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FRONTIER

Framework for internal sensation of pleasure using constraints from disparate findings in nucleus accumbens

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Abstract

It is necessary to find a mechanism that generates first-person inner sensation of pleasure to understand what causes addiction and associated behaviour by drugs of abuse. The actual mechanism is expected to explain several disparate findings in nucleus accumbens (NAc), a brain region associated with pleasure, in an interconnected manner. Previously, it was possible to derive a mechanism for natural learning and explain: (1) Generation of inner sensation of memory using changes generated by learning; and (2) Long-term potentiation as an experimental delayed scaled-up change by the same mechanism that occur during natural learning. By extending these findings and by using disparate third person observations in NAc from several studies, present work provides a framework of a mechanism that generates internal sensation of pleasure that can provide interconnected explanations for: (1) Ability to induce robust long-term depression (LTD) in NAc from naïve animals; (2) Impaired ability to induce LTD in "addicted" state; (3) Attenuation of postsynaptic potentials by cocaine; and (4) Reduced firing of medium spiny neurons in response to cocaine or dopamine. Findings made by this work are testable.

Key Words: Pleasure; Internal sensation; Mind; Memory; Long-term potentiation; Long-term depression; Nucleus accumbens; Drug addiction

Core Tip: Pleasure has been studied by examining animal behaviour and its correlations with molecular and electrophysiological changes. Drugs of abuse generate pleasure along with several seemingly unrelated changes in nucleus accumbens (NAc). When pleasure was examined as a first-person inner sensation, it was possible to arrive at a framework of a causal mechanism for its generation that can also provide inter-

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connected mechanistic explanations for long-term depression (LTD) in NAc in naïve animals, impaired ability to induce LTD in addicted state, attenuation of postsynaptic potentials by both cocaine and dopamine, and reduced firing of medium spiny neurons in NAc by dopamine. Findings made by this work are testable.

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INTRODUCTION

Around 269 million people used drugs of abuse in 2018 and nearly 35.6 million people suffer from drug use disorders globally[1]. Since drugs provide internal sensation of pleasure to which users can get addicted, it is necessary to understand the basic mechanism that generates pleasure and possible ways this leads to addiction. Current studies of brain functions such as perception, memory, fear, anxiety, pleasure, hunger, thirst, reward, aversion, and pain are carried out in animal models by examining behavioural motor actions indicative of those brain functions. During these examinations, there is an implicit assumption that nervous system generates internal sensations of each of those brain functions concurrently with behaviour. Studies have found correlations between behavioural motor actions and sets of neurons that fire and/or their firing rates in brain regions that have a predominant role in those brain functions. In addition, correlations are also found between behaviour and electrophysiological findings in those brain regions. To understand how the brain operates to generate inner sensations of each of the above brain functions, an interconnected framework of explanations is necessary. Even though it is not possible to directly test formation of first-person properties of inner sensations of a brain function, a first step will be to derive plausible mechanisms for their generation using constraints from several disparate findings associated with each brain function.

Learning is expected to generate testable changes that are used for generating first-person inner sensations of memory. By examining fine details of neuronal processes and their properties, it was possible to arrive at a learning mechanism from which inner sensations of memory can be retrieved[2,3]. A summary of the basis of derivation is as follows. Examination of a neuron having thousands of input terminals shows that subsets of nearly 140 input signals can fire that neuron[4,5]. Since input signals attenuate as they propagate towards neuronal soma, it is possible that even a small fraction of one input can fire a neuron, which is being held at a sub-threshold activation state short of that input fraction[6,7]. Associative learning between two stimuli (stimulus 1 and 2) is expected to take place at a location where signals from these stimuli converge. This led to searching for a specific location where learning can generate a specific physical change in millisecond timescales that can be retained for different durations and then enable a cue stimulus (either stimulus 1 or 2 or their components) to generate inner sensation of memory of the second stimulus to explain working, short-term and long-term memories[3].

Input terminals of a neuron are the dendritic spines (spines or postsynaptic terminals) that synapse with output terminals of many neurons in the previous neuronal order. Mean inter-spine distance between spines on the dendrite of a pyramidal neuron is more than the mean spine head diameter[8]. Hence, spines that are abutted to each other most likely belong to different dendrites. Electron microscopic views of cerebral cortex show abutted neuronal processes (including spines) with very minimal extracellular matrix (ECM) space between them. To satisfy requirements of classical conditioning paradigm, interactions between spines that belong to different neurons are necessary[3,9]. This led to the derivation of inter-postsynaptic (inter-spine) functional LINKs (IPLs) between spine heads that belong to different neurons as a general structural change taking place within milliseconds during learning. At a later time when one of the cue stimuli reactivates an IPL, it can depolarize the "inter-LINKed" second spine from a lateral direction. Head region of this inter-LINKed spine gets strongly depolarized during the intermittent arrival of action potentials at its presynaptic terminal when signals from a sensory stimulus

arriving from the environment reach that presynaptic terminal. Head regions of all the spines including the inter-LINKed spines are continuously getting depolarized by the quantal release of neurotransmitter molecules from their corresponding presynaptic terminals, even during sleep. These impart a dominant state that depolarization of a spine results from its presynaptic terminal. Such dominant states of spines of neurons from different neuronal orders can provide a dominant system state that activation of a spine occurs from a stimulus arriving from the environment and that activation of a specific set of spines occurs from arrival of a specific stimulus. In this context, a theoretical possibility is that any instantaneous depolarization of a spine from a lateral direction through an IPL can generate a hallucination (internal sensation of a stimulus in its absence) at the inter-LINKed spine about specific sensory features of the associatively learned second stimulus as a system property[3,9] (Figure 1). This is anticipated of a mechanism that generates memory in the nervous system[10]. This hypothesis called semblance hypothesis is found to agree with the constraints offered by a large number of findings from multiple levels of the system[9].

Ability to induce long-term potentiation (LTP) at a location can be regarded as resulting from the formation of IPLs between abutted spines of different neurons at that location that receive converging excitatory inputs[11]. Since (1) Membrane segments from intracytoplasmic vesicles that carry α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR) subunits can re-organize the cell membrane of lateral spine head region; (2) GluR1 AMPAR subunits are located up to 25 nm beyond the synaptic margin[12], an ideal location for inter-spine interactions; and (3) Endocytosis of GluR1 AMPAR vesicles that uses fragments of membranes from lateral spine head regions is associated with a reversal of LTP (LTP decay)[13] that can be scaled-down to explain the reversal of formed IPLs as a mechanism for physiological forgetting, IPL formation can be viewed as a suitable change triggered by learning[9]. Since (1) Dopamine has a role in motivation-related associative learning [14]; (2) Dopamine lead to the persistence of one-trial hippocampus-dependent memory[15]; and (3) Dopamine cause spine enlargement[16], release of dopamine is expected to augment inter-spine interactions leading to IPL formation and facilitate learning in a motivated state[9].

Application of energy of a different configuration than that is necessary to induce LTP generates long-term depression (LTD) in specific brain regions. An example of such a location is nucleus accumbens (NAc), a brain region associated with generation of pleasure. Cellular changes following LTD stimulation lead to depression of net excitatory postsynaptic potentials recorded from the recording electrode. Since energy is required for stimulation, LTD is an active process and not mere reversal of a mechanism responsible for the decay of LTP[13]. Since experimental results show that it takes several minutes for LTD induction[17,18], it indicates that LTD induction involves time-dependent cellular changes similar to that of LTP induction[11]. Hence, it is necessary to explain time-dependent changes occurring at specific locations where LTD can be induced. Similar to LTP, LTD in the hippocampal synaptic areas is implicated in different types of learning[19-22]. Necessity for stimulation energy and significant delay for induction of LTD following stimulation indicate that several IPLs are formed during LTD induction, similar to that occur during LTP induction[11]. To understand the mechanism that generates internal sensation of pleasure, it is necessary to (1) Examine the neuronal connections to NAc; (2) Examine conditions that allow experimental induction of LTD at this brain region; and (3) Use constraints from all the findings at this region to derive a mechanism for internal sensation of pleasure that can be inter-connected with the remaining findings.

NAc CONNECTIONS

Studies have shown that NAc is primary site mediating reward behaviour and is associated with both reinforcing and addictive behaviours in response to drug use. 95% of cells in the NAc are medium spiny neurons (MSNs). MSNs are called “spiny” due to the abundance of spines on their dendrites. However, visual examination of patterns of distribution of spines on these MSNs[23,24] shows that mean inter-spine distance is comparable to that of the mean spine diameter, which almost matches with the finding in pyramidal neurons that mean inter-spine distance is more than the mean spine diameter[8]. Electron microscopic images of NAc show negligible ECM between cellular processes in many locations[25,26]. Hence, it is possible to infer that the nearest spine to one spine on the dendrite of an MSN is a spine on a different dendrite, which most likely belongs to a different neuron or occasionally to the same neuron.

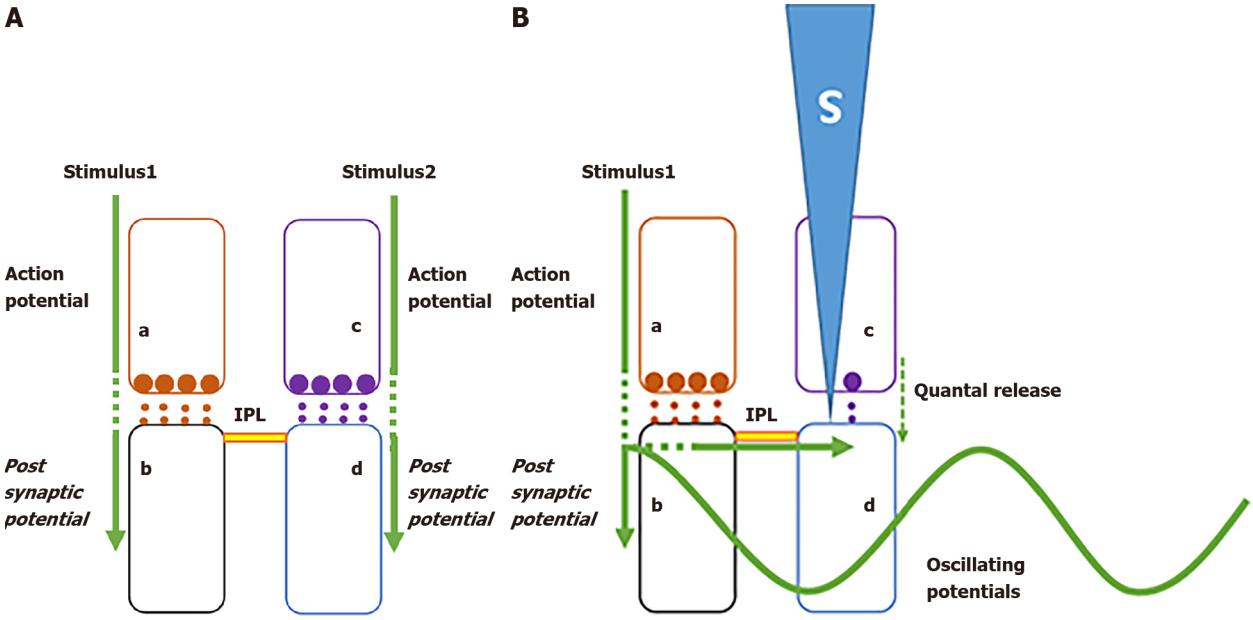

Figure 1 Generation of internal sensation of memory which is used as a reference mechanism to examine internal sensation of pleasure. A: During associative learning between stimulus 1 and 2, signals from these stimuli propagate towards converging locations where inter-postsynaptic functional LINKs (IPLs) between postsynaptic terminals (spines) b and d occur. Spines b and d are depolarized intermittently when action potentials arrive at their presynaptic terminals a and c respectively, and the head regions of these spines are continuously being depolarized by quantally-released neurotransmitter molecules from their presynaptic terminals. These provide a dominant state that a spine is depolarized by its presynaptic terminal that in turn receive signals from stimuli from the environment and is a necessary background condition for generating internal sensation of memory; B: In the above mentioned background state, arrival of stimulus 1 reactivates IPL b-d to cause an incidental lateral activation of postsynaptic terminal d to spark a cellular hallucination (shown using a blue triangle marked S inside) of a sensory stimulus arriving from the environment through its presynaptic terminal c. Details of the method by which sensory qualia of semblions can be determined was described previously[3]. This matches with the expectation of a mechanism for memory[10]. Waveform: Synaptic transmission through synapse a and b and propagation of depolarization through IPL b-d contribute vector components of oscillating extracellular potentials whose frequency needs to be maintained in a narrow range for inducing internal sensation of memory. Specific electrophysiological findings in locations where sensory stimuli converge were found to correlate with behavioural motor actions indicative of specific brain functions. Long-term potentiation (LTP) that can be induced at locations where sensory stimuli converge is an example[87,88]. After application of a high-energy stimulus at a region rich in synapses and following a delay of at least 20 to 30 s[89,90], application of a regular stimulus at the same location generates a potentiated effect when recorded from the postsynaptic dendritic region or postsynaptic neuronal soma. Ability to induce LTP has shown several correlations with animals' ability to learn. It was possible to explain how learning-induced formation of IPLs is artificially produced in a delayed scaled-up manner during experimental LTP induction[11]. By keeping correlation between the ability to generate internal sensation of memory that matches with sensory features of the item whose memory is retrieved and the ability to induce LTP at specific locations[11], specific electrophysiological changes that can be induced at these locations can be examined to arrive at a mechanistic explanation for internal sensation of pleasure. Since there are specific electrophysiological changes that can be induced at locations responsible for different brain functions, a comparative examination can be carried out to understand how different internal sensations are generated (modified from[3]).

Several studies in addiction research have examined changes in synapses on the spines of MSNs in NAc[27-30]. Spines on the dendrites of MSNs receive excitatory inputs from hippocampus, amygdala, thalamus and medial prefrontal cortex. Separate set of spines of MSNs receives inhibitory inputs from ventral tegmental area (VTA) (Figure 2). Dopaminergic inputs from the VTA form additional synapses with the heads or necks of spines that synapse with excitatory inputs[31]. In striatum, certain dopamine functions necessitate spatiotemporal precision between dopamine release sites and receptor locations[32]. It is necessary to find how these connections are related to the generation of internal sensation of pleasure and the ability to generate experimental LTD in NAc.

KEY FINDINGS IN NAc THAT NEED INTERCONNECTED EXPLANATIONS

There are several disparate findings in NAc. Major requirement to understand the mechanism by which pleasure is generated is to reach a single mechanism that can provide inter-connected explanations for all those findings. Constraints offered by all the findings together provide an opportunity to derive a unique solution (Table 1).

Table 1 Key findings in nucleus accumbens and constraints provided by them

Finding	Constraint
LTD can be induced at the spinous region of MSNs of NAc[17,18,28]	Energy applied at the spinous region leads to depression of potentials at the recording electrode placed at the postsynaptic region or on MSN soma
LTD induction has a time delay following stimulation[17,18] comparable to that of LTP induction[13,14]	A time-dependent cellular change is taking place during the delay period following LTD stimulation
Similar to LTP, LTD is also NMDA receptor-dependent[82]	LTD induction takes place through activation of NMDA receptors of glutamatergic synapses
When rewards or conditioned stimuli that predict reward are presented, dopamine neurons in the VTA increase their firing[91,92] releasing dopamine in their terminals that synapse with spines of MSNs in NAc	Dopamine produces certain changes at the spines of MSNs that synapse with excitatory inputs
Drugs of abuse such as cocaine increase dopamine levels in the NAc[28]	Dopamine has certain actions on the spines of MSNs that synapse with excitatory inputs
Dopamine attenuates postsynaptic potentials elicited by stimulation of different excitatory inputs to NAc shell region[40]	Action of dopamine on spines of MSNs that synapse with excitatory inputs attenuates postsynaptic potentials when these excitatory inputs are stimulated through a mechanism
Dopamine reduces excitability of MSNs *in vitro*[93]	Action of dopamine on the spines of MSNs that synapse with excitatory inputs results in inhibition of MSNs through a mechanism
Exposure to cocaine leads to attenuation of postsynaptic potentials[42]	Action of cocaine leads to release of dopamine that acts on spines of MSNs that synapse with excitatory inputs and results in attenuation of postsynaptic potentials
In response to natural rewards and cocaine exposure, a major set of MSNs show depression of firing rate[43-46]	Rewards and drugs cause release of dopamine from VTA and dopamine's action on spines of MSNs that synapse with excitatory inputs result in reduced firing rate of MSNs through a mechanism
Synchronization of membrane potential states in a population of NAc neurons [53]	A mechanism through gap junctions between inhibitory neurons in VTA that provides inputs to NAc neurons and/or a mechanism at the level of spines of MSNs
Brain functions occur optimally in a narrow range of frequency of oscillating extracellular potentials especially that of background alpha rhythm as evident from electroencephalogram (EEG) findings[49]	Regional oscillations of extracellular potentials are expected to be related to oscillating extracellular potentials of the system
Summary of findings	**Inter-connected constraints**
Drugs cause release of dopamine from VTA, which in turn cause attenuation of postsynaptic potentials and depression of MSNs in NAc. Application of energy is able to induce delayed LTD through scaled up changes expected to occur normally at the synaptic region of NAc, which is likely responsible for generating internal sensation of pleasure	Dopamine does certain unique changes at the spines of MSNs of NAc that synapse with excitatory inputs to cause attenuation of postsynaptic potentials, depression of MSNs and promotes experimental induction of LTD. This inter-connected operation is expected to explain a mechanism that generates inner sensation of pleasure

Constraints provided by disparate findings can be used to find inter-connectable explanations for deriving a unique mechanism, which is expected to provide an explanation for the generation of internal sensation of pleasure. NAc: Nucleus accumbens; LTD: Long-term depression; MSNs: Medium spiny neurons; NMDA: N-methyl-D-aspartate; VTA: Ventral tegmental area.

MECHANISM OF PLEASURE AND INTERCONNECTED EXPLANATIONS FOR FINDINGS IN NAc

By keeping (1) the correlation between associative learning and LTP induction[11]; and (2) the ability of inter-LINKed spines of excitatory synapses to induce internal sensation of memory[3] as reference mechanisms, a reasonable expectation is that a mechanism for generating internal sensation of pleasure that satisfies constraints from different findings in NAc (Table 1) will become possible. Dendritic arbors of different MSNs overlap. Energy is applied to induce LTD at the synaptic locations of MSNs of NAc where spines present on different dendrites are abutted. One set of these spines receive inputs from excitatory neurons of different brain regions and another set of spines receive inputs from inhibitory neurons of VTA. In addition, the heads or necks of spines that synapse with excitatory inputs receive dopaminergic inputs[31] (Figure 3). Spines of excitatory synapses that also receive dopaminergic inputs enlarge by the action of dopamine[16]. Furthermore, a scaled-up electrophysiological change responsible for the generation of pleasure is expected to take place during experimental LTD induction at these synaptic locations.

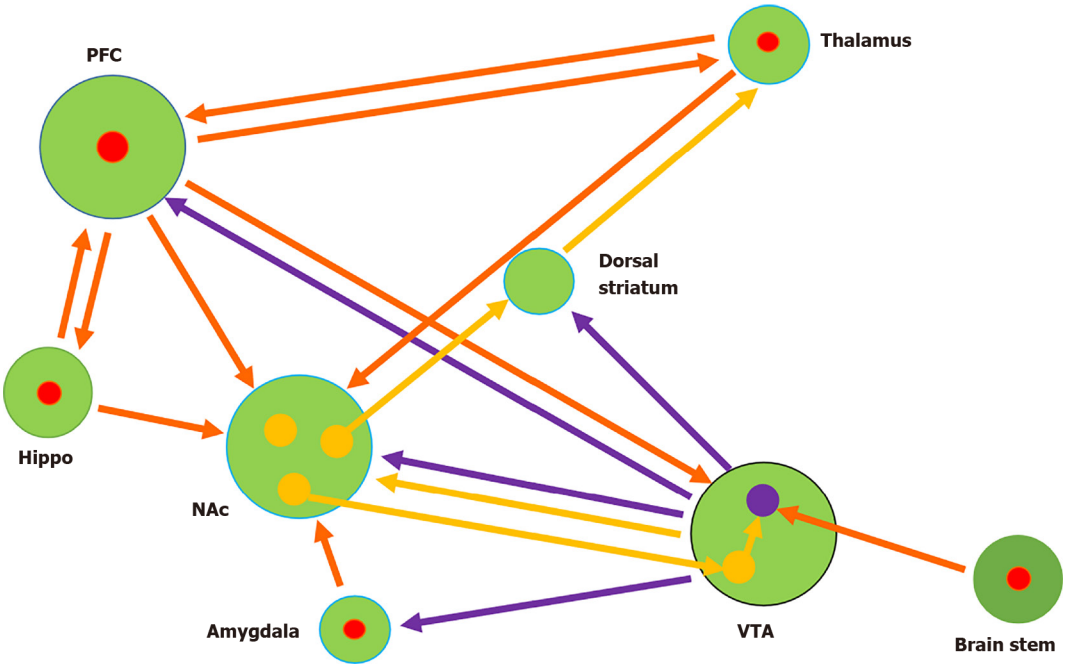

Figure 2 Input and output connections of nucleus accumbens. One set of spines of medium spiny neurons (MSNs) in the nucleus accumbens receive excitatory inputs (red arrows) from several regions. The same spines of MSNs that receive excitatory inputs receive dopaminergic inputs (violet arrows) from ventral tegmental area (VTA). Another set of MSN spines receive inputs from inhibitory interneurons (orange arrow) in the VTA. Large green circles: Different brain regions. Small circles: Predominant cell types within brain regions (Red: Excitatory; Orange: Inhibitory; Violet: Dopaminergic). PFC: Prefrontal cortex; NAc: Nucleus accumbens; VTA: Ventral tegmental area.

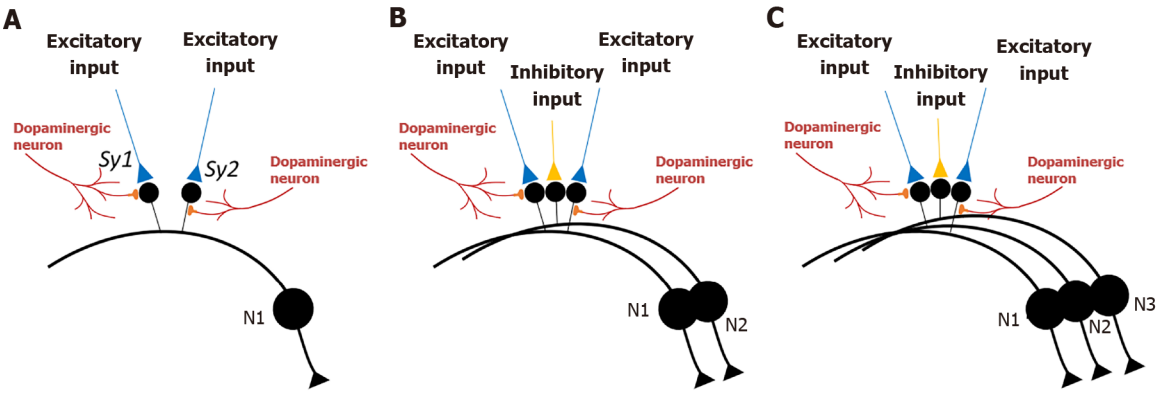

Figure 3 Interactions between spines of medium spiny neurons that synapse with excitatory inputs and spines of medium spiny neurons that synapse with inhibitory inputs. A: Adjacent spines (small black circles) on the dendrite of a medium spiny neuron (MSN) (N1) (cell body is drawn in a large black circle) that synapse with two excitatory inputs (in blue) to form synapses Sy1 and Sy2). Golgi staining shows that spines are physically well separated from each other on the dendrites of MSNs[23,24] such that the inter-spine space is occupied by spines of other dendrites or processes of other neurons or glial cells. This increases the probability that the nearest spine to a spine on the dendrite of a MSN is most likely a spine that belongs to another neuron, or in rare cases belongs to another branch of the same neuron. Note that dopaminergic inputs synapse either onto the head or neck region of spines that synapse with excitatory inputs; B: In between two adjacent spines of MSN N1 shown in figure A, there is a spine that belongs to a second MSN (N2). This spine synapses with an inhibitory input (in orange). All the spines are electrically insulated from each other by fluid extracellular matrix. Natural stimulants or cocaine abuse causes release of dopamine that will cause enlargement of spines that synapse with excitatory inputs. Since the spine that synapses with the inhibitory input is spatially interposed between the expanding spines, inter-postsynaptic functional LINKs are formed between those three spines; C: Same configuration of two spines of MSNs that synapse with excitatory inputs and one middle spine synapsing with inhibitory input. Here, these spines belong to three different MSNs.

There are two main methods by which LTD can be induced. (1) Low-frequency stimulation induces LTD that requires activation of N-methyl-D-aspartate receptors (NMDARs)[33,34]. Modest activation of NMDARs that can be used to induce LTD[28] may involve AMPAR endocytosis[35]; (2) By keeping postsynaptic depolarization below a threshold, a tetanic stimulation that normally induces LTP can induce LTD [36]. Removal of surface AMPARs occurs during induction of both NMDAR-dependent LTD[37,38], and metabotropic glutamate receptor-LTD[39,40]. Since endocytosis of vesicles containing AMPAR subunits during expression of LTD in NAc

[18] is associated with usage of membrane segments from lateral spine head regions that reduces spine size, it can lead to reversal of large number of existing IPLs. Even though reversal of existing IPLs can explain LTD similar to that of LTP decay[13], it is necessary to explain LTD as an active mechanism that requires energy for its experimental induction. Based on findings in NAc (Table 1), it is also necessary to explain (1) Attenuation of postsynaptic potentials by the effect of dopamine on MSN spines that synapses with excitatory inputs[41,42]; and (2) Reduced firing rate of MSNs[43-46], in addition to finding a matching explanation for the generation of internal sensation of pleasure. This has been remaining a challenge.

In the above contexts, main question is whether it is possible to explain internal sensation of pleasure and all the findings in Table 1 in terms of IPL mechanism. It is known that drugs of abuse such as cocaine lead to increased dopamine levels in the NAc[28]. Dopamine is known to cause spine enlargement[16]. Since dopaminergic inputs synapse with spines that receive excitatory glutamatergic inputs, this is expected to cause enlargement of those spines of MSNs. This forces these spines to form IPLs with all their abutted spines. Since some MSN spines synapse with excitatory inputs and others with inhibitory inputs, it is necessary to take into account the possibility for IPL formation between these spines (Figure 3B). In this context, IPL formation between MSN spines that synapse with inhibitory inputs and MSN spines that synapse with excitatory inputs can be examined in the light of the previous view that inhibitory inputs at the input level have a role in information processing[47]. It is necessary to combine all this information to obtain a solution for the challenge described in the previous paragraph.

Since LTP induction in the cortex usually requires low doses of gamma-amino butyric acid$_A$ ($GABA_A$) receptor antagonist bicuculline[48] for concomitant reduction of GABAergic inhibition, it shows the necessity to block activation of spines that synapse with inhibitory inputs. When spines that receive inhibitory inputs are in large numbers, such as in NAc, a mere reduction in GABAergic inhibition alone will not be able to induce LTP. This is because the numbers of spines that receive excitatory inputs are comparatively less to form IPLs between them alone to induce LTP. Now the question is, "What is the effect of application of energy on the MSN spines that receive excitatory inputs and MSN spines that receive inhibitory inputs that are distributed somewhat equally?" This increases the probability for the formation of IPLs between those spines. This can lead to propagation of hyperpolarization from the spines that synapse with inhibitory inputs to neutralize and even hyperpolarize the spines that synapse with excitatory inputs. In experimental LTD stimulation, this will result in depression of net potentials at the recording electrode responsible for LTD.

Now the question is, "Can formation of IPLs between MSN spines that synapse with excitatory inputs and MSN spines that synapse with inhibitory inputs explain the generation of internal sensation of pleasure?" At this juncture, a reasonable inference is that semblance generated at the location where LTD can be experimentally induced is associated with internal sensation of pleasure. Now, one can ask, "What type of a semblance can be anticipated based on the nature of inputs at the spines of MSNs and IPLs that are formed between them?" In physiological conditions, hyperpolarization of spines that receive inhibitory inputs is expected to propagate to spines that receive excitatory inputs through the IPLs formed between them. This is expected to generate a conformational change in the net local semblance induced from all the inter-LINKed spines of MSNs and contribute to internal sensation of pleasure (Figure 4). Brain functions such as pleasure take place only in a state of normal consciousness associated with a narrow range of oscillating extracellular potentials as evident from EEG findings[49]. Synaptic transmission at the synapses and propagation of potentials across the IPLs are expected to contribute vector components to both regional and system level oscillating extracellular potentials[3]. Narrow range of background oscillating extracellular potentials is expected to be generated from continuous reactivation of the large number of IPLs formed from common background stimuli to which nervous system is exposed[50,51]. The latter event continues to generate a background semblance in which internal sensation of pleasure is formed (Figure 4). Explanation for the functional significance of background semblance was explained previously[9].

Several inhibitory neurons in the VTA are expected to get activated through gap junctions between them similar to that contribute to cortical oscillations[52]. It can lead to synchronization of membrane potential states in a population of NAc neurons[53] and can explain how continuous reactivation of newly formed IPLs in NAc maintains pleasure. In physiological conditions, formation of IPLs between MSN spines that synapse with excitatory inputs and MSN spines that synapse with inhibitory inputs can explain how it leads to attenuation of postsynaptic potentials while getting

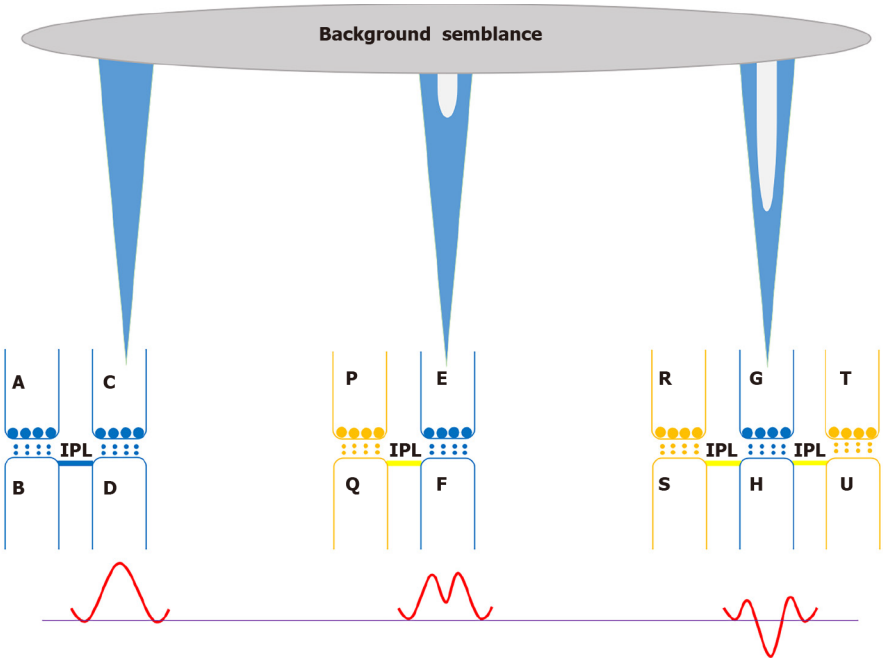

Figure 4 A schematic representation of units of internal sensations whose integral generates pleasure in a background net semblance of the system. Left: Normal semblance as shown in Figure 1. Inter-postsynaptic functional LINK (IPL) between spines B and D that receive excitatory inputs (in blue). An action potential arriving at presynaptic terminal A from a stimulus depolarizes its postsynaptic terminal B, which in turn propagates through the IPL B-D and depolarizes (shown as a positive waveform) inter-LINKed spine D. This generates units of internal sensations (shown as a blue triangle projected upwards from presynaptic terminal C that denotes semblance). Middle: Reactivation of an IPL between spine Q of a medium spiny neuron (MSN) that synapse with an inhibitory input (in orange) and another spine F of a MSN that synapse with an excitatory input (in blue) results in spread of hyperpolarization from spine Q to spine F. This leads to changes in both the waveform of spine depolarization (red waveform) and conformation of semblance (shown as a dip in the blue triangle). Right: Here, spine H that synapses with an excitatory input (in blue) forms IPLs with spines S and U that synapse with inhibitory inputs (orange). Net effect of hyperpolarization results in profound changes in both waveform of spine depolarization (red waveform) and conformation of semblance (shown as a deep dip in the blue triangle). Net effect of changes in semblances from all the inter-LINKed spines of MSNs in nucleus accumbens (NAc) is expected to generate a special semblance of pleasure.

exposed to dopamine[41]. In addition, it can also explain reduced firing of MSNs when animals are exposed to both natural rewards and cocaine[43-46]. The scaled-up change in experimental stimulation that generates LTD is a net effect of depression in the sum of potentials arriving at the recording electrode. A summary of these interconnected findings is shown in Figure 5.

HOMEOSTATIC CHANGES DURING DRUG ABUSE AND WITHDRAWAL

IPL formation involves interaction between outer membranes of spines by excluding the insulating fluid ECM[3]. Exocytosis of intra-cytoplasmic vesicles provides membrane segments that allow re-organization of the cell membrane at the lateral margins of spines that can promote IPL formation. Conversely, endocytosis of GluR1 AMPAR vesicles is associated with a reversal of LTP (LTP decay)[13]. Similar mechanisms can be expected to cause the formation and reversal of IPLs during LTD induction and decay respectively.

After 10 to 14 d of repeated *in vivo* cocaine exposure, both the ratio of AMPAR/NMDAR-mediated excitatory postsynaptic currents (EPSCs) and magnitude of LTD are reduced[17]. One of the reasons for a reduction in the AMPAR/NMDAR - mediated EPSC ratio is a decrease in the number of AMPARs. Based on the IPL mechanism, cocaine exposure results in the enlargement of spines that predisposes the IPLs formed between these spines to undergo fusion pore formation. In this context, endocytosis of vesicles containing GluR1AMPARs following cocaine administration can be viewed as a homeostatic mechanism for preventing IPL fusion. During vesicle endocytosis, usage of membrane segments from lateral spine head regions can reduce the size of spine heads and reverse extreme changes of IPLs such as IPL fusion. Endocytosis of these vesicles observed during experimental LTD induction[18,54,55] can be viewed as a scaled-up physiological response for preventing IPL fusion, especially in locations where dopamine is released. In this context, the finding that a challenge dose of cocaine after weeks of cocaine withdrawal terminates withdrawal

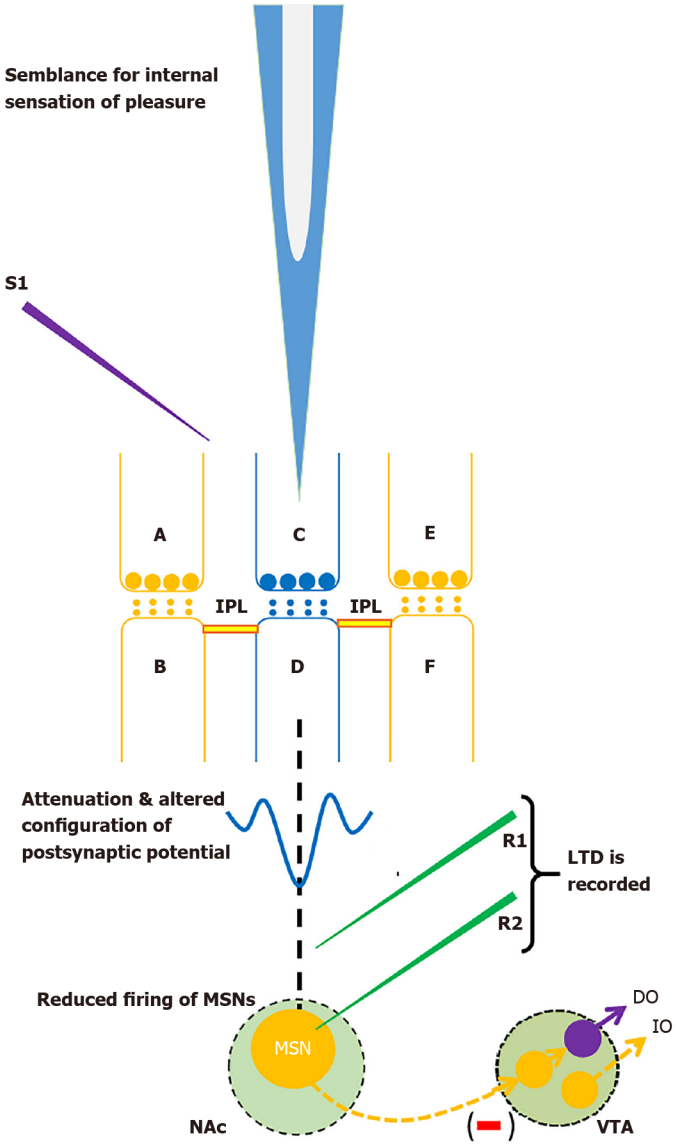

Figure 5 Nucleus accumbens circuitry that matches with constraints from several findings. Spines B and F belonging to different medium spiny neurons (MSNs) synapse with inhibitory inputs arriving through presynaptic terminals A and E respectively. Spine D on a third MSN synapses with excitatory input arriving through presynaptic terminal C. Two inter-postsynaptic functional LINKs (IPLs) are formed between spines B, D and F. These IPLs between spines that synapse with excitatory and inhibitory inputs lead to mixing of depolarization on the spines that synapse with excitatory input and hyperpolarization on the spines that synapse with inhibitory inputs. This leads to alternation of configuration of the net postsynaptic potentials as shown in a trace. Net semblance from a large number of inter-LINKed spines is expected to generate a special semblance for internal sensation of pleasure. Due to propagation of hyperpolarization, sum of potentials reaching many MSNs may not cross the threshold for firing, which leads to reduced firing of MSNs. A specific stimulation pattern applied at the presynaptic region using stimulating electrode S1 results in the formation of a large number of the above-mentioned types of IPLs in a time-dependent manner (inferred from delay between stimulation and long-term depression (LTD) induction[17,18]) resulting in LTD recorded from either recording electrode R1 (extracellular field recording) or R2 (whole-cell recording). Two inhibitory inputs to MSN and one inhibitory output from MSN are shown in orange. Excitatory synapse is shown in blue. Dopaminergic neuron of ventral tegmental area is shown in violet. DO: Dopaminergic output; IO: Inhibitory output; VTA: Ventral tegmental area.

along with endocytosis of AMPARs[28] can be considered as an augmented homeostatic mechanism.

During early withdrawal, administration of dopamine alone restores both spine structure and LTD[56] that can be explained in terms of IPL formation between MSN spines that synapse with excitatory inputs and MSN spines that synapse with inhibitory inputs indicating that the system is highly dynamic. During later periods of withdrawal, an increase in AMPARs at the membrane surface is observed[57,58]. During this time, a strong potentiation of AMPAR-mediated synaptic transmission is observed in the synapses on the spines of NAc MSNs. At this time, a single exposure to cocaine suddenly reverses the synaptic potentiation to depression[59]. This indicates that after a very lengthy drug-free period, the system reaches a near normal state and starts responding like a naïve system by forming IPLs between spines that synapse with excitatory inputs and spines that synapse with inhibitory inputs.

PATHOLOGICAL CHANGES FOLLOWING DRUG ABUSE

Inter-spine fusion is a possible consequence of drug abuse

Based on the IPL mechanism, conditions such as excessive drug use that cause excessive release of dopamine can lead to progression of IPLs to an extreme end of the spectrum of IPL changes, namely IPL fusion[6]. Defects in normal homeostatic mechanisms described in the above paragraph or changes in membrane composition can augment IPL fusion. Fusion between expanding spines matches with the previous observation of dye diffusion between neurons in NAc under the influence of dopamine[60]. Since transcriptomes of even neighboring neurons of similar type are different in the brain[61-63], IPL fusion that occurs between spines that belong to two neurons (Figure 3B and C) can lead to cytoplasmic content mixing and protein precipitation. An initial cellular response is expected to seal off the IPL fusion pore. When this fails, neurons are expected to protect themselves by removing fused spines from them[64], which can explain spine loss during cocaine abuse[65,66]. Loss of spines at the input regions of NAc MSNs in cocaine users will reduce the number of abutted spines and will reduce the probability of IPL formation. This will prevent experimental induction of LTD as evidenced from different studies[67,68].

Drug addiction

Major consequence of IPL fusion is the eventual loss of spines of MSNs[65,66] as a homeostatic mechanism to protect neuronal cells[64]. Since "non-addicted" animals regain the ability to generate LTD after two weeks of discontinuing self-administration of cocaine[68], it indicates that these animals may not have lost their spines. However during early stages of spine loss, the remaining spines can form IPLs to generate internal sensation of pleasure only if they can expand. This necessitates release of dopamine that in turn necessitates the availability of drugs. A natural consequence of this is initiation of drug seeking behavioural motor actions elicited through separate pathways. In later stages when more spines are lost, more amount of drug will become necessary even to maintain internal sensation of normal comfort. At this stage, reduced number of spines on MSNs will lead to persistent impaired LTD in "addicted" animals[68].

DISCUSSION

LTD can be experimentally induced in many brain regions and by different methods. Translating this to understand how it is related to conformational changes in semblance and the nature of internal sensations require examination of all the connections and findings at those regions. Excitatory neurons are controlled by inhibitory neurons both at the output level, for example, in the visual cortex[69] and at the input level[70,71]. The present work has explained a new testable function of inhibitory neurons at their output level. By explaining IPL formation between MSN spines that synapse with inhibitory inputs and MSN spines that synapse with excitatory inputs, it became possible to provide mechanistic explanations for previous assumptions that (1) Increased firing of VTA dopaminergic neurons encode an array of sensory, motor and cognitive variables[72]; and (2) Reduced activity of NAc MSNs encode reward[73-76]. The finding that coupling of potentials between MSNs were found to occur only in neurons that also showed dye coupling[60] matches with the IPL mechanism explained in the present work because IPLs with fusion pores can allow both dye diffusion through the fusion pore and propagation of potentials across the connecting membrane segments. The inference that input-specific filtering of excitatory inputs in the NAc is provided by dopamine[77] can be explained in terms of IPL formation between MSN spines that both synapse with excitatory inputs and enlarge under the influence of dopamine and MSN spines that receive inhibitory inputs.

Further examination is needed to understand the role of cholinergic inputs that synapse with the spines of MSNs in NAc[78]. It is also necessary to examine the difference in dopamine's actions on MSN spines in the shell and core regions of NAc [79,80] for their contributions on pleasure generation. Comparable findings in neurons of lateral hebenula, a brain region associated with reward, whose spines synapse with excitatory, inhibitory and dopaminergic inputs[81]can be examined to further understand this related brain function.

Fast kinetics of AMPA current in glutamatergic synapses allows initial depolarization of the spine head region. It is known that glutamate released from the presynaptic boutons is necessary to depolarize their spines, which will relieve blockage of NMDARs by Mg^{2+}[82]. Furthermore, postsynaptic depolarization below certain threshold induces LTD when tetanic stimulation that normally induces LTP is used[36]. Hyperpolarization from inter-LINKed spines that synapse with inhibitory inputs can provide suitable conditions for the above. It is also possible that timing of hyperpolarization propagating from an inter-LINKed spine that synapse with an inhibitory input also determines the conformation of semblance generated at the spines of excitatory synapses shown in Figures 4 and 5. Understanding details of the mechanism can provide information regarding selection of different types of glutamate receptors, their distribution and functional roles in different brain regions.

Based on the present work, sequence of appearance of neurotransmitters glutamate and GABA[83,84] is likely to provide information about the period when internal sensation of pleasure started appearing during evolution. The enzyme glutamic acid decarboxylase (GAD) catalyzes decarboxylation of glutamate to form GABA. Even though GABAergic interneurons were present in the common ancestor of all amniotes [85], it is difficult to trace the sequence of appearance of glutamatergic and GABAergic neurons. A possibility is that as neurons started receiving a large number of inputs, several combinations of IPLs started generating different internal sensations, which allowed natural selection of neurons that started expressing GAD. By selecting configurations of inputs that led to the formation of IPLs generating internal sensation of pleasure, animals were likely able to seek certain items and perform certain actions that were essential for survival, which those animals would not have performed otherwise.

CONCLUSION

By viewing pleasure as a first-person internal sensation, it was possible to extend IPL mechanism to formulate a framework of a specific mechanism taking place at the dendritic spine regions of MSNs in NAc responsible for pleasure. It matches with constraints provided by disparate findings such as the ability to induce robust LTD in NAc from naïve animals, impaired ability to induce LTD in addicted state, attenuation of postsynaptic potentials by cocaine, and reduced firing of MSNs in response to cocaine or dopamine. IPL mechanism that provided inter-connectable explanations for pleasure and disparate findings in NAc can be subjected to further verification. Since IPLs are expected to be of roughly $10nm^2$ in area as inferred from theoretical studies of membrane bilayers[86], advanced microscopic methods are necessary to detect their real-time formation, stabilization, and reversal in normal conditions and conversion to fusion states in addicted animals.

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REVIEW

Metabolic disturbances associated with antipsychotic drug treatment in patients with schizophrenia: State-of-the-art and future perspectives

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Abstract

Metabolic disturbances and obesity are major cardiovascular risk factors in patients with schizophrenia, resulting in a higher mortality rate and shorter life expectancy compared with those in the general population. Although schizophrenia and metabolic disturbances may share certain genetic or pathobiological risks, antipsychotics, particularly those of second generation, may further increase the risk of weight gain and metabolic disturbances in patients with schizophrenia. This review included articles on weight gain and metabolic disturbances related to antipsychotics and their mechanisms, monitoring guidelines, and interventions. Nearly all antipsychotics are associated with weight gain, but the degree of the weight gain varies considerably. Although certain neurotransmitter receptor-binding affinities and hormones are correlated with weight gain and specific metabolic abnormalities, the precise mechanisms underlying antipsychotic-induced weight gain and metabolic disturbances remain unclear. Emerging evidence indicates the role of genetic polymorphisms associated with antipsychotic-induced weight gain and antipsychotic-induced metabolic disturbances. Although many guidelines for screening and monitoring antipsychotic-induced metabolic disturbances have been developed, they are not routinely implemented in clinical care. Numerous studies have also investigated strategies for managing antipsychotic-induced metabolic disturbances. Thus, patients and their caregivers must be educated and motivated to pursue a healthier life through smoking cessation and dietary and physical activity programs. If lifestyle intervention fails, switching to another antipsychotic drug with a lower metabolic risk or adding adjunctive medication to mitigate weight gain should be considered. Antipsychotic medications are essential for schizophrenia treatment, hence clinicians should monitor and manage the resulting weight gain and metabolic

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disturbances.

Key Words: Antipsychotics; Metabolic disturbances; Weight gain; Schizophrenia; Monitor; Intervention

Core Tip: Metabolic disturbances associated with antipsychotic drug treatment are prevalent in patients with schizophrenia. We herein discuss the epidemiology, the underlying mechanisms, monitoring, and intervention strategies of antipsychotics related metabolic disturbances.

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INTRODUCTION

Patients with schizophrenia have a two to three times higher mortality rate[1,2] and a 20%–25% shorter life expectancy[3] compared with the general population. In addition to the considerably increased risks of suicide, cancer, and respiratory diseases, cardiovascular mortality is a leading cause of excess mortality in patients with schizophrenia[4,5]. Metabolic syndrome and obesity are major cardiovascular risk factors in patients with schizophrenia[5,6].

Before the introduction of the first antipsychotic drug chlorpromazine in 1952, cohort studies noted an increased incidence of abnormal glucose metabolism in patients with schizophrenia[7]. Studies also found that increased fasting and postprandial blood glucose levels in drug-naïve patients with schizophrenia were partly correlated with the severity of their illness[7,8]. Although such metabolic disturbances are partially attributed to unhealthy lifestyle behaviors such as smoking, poor diet, and physical inactivity[9], evidence also indicates a shared pathophysiology between schizophrenia and metabolic disturbances[10]. Meta-analyses of first-episode and drug-naïve patients with schizophrenia have indicated impaired glucose homeostasis and subclinical dyslipidemia before antipsychotic treatment[8,11]. Impaired glucose tolerance in the first-degree relatives of patients with schizophrenia further supports the role of genetic predisposition between schizophrenia and metabolic disturbances[12]. Researchers aim to determine the common susceptible genes that contribute to both schizophrenia and type 2 diabetes mellitus[13-15]. Other pathobiological factors contributing to metabolic disturbances in patients with schizophrenia have also been proposed. Mück-Seler *et al*[16] found that patients with schizophrenia have hypothalamic–pituitary–adrenal axis dysregulation and increased plasma cortisol levels, and evidence shows that hypothalamic–pituitary–adrenal axis dysregulation may play a significant role in the development of metabolic syndrome [17]. Researchers have also suggested that schizophrenia and metabolic syndrome are both related to inflammatory and immune mechanisms[18,19].

Additionally, antipsychotic treatment may exacerbate the metabolic disturbances in patients with schizophrenia. Antipsychotic drugs are the drugs of choice for treating patients with schizophrenia, and certain drugs are also indicated to treat a wide range of mental illnesses, including bipolar disorder, treatment-resistant depression, Tourette syndrome, and aggressive behavior in autism. These drugs are categorized as first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). FGAs act on the dopaminergic system by blocking the dopamine type 2 (D2) receptors. Compared with FGAs, SGAs treat the negative, cognitive, and mood symptoms of schizophrenia more effectively and result in fewer extrapyramidal symptoms at clinically effective doses[20]. Therefore, SGAs may result in greater treatment adherence and psychotic relapse prevention.

Although a meta-analysis indicated that nearly all antipsychotics are associated with weight gain after prolonged exposure[21], certain SGAs are associated with a greater liability of weight gain and metabolic disturbances than high-potency FGAs are[22]. However, studies have shown that antipsychotic use is associated with a decreased risk of all-cause, cardiovascular, and suicide mortality[23,24]. Such findings on long-term mortality outcomes may appear inconsistent with the metabolic side effects of antipsychotic use. This disconnection is likely to due to the improvement of psychopathology associated with antipsychotic treatment, which subsequently may result in healthy lifestyle behaviors and use of health care services for physical illnesses[23,25].

Although antipsychotic medications are essential for treating schizophrenia, clinicians should compare the risks and benefits in choosing the most favorable treatment. This review focused on the adverse effects of weight gain and metabolic disturbances induced by antipsychotic drugs.

ANTIPSYCHOTIC DRUGS AND WEIGHT GAIN

Studies have shown the prevalence of obesity [body mass index (BMI) over 30 kg/m^2] among people with schizophrenia is 42%–60%[26,27]. Several[28,29] but not all[30,31] studies have reported that antipsychotic-naïve patients with schizophrenia are at a higher risk of overweight and obesity. Additionally, weight gain is a well-known side effect of antipsychotic drugs in patients with schizophrenia, influencing 15%–72% of patients[28]. Among FGAs, low-potency ones such as chlorpromazine and thioridazine are related to a greater risk of weight gain than high-potency ones such as haloperidol and fluphenazine[32].

Various SGAs are also associated with varying probabilities of weight gain: Clozapine and olanzapine carry the highest risk; quetiapine, risperidone, and paliperidone an intermediate risk; and aripiprazole, ziprasidone, and lurasidone the lowest risk[20,33,34]. The difference between long-acting injectable and oral SGAs relative to the incidence of weight gain is not significant[35]. Notably, the greatest degree of weight gain in drug-naïve patients with schizophrenia occurs in the first few months after antipsychotic commencement[36]. Although the rate of weight gain then gradually decreases, patients might continue to gain weight for 1–4 years[37]. An early weight gain of > 5% in the first month is the best predictor of long-term weight gain [38].

ANTIPSYCHOTIC DRUGS AND METABOLIC DISTURBANCES

Several attempts have been made by various organizations to establish diagnostic criteria for metabolic syndrome[39]. The World Health Organization proposed the first definition of metabolic syndrome in 1998[40]. In 2001, the National Cholesterol Education Program Adult Treatment Panel III updated the guidelines for metabolic syndrome[41]. The limitation of the aforementioned definitions is that because cutoff values of obesity specific to certain populations are not defined, such cutoff values are not applicable to different ethnic groups. In 2004, Tan *et al*[42] proposed a modified National Cholesterol Education Program Adult Treatment Panel III criteria for metabolic syndrome in Asian populations. In 2006, the International Diabetes Federation provided a worldwide definition of metabolic syndrome with ethnicity-specific criteria for central obesity[43]. Table 1 illustrates the different definitions of metabolic syndrome from different organizations.

Metabolic syndrome is a group of health problems that includes central obesity, hyperglycemia, dyslipidemia, and hypertension, with central obesity being the primary feature[44]. Central obesity is associated with insulin resistance, which finally results in type 2 diabetes mellitus and cardiovascular diseases. Metabolic syndrome is highly prevalent in patients with schizophrenia; the overall prevalence rate being 32.5%[45]. Results from the Clinical Antipsychotic Trials of Intervention Effectiveness schizophrenia trial and comparison with national estimates from the Third National Health and Nutrition Examination Survey revealed that men and women from the Clinical Antipsychotic Trials of Intervention Effectiveness trial were 138% and 251% more likely, respectively, to have metabolic syndrome than patients from the Third National Health and Nutrition Examination Survey matched sample[46].

Table 1 Diagnostic criteria for metabolic syndrome

Organization, Year	WHO, 1988	NCEP/ATP III, 2001	Modified NCEP/ATP III for Asians, 2004	IDF, 2006
Criteria	Glucose intolerance, IGT, diabetes mellitus, or insulin resistance together with two or more of the following:	Three or more of thefollowing:	Three or more of thefollowing:	Central obesity as defined by ethnicity/race, specific WC, but can be assumed if BMI > 30 kg/m^2 and with two or more of the following:
	BP: ≥ 140/90 mmHg	FPG: ≥ 110 mg/dL[1] or on treatment for DM	FPG: ≥ 110 mg/dL[1] or on treatment for DM	FPG: ≥ 100 mg/dL or on treatment for DM
	Abdominal obesity: WHR > 0.9 and > 0.85 for men and women, respectively, and/orBMI: > 30 kg/m^2	BP: ≥ 130/85 mmHg	BP: ≥ 130/85 mmHg	BP: ≥ 130/85 mmHg or on treatment
	Triglycerides: ≥ 150 mg/dL or onTreatment	Triglycerides: ≥ 150 mg/dL or on treatment	Triglycerides: ≥ 150 mg/dL or on treatment	Triglycerides: ≥ 150 mg/dL or on treatment
	HDL-C: < 35 mg/dL for men and < 39 mg/dL for women	HDL-C: < 40 mg/dL for men and < 50 mg/dL for women	HDL-C: < 40 mg/dL for men and < 50 mg/dL for women	HDL-C: < 40 mg/dL for men and < 50 mg/dL for women or on treatment
	Urine albumin excretion rate: ≥ 2 0 μg/min or urine albumin to creatinine ratio: ≥3 0 mg/g	WC: ≥ 102 cm for men and ≥ 88 cm for women	WC: ≥ 90 cm for men and ≥ 80 cm for women	

[1]FPG ≥ 100 mg/dL modified in 2004 according to the International Diabetes Federation definition of impaired fasting glucose. The 2001 definition of National Cholesterol Education Program Adult Treatment Panel III identified fasting plasma glucose ≥ 110 mg/dL as elevated. BMI: Body mass index; FPG: Fasting plasma glucose; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; IR: Insulin resistance; IDF: International Diabetes Federation, NCEP/ATP III: National Cholesterol Education Program Adult Treatment Panel III; WC: Waist circumference; WHR: Waist-to-hip ratio; WHO: World Health Organization.

As mentioned, individual antipsychotic drugs have significant differences in their effects on metabolic disturbances in correlation with their weight gain probabilities [22]. However, some case reports have suggested that substantial weight gain or obesity may not be a factor in up to 25% of cases of new-onset diabetes during antipsychotic treatment[47]. Other studies have reported that olanzapine exerts metabolic changes within days in healthy volunteers without a significant change in body weight[48,49]. Evidence suggests that antipsychotics may directly influence pancreatic beta cells, resulting in time-dependent changes in insulin secretion with initial hypoinsulinemia and subsequent compensatory hyperinsulinemia[50].

MECHANISM UNDERLYING WEIGHT GAIN AND METABOLIC DISTURBANCES DUE TO ANTIPSYCHOTIC DRUGS

Several neurotransmitters and hormones thought to be involved in the management of satiety, feeding, and glucose metabolism have been implicated in the mechanism of antipsychotic-induced weight gain (AIWG) and metabolic disturbances.

Hormones

Various peptide hormones, including leptin, adiponectin, ghrelin, orexin, and cholecystokinin (CCK), play critical roles in the regulation of energy homeostasis and are suggested to be biomarkers of metabolic disturbances. Studies have indicated that serum leptin level increases during antipsychotic treatment[51,52]. Although leptin acts to inhibit food intake, studies have suggested that antipsychotics could induce or exacerbate a leptin-resistance status, which may contribute to aggravated obesity[52]. However, other findings support the possibility of another mechanism involving antipsychotic-induced epigenetic changes to leptin or leptin receptor genes[53].

Adiponectin can also reduce food intake, and a meta-analysis by Bartoli *et al*[54] indicated that treatment with clozapine and olanzapine is associated with decreased adiponectin levels. Decreased adiponectin levels may result in insulin resistance and increased risk of inflammation independent of adiposity[55]. A study revealed that some SGAs, especially clozapine and olanzapine, might exhibit a time-dependent effect on adiponectin levels[56]. Initially, the up-regulation of adiponectin might compensate for the deleterious effect of olanzapine and clozapine on glucose

homeostasis. Then, a new energy balance equilibrium is regained during a short-term treatment, resulting in the return of blood adiponectin levels to the baseline. Finally, the failure of adiponectin up-regulation pushes blood adiponectin levels further below the baseline after long-term treatment.

Ghrelin, however, is a hunger-inducing hormone. Reports on the association between antipsychotic treatment and ghrelin level changes are inconsistent, although three long-term studies reported increased ghrelin levels in patients on SGAs with weight gain liabilities[51]. Acylated ghrelin and desacylated ghrelin are the two main forms of ghrelin and play opposing roles in energy homeostasis. Lower acylated ghrelin/desacylated ghrelin ratios are associated with better metabolic profiles in patients with schizophrenia treated with olanzapine[57]. Leptin, adiponectin, and ghrelin levels differ significantly in patients with schizophrenia receiving clozapine and olanzapine due to the direct effects of the medications, rather than due to weight gain[58]. Additionally, the leptin/adiponectin ratio seems to be a preferential marker of metabolic syndrome in patients with schizophrenia compared with leptin or adiponectin alone[59].

Orexins, also known as hypocretins, have been suggested to regulate wakefulness, feeding, and metabolic homeostasis[60]. A study found that orexin-A level was elevated in patients with schizophrenia treated with antipsychotics, particularly in those taking fewer obesogenic antipsychotics[61]. The potential protective role of orexin-A against antipsychotic-related metabolic abnormalities may be attributable to the thermogenesis resulting from increased sympathetic tone and reduced peripheral insulin resistance[61].

CCK plays an important role in induction of gallbladder contraction, stimulation of pancreatic secretion, regulation of gastrointestinal motility, and induction of satiety [62]. Studies found that CCK is related to obesity and metabolic syndrome in the general population[63,64]. Animal studies reported that olanzapine could counteract the satiating effect of CCK[65] , and clozapine could reduce hypothalamic messenger RNA of CCK-2 receptor[66]. In contrast, human studies found that CCK level did not change significantly after olanzapine treatment[67,68]. The role of CCK in antipsychotic-induced metabolic disturbances warrants further investigations.

Neurotransmitters

Histamine H_1 receptor antagonism promotes feeding, and the affinity for H_1 receptors is closely correlated with AIWG[69], with clozapine and olanzapine having the highest affinity. Researchers have also proposed that drugs with H_1 receptor antagonism may also induce weight gain because of their sedative effects and consequential reduced mobility[70].

Serotonin is known to provide a satiety signal, and serotonin 5-HT_{2C} receptors are integral to the regulation of energy homeostasis by working together with the melanocortin and leptin signaling pathways[71]. Several SGAs, including clozapine and olanzapine, are potent 5-HT_{2C} inverse agonists and cause significant weight gain. However, ziprasidone, which also has a high affinity for 5-HT_{2C} receptors, is associated with limited weight gain, indicating that no single neurotransmitter system can fully explain AIWG. Conversely, the 5-HT_{1A} receptor exhibits the opposite effect of the 5-HT_{2C} receptor on food intake. The 5-HT_{1A} partial agonism, the common mechanism between aripiprazole, lurasidone, and ziprasidone, may reduce the risk of metabolic disturbances[72].

One study reported that bromocriptine, a specific dopamine D_2 receptor agonist, can counteract antipsychotic-induced hyperphagia and body weight gain in rats[73]. Dopamine D_2 receptor antagonism can enhance the 5-HT_{2C}-mediated effects on food intake and influence glucose metabolism by disinhibiting prolactin secretion[74]. Prolactin, which can stimulate pancreatic β-cell proliferation and insulin production and secretion, may be inversely associated with diabetes mellitus risk[75]. Moreover, prolactin generally suppresses lipid storage and adipokine release[76]. These characteristics may explain the reason that FGAs, risperidone, and amisulpride, which exhibit a higher hyperprolactinemia incidence than do other SGAs, have a lower propensity to develop metabolic disturbances.

Cholinergic muscarinic M_3 receptors are highly expressed by pancreatic β-cells, and low olanzapine and clozapine concentrations, both potent M_3 antagonists, can considerably and selectively impair cholinergic stimulated insulin secretion by blocking muscarinic M3 receptors in isolated rat islet cells[77]. The affinity for the cholinergic muscarinic M_3 receptor is therefore suggested to be the predictor of the propensity of antipsychotic-induced type 2 diabetes mellitus[78].

The support for α1- and α2- adrenergic receptor involvement in the etiology of AIWG is not as well developed as that for the aforementioned receptors. However, evidence indicates that these receptors may be associated with glucose control and may be synergistic with other receptor activities in contributing to AIWG[79].

Numerous pharmacogenetic investigations have identified the role of genetic polymorphisms associated with metabolic disturbances. The most-studied candidate genes that derive from receptors considered to mediate antipsychotic effects on food intake include serotonin 5-HT_{2C}, histamine H1, *ADRA1A*, and dopamine D_2 receptors [80]. Other genes that have been investigated in association with metabolic disturbances include leptin (*LEP*), leptin receptor (*LEPR*), ghrelin (*GHRL*), adiponectin (*ADIPOQ*), insulin-induced genes 1 and 2 (*INSIG1* and *INSIG2*), cannabinoid receptor 1 (*CNR1*), fat-mass and obesity-associated protein (*FTO*), methylenetetrahydrofolate reductase (*MTHFR*), and melanocortin-4 receptor (*MC4R*)[71,81].

Gut microbiota

The gut microbiome can interact with the central nervous system tract through the gut–brain axis. Compared with healthy controls, patients with schizophrenia exhibited a lower gut microbial richness index and diversity index[82]. Several studies have reported an association between metabolic disturbances and gut microbiota in patients with schizophrenia[83,84]. The mechanisms underlying antipsychotic-induced metabolic disturbances mediated through gut microbiota might involve an influence on energy homeostasis and aggravation of chronic inflammation[85,86]. Maier *et al*[87] reported that antipsychotic drugs exhibit antimicrobial activity and may disturb the gut ecosystem. Gut microbiota that may modulate the gut hormone system include ghrelin, peptide YY, glucagon-like peptide-I, and CCK, which play critical roles in adjusting energy homeostasis relative to glucose metabolism, fat storage, and appetite control[85]. Antipsychotic-induced dysbiosis can produce several inflammatory cytokines, including interleukin 1, interleukin 6, and tumor necrosis factor alpha, which are essential in mediating the relationship between gut microbiota and metabolic disturbances[88].

Potential predictors

Several predictors of AIWG and metabolic disturbances have been identified, including female gender and younger age[89]. Debate is ongoing regarding the relationship between baseline BMI and AIWG, even though low-baseline BMI and normal weight status (*i.e.* BMI < 25) have been frequently associated with greater AIWG[90]. Lan *et al*[91] applied artificial intelligence to develop a neurofuzzy model, including physical factors (baseline weight, height, and waist and hip circumferences), lifestyle factors (smoking, dietary patterns, and exercise levels), genetic factors (*ADRA1A*, *ADRB3*, *ADRA2A*, *5-HTR_{2A}*, and *5-HTR_{2C}*), and psychopathology severity as predictor variables, with a 93% prediction rate for weight gains among patients with schizophrenia treated with antipsychotics.

METABOLIC MONITORING

National and international groups have developed guidelines for screening and monitoring AIWG and metabolic disturbances, but studies have indicated that these guidelines are not routinely implemented in clinical care[92]. Table 2 illustrates the comparison between two guidelines proposed by the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity[32], and the British Association for Psychopharmacology[93]. Notably, the monitoring frequency should be adjusted according to the clinical situation or after a change in antipsychotic medication.

Lin *et al*[94] developed an artificial neural network and multiple logistic regression models without biochemical parameters to identify rapidly metabolic syndrome in SGA-treated patients. The researchers suggested that waist circumference and diastolic blood pressure were the most predictive variables. Other risk factors for antipsychotic-induced metabolic syndrome should also be evaluated, including smoking, dietary habits, and physical activity levels as well as personal and family history of obesity, diabetes mellitus, and cardiovascular diseases[95].

Table 2 Metabolic monitoring guidelines as proposed by various organizations

	US consensus[32]	BAP guidelines[86]
Weight	At 4 wk, 8 wk, and 12 wk after initiating or changing SGA therapy, then quarterly	BMI weekly for the first 4–6 wk, then every 2–4 wk for up to 12 wk. At a minimum, once every 4 wk for the first 12 wk, then at 6 mo and at least annually
Blood glucose	Assessed fasting plasma glucose at 3 mo, then annually	Assessed fasting or random plasma glucose in the initial weeks and glycated hemoglobin at 12 wk, 6 mo, and then annually
Lipid profile	At 3 mo, then repeated at 5-yr intervals if normal	At 12 wk, 6 mo, and then annually. The total cholesterol/high-density lipoprotein cholesterol ratio should be required.
Blood pressure	At 3 mo, then annually	At 12 wk, 6 mo, and then annually

US consensus: Consensus proposed by American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity[32]; BAP guidelines: Guidelines proposed by the British Association for Psychopharmacology[86]; SGA: Second-generation antipsychotics; BMI: Body mass index.

INTERVENTIONS

The National Institute for Health and Care Excellence guidelines on psychosis and schizophrenia in adults suggest that these patients, particularly when taking antipsychotics, should be offered combined dietary and physical activity programs as well as help for smoking cessation from a psychiatric multidisciplinary care team[96]. Studies have reported that these nonpharmacological strategies for AIWG are beneficial and cost-effective and therefore should be a priority, particularly in early antipsychotic treatment stages[97,98].

Although lifestyle interventions are always crucial, switching to a different antipsychotic medication with a lower propensity for weight gain could also be effective for managing metabolic adverse effects. Studies have shown that switching to aripiprazole, amisulpride, ziprasidone, and lurasidone is beneficial for weight or metabolic measurements[99].

Because switching antipsychotics may result in psychosis decompensation and relapse, another strategy that involves adding adjunctive medication to mitigate weight gain and metabolic changes has been studied extensively. The proposed medications are listed and discussed subsequently.

Metformin

Metformin, probably the most hopeful drug to attenuate antipsychotic-induced metabolic abnormalities[100], is a hypoglycemic drug for treating type 2 diabetes mellitus and employs a mechanism for reducing hepatic glucose production and improving insulin sensitivity without causing overt hypoglycemia. Metformin has also been effective in improving lipid metabolism by reducing triglyceride levels[101].

A meta-analysis of 12 randomized controlled trials (RCTs) concluded that adjunctive metformin is effective in treating AIWG and metabolic disturbances; the doses used in these trials ranged from 500 mg/d to 2550 mg/d[100]. Wu *et al*[102] conducted a RCT to test the efficacy of metformin alone, lifestyle intervention alone, and in combination in 128 first-episode patients with schizophrenia who added > 10% to their weight after receiving antipsychotic medications. After 12 wk, lifestyle intervention alone, metformin alone, and in combination were effective in attenuating AIWG and metabolic disturbances. Lifestyle intervention plus metformin demonstrated the greatest effect on weight loss, whereas metformin alone was more effective for reversing weight gain and increasing insulin sensitivity than lifestyle intervention alone[102].

Topiramate

Topiramate, a medication for epilepsy treatment and migraine prevention, is observed to reduce weight by poorly understood mechanisms likely related to glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonism in the hypothalamus and modulation of hypothalamic concentrations of neuropeptide Y, galanin, and corticosteroid concentrations; topiramate also stimulates lipoprotein lipase and inhibits carbonic anhydrase[103,104]. A meta-analysis of 17 RCTs indicated that 50–400 mg/d adjunctive topiramate significantly reduced weight or BMI and psychopathology in patients with schizophrenia[105].

Amantadine

Amantadine, an antiviral agent for influenza A treatment, has been shown to reduce extrapyramidal adverse effects. Evidence shows that amantadine enhances dopamine release indirectly through antagonism of the N-methyl-D-aspartic acid glutamate receptor[106]. According to a meta-analysis of five RCTs, adjunctive amantadine moderately outperformed placebo in terms of weight reduction[100]. Amantadine augmentation does not seem to exacerbate psychosis and may even be effective in alleviating negative symptoms[107].

Aripiprazole

Aripiprazole, which acts as partial agonist of dopamine D_2 and serotonin 5-HT_{1A} receptors as well as an antagonist of 5-HT_{2A} receptors, is categorized in the group with the lowest propensity for weight gain. A meta-analysis of nine RCTs indicated that adjunctive aripiprazole with SGAs results in significant weight reduction compared with placebo[108]. Reviews have also reported a protective effect of adjunctive aripiprazole with other antipsychotics for dyslipidemia and diabetes mellitus when compared with antipsychotic monotherapy or other antipsychotic combinations[109]. Combining aripiprazole with other low metabolic risk antipsychotics such as ziprasidone, amisulpride, or lurasidone to mitigate weight gain warrants exploration.

Fluvoxamine

Fluvoxamine, a potent cytochrome P450 1A2 inhibitor, blocks the major metabolism pathway of clozapine, resulting in a 5–12-fold increase in plasma clozapine levels and a decrease in the levels of its major active metabolite norclozapine. Norclozapine, not clozapine, is associated with increases in weight and plasma glucose and triglyceride levels[110]. Lu *et al*[111] randomized patients with schizophrenia to receive either 50 mg/d fluvoxamine plus 100 mg/d clozapine or 300 mg/d clozapine. The authors found that the clozapine–fluvoxamine combination significantly attenuated increases in body weight and insulin resistance as well as in insulin, glucose, and triglyceride levels compared with clozapine monotherapy. The combination also significantly reduced psychopathology compared with clozapine monotherapy[111]. As a clinical implication, clinicians should reduce clozapine dosage and carefully monitor clozapine levels if this combination is applied.

SUPPLEMENTAL PRODUCTS

Omega-3 polyunsaturated fatty acids

Omega-3 polyunsaturated fatty acid (n-3 PUFA) supplementation could produce favorable hypolipidemic effects, a reduction in pro-inflammatory cytokine levels, and improvement in glycemia in patients with type 2 diabetes mellitus[112]. Proposed mechanisms by which n-3 PUFAs may counteract metabolic disturbances include modulating lipid metabolism, regulating adipokines such as adiponectin and leptin, alleviating adipose tissue inflammation, promoting adipogenesis, and altering epigenetic mechanisms[113]. According to a meta-analysis of 19 RCTs, adjunctive n-3 PUFAs could improve psychopathology and reduce triglyceride levels in patients with schizophrenia[114].

Melatonin

The efficacy of melatonin in reducing SGA-related metabolic adverse effects is inconsistent. Modabbernia *et al*[115] reported that melatonin was effective in alleviating olanzapine-induced weight gain and hypertriglyceridemia, whereas Agahi *et al*[116] noted that melatonin significantly increased HDL levels and decreased fasting blood sugar levels but increased weight in patients receiving SGAs compared with the placebo group. Romo-Nava *et al*[117] reported that melatonin is effective in attenuating SGA-induced metabolic adverse effects in patients with bipolar disorder but not in patients with schizophrenia. A recent review manuscript reported that adjunctive melatonin therapy has positive outcome for attenuating antipsychotic-induced metabolic disturbances in patients with schizophrenia[118]. Additional studies on the effect of melatonin on antipsychotic-related metabolic side effects are warranted.

CONCLUSION

Studies have demonstrated that antipsychotic drugs potentially induce or trigger metabolic disturbances, which are a major cardiovascular risk factor for patients with schizophrenia. In general, SGAs carry a higher risk of metabolic disturbances than do FGAs. Various SGAs are also associated with varying potentials for weight gain and can be roughly categorized into three groups: Clozapine and olanzapine (highest risk); quetiapine, risperidone, and paliperidone (intermediate risk); and aripiprazole, ziprasidone, and lurasidone (lowest risk).

Notably, Wu and Gau[119] found that patients with schizophrenia and type 2 diabetes mellitus develop few advanced diabetes mellitus complications after receiving regular antipsychotic treatment. The authors proposed that appropriate antipsychotic treatment can improve the patients' conditions and thereby increase the frequency of healthy behavior.

Despite a growing knowledge of the biochemical profiles of antipsychotic agents, the underlying mechanisms of their association with metabolic disturbances remain inconclusive. The binding affinities of antipsychotics to several neurotransmitter receptors, such as H_1, 5-HT_{2C}, 5-HT_{1A}, D_2, M_3, and adrenergic receptors, might be associated with induction of metabolic disturbances. Studies have revealed a positive association between AIWG and therapeutic benefits, particularly in patients treated with olanzapine and clozapine, which suggests that these medications may possess a shared mechanism related to their metabolic liability[120]. Various peptide hormones, including leptin, adiponectin, ghrelin, and orexin, are also suggested to be metabolic disturbance biomarkers. Notably, an increasing amount of evidence indicates that genetic polymorphism has a strong influence on AIWG and metabolic disturbances, further highlighting the complexity and multiplicity of the mechanisms.

Despite established guidelines and recommendations, patients treated with antipsychotic drugs have not adequately received the baseline and follow-up assessments of metabolic and cardiovascular risk factors. Moreover, psychiatrists and members of multidisciplinary care team should motivate patients to pursue healthy lifestyle behaviors, including dietary and physical activity programs. If lifestyle interventions do not succeed, switching to another antipsychotic drug with a low metabolic risk or including an adjunctive medication to mitigate weight gain can be an effective intervention option. All interventions should be adequately monitored, as individual patients may respond unpredictably to any of these pharmacological and natural agents.

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REVIEW

Alternative models for transgenerational epigenetic inheritance: Molecular psychiatry beyond mice and man

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Abstract

Mental illness remains the greatest chronic health burden globally with few inroads having been made despite significant advances in genomic knowledge in recent decades. The field of psychiatry is constantly challenged to bring new approaches and tools to address and treat the needs of vulnerable individuals and subpopulations, and that has to be supported by a continuous growth in knowledge. The majority of neuropsychiatric symptoms reflect complex gene-environment interactions, with epigenetics bridging the gap between genetic susceptibility and environmental stressors that trigger disease onset and drive the advancement of symptoms. It has more recently been demonstrated in preclinical models that epigenetics underpins the transgenerational inheritance of stress-related behavioural phenotypes in both paternal and maternal lineages, providing further supporting evidence for heritability in humans. However, unbiased prospective studies of this nature are practically impossible to conduct in humans so preclinical models remain our best option for researching the molecular pathophysiologies underlying many neuropsychiatric conditions. While rodents will remain the dominant model system for preclinical studies (especially for addressing complex behavioural phenotypes), there is scope to expand current research of the molecular and epigenetic pathologies by using invertebrate models. Here, we will discuss the utility and advantages of two alternative model organisms–*Caenorhabditis elegans* and *Drosophila melanogaster*–and summarise the compelling insights of the epigenetic regulation of transgenerational inheritance that are potentially relevant to human psychiatry.

Key Words: Transgenerational inheritance; Epigenetics; Invertebrate models; *Caenorhabditis elegans*; *Drosophila melanogaster*; Environmental stress

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Core Tip: Psychiatry research is only beginning to identify the complex epigenetic pathologies across various conditions that may regulate symptomatology. Epigenetics may account for certain conditions that are highly heritable but are not fully accounted for by genetics. Preclinical animal models are a necessary tool to accelerate our understanding of molecular mechanisms and for developing new therapeutic options. Simple behavioural and neurobiological assays combined with high levels of functional gene conservation and rapid generation time in easily genetically manipulated organisms make *Caenorhabditis elegans* and *Drosophila melanogaster* excellent systems to model transgenerational epigenetic inheritance phenotypes.

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INTRODUCTION

Advances in genomic technologies have led to a rapid increase in the number of known genomic variants linked to human psychiatric illnesses. However, we still know little of the molecular and genetic functions of many of these genes or their mode of inheritance. The wealth of genetic information and experimental techniques associated with laboratory model organisms that have not been traditionally utilised for analysis of psychiatric illnesses provide an untapped resource that promise to revolutionise our understanding of these conditions.

At the turn of the 18th century, the French naturalist Jean-Baptiste Lamarck proposed that environmentally adaptive traits could be acquired by an individual over a lifetime and, more importantly, inherited by their progeny. It was not until the 21st century that Lamarckian theory re-emerged from the shadows of Darwin's theory of natural selection and the principles of genetic inheritance. This recent revival has been driven by growing evidence of unusual inheritance patterns across a wide number of species, which collectively indicate the presence of biological mechanisms that govern how the physical environment, diet and individual experiences not only influence our individual constitution, but the health of our descendants as well. In the past decade, preclinical studies of mammalian models of human disease have uncovered robust evidence of transgenerational shifts in health. However, alternative animal models should be considered as a means of conducting more time- and cost-effective transgenerational research. Here, we summarise recent advances in transgenerational epigenetic inheritance stemming from non-mammalian models that have revealed epigenetic processes potentially relevant to psychiatry. We hope to convince readers that research based on these non-mammalian organisms have the capacity to provide novel insights into the molecular pathologies of different neuropsychiatric conditions.

Epigenetic inheritance drives the adaptation of phenotypic traits and plays a significant role in directing human health outcomes across generations. For example, the accumulation of specific epigenetic modifications is proposed to contribute to the increasing prevalence of cardiovascular and metabolic diseases[1,2]. Separately, epigenetic modifications have been demonstrated in the transgenerational transmission of risk for mental illness, and possibly contributing to the increasing prevalence of a range of psychiatric disorders[3-6]. However, non-mammalian models have also contributed by extending our understanding of the molecular pathologies in human disease. For example, studies of the nematode *Caenorhabditis elegans* (*C. elegans*) have not only provided us enlightening perspectives on the molecular regulation of aging[7,8] but also revealed how stress and nutrition are transgenerational modifiers of progeny survival[9-11].

Briefly, transgenerational inheritance broadly describes the process of a parental generation undergoing experiences and exposures that are subsequently linked to altered phenotypes and behaviours in future generations (in F2s at the very least). Note that the phrase 'intergenerational inheritance' describes transmission that is

limited (or only studied up till) to the very next F1 generation (see Figure 1 for further patrilineal and matrilineal distinctions). While the full spectrum of biological processes underlying transgenerational inheritance is yet to be fully elucidated, a multiplex of epigenetic modifications has been implicated. Importantly, epigenetic inheritance specifically excludes the reorganisation of genome sequence through DNA mutations, and some epigenetic marks are species-specific (further emphasizing the importance of multi-species research). The most widely studied epigenetic modifications include DNA methylation, histone protein modifications (such as methylation, acetylation), as well as short and long non-coding RNAs (sncRNAs and lncRNAs, respectively) that moderate transcriptional activity. Due to space constraints, we refer readers to the following reviews that comprehensively discuss the biochemistry of epigenetic modifications relevant to the neuropsychiatric field[12-16]. The epigenome is subject to modification following exposure to stressors that challenge survival, ranging from environmental (exposure to toxic chemicals)[17] to physical (heat stress) to psychological (fear of predation)[18,19]. We now know that offspring can inherit a range of epigenetic modifications that alters their physical or behavioural traits. Over the past decade, preclinical studies of rodent models of chronic stress[20,21] and trauma[22-24] have demonstrated this phenomenon, but could alternative non-mammalian models of stress offer further insight into the relevant epigenetic pathologies? These tools offer the field of psychiatry the opportunity to clarify the extent to which the risk for mental illness may be moderated by parental or ancestral exposures to such stressors and life events, and understand the molecular mechanisms mediating such forms of transgenerational inheritance. Epidemiological studies have reported a range in heritability of neuropsychiatric disorders (although readers should note that there have been relatively few studies given the challenges of conducting such large-scale research). For example, a high degree of heritability (81%) was initially estimated for schizophrenia (SZ) based on twin studies[25], while subsequent estimates based on the Danish and Swedish populations were comparatively lower at approximately 60%[26, 27]. Those latter studies also estimated that heritability of bipolar disorder (BP) was similar to SZ. However, the potential that epigenetic inheritance moderates the heritability of certain neuropsychiatric conditions has yet to be thoroughly investigated. Of course, in contrast, other psychiatric disorders such as alcohol dependence or major depression display low-moderate degrees of heritability[28] so while those disorders may involve aspects of epigenetic pathology, it is less likely that epigenetic inheritance would be a significant causal factor.

While studies of *C. elegans* and *Drosophila melanogaster* (*D. melanogaster*) may be initially dismissed as far removed from relevance to human physiology, and although most preclinical drug testing is performed with rodent models, these invertebrate model systems provide alternative approaches to conducting complementary research of common epigenetic mechanisms and biochemical processes that may be fundamental to neuropsychiatric pathologies. One should not forget that mammalian transgenerational research can trace its roots to historically rich and revealing studies of plants. Some of the earliest evidence for the phenomenon include Barbara McClintock's ground-breaking studies of retrotransposition in maize and the transgenerational inheritance of transposon phases. While we tend to associate 'stress' with the notion of psychosocial stress, this term can be used to encompass any extrinsic condition that disturbs the normal function of the biological system, or a condition that decreases fitness, including thermal stress, desiccation, UV stress, starvation, chemical exposure and overcrowding. In using alternative animal models, it is crucial that etiologically relevant stressors are applied in the appropriate manner. Heat stress is well known to impact a wide range of physiological and behavioural parameters, which can result in gastrointestinal dysfunction[29], increased blood pressure and disordered metabolic function[30]. In particular, elevated temperatures cause profound disruptions to various aspects of reproduction in both mammals and invertebrates including mating behaviours[31,32], spermatogenesis and oogenesis, egg/foetal development and viability, and offspring body size[33,34]. With mounting concerns about climate change, and recent increases in unusual climate events, understanding how we adapt to such environmental changes and the implications for global population health trends have become more important than ever. A recent systematic review of the impacts of climate change on mental health reported on the complexities in attempting to consolidate the data, but highlighted more common psychopathologies such as anxiety and trauma[35]. It is unclear if and how climatic factors could influence human health outcomes through epigenetic modifications. Understandably, designing and conducting human studies of this nature would be highly challenging due to the inherent complexities *e.g.* having to account for geographical and ethnic diversities. However, research based in the primary

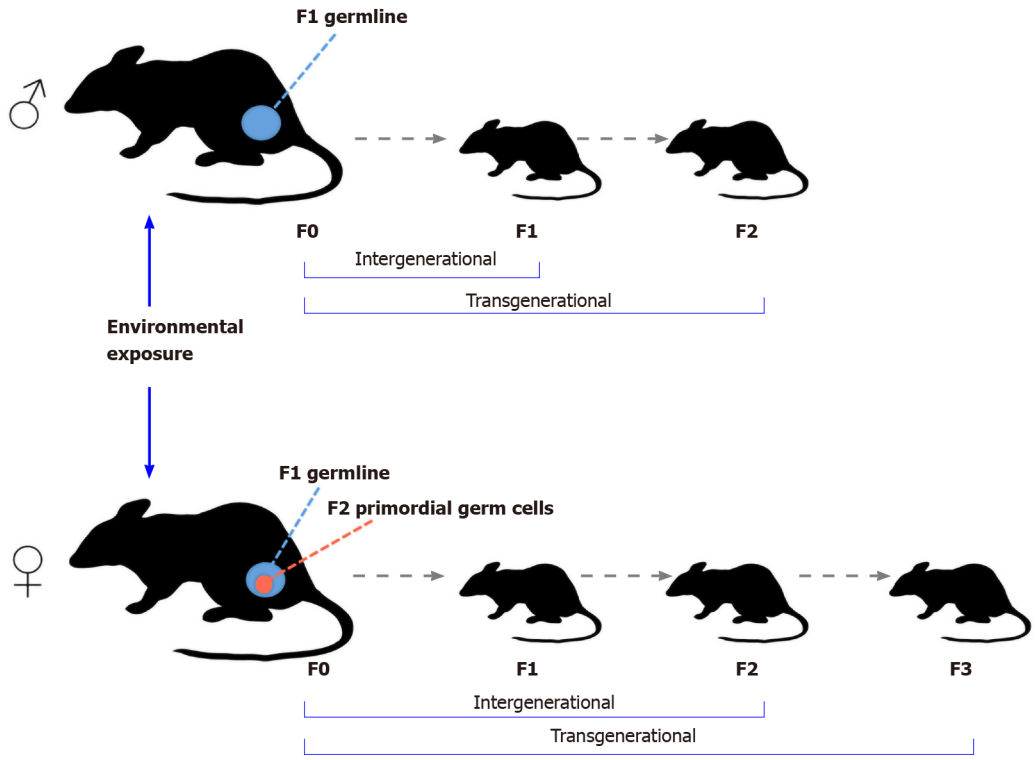

Figure 1 Differences between the definition of transgenerational and intergenerational inheritance through the male and female germ lines.

production industries may be an unexpected source of early clues as to how these occur. Afterall, developing the knowledge to control the effects of heat stress has been crucial to the field of agriculture for maximising crop yield[36,37] and maintaining livestock fecundity and fitness[38,39].

There are mounting calls to recognize that ancestral health is a significant contributing factor of current day human health and phenotypes, and this would require maintaining detailed individual medical records for longitudinal epidemiological studies. On a large scale, such a perspective shift would aid us in identifying the determinants of public health issues and evaluating possible interventions and treatments. Furthermore, elucidating the mechanisms driving environmentally-induced epigenetic changes linked to specific aspects of health and disease may promote a shift towards the development of personalised treatments and drugs based on these signatures[40]. With numerous epigenetic processes conserved from invertebrates to humans, it is unsurprising that many fundamental epigenetic processes are also shared by humans and non-mammalian animals. Therefore, there is valid argument for utilising non-mammalian species as viable alternative animal models to investigate environmentally induced changes in human health, stress response and behavioural adaptations. We will now summarise recent evidence from transgenerational studies of key two non-mammalian models-*C. elegans* and *D. melanogaster*–focussing on environmental stressors and highlight their potential utility for investigating the molecular pathologies of psychiatric conditions.

EPIGENETIC MODIFICATIONS IDENTIFIED BY TRANSGENERATIONAL STUDIES OF *C. ELEGANS* RELEVANT TO PSYCHIATRY

In contrast to mammalian models where multigenerational studies are impeded by long generational times, logistical difficulties and confounding factors, invertebrate models breed rapidly with large progeny cohorts, making them ideal models for performing multi-generational studies. There are the obvious limitations of *C. elegans* as a model, primarily that it is a relatively simple organism lacking many organ systems found in vertebrates. However, the *C. elegans* genome possesses homologs of about two-thirds of all human disease genes. Thus, it is widely used as a model system for studying aging, age-related diseases[41] and neurogenerative conditions[42].

Transgenerational studies of *C. elegans* could therefore provide insight into the molecular pathologies and epigenetic modifications that could be accumulating across generations in humans. Here, we will summarise recent advances in our understanding of the transgenerational responses of *C. elegans* involving thermal stress and starvation and highlight their relevancy to human psychopathologies (Table 1).

The most impressive finding to-date was that exposure of a single progenitor generation to an elevated rearing temperature (25 °C instead of 20 °C) caused transcriptome-wide expression changes that persisted for a further seven generations after temperature normalisation[43]. Importantly, it was identified that the ancestral exposure to a higher temperature was associated with a reduction in the repressive histone modification H3K9me3 (trimethylation of lysine 9 residue in histone H3) in both oocytes and sperm, before onset of zygotic transcription. What could be of importance to the psychiatry field was the revelation that there was de-repression of endogenously repressed repeat sequences, and increased expression of two DNA transposons remained for up to five generations. The role of repetitive elements in human health and disease is still unclear but they have been speculated to be potential etiological factors for SZ, BP and major depressive disorder (MDD)[44], despite a present lack of consistent evidence. For example, there has only been a single report of a repetitive element insertion in three monozygotic twin pairs discordant for SZ[45] but similar observations have not been detected in other studies. However, subsequent studies have reported elevated levels of Class I retrotransposon RNA in cerebrospinal fluid, whole blood and serum samples from SZ patients[46-48]. It should be noted that these latter studies were conducted by the same research group and further independent verification is still required. At the present time, there are also no available rodent models of abnormal repetitive element expression so determining its relevance to neuropsychiatric pathologies is impossible. *C. elegans* would therefore be a prime model organism to investigate environmental factors associated with the aforementioned psychiatric conditions, with the dysregulation of repetitive element expression as a primary outcome measurable. Such studies would either cement their causal roles or establish them as secondary molecular pathologies.

Separately, another repressive histone mark linked to *C. elegans* lifespan[49], di methylation of lysine 9 residue in histone H3 (H3K9me2), has also been implicated in various psychiatric conditions. Increased levels of H3K9me2 were found in post mortem SZ brains and in peripheral blood cells[50]. However, the directionality of this change in expression may vary depending on the specific psychopathology, according to evidence from rodent studies. For example, stress-induced depression was associated with reduced H3K9me2 occupancy at the oxytocin and arginine vasopressin gene promotors, both of which were normalised by physical exercise[51]. Thus, the outcomes linked to the manipulation of H3K9me2 levels are also gene specific. This is further exemplified by the capacity for Cdk-5 targeted H3K9me2 to attenuate cocaine-induced locomotor behaviour and conditioned place preference[52]. These clearly showcase the complexity to epigenetic regulation of gene transcription and the significant challenges faced when attempting to treat psychiatric conditions by targeting a single histone modification. However, armed with precise knowledge of the molecular pathologies, aiming to modify negative behaviours in addiction through gene-targeted histone modification could be an intriguing prospect for the future.

A recent study examined a more severe temperature perturbation through acute heat shock (34 °C for 5 min) and discovered that this caused maternal neurons to release the neurotransmitter 5-HT, which facilitated transcription factor heat shock factor 1 (HSF-1)-mediated mRNA production in soon-to-be fertilized germ cells[9]. The authors proposed that this timely activation of HSF-1 in germ cells ensures viability and future stress tolerance since embryos that arose from heat-shocked mothers contained an excess of protective mRNA and their F1 progeny were more resilient to subsequent temperature insults. It was found that HSF-1 recruited the histone chaperone FAcilitates Chromatin Transcription (FACT) complex to alter histone dynamics and promote transcription of the heat shock protein Hsp70. Interestingly, several studies have identified an accumulation of Hsp70 associated with MDD. In a study of post-mortem brain samples from patients with MDD, Hsp70 was significantly elevated in the dorsolateral prefrontal cortex, while antidepressant treatment did not have any modulatory effect[53]. Separately, elevated serum Hsp70 levels were reportedly predictive of premenopausal women who would go on to develop MDD [54], although Hsp70 levels subsequently decreased for women who did not develop MDD. Collectively, this suggests that Hsp70 could be a useful biomarker for MDD risk but it remains to be verified in a younger, or even a healthy, population.

Table 1 Studies of transgenerational epigenetic inheritance in *Caenorhabditis elegans* of relevance to neuropsychiatric conditions and mammalian preclinical models

Type of stress (if applicable to study)	Transgenerational shifts in progeny phenotypes	Epigenetic modifications implicated in the inheritance process	Ref.	Psychiatric conditions with similar epigenetic pathology	Ref.
Elevated temperature	Temperature-induced transcriptome changes potentially up to F14 generation	Heat shock reduces H3K9me3 to facilitate de-repression of endogenously repressed repeats (DNA transposons)	Klosin *et al* [43], 2017	Repetitive elements as etiological factors for schizophrenia (SZ), bipolar disorder and major depression (review)	Darby and Sabunciyan 2014[44]
		No difference in another repressive mark, H3K27me3		Altered expression of human endogenous retroviruses associated with autism spectrum disorder and SZ (review)	Misiak *et al* [169], 2019
		Active histone marks H3K36me3 and H3K4me2 both unchanged		Tissue-specific repetitive elements expression differences in Parkinson's disease	Billingsley *et al* [170], 2019
Heat shock	Maternal heat shock altered survival of F1 progeny through 5-HT dependent HSF-1 recruitment to heat shock protein gene promotors. Persistence of phenotypic changes not investigated	Histone H3 occupancy at *hsp70* genes decreased following heat shock	Das *et al* [9], 2020	MDD associated with increased hsp70 expression in post mortem dorsolateral prefrontal cortex	Martín-Hernández *et al*[53], 2018
				Elevated serum HSP70 levels predicted development of MDD for premenopausal women. Serum HSP70 decreased over time for women who did not develop MDD	Pasquali *et al* [54], 2018
				Decreased Hsp70 expression in CA4 associated with complete seizure remission for temporal lobe epilepsy	Kandratavicius *et al*[171], 2014
NA	NA	Transgenerational inheritance of H3K36me3 is regulated by two distinct histone methyltransferases, MES-4 and MET-1	Kreher *et al* [172], 2018	H3K36me3 implicated in SZ susceptibility SNPs. But histone lysine methyltransferases yet to be investigated in the context of SZ	Niu *et al*[65], 2019
NA	NA	Lifespan regulated by the H3K9me2 methyltransferase MET-2	Lee *et al* [49], 2019	H3K9me2 elevated in post-mortem SZ brains and peripheral blood cells. Treatment with histone methyltransferase inhibitor BIX-01294 decreased H3K9me2 levels and rescued expression of SZ risk genes	Chase *et al*[50], 2019
				Reduced H3K9me2 at oxytocin and arginine vasopressin gene promotors in a rodent model of stress-induced depression. Rescued by physical exercise	Kim *et al*[51], 2016
				Cdk-5 targeted H3K9me2 attenuates cocaine-induced locomotor behaviour and conditioned place preference in a rodent model of addiction	Heller *et al*[52], 2016
NA	Decline in fertility	H3K4me2 demethylase *spr-5*	Greer *et al* [173], 2014	Treatment with antipsychotic drug olanzapine increased H3K4me2 binding on gene loci associated with adipogenesis and lipogenesis in a rat model	Su *et al*[174], 2020
				KDM5C gene that encodes the H3K4me2/3 histone demethylase linked to autism and intellectual disability	Vallianatos *et al* [175], 2018
Heavy metal (arsenite) stress	Increased resistance to oxidative stress up to F2 generation; no change in reproduction or lifespan	H3K4me3 complex components (*wdr-5.1*, *ash-2*, *set-2*), and transcription factors *daf-16* and *hsf-1*	Kishimoto *et al*[10], 2017	Increased H3K4me3 associated with three *synapsin* gene variants in bipolar disorder and major depression	Cruceanu *et al* [63], 2013
				SZ risk variants are over-represented in association with	Girdhar *et al* [64], 2018

				H3K4me3 in human frontal lobe	
				H3K4me3 implicated in SZ susceptibility SNPs	Niu *et al*[65], 2019
				Increased H3K4me3 associated with increased *Oxtr* gene expression in a rat model of methamphetamine addiction	Aguilar-Valles *et al*[68], 2014
Hyperosmotic stress	Increased resistance to oxidative stress up to F2 generation	Not further investigated in study	Kishimoto *et al*[10], 2017	Relevance to human health presently unclear	
Larval starvation	Increased resistance to oxidative stress up to F2 generation	Not further investigated in study	Kishimoto *et al*[10], 2017	Relevance to human health presently unclear	
Larval starvation	NA	Thirteen miRNAs up-regulated (miR-34-3p, the family of miR-35-3p to miR-41-3p, miR-39-5p, miR-41-5p, miR-240-5p, miR-246-3p and miR-4813-5p); Two miRNAs down-regulated (let-7-3p, miR-85-5p)	Garcia-Segura *et al*[77], 2015	Eight differentially expressed blood miRNAs linked to PTSD. Four up-regulated (miR-19a-3p, miR-101-3p, miR-20a-5p, miR-20b-5p). Four down-regulated (miR-486-3p, miR-125b-5p, miR-128-3p, miR-15b-3p)	Martin *et al*[78], 2017
				Deletion of miR-34 family in mice facilitates resilience to stress-induced anxiety and extinction of fear memory	Andolina *et al*[84], 2016
				miR-34 differentially expressed in induced pluripotent stem cells derived from schizophrenia patients	Zhao *et al*[176], 2015
				miR-34a regulates expression of p73, a p53-family member, that is implicated in neuronal differentiation	Agostini *et al*[86], 2011
Starvation	Increased longevity of progeny up to F3 generation	Inheritance of small RNAs through at least 3 generations.	Rechavi *et al*[11], 2014	miRNAs and rRNAs make up the majority of exRNAs in human plasma	Danielson *et al*[91], 2017
		Small RNAs regulating expression of genes involved in nutrition, metabolic health and lipid transport		1 specific exRNA predicted diagnosis of Alzheimer's disease	Yan *et al*[94], 2020
				exRNAs are potentially involved in the paternal intergenerational influence on offspring metabolic health (mouse model)	van Steenwyk *et al*[93], 2020

HSF-1 activity is also associated with elevated histone H4 protein levels in somatic tissue during development, leading to reduced transcription of mitochondrial complex IV genes and decreased respiratory capacity[55]. While it has not been linked specifically to histone H4 only, a similar role of neuronal heat shock proteins in moderating the response to oxidative stress is evidenced in *D. melanogaster* with increased resistance to oxidative stress and extended organismal lifespan, in addition to ameliorating phenotypes associated with Parkinsonism-type genetic models[56]. Collectively, it emphasizes the conserved association between heat shock proteins, oxidative stress and neuronal damage. However, the precise regulatory roles that histone H3 and H4 proteins provide independently to the overall oxidative stress response remain unclear and warrants further investigation. Mitochondrial dysfunction and the accumulation of oxidative stress are crucial factors in the pathophysiology of MDD[57-59], and biomarkers of oxidative stress are elevated in drug-naïve first episode SZ patients[60]. Thus, there is strong interest in targeting oxidative stress deficiencies in MDD, BP and SZ[61] through antioxidant treatments such as N-acetylcysteine[62]. Future studies could use *C. elegans* to explore the efficacies of various antioxidant compounds in treating heat shock-induced oxidative stress, as well as their underlying modes of action. Studies could also be extended to heat shocking *C. elegans* pre-treated with antioxidants to better understand the epigenetic regulation of 5-HT neurotransmission.

The dysregulation of transcriptional activity is widely reported in a swathe of psychiatric conditions but the causes have yet to be precisely identified. For example, H3K4me3 has been implicated in the pathophysiology of SZ, BP and MDD, with increased H3K4me3 is associated with three *synapsin* gene variants in BP and MDD[63] while SZ risk variants are over-represented in association with H3K4me3 in human frontal lobe samples[64]. The latter is a consistent with a separate study examining H3K4me3 association with SZ susceptibility SNPs[65]. While there have been several independent GWAS studies of SZ, there has yet to be an attempt to reconcile the genomic data with epigenomic variation. That would undoubtedly be a tremendous undertaking, but it could further streamline and identify more robust gene candidates in our attempts to pinpoint the primary molecular pathologies underlying SZ. *C. elegans* could be used to first establish the molecular consequences of such an abnormal epigenetic landscape and resulting transcriptional dysregulation (matched to existing human data), before further behavioural studies are extended to mammalian models. Incidentally, H3K4me3 was identified by Kishimoto *et al*[10] as being involved with the transgenerational adaptations to other forms of environmental stressors aside from thermal stress, namely heavy metal exposure, hyperosmotic conditions, and transient starvation[10]. Following progenitor exposure to all three stressors, there were consistent increases in progeny fitness up till the F2 generation; however only the epigenetic mechanism mediating adaptation to arsenite exposure was further investigated. Unlike the repressive histone modifications mentioned above, H3K4me3 predominantly marks transcriptional start sites and is part of a regulatory complex that facilitates access and assembly of RNA polymerase 2[66,67]. Kishimoto *et al*[10] reported that the genetic components (*wdr-5.1*, *ash-2* and *set-2*) of the H3K4me3 regulatory complex were required to manifest the transgenerational adaptations, implicating histone H3-dependent gene transcription in transgenerational inheritance. Therefore, future work on H3K4me3-regulation transcriptional activity could provide new insight into the molecular pathways affected in SZ, BP and MDD by targeting *C. elegans* homologs of human risk genes for more specific investigations.

Finally, in a rat model of methamphetamine addiction, there was greater H3K4me3 association with the oxytocin receptor gene that corresponded to increased *Oxtr* gene expression[68]. As discussed above, strategies to treat addiction-related molecular pathologies by targeting histone modifications will be challenged by having to account for both active and repressive histone marks. The viability of such interventions and their molecular consequences would be ideally be first tested in *C. elegans* before proceeding to trials in mammalian models.

Malnutrition and starvation at different stages of life have a dramatic impact on mental health. For example, famine exposure *in utero* was associated with an increased risk for mental illness in females, though surprisingly with no apparent significant effect on males[69]. Developmental malnutrition driven by abnormalities in oxidative stress pathways has been linked to an increased risk for SZ and other psychiatric illness later-in-life[70]. Nutrition ultimately dictates metabolic health and more recent studies reported that fasting insulin levels and body mass index at different ages were predictive of at-risk status for psychosis or depression[71], while fasting blood glucose and serum lipid levels predicted suicide attempters in young patients with MDD[72]. At the opposite end of the age spectrum, geriatric deficiencies in micronutrients such as folic acid, thiamine or cobalamin have been linked to worsened mental health symptoms[73,74]. However, careful regulation of nutrition through caloric restriction or fasting has been proposed to be effective in improving symptoms of MDD[75], indicating that dietary interventions where appropriate would benefit patients. This could be particularly important in conditions whereby medications could have unavoidable metabolic side effects[76]. While epidemiological data flags the importance of nutrition for mental health, we continue to have a very poor understanding of this interactive relationship in the absence of evidence of causality and the underlying molecular mechanisms. Human studies of that nature would be severely limited by inherent genetic and cultural heterogeneities within populations, and there would be strong ethical arguments against the manipulation of subjects' diets. These issues are circumvented in studies of *C. elegans* wherein genetic homogeneity is controlled and dietary manipulations are feasible, although as *C. elegans* feed upon bacteria subtle dietary manipulations may be more easily accomplished using the chemically controlled diets that have been formulated for *D. melanogaster*. Transgenerational studies of starvation in *C. elegans* have already been conducted with clear evidence of downstream impacts on progeny fitness. More importantly, these studies have identified epigenetic mechanisms regulating the transgenerational adaptations, and these could potentially be regulating the molecular pathologies driving the malnutrition-related increase in risk for mental illness.

Kishimoto *et al*[10] reported that progenitor larval starvation triggered increased resistance to oxidative stress of two generations of progeny[10] but did not pursue the underlying epigenetic mechanisms and their associated molecular adaptations. However, previously, it was reported that starvation during the early L4 Larval stage altered the expression of 13 miRNAs in *C. elegans*[77]. Of the 13, only 2 were downregulated while the miRNAs of the miR-35 family were most highly upregulated. Being a simple organism, there are only 302 known miRNAs in *C. elegans* compared to over 2000 human miRNAs, so studying their role in transgenerational inheritance and phenotype adaptations is comparatively straightforward. miRNAs are now established to be dysregulated in different human conditions and are the subjects of interest for severe stress-related anxiety disorders such as post-traumatic stress disorder and SZ, as prognostic biomarkers and therapeutic targets. However, their role as epigenetic regulators of pathogenesis are unclear and systematic profiling of individual miRNAs to neuronal circuitry could be one approach to identifying their potential pathogenic roles in psychiatric conditions.

In a cohort study of military combat veterans, 8 differentially expressed blood miRNAs were associated with the diagnosis of post-traumatic stress disorder (PTSD)[78], and their predicted gene targets were implicated in neurotransmission and maintenance of the neural circuitry. Indeed, multiple functional magnetic resonance imaging studies have clearly demonstrated that brain function is compromised in PTSD[79,80]. There is initial evidence to suggest that paternal PTSD may also have the capacity to influence the neural function and behaviour of progeny, and that this is through the inheritance of sperm-borne miRNAs. In the social defeat mouse model of PTSD, both male and female progeny displayed significant anxiety and depression-related behaviours despite themselves not having been subject to stressful interventions[81,82]. It was later independently reported that modelling paternal early life trauma alters sperm miRNAs and exerts significant intergenerational alterations of target genes in the brains of progeny (*e.g. ctnnb1*, catenin β1 in the hippocampus)[22]. Our own studies have extended that line of evidence by demonstrating the transgenerational effects of paternal stress exposure and altered sperm miRNAs resulting in significant expression differences of the imprinted gene insulin-like growth factor 2, *Igf2* in the hippocampus of two generations of progeny[21]. While their downstream target genes may have been discovered to be dysregulated, there is still some controversy regarding the intergenerational inheritance of sperm miRNAs because having altered levels of miRNAs in sperm does not translate to those same miRNAs being dysregulated in offspring brains[23]. Despite the transgenerational implications of paternal PTSD on brain function of their children remaining unknown at this time, a bigger unresolved question is how traumatic stress alters miRNA expression , with one possibility being dysregulation of histone protein modifications and altered chromatin state. Unlike PTSD, which is caused by an external trigger, miRNAs appear to be co-regulated with susceptibility risk genes in SZ. For example, one study has reported an over-representation of miR-9-5p-targeted risk genes while miR-9-2 is located in a genomic region strongly associated with SZ[83]. Given the strong environmental component to both PTSD and SZ, continuing research into stress-induced miRNA changes in *C. elegans* could be used to further our understanding of the relevant environment x gene interactions underlying the molecular pathogenesis of PTSD and SZ. Other miRNAs have been implicated in stress-related disorders such as members of the miR-34 family, which are differentially expressed in induced pluripotent stem cells derived from SZ patients[41,84]. Among these, and consistent with the neurodevelopmental hypothesis of SZ[85], miR-34a is a key regulator of p73 expression, a p53-family member that is implicated in neuronal differentiation[86]. However, causal evidence is lacking to demonstrate that miR-34a is an epigenetic conduit for environmental stress to impact on brain development resulting in a schizotypy brain phenotype. One feasible experiment to propose would be ablating expression of the *C. elegans* homolog of miR-34a or the miR-34 family and study the impacts on neuronal differentiation, development and circuit maturation.

Interestingly, Rechavi *et al*[11] report that progenitor larval starvation was associated with extended longevity in three generations of progeny through the inheritance of small RNAs that regulate genes involved in nutrition, metabolic health and lipid transport[11]. It has been demonstrated in *C. elegans* that extracellular RNAs (exRNAs) are transported from one generation to the next through intracellular vesicles or even as unpackaged extracellular material[87]. The transgenerational effects of paternal stress exposures[21-23] involve altered small non-coding RNA content of sperm transmitted in microvesicles within the male reproductive organs[88,89], but so far this has only been demonstrated in mouse models[90]. Perhaps not so coincidentally, miRNAs are one of two major exRNA species in human plasma (the other

being ribosomal RNAs)[91]. Their presence and relative stability have led to an emerging recognition of their promise as 'liquid biopsies' for diseases, but while early adoption has targeted metabolic pathology[92], the correlation of biofluid exRNA levels with psychiatric conditions remain untested. Interestingly, it was reported that chronic injection of serum from a mouse model of trauma into healthy controls was sufficient to recapitulate the intergenerational impact on offspring metabolism[93]. However, miRNA profiling of the serum content was not performed in that study. Very recently, an investigation profiling exRNAs isolated from the plasma of elderly individuals up to 15 years prior to death revealed that the early presence and progressive increase of phosphoglycerate dehydrogenase (PHGDH) exRNA predicted eventual diagnosis of Alzheimer's disease (confirmed with post mortem pathology testing)[94]. Studies of *C. elegans* could be used to first determine how stress triggers an elevation of circulating exRNAs. Subsequently, given that biofluid screening of exRNAs is already being used to aid diabetes and AD diagnoses, there appears to be untapped potential for this methodology as a presymptomatic screening tool in psychiatry.

Overall, recent studies have demonstrated the complexity of epigenetic responses implicated in the transgenerational responses to progenitor stress exposure. These include histone modifications, dysregulation of DNA repetitive elements and altered expression of non-coding RNAs. These are also molecular processes shared by humans and have been identified as molecular pathologies of various psychiatric conditions. Thus, studying the epigenetic response of *C. elegans* to etiologically relevant environmental stressors and the corresponding physiological and behavioural responses will continue to provide further insight into human molecular psychiatry.

EPIGENETIC MODIFICATIONS IDENTIFIED BY TRANSGENERATIONAL STUDIES OF D. MELANOGASTER RELEVANT TO PSYCHIATRY

D. melanogaster has been established as an invertebrate model organism for studying human neurological disorders due to the remarkable evolutionary conservation of multiple human disease-causing genes. *D. melanogaster* have a higher degree of concordance with humans than *C. elegans*, with 75% of human diseases estimated to have a *D. melanogaster* homologue[95]. While also displaying sexual dimorphism in its physiology and behaviour, *D. melanogaster* have a generational time of only 10-12 d as opposed to approximately 6-9 wk for mice. Thus, in a protracted timeframe and at much lower cost compared to using rodents, multi-generational studies can also be performed to assess transgenerational effects and adaptations of *D. melanogaster* offspring to various environmental stressors. Additionally, a wide range of established transgenic strains, gene manipulation techniques and tools are readily available[96]. Here, we refer readers to several broad reviews discussing the utility of *D. melanogaster* research in advancing the understanding of the complex genetic basis for human traits, psychiatric disorders, neurodegeneration, and for drug discovery and screening[97-100]. Of course, the significant limitations of modelling complex neuropsychiatric conditions in *D. melanogaster* must also be acknowledged. Despite the relative ease in genetic manipulation, neuropsychiatric conditions such as SZ are driven by a combination of multiple genetic and environmental factors, and cannot be simply reduced to and reproduced in single, double or even triple transgenic knockout strains. Furthermore, the myriad of behavioural symptoms requires higher brain function to manifest, for which only mammalian models could be considered as appropriate. However, these reasons should certainly not diminish the utility value of *D. melanogaster* as a high throughput screening tool for basic neuropathological, molecular or epigenetic markers of disease. Most recently, *D. melanogaster* have even been used to model insomnia in order to examine the effectiveness of sleep restriction therapy[101]. However, despite these advantages, transgenerational studies in *D. melanogaster* aimed at examining mechanisms of epigenetic inheritance remain relatively sparse. Yet, the limited research has produced some compelling evidence, nonetheless. In this section, we will summarise key findings by highlighting the transgenerational outcomes of environmental and chemical stress exposures on offspring phenotypes paired with the reported epigenetic processes implicated. We will then flag the neuropsychiatric conditions for which further *D. melanogaster* research could potentially shed new light on the pathological origins.

D. melanogaster are sensitive to the climate and temperature fluctuations[102,103] and have been instrumental in advancing our understanding of the heat stress response. Heat stress-associated deleterious effects on physiology and behaviour are

largely attributed to its denaturing effect on proteins, which undergo abnormal folding, entanglement and unspecific aggregation[104]. In addition to the disruption of singular proteins, heat stress can also disrupt other cellular mechanisms with the culmination of these individual disruptions being cell death[105]. The ubiquitous and highly conserved heat shock response is a complex cascade of different processes, the most central being the transcriptional up-regulation of genes coding for the family of heat shock proteins that were in fact first discovered in *D. melanogaster*[106,107]. In addition to the metabolic and physiological effects on the exposed organism[108,109], selective thermal variations can dramatically shift *D. melanogaster* physical phenotypes such as flight ability over generations (impaired by F2 generation and maintained till the F4 generation) in a sex-dependent manner[110,111]. Thus, imposing a suboptimal ambient environment for survival either by changing the housing temperature or through a transient shift of temperature represents the most etiologically relevant approaches to stressing *D. melanogaster*. These encapsulate studies of both cold tolerance[112] and heat tolerance (discussed in detail below, Table 2), and these allow us to investigate how genetic variation dictates response to the environment or *vice versa*. Research into the transgenerational effects of heat stress in *D. melanogaster* have yielded intriguing and robust evidence of altered offspring physiology and heat stress responses. More importantly, those studies have also revealed epigenetic mechanisms that are of particular interest to psychiatry. Perhaps the most compelling demonstrations of environment-directed modifications of *D. melanogaster* epigenetics resulting in altered gene expression are the transgenerational studies of *white* gene expression following heat stress. The X chromosome residing *white* gene encodes for an ATP-binding cassette transporter that facilitates transport of the eye pigment precursors, guanine and tryptophan (red and brown pigment precursors, respectively) into the developing eyes during pupation[113]. Repression of *white* achieved by inserting the cellular memory module Fab-7 upstream of *white* to enhance chromatin silencing results in the loss of eye pigmentation[114]. Importantly, the Fab-7-mediated silencing process involves recruitment of *Polycomb* Group (PcG) proteins, which are essential in the propagation of chromatin structures and regulate gene silencing through S-phase of the cell cycle[115-117]. The mere developmental exposure to a mildly stressful temperature of 29 °C (typical housing temperature is 25 °C) suppressed Fab-7 expression, resulting in the de-repression of *white* and recovery of red eye pigmentation[118]. Importantly, that de-repression event was heritable down both male and female germ lines up till the F4 generation. That "founder effect" and maintenance of a de-repressed state across multiple generations indicates that inheritance of the temperature-modified chromatin state is maintained by the PcG protein complex. Of relevance to the human epigenome, the PcG protein complexes catalyse the formation and maintenance of the inactive histone mark H3K27me3[118], which as previously mentioned, is widely associated with neuropsychiatric conditions with abnormal histone modification patterns and aberrant gene transcriptional profiles [119]. Yet, the regulation of differentially expressed genes by PcG protein complexes in neuropsychiatric conditions has not been reported. While PcG protein complex function has been of great interest to the oncology field given the tell-tale features of DNA hypermethylation and aberrant transcriptional silencing of tumour suppressor genes[120], a causative role in psychiatric disorders has yet to be established. PcG protein complexes serve as a master regulator of active gene transcription so understanding the intricacies of PcG regulation of chromatin states will be essential if targeting aberrant histone modifications are to be a major therapeutic focus of the future. Aside from changes at the *white* gene locus, the multi-generational effects of heat shock on other behavioural (social interaction, mating) and physiological (metabolic and endocrine health) parameters in *D. melanogaster* are yet to be comprehensively studied. It would be very interesting to investigate if PcG protein complexes also have the capacity to affect the social behaviour, cognition and physical attributes of *D. melanogaster* by manipulating the extent of histone methylation associated with neuropsychiatric risk genes.

Interestingly, and in contrast to the stable inheritance pattern mediated by PcG protein complexes, heat shock-induced de-repression of *white* gene expression involving disruption of the heterochromatin assembly was maintained through three generations of embryos but contingent on repeated exposure of the offspring themselves to heat stress[121]. In that study, the transgenerational effects of heat shock were associated with increased phosphorylation of ATF-2, a member of the CREB/ATF family of transcription factors. Interestingly, levels of phosphorylated ATF-2 are reported to be increased in the ventral parieto-occipital region of post-mortem human brains when comparing between medicated and unmedicated patients with depression[122]; it is unknown if pATF-2 Levels could be predictive of a familial

Table 2 Studies of transgenerational epigenetic inheritance in *Drosophila melanogaster* of potential relevance to psychiatric conditions and mammalian preclinical models

Type of stress (if applicable to study)	Transgenerational shifts in progeny phenotypes	Epigenetic processes implicated in the inheritance process	Ref.	Potentially relevant psychiatric conditions	Ref.
Thermal stress (selection based on intolerance to heat stress)	Reduced ability to fly by F2 generation, maintain through to F4 generation	Epigenetic mechanism not investigated; aspects of stress physiology that affect flight still unclear	Krebs and Thompson [111], 2006	Relevance to human health presently unclear.	
Mild heat stress(embryos maintained at 29 °C)	De-suppression of *white* gene up to F4 generation	Disruption of polycomb group (PcG) protein complex affecting H3K27me3	Bantignies *et al*[114], 2003	Despite multiple reports of altered H3K27me3, the involvement of PcG protein complexes in human psychopathologies has not been established	
Heat shock (flies exposed to 37 °C for 1 h)	De-suppression of *white* gene sustained up to F3 generation required repeated exposure to the same paternal stressor. Gradual return to normal upon removal of heat shock	Disruption of pATF-2 mediated heterochromatin assembly	Seong *et al* [121], 2011	Rat model of chronic stress reported increased ATF-2 gene expression in the frontal cortex of chronically stressed rats, which is decreased following chronic antidepressant treatment	Laifenfeld *et al* [122], 2004
				pATF-2 levels are increased in post mortem samples of unmedicated *vs* medicated patients with MDD. No differences detected for bipolar disorder or schizophrenia	Gourzis *et al* [177], 2012
				Case report of decreased chromosome 1 heterochromatin in FTLD, misdiagnosed as SZ. Altered size distribution of chromosome 1 heterochromatic region in unrelated SZ patients compared to controls	Kosower *et al* [178], 1995
				Risperidone inhibition of heterochromatin formation in human liposarcoma cells *in vitro*, in a process involving PKA signalling; extent of dysregulated heterochromatin in psychosis yet to be explored	Feiner *et al* [125], 2019
				Parental exposure to risperidone led to intergenerational effects on F1 predator avoidance behaviours in zebrafish; potential human effects have not been investigated	Kalichak *et al* [179], 2019
Heat stress (flies raised at 29 °C)	Suppression of BX2 transgene cluster over multiple (50) generations	Paramutation of BX2 *via* maternally inherited piRNAs, triggered by heat stress which resulted in active transcription of piRNAs within that gene locus	de Vanssay *et al*[126], 2012	Paramutation is not regarded as an established epigenetic process in mammals	
				However, readers should be aware of this proof-of-concept study in mice	Yuan *et al* [180], 2015
			Casier *et al* [127], 2019	Paternal transmission of "white-tail-tip" phenotype caused by paramutant allele in mice limited to one generation. Maternal miRNAs and piRNAs regulate (inhibit) germline transmission of paramutation	
				14 piRNAs differentially expressed in AD prefrontal cortex samples *vs* controls	Qiu *et al*[128], 2017
				Sequencing of CSF-derived exosome sncRNA revealed combination of 3 miRNAs and 3 piRNAs detected AD and predicted the conversion of mild–cognitive impaired (MCI) patients to AD dementia. Greater predictive confidence when combining the smallRNA signature with pTau and Aβ 42/40 ratio pathology	Jain *et al*[129], 2019
Forced cohabitation with predator or	Stressed females shift behaviour to laying eggs on	Maternal inheritance of chromosome III and NPF (	Bozler *et al* [136], 2019	Dysregulation of NPY levels in the brain is a key pathophysiology of drug	Gonçalves *et al* [181], 2016

endoparasitoid wasps	food rich in ethanol, and that preference is inherited through five generations	*Drosophila* homolog of NPY) gene locus, reduced NPF expression in the fan shaped body of the adult brain drives ethanol preference		addiction. Manipulation of NPY neurotransmission has potentially beneficial behavioural outcomes, depending on the drug in question	
				NPY is implicated in human alcohol misuse disorders	Mayfield *et al* [137], 2002
				NPY is also implicated in rodent models of alcohol misuse disorder	Mottagui-Tabar *et al* [138], 2005
					Thorsell and Mathe[139], 2017
					Badia-Elder *et al*[140], 2003
					Schroeder *et al* [142], 2005
					Robinson *et al* [141], 2019
Restraint stress	Paternal restraint stress affects epigenome, transcriptome and metabolome of F1 progeny	Stress-induced up-regulation of *Upd3* (*Drosophila* homolog of IL-6) in somatic cells and testes, activating JAK/STAT pathway	Seong *et al* [145], 2020	Metabolic dysregulation in the F1 offspring derived from male breeders exposed to early postnatal stress	van Steenwyk *et al*[146], 2018; van Steenwyk *et al*[93], 2020
		Subsequent p38 activation results in dATF-2 deactivation in germ cells leading to decreased H3K9me2 (repressive mark) at target genes. Repressive histone marks inherited by F1 progeny		Review of epigenetic mechanisms proposed to underlie intergenerational transmission of paternal trauma	Yehuda and Lehrner[182], 2018
				Childhood adversity associated with altered DNA methylation of HPA axis and immune system genes; potentially inherited by offspring	Bick *et al*[154], 2012
Methylphenidate (MPH) treatment	Behavioural response to MPH is genetically variable and intergenerational effects can be observed in F1 offspring	Mechanism is unknown but MPH resulted in alterations to expression of many histone modifying genes	Rohde *et al* [158], 2019	ADHD is highly heritable, but the reasons are unclear despite the identification of candidate genes. Future studies should attempt to identify transgenerationally heritable epigenetic modifications as the basis for genetic vulnerability	
				Non-human primate studies indicate that MPH treatment affects normal puberty. The transgenerational implications of this finding for humans needs to be followed-up	Mattison *et al* [155], 2011
G418 treatment (toxic stress)	Exposure of F0 females to G418 resulted in reduction of *Polycomb* group gene expression in up till F3 generation	Maternal *Polycomb* group expression in early embryogenesis affects expression of the zygotic genome, which can be inherited	Stern *et al* [168], 2014	G418 has been successfully used to rescue PTC deficiencies in a cell culture model for frontotemporal dementia. However, its broader utility for treating neuropsychiatric conditions remains unknown	Kuang *et al* [164], 2020
				PTC mutations of neuronal *UPF3B* gene associated with nonspecific mental retardation with or without austism	Laumonnier *et al*[183], 2010

PTC: Premature termination codon; IL: Interleukin.

history of MDD or other forms of stress-related psychopathology. The *D. melanogaster* ATF-2 is known to be an essential regulator of heterochromatin assembly through its co-localisation with HP1, a crucial adaptor molecule for DNA methyltransferases that are recruited along the heterochromatin assembly by H3K9me marks. Thus, despite the lack of evidence at this time, it has been speculated that the general disruption of gene expression in psychiatric conditions such as SZ involves a combination of abnormal DNA methylation and histone methyltransferase activity[123,124], and that recurring environmental stress could be key triggers for the familial manifestations of psychosis. It is especially important that this aspect of epigenetic pathology be examined given more recent *in vitro* evidence that antipsychotics such as risperidone

have the capacity to inhibit heterochromatin formation[125].

Studies of heat stress have also uncovered other heat-induced epigenetic responses involving paramutation and the resulting transgenerational inheritance of small non-coding RNAs *via* the maternal lineage. de Vanssay *et al*[126] described a paramutation event involving P-transposable-element repression in the germ line (termed trans-silencing effect, TSE) that converted other homologous clusters typically incapable of TSE into strong silencers[126]. The transgenerational effects of this paramutation persisted through 50 generations of progeny and was found to specifically require *aubergine* gene-mediated piRNA biogenesis but not Dicer-2 mediated siRNA production. Interestingly, this paramutation is triggered by heat stress and the pattern of piRNA up-regulation is transmitted *via* the maternal lineage[127]. Thus, one of the persistent epigenetic modifications in response to stress in humans could be the emergence of actively transcribed piRNA loci. While piRNAs are not a core focus of molecular psychiatry, piRNAs have started to gain attention in the domain of neurodegenerative diseases after having been found to be differentially expressed in prefrontal cortical tissue of post-mortem AD brains[128]. That has led to questions of their role in disease pathogenesis and the possibility of using them as a reliable biomarker for human disease. In support of the latter notion, miRNA and piRNA profiling of human cerebrospinal fluid-derived exosomes has more recently been proposed to have utility in diagnosing AD, as well as predicting the conversion from mild cognitive impairment to AD dementia[129]. There is sexual dimorphism in the clinical manifestation of AD with more women than men being diagnosed and maternal transmission is more frequently observed than paternal transmission[130]; but the potential involvement of maternally inherited miRNAs or piRNAs to confer AD risk is completely unknown at this time. In *D. melanogaster* it has been established that piRNAs are maternally inherited and aging is associated with an increased presence of novel heterochromatic-only secondary piRNAs[131-134]. However, evidence of a similar pattern of inheritance role in humans has yet to be discovered. Our understanding of piRNA in the context of psychiatry and behaviour is barely in its infancy, and there remains much to be uncovered regarding the piRNA pathogenesis and its direct consequences across the range of neuropsychiatric diseases. Perhaps further studies in *D. melanogaster* can uncover novel piRNA-mediated disease mechanisms for psychiatry conditions that are skewed to maternal transmission.

Predator stress is another form of environmental stress that applies to *D. melanogaster* and studies have revealed that it is sufficiently severe to induce shifts in reproductive behaviours. Females housed in cohabitation conditions with endoparasitoid wasps develop a preference to lay eggs on ethanol-rich food as ethanol protects the larvae from wasp infection[135]. That change in oviposition behaviour was found to be driven by neuropeptide F (the *D. melanogaster* homolog of Neuropeptide Y, NPY) and persisted despite removal of the endoparasitoid wasps. More impressively, a recent study reported that exposure to predatory wasps is also an environmental stressor that triggers a similar transgenerational modification of egg laying behaviour over five generations[136]. That shift towards ethanol-rich substrates was established to be superficially maternally transmitted and involved inheritance of Chromosome III within which resides the *NPF* gene that is differentially expressed in the fan shaped body of the adult female brain. Here, it is worth noting that NPY is of major interest to substance misuse disorders and has been implicated in human alcohol use disorder [137-139] as well as in rodent models[140-142]. Since genetic vulnerability remains the core disease-causing factor for humans, and given that unbiased genetic screening, QTL analyses or GWAS studies are easily paired with functional studies in *D. melanogaster*[143,144], the latter presents as a viable alternative organism to study gene-environment interactions and the triggers that drive alcoholism, with perhaps the next step being a pursuit of the epigenetic mechanisms underlying those pathologies.

Interestingly, by using restraint stress to model strong psychological stress, Seong *et al*[145] found that paternal stress altered the epigenome, transcriptome, and metabolome in a dATF2 pathway-dependent manner[145]. A host of genes involved in metabolic health (amino acid metabolism, glycolysis, TCA cycle) were differentially expressed in the F1 offspring, which is consistent with the observations of similar paternal stress studies in mice[93,146]. The intergenerational effects in *D. melanogaster* were proposed to be caused by stress-induced up-regulation of *Upd3* gene in the testes [the *D. melanogaster* homolog of the pro-inflammatory cytokine Interleukin-6 (IL-6)], which was confirmed by overexpression studies of *Upd3* in paternal somatic cells with corresponding studies of the offspring outcomes. The overall intergenerational effects were proposed to be mediated by stress-induced increases in Upd3 that causes abnormal phosphorylation of dATF-2 in *D. melanogaster* germ cells, resulting in decreased H3K9me2 repressive marks that are inherited by the F1 offspring to

ultimately disrupt heterochromatin assembly and gene transcription. In humans, it remains to be clarified whether IL-6 (or other pro-inflammatory cytokines) correlates with sperm DNA damage[147,148]. However, it is well-established that inflammation has a significant role in the pathogenesis of various neuropsychiatric conditions including MDD[149-151] and SZ[152,153]. It would be interesting to elucidate the relationship of SNPs and risk gene loci with H3K9me2 repressive marks, and its contribution to the development of those conditions especially in familial cases. Additionally, given initial evidence suggesting that traumatic stress has long-term epigenetic consequences including altering the DNA methylation patterns of genes relevant to HPA axis function and the immune (inflammation) response[154], future *D. melanogaster* studies should also focus on DNA methylation as a key epigenetic mechanism mediating the transgenerational inheritance of stress-induced pathologies.

Methylphenidate (Ritalin) is a frontline prescription psychostimulant for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. The increasing frequency of prescription has been the cause for concern regarding over-prescription and overdiagnosis. Methylphenidate treatment has been reported to result in significant developmental delay to puberty with hormonal imbalance in non-human primates[155]. While the impacts on spermatogenesis or sperm health were not investigated in that study, separate work on the major metabolite of methylphenidate, ritalinic acid, has found a significant increase of human sperm motility and viability *in vitro*[156]. However, any effects of long-term methylphenidate treatment on pubertal growth, sperm development *in vivo* and the sperm epigenome are unknown presently. *D. melanogaster* studies have contributed tremendously to advancing our understanding of the genetics of neuropsychiatric conditions. A prime example is they have been used to identify ADHD candidate genes[157] and to determine the transcriptomic response to methylphenidate, which correlate to their locomotor responses to drug treatment[158]. The latter study also identified putative candidate genes through whole genome transcriptomic analysis that accounted for the variability in drug response. Collectively, that body of work establishes *D. melanogaster* as a valid organism to further probe the transgenerational effects of methylphenidate exposure on male reproductive health and progeny behaviours. The aetiology of ADHD remains poorly understood but epidemiological data indicates approximately 80% heritability for both adults and children[159,160] despite only 22% of the disease liability being linked to common gene variants[161]. Given that knockdown of *D. melanogaster* homologues of ADHD candidate genes produces abnormal locomotor phenotypes that are also responsive to treatment by ADHD prescription compounds [162,163], *D. melanogaster* would continue to serve as an ideal organism for future investigations into the epigenetic factors underlying the high degree of heritability of ADHD.

Recently, one study investigating new therapeutic options for treating fronto-temporal dementia (FTLD)[164] explored the use of aminoglycosides–a class of gram-negative bacilli antibiotics that have the capacity to induce eukaryotic ribosomal readthrough of premature termination codon (PTC) sequences to yield a full-length protein. Aminoglycosides have successfully been used to treat various diseases involving PTC mutations such as cystic fibrosis[165], Duchenne muscular dystrophy [166] and Rett syndrome[167], but have yet to be employed for neuropsychiatric conditions. In using a cell culture screening assay to conduct proof-of-principle studies with non-sense mutations of *progranulin* associated with FTLD, Kuang *et al*[164] identified two aminoglycosides that rescued the expression of the *progranulin*. It is worth noting that one of those aminoglycosides, G418 (also known as geneticin), has previously been reported to exert transgenerational effects on maternal *Polycomb* levels in *D. melanogaster* F2 embryos that persisted into the F3 generation[168]. Importantly, G418 exposure lead to growth retardation and delay in pupation times. While the transgenerational implications of G418 would be minimal since FTLD is associated with advanced aging, we believe it is important that readers be aware of such potential risks to offspring should aminoglycosides continue to be explored as therapeutic options for conditions in a younger fertile population.

CONCLUSION

Looking towards the future, improving the prospects for neuropsychiatric patients requires the field of psychiatry to have a more comprehensive understanding of the causes of various conditions, especially regarding how basic molecular and epigenetic pathologies interact and contribute to the overall disease phenotype. A major step

would be the incorporation of epigenome profiling since it is the key molecular intermediary linking genetics (susceptibility) to the environment (stress-related triggers). In highlighting the key findings of studies of *C. elegans* and *D. melanogaster*, we hope readers can come to appreciate the value of conducting basic research employing these two key non-mammalian organisms to potentially uncover novel molecular and epigenetic pathologies. Multiple stress-induced epigenetic modifications that affect the individual have significance in a variety of human neurological conditions, but further findings that progeny are also transgenerationally affected will have broader implications for health projections for future generations. At a time when stress (physical and mental) is prevalent and largely unavoidable, there is great urgency to understand the current mental health crisis and work towards new approaches for treatment and prevention. Of course, it is openly acknowledged that complex human behavioural responses and adaptations related to psychopathologies cannot be modelled in simple organisms. However, many fundamental molecular mechanisms that regulate neuronal behaviour have been conserved across phyla, and those molecular and neuronal circuitries can be interrogated in a rapid manner in simple model organisms Therefore, invertebrate research should be regarded as being tremendously beneficial and highly complementary to human and mammalian model research, and further investments should be made in this regard. An expanded combination of clinical studies, rodent models and molecular studies in model organisms provides an extremely powerful multi-tiered approach to understanding the molecular basis of psychiatric disorders. Focusing on the epigenetic pathologies associated with neuropsychiatric conditions will undoubtedly lead to the development of novel approaches for treatment.

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REVIEW

Antipsychotics cardiotoxicity: What's known and what's next

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Abstract

Chronic use of antipsychotic medications entails a dilemma between the benefit of alleviating psychotic symptoms and the risk of troubling, sometimes life-shortening adverse effects. Antipsychotic-induced cardiotoxicity is one of the most life-threatening adverse effects that raises widespread concerns. These cardiotoxic effects range from arrhythmia to heart failure in the clinic, with myocarditis/cardiomyopathy, ischemic injuries, and unexplained cardiac lesions as the pathological bases. Multiple mechanisms have been proposed to underlie antipsychotic cardiotoxicity. This review aims to summarize the clinical signs and pathological changes of antipsychotic cardiotoxicity and introduce recent progress in understanding the underlying mechanisms at both the subcellular organelle level and the molecular level. We also provide an up-to-date perspective on future clinical monitoring and therapeutic strategies for antipsychotic cardiotoxicity. We propose that third-generation antipsychotics or drug adjuvant therapy, such as cannabinoid receptor modulators that confer dual benefits — *i.e.*, alleviating cardiotoxicity and improving metabolic disorders — deserve further clinical evaluation and marketing.

Key Words: Antipsychotics; Cardiotoxicity; Sudden cardiac deaths; Cannabinoid receptor; Adrenoceptor

Core Tip: Antipsychotic drug-induced cardiotoxicity is troubling and sometimes life-threatening, which restricts their clinical application. Herein, we summarize the clinical signs and pathological changes of antipsychotic cardiotoxicity and introduce recent progress in understanding the underlying mechanisms at both the subcellular organelle level and the molecular level. Future perspectives regarding clinical monitoring and therapeutic strategies for antipsychotic cardiotoxicity are also discussed.

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INTRODUCTION

The use of antipsychotics is an important and integral part of psychiatric care and often lasts for a lifetime. Antipsychotics are primarily prescribed for the treatment of schizophrenia and other psychotic diseases[1] and are commonly categorized as first-generation antipsychotics (FGAs, or typical antipsychotics) and second-generation antipsychotics (SGAs, or atypical antipsychotics). Recently, several new and emerging antipsychotic medication strategies, termed third-generation antipsychotics (TGAs), have been marketed or are under clinical development for the treatment of mental disorders[2]. Generally, the evolution of antipsychotics has largely improved therapeutic outcomes in the clinic. However, inevitable side effects remain a clinical limitation that unfortunately results in drug withdrawal or discontinuation of potentially successful regimens[3]. These toxic effects range from minor issues (*e.g.*, mild sedation or dry mouth) to troubling issues (*e.g.*, weight gain or metabolic disturbances) to even life-threatening issues (*e.g.*, cardiotoxicity).

Clinical statistics have reported a clear link between the use of antipsychotics and increased incidence and mortality of sudden cardiac death (SCD)[4]. In a large Danish retrospective study, the incidence of SCD was 14.8 deaths per 100000 person-years in psychiatric individuals[5]. Current users of FGAs and SGAs had higher rates of SCD than nonusers of antipsychotic drugs, with adjusted incidence-rate ratios of 1.99 [95% confidence interval (CI): 1.68 to 2.34] and 2.26 (95%CI: 1.88 to 2.72), respectively[6]. Autopsy-based evidence also confirmed that approximately 3.5% of schizophrenia patients under antipsychotic use died from cardiac causes[7]. Moreover, SGAs seem to predispose patients to a mildly higher risk of SCD than FGAs, with an incidence-rate ratio of SGAs to FGAs of 1.14 (95%CI: 0.93 to 1.39). The incidence of antipsychotic-induced SCD is also dose-related. The incidence-rate ratios of FGA users increased from 1.31 (95%CI: 0.97 to 1.77) for those taking low doses to 2.42 (95%CI: 1.91 to 3.06) for those taking high doses ($P < 0.001$). Among users of SGAs, the incidence-rate ratios increased from 1.59 (95%CI: 1.03 to 2.46) for those taking low doses to 2.86 (95%CI: 2.25 to 3.65) for those taking high doses ($P = 0.01$)[6].

In recent decades, our knowledge of antipsychotic cardiotoxicity has been increasingly improved. This review aims to provide an up-to-date summary of recent progress in understanding the clinical manifestations, pathological alterations, and cellular and molecular mechanisms underlying this critical issue. We also propose future perspectives that await implementation.

CLINICAL MANIFESTATIONS OF ANTIPSYCHOTICS CARDIOTOXICITY

Multiple studies have reported antipsychotic cardiotoxicity from clinical perspectives. These cardiovascular effects range from heart rate (HR) changes and blood pressure (BP) alterations to more severe and fatal issues such as QTc prolongation and congestive heart failure. These manifestations and their closely associated drugs are illustrated in Figure 1.

Heart rate changes

Tachycardia: Antipsychotic agents have anticholinergic properties and thus could cause cardiovascular side effects when vagal tone is significantly decreased by antagonism of type 2 muscarinic receptors. The anti-muscarinic effects include sinus tachycardia and other systemic anticholinergic effects, such as dry mouth, constipation, and urinary retention. Antipsychotic-induced tachycardia is most commonly observed in low-potency FGAs (*e.g.*, chlorpromazine and thioridazine) and some SGAs (*e.g.*, clozapine). Compared with an average of 72 ± 14 beats/min in 42 unmedicated controls, the mean HR significantly increased to 83 ± 14 beats/min in the 111 patients receiving FGAs. It has been estimated that an increase in HR of 10-15 beats/min could be observed in 1/4 of patients taking clozapine. Consistently, data showed that treatment with clozapine (21 d under 200-600 mg/d), haloperidol (18 d

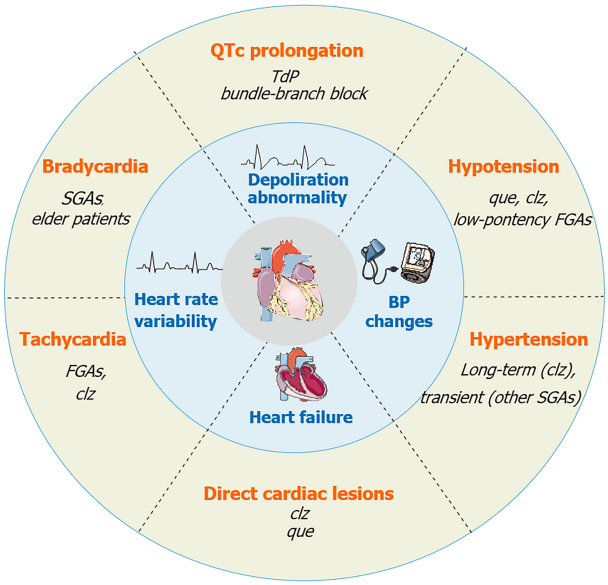

Figure 1 Summary of clinical manifestations of antipsychotic cardiotoxicity. Typical characteristics for each manifestation are concisely listed in black texts. SGA: Second-generation antipsychotic; FGA: First-generation antipsychotic; TdP: Torsades de pointes.

under 5-10 mg/d), and olanzapine (17 d under 5-20 mg/d) increased patients' HRs to 107, 86, and 89 beats/min, respectively, which were significantly higher than those of their matched control subjects (62 beats/min)[8]. Of note, clozapine-induced tachycardia does not seem to be dose-dependent. In a rat model receiving different doses of clozapine administration, a low dose (1.5 mg/kg) and a high dose (5 mg/kg) of clozapine increased the HR by 51 ± 8 and 47 ± 15 beats/min, respectively[9]. This effect was distinct from those of haloperidol and risperidone[8].

Most patients may develop milder tachycardia with drug treatment extension, a phenomenon referred to as drug tolerance, with clozapine being the sole exception. Clozapine-induced tachycardia may be persistent and requires the addition of β-adrenergic receptor antagonists to avoid severe cardiovascular effects for symptomatic patients with HRs over 110-120 bpm[10]. In addition, antipsychotic-induced tachycardia may increase myocardial oxygen demand and aggravate cardiac ischemia in patients with basic cardiovascular diseases. Persistent tachycardia may also contribute to cardiomyopathy[11]. All of these outcomes mandate clinical interventions.

Bradycardia: Some cases also reported antipsychotic impacts on lowering the HR, particularly SGAs such as risperidone[12], quetiapine[13], amisulpride[14], olanzapine [15], and paradoxically clozapine[16]. These cases were mostly elderly patients with signs abated after discontinuation of drugs. It has been reported that risperidone induced bradycardia in an 82-year-old woman (43 beats/min) and 69-year-old man (39 beats/min). Prompt initiation of appropriate resuscitative and supportive measures, along with discontinuation of the offending medication, led to clinical improvement [12]. Quetiapine-induced bradycardia has also been reported in elderly patients, in which settings, a time sequential improvement was achieved after decreasing the drug dosage[13]. A male patient developed symptomatic bradycardia during usage of amisulpride (400-800 mg/d), which dramatically improved after the complete termination of amisulpride usage[14]. An 84-year-old patient presented with conscious depression, bradycardia (40 beats/min), hypotension, miosis, and hypothermia after 2.5 mg/day olanzapine therapy, and his condition improved with supportive therapy [15]. Clozapine also induced bradycardia in elderly patients[16], albeit with more reports of clozapine-induced tachycardia.

Antipsychotics-induced bradycardia may be explained by age-related changes in the pharmacokinetics and pharmacodynamics of drugs in older patients that increase their susceptibility to the side effects of psychotropic medications[16]. The antipsychotic-induced slowdown of HR may lead to more severe outcomes, such as cardiac arrest and SCD. It is hence strongly suggested that clinicians remain vigilant for the signs or symptoms of adverse effects such as bradycardia in their elderly patients who take SGAs.

Blood pressure

Hypertension: In a 24-wk follow-up study, only four (22%) of the 18 patients fulfilled the criteria for hypertension at baseline levels. However, 12 (67%) in 18 patients developed hypertension ($\chi^2 = 6.25$, $df = 1$, $P = 0.0124$) with regard to both systolic BP (SBP) and diastolic BP (DBP) during clozapine treatments[17]. Consistently, a 5-year follow-up observation of 82 patients showed significant increases in SBP ($P = 0.0004$) and DBP ($P = 0.0001$) after clozapine therapy. In these patients, 27% developed hypertension, the rate of which significantly surpassed that in FGA therapy (4%) or in other SGA (olanzapine and risperidone) therapies (9%)[18].

Interestingly, clozapine tended to reduce SBP in the early period after drug initiation, whereas olanzapine and risperidone raised SBP to a statistically significant degree within 3 d of initiation[19]. Aripiprazole, another SGA, was also observed to induce arterial hypertension shortly after drug initiation in two geriatric patients[20]. Both somatic and psychiatric outcomes were favorable after discontinuation of aripiprazole or the introduction of FGAs.

Orthostatic hypotension: Orthostatic hypotension is one of the most common cardiovascular adverse effects of antipsychotics and is more common in elderly patients[21,22]. In a cardiovascular health study enrolling 5201 patients over 65 years old, the prevalence of asymptomatic orthostatic hypotension was 16.2% to 18%, although only 2% were symptomatic[23]. The risk of orthostatic hypotension associated with antipsychotics is increased in patients with autonomic nervous system diseases and fluid imbalance and in those taking concomitant drug therapy that affects hemodynamic tone. Elderly individuals taking multiple medications, such as antipsychotics and hypotensive drugs, constitute a higher risk factor for symptomatic orthostatic hypotension. The incidence of FGA-induced orthostatic hypotension is approximately 77% compared with only 15% in patients receiving placebo[24], with the accepted mechanism being α1 adrenergic blockade and other putative mechanisms such as calcium blockade, inhibition of centrally mediated presser reflexes, and negative inotropic effects[25]. Low-potency phenothiazine antipsychotics (*i.e.*, chlorpromazine and thioridazine) are generally considered the most common FGAs that cause orthostasis[26].

Unlike FGAs, most SGAs, with the exception of clozapine and quetiapine, are less likely to cause orthostatic hypotension due to their low affinity for α_1-adrenergic receptors[26]. Based on available data, the hierarchy of hypotension production was quetiapine (27%) > clozapine (24%) > iloperidone (19.5%), compared with 8.3% in patients taking placebo, while other SGAs (*i.e.*, risperidone, olanzapine, and ziprasidone) barely cause orthostatic hypotension[26,27]. Of note, orthostatic hypotension is dose-dependent and transient. The long-term effect of SGAs may be more associated with hypertension, as mentioned above. Therefore, orthostatic hypotension can frequently be overcome with close monitoring and conservative dosing[28].

Ventricle repolarization abnormalities

QT prolongation: Antipsychotic agents are commonly correlated with repolarization abnormalities, which manifest as iatrogenic prolongation of the QT interval. The QT interval is measured on the electrocardiogram (ECG) from the beginning of the QRS complex (initial deflection or Q wave) to the end of the T wave, which reflects depolarization and repolarization of the ventricles, respectively[29]. An imbalance in ion flow across the cell membrane, especially potassium current impairment, can result in delayed repolarization manifesting a prolonged QT interval[30]. Since this interval is inversely proportional to HR, the QT interval is typically corrected for HR (QTc). The QTc interval in healthy people ranges from 380 ms to 450 ms under the combined impact of age and gender. Some antipsychotic medications are associated with the prolongation of QTc interval (> 450 ms in men and > 460 ms in women). In a cohort study enrolling 4825345 patients, approximately 40% were prescribed an antipsychotic medication and later presented with QTc prolongation[31]. In particular, the Pfizer 054 study conducted by Pfizer Inc. reported the order of QTc interval elongation to be thioridazine (35.6 ms), ziprasidone (20.3 ms), quetiapine (14.5 ms), risperidone (11.6 ms), olanzapine (6.8 ms), and haloperidol (4.7 ms)[32,33]. The U.S. FDA has therefore increased concerns of this serious issue; five different medications have been withdrawn from the market, and several others have received different kinds of product warnings[34].

It is noteworthy that although most antipsychotics are associated with QTc prolongation, it is rather difficult to rank the risk of malignant arrhythmia for the individual antipsychotic drug since ECG measurement methods vary across studies. A

recent clinical review therefore integrated pharmacovigilance data from several international databases. Data from various authorities on the risk of arrhythmia associated with psychotropic medications were weighted and categorized into three risk categories. Aripiprazole, olanzapine, perphenazine, and zuclopenthixol were categorized as class A drugs [no risk of QTc prolongation or torsades de pointes (TdP)]. Amisulpride, chlorprothixene, clozapine, flupentixol, levomepromazine, paliperidone, quetiapine, risperidone, and sulpiride were categorized as class B drugs (a drug with a propensity of QTc prolongation). Finally, haloperidol, pimozide, sertindole, and ziprasidone were categorized as class B* drugs (a drug with pronounced QTc prolongation, documented TdP cases, or other serious arrhythmias) [35].

Serious conduction abnormality: QT prolongation is associated with ventricular arrhythmias, specifically TdP, and SCD. TdP can be inherited (congenital long-QT syndrome, LQTS) or acquired, with the most common reason being medications[36]. The following conditions increase the risk of drug-induced TdP: (1) Disease states/electrolyte levels (heart failure, structural cardiac disease, bradycardia, and hypokalemia); (2) pharmacogenomic variables (presence of congenital LQTS, subclinical ion-channel mutations, and history of or having a relative with history of drug-induced long QT/TdP); and (3) pharmacodynamic and kinetic factors (high doses, women, being elderly, metabolism inhibitors, combining two or more QT prolonging drugs, drugs that prolong the QT and increase QT dispersion, and drugs with multiple actions on ion channels)[37]. Until now, QT prolongation has remained the most extensively used surrogate marker for TdP, while the existing means for precisely measuring prolongation have been debated[38,39]. Moreover, TdP is known to occur at therapeutic doses of SGAs when the QTc interval is < 500 ms. Thus, establishing a clinically standardized threshold of the QTc interval is difficult but important.

Serious conduction system alterations also include right and left bundle-branch block (RBB and LBB) and partial or complete atrioventricular block. It has been reported that an abnormal cardiac conduction system was the second most common cause of death in 24 patients dying suddenly from long-term antipsychotic use[40]. The main mechanisms are antipsychotic-induced pericarditis involving the sinus node, atrial muscle, and atrioventricular node or endocarditis involving the RBB, LBB, and Purkinje fibers.

Heart failure

Antipsychotic-induced heart failure is a consequence of prior direct cardiac lesions in response to drug stimuli. These pathological lesions included myocarditis, cardiomyopathy, ischemic heart diseases (IHD), *etc.*[41].

Currently available reports have mainly linked clozapine with an increased risk of heart failure. A psychiatric patient on chronic low-dose clozapine (75 mg/d) therapy presented with congestive heart failure secondary to the cardiotoxic effects of psychiatric medication, a condition that failed to be corrected by conventional heart failure treatments. Drug discontinuation is commonly issued when confronting clozapine-induced heart failure[42]. An exclusive report also presented the case of a 37-year-old woman who developed cardiomyopathy under high doses of quetiapine and recovered in the course of the next months after quetiapine was stopped[43]. While temporary cessation of treatment can lead to severe psychotic exacerbation and nonengagement with cardiac specialists, more evidence is required for continued use of antipsychotics in patients with cardiac complications[42].

PATHOLOGICAL CHANGES OF ANTIPSYCHOTICS CARDIOTOXICITY

Chronic exposure to antipsychotics may directly damage cardiac muscles that lead to irreversible cardiac remodeling, pathologically diagnosed as myocarditis, dilated cardiomyopathy (DCM), and some other conditions, including ventricular hypertrophy, IHD, and pulmonary thromboembolism (PTE). In addition, emerging studies have reported that substantial fatal cases are negative for autopsy findings or with only mild pathological lesions, the causes of which are referred to as cardiac arrhythmia (summarized in Figure 2).

Myocarditis and DCM

Myocarditis is defined as inflammation of the myocardium. Clozapine is by far the

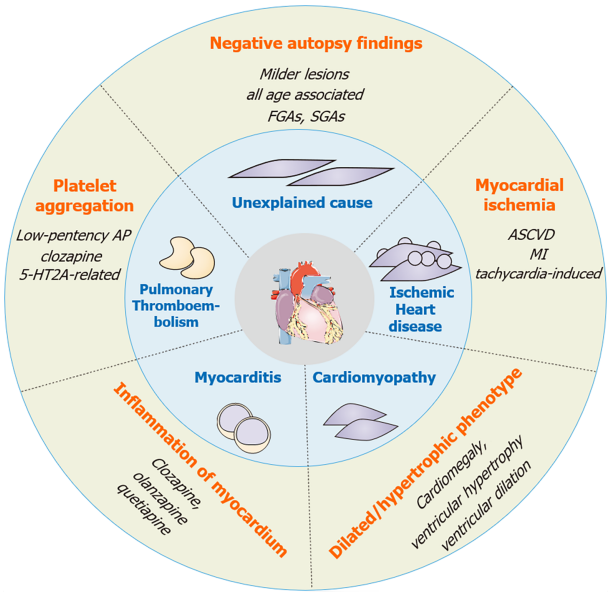

Figure 2 Summary of cardiac pathological changes in response to antipsychotic treatments. Typical characteristics of each pathological change are concisely listed in black text. SGA: Second-generation antipsychotic; FGA: First-generation antipsychotic; ASCVD: Atherosclerotic cardiovascular disease; MI: Myocardial infarction.

most commonly used antipsychotic that has been associated with myocarditis. The World Health Organization has suggested that clozapine, which caused over 200 cases of myocarditis and cardiomyopathy in 2001[44], has a closer association with myocarditis and cardiomyopathy than any other kind of antipsychotic drug[45]. According to statistics, clozapine-associated myocarditis has been estimated to increase from 1 in 10000 to 1 in 500 patients. Most of these cases occurred in the first 2 mo after clozapine therapy[46], while at the beginning of drug use, the incidence of clozapine-related myocarditis is between 0.03% and 0.19%[47]. Furthermore, the death rate caused by clozapine-induced acute myocarditis is approximately 25%[48]. An autopsy report also confirmed antipsychotic-induced myocarditis, which showed that in 24 sudden death cases, 11 (45.8%) died from myocarditis, and 7 (29.2%) were on clozapine medication[49].

The histopathological features in the case of clozapine-related myocarditis are myocytolysis and necrosis with florid infiltration, accompanied by lymphocytes, neutrophils, and prominent eosinophils[41]. If acute myocarditis is not recognized at the early stage, it may progress to DCM, a disease characterized by ventricular dilation and heart dysfunction. According to Kilian *et al*[41], the incidence of DCM in the general population was 0.75% to 1%, while that in clozapine-treated patients was approximately 5.15% (over a 5-fold increase compared with the general population). In an autopsy report, 6 (42.9%) in 14 cases died suddenly from DCM, which developed after chronic antipsychotic use[50].

The mechanism by which antipsychotics induce myocarditis or DCM remains unclear. Numerous hypotheses have been proposed, including immunoglobulin (Ig)E-mediated pathways, cytokine-driven responses, and oxidative stress-related hypercatecholaminergic states[51]. While IgE-mediated hypersensitivity used to be considered the main attributor, a recent study found that clozapine treatment caused an elevated plasma catecholaminergic state, and the blockade of β-adrenoceptors may be helpful in decreasing the occurrence and severity of clozapine-induced myocarditis, implicating a membrane receptor-involved mechanism[52]. We also reported that myocarditis is not always accompanied by aberrant eosinophils in experimental murine models[53], implying IgE-independent mechanisms underlying antipsychotic-induced cardiac muscle disorders.

Olanzapine- and quetiapine-induced myocarditis has also been sparsely reported due to their chemical structure similarity with clozapine. Quetiapine induced cardiomyopathy in a 37-year-old woman after high dosages[43]. From the spontaneous adverse drug reports database of the Danish Health and Medicines Authority, two fatal cases of eosinophilic myocarditis were associated with the use of olanzapine [54]. Another case report with 10-year olanzapine intake also suggested that the use of olanzapine may cause DCM since echocardiography shows decreased global biventricular function[55]. It has also been mentioned in another report that the

adverse drug reaction of psychotropic drugs (clozapine and olanzapine) is very likely to be related to DCM[56].

Ischemic heart diseases

It has been reported that most patients with schizophrenia do not die from suicide or during psychotic episodes but from IHD[57]. IHD has become the primary cause of death among schizophrenia patients[58] and tends to be sex biased. According to a statistical analysis, antipsychotics increased the prevalence of acute IHD by 32% among women but caused no significant changes among men[59]. The four antipsychotic drugs associated with high mortality of IHD were clozapine, quetiapine, olanzapine, and thioridazine, all of which share high affinity to the 5-HT2A receptor [60], and blockade of the 5-HT2A receptor might confer protection against IHD and buffer the deleterious metabolic effects of antipsychotics[61].

Among IHDs, myocardial infarction (MI) is a severe pathological alteration after the use of antipsychotic drugs[62]. It has been reported that antipsychotic users were 1.88-fold more likely to have MI[63], although this conclusion was challenged by a meta-analysis reporting no significant association with antipsychotic drugs[62]. The high incidence of MI might be attributed to atherosclerotic cardiovascular diseases (ASCVDs), which account for 67.3% of the natural deaths among schizophrenia patients in Maryland, USA[58]. ASCVD may manifest ischemic syndromes, including acute coronary syndromes, congestive heart failure, and sudden and nonsudden cardiac death[64]. The mechanism of ASCVD being common among schizophrenia patients is multifaceted, with the gut microbiome interrupted by antipsychotic use being recently introduced as a novel mechanism[65]. Interestingly, a study showed that haloperidol, a representative FGA, inhibited atherosclerosis in mice lacking LDL receptors by decreasing ABCA1-mediated cholesterol efflux from macrophages to apolipoprotein A1[66]. Another contributor to myocardial ischemia might be antipsychotic-induced tachycardia that increases myocardial oxygen demand and aggravates cardiac ischemia in schizophrenia patients[35].

Ventricular hypertrophy

In an autopsy-based study, two (14.3%) in 14 cases were found to have remarkable left ventricular hypertrophy, leading to the diagnosis of hypertrophic cardiomyopathy [50]. We also reported a case of sudden death from hypertrophic cardiomyopathy after over 20 years of chlorpromazine therapy[40]. Ventricular hypertrophy might be an adaptive response in the early stage of antipsychotic stimuli. When maladapted, the heart may progress to pathological hypertrophy, a condition that predisposes patients to sudden death.

Pulmonary thromboembolism

Antipsychotic drugs have also been reported to cause thrombotic complications such as lupus-like syndromes. Both typical and atypical antipsychotics can cause PTE[67]. Female sex and the use of antipsychotics were two risk factors for PTE, with odds ratios of 4.22 (95%CI: 1.82-9.78) and 10.49 (95%CI: 3.95-27.85), respectively[68]. Among 28 patients who died of PTE, eight (28.6%) used antipsychotics, and all were female [68]. High-dose and parenteral administration were also more likely to cause PTE. For oral administration, the odds ratio was 1.07 for the low dose ($P = 0.04$) and 1.40 for the high dose ($P < 0.001$). For parenteral administration, the odds ratio was 1.18 for the low dose ($P < 0.001$), while it was 1.43 for the high dose ($P < 0.001$)[69]. In particular, the use of low-potency antipsychotic drugs was associated with a higher risk of venous thromboembolism (risk ratio = 1.90, 95%CI: 1.04-3.47), a condition that predisposes patients to PTE[70]. Generally, chlorpromazine, thioridazine, and clozapine are common antipsychotics that cause PTE.

The development of PTE has been associated with increased platelet aggregation due to the strong affinity of these drugs for 5-HT2A receptors. According to statistics, atypical antipsychotic drugs have a more than 10-fold greater affinity for 5-HT2A receptors than for D2 receptors[68]. Antipsychotics may also block dopamine and then cause hyperprolactinemia, which is a significant risk factor for PTE in patients using antipsychotics. Of note, although aripiprazole and quetiapine act on 5-HT2A receptors, they did not increase the risk of PTE. Another report also showed no increase in platelet aggregation caused by haloperidol, olanzapine, and risperidone[71], although this finding contradicts sporadic case reports of olanzapine and risperidone-associated PTE[72]. These studies imply extra 5-HT2A receptor-independent mechanisms or potential between-study heterogeneity.

Sudden unexplained death

It is noteworthy that even after systemic autopsy and toxicological screening, some cases may have no definitive cause of death, the so-called "unexplained" autopsy-negative cases that are probably caused by cardiac arrhythmia. Many autopsy-based studies have documented unexplained cases among sudden deaths of schizophrenia, with rates ranging from 2.8%[58] to 52%[73]. A nationwide cohort study from Denmark found that SCDs in psychiatric patients were more often unexplained than those in nonpsychiatric patients (65% *vs* 40%, P = 0.02)[5]. The incidence of unexplained deaths tends to increase across years, as the deaths per 100000 patient-years dramatically increased from 7 (95%CI: 3.7-19.4) in 1984-1998 to 125 (95%CI: 88.9-175.1) in 2005-2009[73]. The unexplained cases were similar to the explained cases regarding demographic features, psychiatric diagnoses, and use of psychotropic classes (FGAs and SGAs). Dyslipidemia (P = 0.012), diabetes (P = 0.054), and comorbid dyslipidemia and diabetes (P = 0.006) were more common in the unexplained group [73].

In particular, there have been six autopsy-based reports that highlight unexplained deaths. The detailed forensic characteristics are documented in Table 1. Specifically, these unexplained cases were found at all ages, ranging from 2 to 86 years old. Male decedents were more common (57.8%). All decedents were overweight or worse, which conforms to the notion that dyslipidemia and diabetes were more common in unexplained deaths[73]. Approximately half of these unexplained deaths were negative for any autopsy findings. Before the introduction of SGAs, the FGAs chlorpromazine and haloperidol were common drugs, while after the introduction of SGAs, quetiapine, olanzapine, and clozapine were the primary drugs associated with unexplained deaths. Most of these cases were at a therapeutic dose, with the exception of the eight unexplained cases whose postmortem levels of antipsychotics were up to toxic concentrations[74].

MECHANISMS UNDERLYING ANTIPSYCHOTICS CARDIOTOXICITY

Subcellular organelles

Mitochondria: It has been reported that the antipsychotic drug clozapine undergoes bioactivation to a reactive nitronium ion by dehydrogenation in mitochondria; subsequently, this electrophilic intermediate is detoxified by conjugation with reduced glutathione[76]. The clozapine-glutathione conjugates are then eliminated in the bile of rats and mice over a 3-h period[77]. Thus, cardiac mitochondria may be a target for antipsychotic-associated adverse cardiac effects. Drug-induced functional and/or structural variations of cardiac mitochondria may result in myocarditis and cardiomyopathy by various approaches[78]. One possible mechanism of cardiac mitochondrial damage may involve antipsychotic bioactivation by cardiac tissue-specific microsomal CYPs and/or soluble oxidases/peroxidases, translocation of the resultant reactive metabolite to mitochondria, and alkylation of mitochondrial proteins[79], a mechanism similar to paracetamol-induced hepatoxicity[80]. Furthermore, the parent drug and/or its metabolite(s) may enter cardiac mitochondria to form nitronium ions, which localize within this organelle and consequently cause drug accumulation in the heart [79]. In addition, chronic dosing with haloperidol and some SGAs (*i.e.*, clozapine and risperidone) could result in loss of complex I, the electron transport chain component in mitochondria, to generate side effects[81,82] and negatively affect mitochondrial bioenergetics[81]. Proteomic profiling revealed that mitochondrial function and oxidative phosphorylation were significantly affected in risperidone- and olanzapine-treated mouse hearts, additional evidence supporting risperidone-altered cardiac mitochondrial oxygen consumption[83].

Lysosomes: Lysosomes contain over 30 acid hydrolases and are a significant acidic compartment to digest and phagocytose during antipsychotic metabolism[84]. Most antipsychotics are basic lipophilic compounds, the distribution of which is determined by cellular membrane phospholipid binding[85] or by lysosomal trapping[86]. For lysosomal trapping, basic lipophilic drugs permeate membranes and aggregate in lysosomes. The acidic interior of lysosomes then protonates the parent drugs or metabolites, preventing them from returning to the cytosol, an approach directly leading to detoxification of drugs[84]. Unfortunately, unlike the liver, lung, and kidney, the heart is a lysosome-deficient organ that exerts a very weak capacity to capture and protonate drugs[87]. This natural defect directly results in failure of drug protonation after entering cardiac cells and explains the exclusive cardiotoxicity of

Table 1 Six autopsy-based studies assessing demographic and forensic characteristics of sudden unexplained deaths after antipsychotic use

Category	Sweeting *et al* [7]	Ifteni *et al*[75]	Sun *et al*[58]	Ye *et al*[40]	Jusic and Lader[74]	Manu *et al*[73]
Publication year	2013	2014	2019	2018	1994	2011
Case region	Sydney, Australia	Brasov, Romania	MD, United States	Shanghai, China	London, United Kingdom	New York, United States
Reported case number	72/683	6/57	11/391	5/24	8 case reports	52/100
Age, yr (mean ± SD)	53 ± 14	55 ± 13	36 ± 17	57 ± 5	36 ± 14	50 ± 13
Males, *n* (%)	41 (56.9)	4 (66.7)	7 (63.6)	1 (20.0)	5 (62.5)	31 (59.6)
BMI (kg/m^2)	26.0 ± 7.1	26.0 ± 4.8	31.0 ± 7.2	NA	NA	NA
Autopsy finding[1], *n* (%)	NA					NA
Mild atherosclerosis		3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Chronic pericarditis		1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Myocardial dystrophy or fibrosis		1 (16.7)	2 (18.2)	0 (0.0)	1 (12.5)	
Ventricular dilation		0 (0.0)	2 (18.2)	0 (0.0)	0 (0.0)	
Cardiomegaly		0 (0.0)	2 (18.2)	0 (0.0)	0 (0.0)	
Conduction system abnormality		0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	
Lung edema, congestion		1 (16.7)	0 (0.0)	0 (0.0)	4 (50.0)	
None		0 (0.0)	5 (45.5)	3 (60.0)	4 (50.0)	
Postmortem toxicology[1], *n* (%)	NA	NA				
First-generation						4 (7.7)
Chlorpromazine			0 (0.0)	2 (40.0)	5 (62.5)	
Haloperidol			0 (0.0)	1 (25.0)	5 (62.5)	
Thioridazine			0 (0.0)	0 (0.0)	1 (12.5)	
Droperidol			0 (0.0)	0 (0.0)	2 (25.0)	
Promazine			0 (0.0)	0 (0.0)	1 (12.5)	
Trifluoperazine			0 (0.0)	0 (0.0)	1 (12.5)	
Pimozide			0 (0.0)	0 (0.0)	2 (25.0)	
Fluphenazine			0 (0.0)	0 (0.0)	2 (25.0)	
Second-generation						
Olanzapine			0 (0.0)	2 (40.0)	0 (0.0)	2 (3.8)
Quetiapine			4 (36.4)	1 (25.0)	0 (0.0)	11 (21.2)
Clozapine			2 (18.2)	1 (25.0)	0 (0.0)	5 (9.6)
Risperidone			0 (0.0)	0 (0.0)	0 (0.0)	4 (7.7)
Ziprasidone			0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Negative			5 (45.5)	0 (0.0)	0 (0.0)	0 (0.0)

[1]Some cases are presented with ≥ 2 autopsy findings or drugs, so the sum may exceed the total number of columns. BMI: Body mass index; NA: Not available.

antipsychotics. Moreover, polypharmacy is common among patients with mental disorders. When two or more basic lipophilic drugs are trapped by lysosomes, the pH increases more than when a single drug is trapped. Lysosomes are then oversaturated and diminish the drug intake capacity[84]. This is a phenomenon called synergistic

effect.

Molecular mechanisms

Ion channels: Cardiac action potentials are generated by transmembrane movements of ion species, flowing principally through specific channels. Antipsychotics can affect a variety of cardiac ion channels, especially the potassium channel (particularly the potassium rapid delayed rectifier channel, K_r), which is associated with QT interval prolongation and lethal cardiac arrhythmias such as TdP[88]. The K_r channel, also known as the hERG channel, is encoded by the human ether-a-go-go related gene (*hERG*). Almost all antipsychotics could modulate cardiac K_r channels. Risperidone and its active metabolite paliperidone inhibited the potassium current by interacting with the open and inactivated states of the I_{Kr} channel without affecting channel protein trafficking[89]. FGAs (chlorpromazine and thioridazine) and clozapine suppress the current of the K_r channel and consequently result in QT prolongation. Olanzapine, a first-line SGA in the clinic, blocked the K_r current in a concentration-dependent manner with a tail current decrease of 50% at 3.8 mmol/L olanzapine[90]. Of note, the 50% inhibition concentration (IC_{50}) of this iron channel has drug-based differences, ranging from 1 nmol/L (haloperidol)[91] to 6 μmol/L (olanzapine)[92]. This variation is not related to a class effect (FGAs *vs* SGAs) but seems to relate to the potency of antipsychotics to block hERG channels[93].

Genetic susceptibility, namely, mutations in the genes encoding potassium ion channel proteins (*i.e.*, *KCNH2*, *KCNQ1*, and *SCN5A*) is also directly associated with an increased risk of malignant arrhythmias[94]. In addition to the inherited *hERG* mutations that are associated with congenital long QT syndrome, suppression of native I_{Kr} by psychotropic therapy also predisposes individuals to polymorphic ventricular tachycardia of the TdP type[95]. Hence, genetic screening should be implemented in selected patients who have previous episodes of drug-induced arrhythmias.

Biological membrane receptors: As mentioned above, due to their lipophilic nature, antipsychotics might exert their cardiac effects by perturbing the physical properties of biological membranes[96]. The membrane-resided receptors may thus be involved.

Adrenoceptors: There are many antipsychotics that have a strong affinity for adrenoceptors. For example, the FGA droperidol competitively interacts with vascular α-adrenoceptors but has no effect on β-adrenoceptors[97]. The potency of binding to α1- and α2-adrenergic receptors varies among these medications, with a 532-fold range for α1 antagonism and a 400-fold range for α2 antagonism among atypical antipsychotics [98]. There are several lines of evidence for the involvement of adrenoceptors in antipsychotic cardiotoxicity. First, as the endogenous ligand of adrenoceptors, plasma noradrenaline levels significantly increased in patients upon clozapine maintenance treatment[99]. Similarly, in a rat model receiving multiple doses of the FGA haloperidol and SGAs (risperidone, clozapine, and olanzapine), the plasma catecholamine levels were found to be significantly elevated by all antipsychotics, although the elevation was drug- and dose-dependent[100]. Compared to other antipsychotics, intravenous injection of olanzapine and clozapine seemed to cause a more significant increase in plasma epinephrine. Second, a β-adrenergic blocking agent, propranolol, was found to significantly attenuate clozapine-induced myocarditis in a murine model[52], posing a direct linkage of adrenoceptors to antipsychotic cardiotoxicity.

Cannabinoid receptors: Given that β-adrenoceptor blockade produced only a partial reduction in clozapine-induced TNF-α levels[52], other receptors were later proposed to be functional. In our serial works, we found that clozapine[53] or quetiapine[101] treatments caused a decrease in cannabinoid receptor 1 (CB1R) while increasing CB2R expression within approximately 2 wk of treatment in mice. The ligands of these receptors were disrupted in a dose- and time-dependent manner. Furthermore, in cultured cardiomyocytes, the CB1 receptor was observed to translocate from the cytomembrane in intact cells to the cytoplasm/nuclei in SGA-treated cells, whereas the CB2 receptor went the opposite way in SGA-treated cells[53,101], suggesting a functional rivalry between the cannabinoid receptor subtypes[102]. Furthermore, both cannabinoid receptors regulated a new type of necrotic cell death[101], termed necroptosis, which explained the clinical association of antipsychotic use with inflammatory states. The opposite roles of cannabinoid receptors suggested that the treatment of antipsychotic cardiotoxicity might only be beneficial when based on single-receptor agonism or antagonism[102].

Other molecular mechanisms: Several pathways were also reported to be associated with clozapine-induced myocarditis. Clozapine, particularly at relatively high doses, has a clear cardiotoxic effect, as evidenced by increased myocardial oxidative stress, inflammatory cytokines, DNA damage, and apoptosis with attenuation of antioxidant defenses. The use of captopril, an angiotensin-converting enzyme inhibitor, significantly protected against the above clozapine-induced effects in rats[103]. In a rat model, olanzapine-induced cardiotoxicity was reported to be associated with increased acetyl-CoA carboxylase phosphorylation and tissue ATP levels and lower phosphorylation levels of Akt and its downstream product AS160[104]. These generally descriptive studies reinforced the mitochondria-involved mechanisms and implied that inflammatory cell death might be critically involved in antipsychotic cardiotoxicity. By integrating proteomic and transcriptomic approaches, we recently further found that representative SGAs share a similar cardiac pathological basis to cause cardiotoxicity, and spliceosome signaling represents a common intracellular mechanism underlying SGA-induced cardiotoxicity[105]. SGA-dysregulated spliceosome signaling was only partially rescued by pretreatment with an agonist of histamine 1 receptor (HRH1)[105], implying additional membrane receptor-involved mechanisms.

FUTURE PERSPECTIVES

Clinical monitoring

Many approaches have been recommended for the clinical monitoring of antipsychotic cardiotoxicity, including biomarker detection (*i.e.*, CRP, creatine kinase, and cardiac troponins), ECG monitoring, echocardiogram monitoring, and B-type natriuretic peptide (BNP) detection.

Creatine kinase has been found to be less useful than troponin to assess myocardial injury due to its low sensitivity (approximately 22%)[106]. Troponins appear to have a higher sensitivity of approximately 39% but can only be true-positive in the first month after disease onset. The specificity of troponin is approximate 89%[107]. The sensitivity of ECG monitoring is approximately 35% (equal to that of peripheral eosinophilia detection), while creatine kinase isoenzyme (CK-MB) only has a 5.7% sensitivity rate[107]. The test with the highest sensitivity is left-ventricle hypokinesis and/or reduced ejection fraction by echocardiogram, although only 48%[108]. A clinical study over the years 1994-2009 concluded that combining troponin (over twice the upper limit) and CRP (over 100 mg/L) had an estimated diagnostic sensitivity of 100% for symptomatic clozapine-induced myocarditis[109]. A recommendation was also proposed to regularly monitor CRP, troponins, and ECG at baseline and at weeks 1, 2, 3, and 4 to improve the early detection of clozapine-induced myocarditis[110].

The above approaches have been clinically practiced for decades and, however, are not exclusive for monitoring antipsychotic-induced cardiotoxicity. BNP is a 32-amino acid vasoactive peptide that is primarily secreted by the ventricular wall[111]. It acts as a key response to increased wall stress and a vital regulator in the homeostasis of water and salt excretion[112]. A clinical study has documented the potential of using an N-terminal fragment of BNP (NT-proBNP)[113] in combination with QTc measurement as a highly accurate marker for the early detection of acute antipsychotic drug-induced cardiotoxicity. Of note, these clinical studies are limited to a small number of patients. Multicenter studies with larger sample sizes are mandated to verify the association between NT-proBNP levels and acute cardiac toxicity.

In recent years, implantable cardioverter defibrillators (ICDs) have been considered the most effective treatment for patients at high risk of SCD[114]. Individual wrist-worn medical devices with the capability of monitoring several fatal biometrics, such as HR and BP, as well as ECG have also been recommended[115]. This high-tech wrist-worn device has multiple advantages over other biochemical tests due to better prediction and management of patients and the real-time notice of irregular heart rhythm and other warnings to users receiving antipsychotic therapy.

Therapeutic agents

Some studies have reached a consensus that the addition of β-blockers has been an effective clinical alternative for the treatment of clozapine-associated tachycardia[116]. Taking low doses of bisoprolol, for example, can be well tolerated and may offer symptomatic relief in patients who are aware of and suffer from tachycardia[117].

In addition, we have provided profound data that two subtypes of cannabinoid receptors (CB1R and CB2R) are critically involved in antipsychotic cardiotoxicity. Specific antagonists of CB1R or agonists of CB2R bring beneficial effects, including inflammation suppression and fibrosis remission in the heart[53,101]. Meanwhile, it would not profit from dual antagonists or agonists since dual binding might neutralize the effect of each other. Therapeutics should be mono-receptor based[53,101]. In particular, antagonists of CB1R have been marketed for weight loss, and CB2R agonists have also been associated with a welcome metabolic process[118]. Since metabolic and cardiovascular adverse effects are the major dilemma associated with antipsychotic drug use[119], the use of CB1R antagonists or CB2R agonists in combination with antipsychotics might be conceived to exert dual protection: One to inhibit drug cardiotoxicity and the other to ameliorate antipsychotic-induced weight gain. Of note, individual CB1R antagonists may cause additional psychiatric disorders due to brain penetrance and have been withdrawn from clinical use (*i.e.*, rimonabant [120]). Therefore, the development of peripherally restricted CB1R antagonists or CB2R agonists would provide dual protection against these clinical concerns without causing additional toxicity[121].

Third-generation antipsychotics

There are several new and emerging antipsychotic medications, termed TGAs, recently marketed or under clinical development for the treatment of several mental disorders [2]. Overall, TGAs display a good safety profile, with a well-demonstrated lower metabolic liability than SGAs. Furthermore, TGAs appear to specifically target negative symptomatology and improve cognitive domains[2].

Comparing the cardiac adverse effects of recently developed antipsychotics (brexpiprazole, cariprazine, lurasidone, pimavanserin, and roliperidone)[122], roliperidone showed the lowest incidence of cardiovascular effects and metabolic influences, such as hypotension, QTc prolongation, weight gain, and metabolic syndrome, which indicates a potential therapeutic method to offset the defects of SGAs. Further clinical trials are needed for safety and efficacy evaluation.

CONCLUSION

This review introduces the clinical manifestations and pathological lesions in antipsychotic cardiotoxicity. Although largely unknown, many mechanisms at the subcellular organelle level (mitochondria and lysosomes) and at the molecular level (membrane receptors and ion channels) have been independently reported. This merits future evaluation of the efficacy (sensitivity and specificity) of the recently developed monitoring approaches. To avoid drug discontinuation or withdrawal from the market, drug adjuvant therapy to alleviate both cardiotoxic and metabolic effects is preferentially favorable. TGAs, particularly those with favorable cardiac and metabolic outcomes, deserve clinical application. Larger cohort-based clinical evaluations are needed for the development of receptor-targeted adjuvant drugs.

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REVIEW

Therapeutic role of yoga in neuropsychological disorders

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Abstract

Yoga is considered a widely-used approach for health conservation and can be adopted as a treatment modality for a plethora of medical conditions, including neurological and psychological disorders. Hence, we reviewed relevant articles entailing various neurological and psychological disorders and gathered data on how yoga exerts positive impacts on patients with a diverse range of disorders, including its modulatory effects on brain bioelectrical activities, neurotransmitters, and synaptic plasticity. The role of yoga practice as an element of the treatment of several neuropsychological diseases was evaluated based on these findings.

Key Words: Complementary medicine, depression; Bipolar disorder; Schizophrenia; Anxiety; Migraine; Parkinson's disease; Alzheimer's disease; Epilepsy; Multiple sclerosis

Core Tip: A multitude of beneficial effects of yoga practice and the underlying mechanisms of action have been reported and point out its role as an influential element in the integrative therapy of various neuropsychological disorders. In the planning of further investigations, studies should be designed to achieve more accuracy and precision in the heterogeneous field of yoga practices and potential fields of application.

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INTRODUCTION

Several neurological disorders affect mental health and lead to various degrees of impairment in cognitive functions. The use of complementary and alternative medicine, practices that improve the mind's capacity and body function, amongst patients with neuropsychological disorders is increasing worldwide[1,2]. Biofeedback, homeopathy, acupuncture, meditation, and yoga are among the different categories of these interventions[3]. Yoga is a form of mind-body technique that involves and contributes to both mind and body[4] and has been used as a therapeutic intervention in various neurological and psychological disorders[5]. The word "Yoga" is derived from the Sanskrit origin "yuj" meaning "yoke" or "union," and it is assumed that yoga describes the union between mind and body[5]. As an ancient Indian non-religious mind-body method[2,6], yoga is considered a philosophical and spiritual discipline that alleviates suffering and promotes human health[4]. Yoga has been practiced in Eastern cultures as a spiritual healing method for over 4000 years. The "Yoga sutra," a 2000-year-old guidebook, is the earliest known document of yoga that provides the framework of all branches of yoga. This book conceptualized yoga as eight limbs, which were designed to be practiced in sequence[7-9]. There are several styles of yoga, and no one is superior to another (Table 1).

A rapid increase of interest in yoga in Western countries occurred in the first decades of the 19th century, which has continued to this day. The National Health Interview Survey has reported that the number of people in the United States who practice yoga has increased dramatically among all age groups between 2002 to 2012[9,10]. Yoga practice can be a treatment for a variety of disorders as well as physical exercise[9]. This leads to an increase in investigations focusing on the mechanism of action and effect of yoga intervention on various mental and physical conditions[9-11]. Yoga interventions can maintain brain health through various mechanisms, such as the improvement of cerebral oxygenation[12], enhancement of neurotrophic and angiogenic factors (such as angiogenin)[13], balancing the excitatory/inhibitory neurotransmitter equilibrium[14], modulation of immune responses[15], and prevention of oxidative stress[16]. In the present review, we first show data that point out the effect of yoga on the brain under physiological conditions. Then, we review the effect and potential mechanism of action of yoga in the treatment of neurological and psychological disorders.

EFFECT OF YOGA ON THE BRAIN

Yoga is a movement-based embodied contemplative activity that can lead to a variety of neurobiological alterations in different brain regions. Yoga exerts a regulatory effect on brain synaptic plasticity and promotes cognitive tasks, particularly working memory[17,18]. Furthermore, yoga increases inter-hemispheric coherence and symmetry and improves neurocognitive functions[19]. Yoga may also exert pronounced anatomical changes in different brain regions, especially in the limbic system[20].

Effect of yoga on brain neurotransmitters

γ-aminobutyric acid (GABA) is considered the main inhibitory neurotransmitter responsible for the regulation of cortical excitability and neural plasticity[21,22]. Multiple lines of evidence suggest that yoga promotes cortical GABAergic inhibitory tone and modulates downstream brain regions[14,23]. A 12 wk yoga practice markedly enhanced the thalamic GABA values, accompanied by improved mood and reduced anxiety[24]. Higher thalamic GABA levels could be the result of enhanced (regional) cerebral blood flow in the prefrontal cortex of yoga practitioners[25], which can lead to the activation of the reticular nucleus of the thalamus and higher GABA production [26,27]. A magnetic resonance spectroscopy study has shown that yoga practitioners exhibited greater brain GABA values after a 60 min session of yoga training compared

Table 1 Different types of yoga interventions

Type of yoga	Description
Ashtanga	Six series of postures during breathing exercises
Bikram	Twenty-six poses and a sequence of two breathing exercises that take place in heated rooms with high humidity
Hatha	Basic postures and poses with breath regulation and meditation
Iyengar	Focuses on the precise structural alignment of the body
Jivamukti	Physically intense challenging postures with meditation
Kripalu	Breathing exercises at the beginning, gentle stretches, and series of poses before final relaxation
Kundalini	Chanting at the beginning and meditation aiming to release energy
Sivananda	Based on a 5-point approach, including proper breathing, diet, relaxation, exercise, and positive thinking
Vini	Based on in-depth training aiming to be an expert on anatomy and yoga therapy
Prenatal	A type of yoga helping mothers with physical training and meditation
Yin	Focuses on releasing tension through different joints

to controls[28]. In addition to GABA, an enhancement of dopamine has been observed in the ventral striatum of subjects who practice yoga[25,29,30]. It has been suggested that yoga could cause a rise in serotonin. Several investigations performed on participants after their meditation sessions have shown an elevation of the serotonin metabolite levels in urine[25,31]. Moreover, a regular yoga practice may cause a reduction in norepinephrine values. Patients with heart failure who practiced weekly yoga displayed lower levels of norepinephrine in blood samples[30,32] (Figure 1).

Effect of yoga on the bioelectrical activities of the brain

Yoga practices regulate electroencephalogram (EEG) signals through switching off non-relevant neural circuits for the preservation of focused attention and blockade of inappropriate signals[33]. Studies on the effects of yoga on brain waves revealed that breathing, meditation, and posture-based yoga practice increase overall brain activity [19], particularly in the amygdala and the frontal cortex. Alpha brain waves predominate during active attention and thinking as well as in some meditative conditions and correlate with basic cognitive processes[34]. Alpha waves could reflect the physiological and pathological changes of the relevant neural network activity during conscious perception and working memory[35]. Investigations on brain waves in meditators concluded that meditation leads to the alterations in anterior cingulate and dorsolateral prefrontal cortices and the enhancement of alpha wave activity[36]. Beta brain waves are dominant during wakefulness with open eyes, which could be affected by stressful conditions[37,38]. An enhancement of EEG beta wave activity has also been observed after yoga meditation practices[39]. Beta wave activity is present throughout the motor cortex during isotonic contractions and slow movements and is related to gains in academic performance and high arithmetic calculation ability[19, 40]. Theta waves assist with alertness and the ability to process information quickly [36]. The occurrence of the higher theta wave activities is associated with lower levels of anxiety[36,41]. An increase in theta wave activity has been reported during meditation[30,36]. Longer duration of meditation is associated with higher theta and alpha wave activities[30,33,36].

Effect of yoga on brain structure and neural connectivity

Yoga intervention seems to be associated with brain structural alterations, particularly in the frontal cortex, amygdala, hippocampus, insula, and anterior cingulate cortex [42]. An investigation on regional differences in grey matter volume associated with the practice of yoga has shown a greater grey matter volume in different areas of the dominant hemisphere, including the ventromedial orbitofrontal, ventrolateral prefrontal, and inferior temporal and parietal cortices as well as the left insula in skilled practitioners of yoga[43]. Furthermore, elderly yoga practitioners with several years of yoga experience have shown greater neocortical thickness in the left prefrontal complex cluster, which includes part of the lateral middle frontal gyrus, dorsal superior frontal gyrus, and anterior superior frontal gyrus compared to healthy non-practitioners[44]. A magnetic resonance imaging study revealed the greater volume of gray matter in the left hippocampus in skilled yoga practitioners with at least 3 years

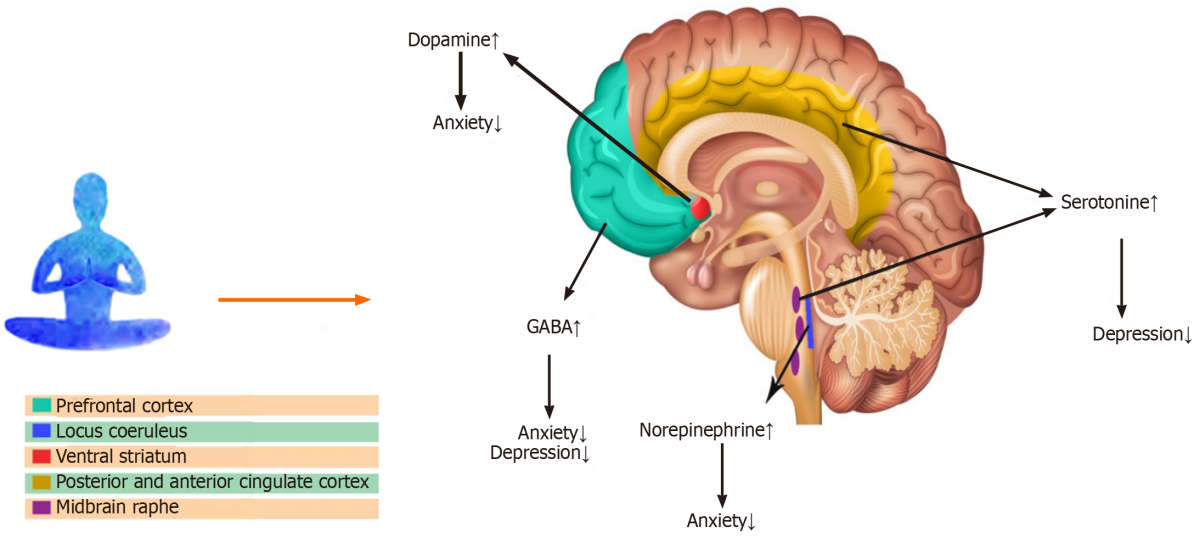

Figure 1 The effect of yoga intervention on various neurotransmitters in different brain regions. GABA: γ-aminobutyric acid.

of experience compared to the sex- and age-matched control subjects[18]. A population-based study on 3742 subjects revealed a lower right amygdala volume and a lower left hippocampus volume in those who participate in meditation and yoga practices[45] (Figure 2).

THE CLINICAL EFFECT OF YOGA

The clinical role of yoga on neurological disorders

Yoga and headaches: Several studies have suggested the beneficial effects of yoga in reducing the frequency and intensity of various forms of headaches, particularly migraine and tension headaches[46]. Yoga has been suggested as a potential complementary therapeutic intervention for headaches[47]. A meta-analysis on yoga for tension-type headaches and migraine has shown preliminary evidence of a short-term beneficial effect of yoga on tension-type headaches. This study revealed a significant improvement in the frequency, duration, and intensity of pain in patients with tension-type headaches[48]. A randomized controlled trial evaluating the beneficial effects of yoga on 114 patients with migraines has shown a significantly greater improvement in various migraine measures, including headache frequency, intensity, and use of rescue medications[49]. Another randomized controlled study with 19 subjects suffering from episodic migraine has shown a reduction in headache intensity, duration, depression, and anxiety as well as an improvement of self-efficacy, migraine-related disability, and quality of life from baseline to initial follow-up[50]. A significant improvement of self-perceived pain frequency, pain intensity and duration, and psychological status as well as a reduction in medication consumption was observed in 31 patients with chronic migraine[51]. Furthermore, a significant decrease in headache frequency, medication intake, and stress perception has been reported in 20 patients with migraine or tension headaches[52]. Yoga has been suggested as a potentially effective approach to reducing headaches associated with menopause[53].

Multiple investigations have explored the mechanisms of action of yoga on headaches. Migraine is a neurovascular disorder with significant upregulation of endothelial adhesion molecules[2,54]. It has been suggested that yoga intervention alleviates pain primarily *via* modulation of the pain perception system, including the anterior cingulate cortex, insula, sensory cortex, and thalamus[55]. A study on 42 women with migraines evaluated the effect of yoga on endothelial dysfunction in migraine patients. A 12 wk yoga training program increased delivering O_2 to the body and reduced peripheral vascular resistance with a significant reduction in plasma values of vascular cell adhesion molecule, which suggests an improvement of vascular function in patients with migraine[8,51,56,57]. The amplitude of the contingent negative variation, an ultra-slow neocortical event-related potential, is significantly greater in patients with migraine compared to healthy controls, which indicates higher cortical excitability[58]. Subjects with migraines, who practice meditation, including

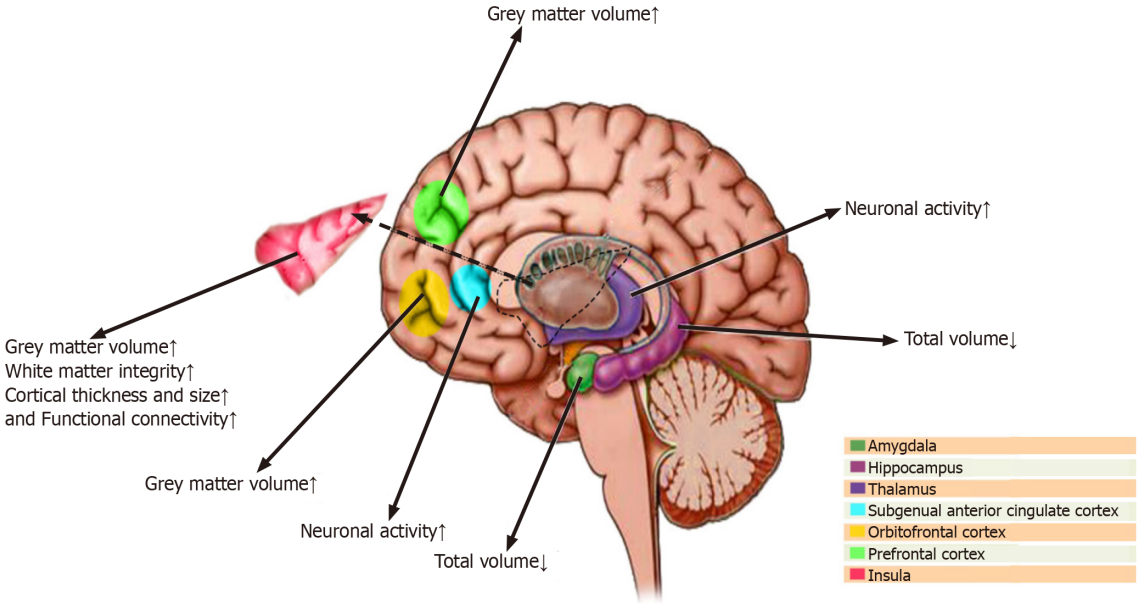

Figure 2 The effect of yoga practice on the functional activities of various brain regions.

yoga, have shown significantly lower amplitude of contingent negative variation[59].

Yoga and Alzheimer's disease: Alzheimer's disease (AD) is characterized by neuronal loss, mostly in the neocortex and the hippocampus[2,60], and is associated with memory and cognitive impairments and neuropsychiatric dysfunctions[2,60]. It has been suggested that yoga exerts a beneficial impact on overall brain health in healthy elderly subjects, older people with mild cognitive dysfunction, and subjects with dementia[61]. Yoga practice promotes cognitive function, affective interaction, and physical abilities of the healthy elderly population[62] and exerts a positive impact on total brain volume, neocortical grey matter thickness, and functional connectivity between different brain regions in subjects with mild cognitive dysfunction[63]. Using magnetic resonance imaging volumetric analysis, a trend toward decreased hippocampal volume atrophy has been observed after an 8 wk of yoga practice in patients with mild cognitive dysfunction[64]. A randomized neuroimaging study with 14 subjects has shown that yoga and mindfulness meditation may decrease hippocampal atrophy and promote functional connectivity between different brain regions, including the posterior cingulate cortex, the medial prefrontal cortex, and the hippocampus in adults susceptible to dementia[64]. Furthermore, it has been shown that mind-body interventions, such as yoga, can restore cognition in persons with mild cognitive impairment and delay the onset of AD[65,66]. Elderly subjects suffering from mild to moderate dementia have exhibited an improvement of behavioral impairments after a 12 wk yoga training program[67]. Metabolic enhancement for neurodegeneration, a novel therapeutic approach for AD, has merged yoga and meditation into other treatments of early AD pathology and achieved sustained cognitive improvement in 90% of patients[68]. Yoga may enhance blood flow to areas of the brain that modulate memory functions, reduce neuronal injury, promote the symptoms of early dementia, and delay the onset of AD[69]. Yoga can also improve the physical disability of patients with AD, such as walking, gait speed, and balance [70].

Although the mechanism of yoga action on AD needs to be elucidated, some possible mechanisms have been suggested. The serum values of several neurotrophic factors, such as brain-derived neurotrophic factor, increase after yoga practice in healthy individuals[71]. This may also occur in patients with mild to moderate AD and exerts a neuroprotective effect on the neurodegenerative process of AD[61]. The long-term practice of yoga also increases the serum value of serotonin[72]. The neuroprotective effects of yoga may be due to the enhancement of serotonin. Serotonin significantly destabilizes Aβ fibrils and protects neuron Aβ-induced cell injury and death[73]. The serum levels of melatonin significantly increased after a 3 mo period of yogic practices[74]. Melatonin reduces the Aβ level[75] and promotes microvessel abnormalities in the neocortex and the hippocampus[76] in experimental AD models.

Yoga and epilepsy: The goal of therapeutic approaches for epilepsy, a common neurological disorder characterized by abnormal electrical brain activity[77], is to eliminate or decrease the number and duration of seizures and improve the quality of life[2,78]. Several studies suggest that yogic practices can ameliorate seizures in patients with different types of epilepsy. An investigation on the effects of yoga intervention on seizures and EEG of 32 patients suffering from idiopathic epilepsy has revealed 62% and 83% reduction of seizure frequency 3 and 6 mo after the intervention, respectively. Furthermore, this study has shown a significant shift of EEG frequency from 0-8 Hz toward 8-20 Hz[79]. Another randomized controlled trial conducted on 20 children aged 8-12 years with epilepsy has suggested that a 6 mo yoga intervention as an additional therapy in children with epilepsy may lead to seizure freedom and a significant improvement of epileptiform EEG signals[80]. The evaluation of the effect of yoga on clinical outcomes of 300 patients with epilepsy has suggested that yoga is a helpful approach for patients to manage their disease[71]. Contrary to these reports, a clinical study reported no significant differences between the frequency of seizures between the yoga and control groups. Nonetheless, the yoga group showed significant improvements in their quality of life[81]. An analysis of the data of two clinical trials that evaluated the effect of yoga on 50 epileptic patients suggests a possible beneficial effect of yoga in the control of seizures[82].

Yoga and multiple sclerosis: Several clinical trials investigated the potential beneficial effects of yoga therapy in patients with multiple sclerosis (MS), an autoimmune neuroinflammatory demyelinating disorder of the central nervous system[83]. A study tested the effects of a 6 mo yoga intervention on the improvement of different aspects of physical as well as psychosocial conditions in 44 patients with MS and 17 healthy relatives. This investigation has shown significant improvements in the quality of life, walking speed, fatigue, and depression values. However, yoga did not promote the pain, balance, and physical status of these patients[84]. A pilot study on 12 patients suffering from MS has suggested that various yoga trainings for 6 mo may lead to a significant improvement in postural balance and daily physical activities[85].

Another clinical study on 24 participants diagnosed with mild to moderate MS, which underwent an intensive yoga practice for more than 4 mo, has shown marked improvements in the peak expiratory flow rate, physical conditions, mental health, and quality of life of patients with MS[86]. A study conducted on 60 female patients with MS revealed that yoga training significantly improved physical abilities and sexual satisfaction[87]. Yogic training and relaxation have also been suggested for the improvement of neurogenic bladder dysfunction in patients with MS[88].

A qualitative case investigation on a woman with MS suggested that individualized yoga intervention for 6 mo could be beneficial for the improvement of muscle tone and strength as well as self-confidence and stamina[89]. A significant improvement in balance, gait, fatigue, walking speed, and step length has been reported in 18 patients with relapsing-remitting MS after a 12-wk yoga training[90]. Yoga intervention has also exerted a beneficial role on improvements of postural balance and reduction of the influence of postural balance impairment during daily activities in patients diagnosed with MS after yoga practice for 6 mo[85]. A meta-analysis of 10 randomized controlled trials with overall 693 patients with MS who trained with different forms of yoga has revealed a significant improvement of fatigue but no effects on the overall quality of life, sexual function, and psychosocial condition[91].

Yoga and Parkinson's disease: The potential beneficial therapeutic effects of a yoga intervention for Parkinson's disease (PD), a chronic and debilitating neurodegenerative disorder, have been investigated. Yoga exerts a range of beneficial effects on different symptoms of PD[92]. A question-based survey on 272 patients with PD has shown that the majority of patients found yoga and meditation helpful for the alleviation of both motor and non-motor (fatigue, sleep difficulties, pain) symptoms [93]. A randomized clinical study on 126 patients with mild to moderate PD who underwent weekly yoga training for 8 consecutive weeks has shown a significant alleviation of psychological symptoms, improvement of the quality of life, and reduction of motor symptoms[94]. Yoga exercises can improve flexibility and balance, decrease muscle rigidity, increase the range of motion, and promote muscle strength in patients with PD[95]. Yoga intervention effectively improves balance and proprioceptive acuity in 33 patients with mild to moderate PD[96]. It has been suggested that incorporating yoga and occupational therapy may promote balance and decrease falls in patients with PD[97]. Yoga training decreases the back pain associated with a lower postural instability, which may reduce falls in patients with PD[98]. Furthermore, yoga as adjunctive therapy in patients with PD has been suggested as an effective treatment

for the reduction of psychological complications, particularly anxiety and depression [99-101].

Yoga and neuropathy: Peripheral neuropathy is a common neurological condition due to physical nerve injury, diabetes mellitus, autoimmune disorders, malignancy, kidney failure, nutritional deficiencies, systemic disorders, and idiopathic neuropathies, which can implicate the motor, sensory, and/or autonomous peripheral nerves[102, 103]. Several lines of evidence suggest that yoga may alleviate symptoms of various neuropathies[104,105].

Several reports suggest the beneficial effects of yoga practices in patients with neuropathy. Yoga practices were shown to improve numbness and weakness in lower extremities after a stretch or compression injury of the gluteal nerves[106], alleviate chronic pain due to diabetic neuropathy[107], and promote sensory functions and muscle movement in subjects with diabetic peripheral neuropathy[108]. However, it should be noted that some reports indicate yoga-induced nerve injury and neuropathy [109-111], particularly in patients who take sedative medications, people with benign hypermobility of their connective tissue, and the elderly[110,112,113]. Furthermore, yoga may ease compression and decrease nerve compression in carpal tunnel syndrome, which could lead to the improvement of numbness after a few weeks of practice[114,115]. Yoga mediation therapy improved the nerve conduction velocity, which was associated with glycemic control, in patients with diabetic neuropathy[116, 117]. A reduction of the impact of chemotherapy-induced peripheral neuropathy symptoms on the lives of patients with breast cancer as well as on the pain intensity after yoga intervention has been reported[118,119].

The clinical role of yoga in psychological disorders

Yoga, stress, and anxiety: Stress and anxiety are increasing in incidence worldwide. Approximately 34% of the general population is affected by an anxiety disorder during their lifetime[120]. Several investigations were performed on the feasibility and potential efficacy of different forms of yoga on anxiety- and stress-induced symptoms in both children and adults. It has been suggested that yoga may promote mental and physical strength, increase stress resilience, and reduce anxiety[121]. Although some studies do not show any effect[122,123], most investigations indicate that yoga can be effective in the alleviation of anxiety in the form of monotherapy or adjunctive therapy [124-127]. Functional magnetic resonance imaging evaluation revealed that yoga interventions modulate the activity of various brain areas that are crucial to emotion regulation, such as the superior parietal lobule and supramarginal gyrus, and lead to a diminished sympathetic response to stressful emotional stimulations[128]. Training of mindfulness- and yoga-based programs has shown a significant reduction of anxiety symptoms, which was associated with a marked decrease of structural connectivity of the right amygdala[129]. Furthermore, it has been suggested that yoga intervention modulates stress-induced autonomic regulatory reflex and inhibits the production of adrenocorticotropic hormone from the anterior pituitary gland[130], resulting in decreased production of cortisol from the adrenal gland[131].

A meta-analysis revealed that more yoga exercises were accompanied by greater benefits, particularly when subjects were suffering from higher values of anxiety at the early stages[132]. Another meta-analysis of eight trials with 319 adults diagnosed with anxiety disorders who underwent yoga training indicates that yoga could be a safe and effective intervention to reduce the intensity of anxiety[133]. Rhythmic yoga meditative interventions resulted in a reduction of stress associated with a higher plasma dopamine level together in 67 healthy subjects who regularly engaged in mind-body training[134]. Enhancement of dopamine values following yoga practice leads to a suppression of corticostriatal glutamatergic transmission and regulation of conscious states[29]. Yoga interventions have been suggested to enhance vigilance, improve sleep, and reduce anxiety in healthy security personnel[135].

Yoga-based exercises in schools have been suggested to reduce stress and challenging behavioral and cognitive responses to stress, promote physical ability, and strengthen cognitive performance among students[136,137]. Yoga interventions for a period of 8 wk have shown a significant impact on reducing anxiety in school-age children[138]. Using a yoga-based relaxation method (mind-sound resonance technique) alleviated state anxiety and mind wandering and promoted state mindfulness and performance in school children[139]. High-frequency yoga breathing training promotes attention and reduces anxiety in students aged 11-12 years[140]. Furthermore, evaluation of the effect of yoga intervention on stress perception and anxiety levels in college students has shown a significant reduction in anxiety and

stress scores associated with a marked enhancement of total mindfulness[141]. Yoga can also help adolescents hospitalized in an acute care psychiatric ward to lessen their emotional distress[142]. Yoga exerts a bifacial effect on the reduction of anxiety and improvement of self-esteem in orphanage residents[143].

Practicing yoga in patients suffering from post-traumatic stress disorder for at least 4 wk resulted in a significant reduction of cortisol values[144]. Yoga practices significantly reduce stress and anxiety in subjects living with human immunodeficiency virus[145], people with cancer[146], such as survivors of lung cancer[147] and patients with breast cancer[148], patients with systemic disease, like rheumatoid arthritis[149,150], and patients with neurologic disorders, such as PD[100]. Yoga exercises have also been suggested as a promising stress-relieving approach in pregnant women[151,152], in women receiving treatment for infertility[153], and in women who are trying to quit smoking[154,155].

Yoga and depression: Depression is the most common psychiatric disorder that affects 25% of women and 12% of men during their lifetime[156-159]. This disorder is commonly treated by antidepressants and psychotherapy[156,160]. Yoga interventions have been suggested as effective adjuvant therapy[161,162] as well as monotherapy [163] for depression.

A narrative review on the efficacy of yoga and mindfulness as an adjuvant treatment in severe mental illnesses including major depressive disorder (MDD) indicated that both yoga and mindfulness have significant and beneficial effects on reducing the severity of depressive symptoms[164]. Yoga practices in combination with the application of conventional antidepressants significantly improved depression symptoms and reduced the remission rate in patients with MDD compared to control patients[165]. A significant decrease in self-reported symptoms of depression after practicing yoga has been observed in individuals aged 18-29 with mild levels of depression[166]. A meta-analysis has shown a more significant reduction in depression compared to psychoeducation[167].

In addition to the improvement of depression, yoga interventions promote mental health and quality of life and interrupt negative thinking in patients with depression [168,169]. A meta-analysis of 10 studies has shown that yoga practices have a statistically significant effect as an adjunct treatment in patients with MDD[162]. In an investigation of hospitalized patients with severe MDD, the effect of yoga intervention was equivalent to treatment with a tricyclic antidepressant[170]. It has been suggested that yoga modulates cortical inhibition *via* the regulation of the GABAergic system and exerts beneficial effects in MDD[171]. Furthermore, increased GABA-mediated neurotransmitter activity induced by transcranial magnetic stimulation, and multiple yoga therapy sessions was associated with a significant improvement of depression symptoms in patients with MDD[172]. Enhancement of thalamic GABA values has also been suggested as a potential mechanism for the improvement of mood in patients with MDD[173]. Enhancement of serum neurotrophic factors, such as brain-derived neurotrophic factor, in patients with MDD who practiced yoga, pointed to the possible role of increased neuroplasticity in the improvement of depression symptoms [174]. Yoga practices in post-menopausal women resulted in reduced values of follicle-stimulating hormone and luteinizing hormone, which was associated with decreased stress levels and depression symptoms as well as improved quality of life[175]. Yoga practices in association with coherent breathing intervention have been shown to resolve suicidal ideation in patients with MDD[9,176].

Yoga and bipolar affective disorder: Bipolar affective disorder (BD) is a chronic illness with recurrent episodes of manic or depressive symptoms[177,178]. Although most patients with BD are free of symptoms during remission, many of them continue to experience mild symptoms and suffer from functional behavior impairments[177,179]. Studies on the role of yoga in the treatment of BD are scarce. However, some studies have recommended yoga as a specific self-management strategy for BD[5,180]. Patients with BD have shown a significant alleviation of depression and anxiety symptoms, reduction in difficulties with emotion regulation, and improvement of mindfulness skills during the remission phase following several weeks of yoga practices[181]. Yoga interventions have been suggested to decrease negative emotions in patients with BD [182]. Yoga has also been suggested as an adjuvant therapy that improves residual depression symptoms[183] as well as manic symptom severity[184] of patients with BD. An extensive multicenter, randomized controlled study on 160 adults with BD has shown that mindfulness-based cognitive therapy, including yoga practices, improves the severity of manic symptoms and anxiety, promotes mental health and overall functioning, and reduces relapse rates[185].

Yoga and schizophrenia: Schizophrenia (SZ) is a severe mental disorder, which often exhibits itself by positive symptoms, including hallucinatory experiences and delusional beliefs and negative symptoms, such as lack of motivation and social contacts as well as the absence of spontaneous speech and affective flattening[186-188]. A growing body of evidence suggests that yoga training as an add-on therapy could improve both the negative and positive symptoms and promote cognitive functions and emotional recognition of SZ[189-194].

The analysis of yoga intervention effects on the mood of 113 patients with psychosis has revealed significant improvements in tension-anxiety, depression, anger, fatigue, and confusion[195]. Another study on 66 antipsychotic-stabilized patients with SZ has revealed a significant improvement in positive and negative symptoms, socio-occupational functioning, and performance following yoga training[190]. A meta-analysis of 13 investigations with 1159 patients revealed the importance of the frequency of yoga interventions with an improvement of positive symptoms as well as the duration of each session with the alleviation of negative symptoms in patients with SZ[196]. Yoga practices in the patients with SZ who were taking antipsychotic medications and were in a stable condition significantly decreased drug-induced parkinsonian symptoms and improved executive functions and negative symptoms[192]. Long-term yoga intervention in patients with SZ resulted in greater social and occupational functioning and promoted the quality of life[197]. Yoga training in patients with SZ resulted in an improvement of negative and positive symptoms associated with a reduction of paranoid beliefs and promoting quality of life[198]. Yoga as an add-on treatment has shown a greater improvement of the negative symptoms of SZ in comparison to physical exercise therapy[197]. Furthermore, yoga therapy led to a significant reduction in burden scores and an improvement in the quality of life among patients with psychosis[199]. Yoga intervention in patients with SZ significantly improved cognitive dysfunction, presumably through the correction of autonomic dysfunction [200,201].

It has been suggested that yoga may improve SZ symptoms by strengthening the synaptic network of the lateral and medial prefrontal areas and augmentation of the premotor and parietal mirror neuron circuitry[202]. Oxytocin values increased significantly following yoga practice[203]; an effect that has been suggested to play a potential role in the improvement of social cognition after yoga intervention in patients with SZ[204]. Yoga practice in patients with SZ was also associated with a significant decrease in blood cortisol levels, suggesting a beneficial effect of yoga in the reduction of sociophysical stress of patients[204].

Yoga and other psychological disorders: Several other studies indicate the potential beneficial effects of yoga practices on other psychological disorders and syndromes, such as obsessive-compulsive disorder (OCD), burnout, somatoform disorders, and hypochondriasis[205]. The treatment of OCD with yoga together with the pharmacological interventions improved the obsessive thoughts and compulsive behavior of patients with OCD[206,207]. Furthermore, several clinical trials have suggested the promise of yoga intervention as an adjunct therapy for patients with OCD, who were unresponsive to conventional treatments[208,209]. Moreover, yoga training enhanced general satisfaction, improved work exhaustion, and led to greater work engagement and empathy among teachers[210], nurses[211], hospice professionals[212], and physicians[213,214], who were suffering from job burnout. Yoga can promote the psychological and physical well-being of subjects with burnout, particularly when combining it with other activities, such as art and music-therapy[215,216]. Furthermore, yoga-based interventions have been recommended as an effective therapeutic approach in somatoform disorders[217]. A 6 mo trial of yoga practices led to a significant improvement of somatoform symptoms, such as gastrointestinal, cardiovascular, and urogenital symptoms, in women with the menstrual disorder [218]. Several studies have revealed the beneficial effects of yoga interventions on the psychological health of the population during the global pandemic of coronavirus disease 2019[219].

ADVERSE EFFECTS OF YOGA

While yoga practice may exert various physical and psychological health benefits, there are some reports on its adverse effects. Intensive yoga training may lead to altered perceptions and beliefs in possessing supernatural powers. However, these psychological alterations can be interpreted as a part of spiritual enlightenment in

Eastern meditative culture[220]. Furthermore, yoga training may transiently increase the intraocular pressure and lead to progressive optic neuropathy, particularly in patients with glaucoma[109]. The musculoskeletal complications, including back, shoulder, or neck pain, osteoarthritis, joint injuries and dislocations, fractures, disc herniation, and tendon deformities have been reported as a common adverse effects of yoga practice[221-223]. However, the frequency of severe injuries associated with yoga is low (less than 5%), and both acute and chronic injuries recover fully[224,225]. Moreover, there are several reports of peripheral nerve injuries after a yoga practice, particularly in the elderly subjects who take sedative medications and patients with hypermobility of the connective tissue[104-106].

CONCLUSION

Most scientific publications on yoga deal with the efficacy of said programs to gain an understanding of the subject to counsel patients appropriately. However, the usefulness of meditation specifically for clinicians, as an occupation group that is particularly associated with physical and mental health risks, still needs more accurate evidence. Although most investigations are in favor of the beneficial effects of yoga on neuropsychological disorders, some studies have not found this meditative procedure useful.

Several points in the studies that have shown the beneficial impacts of yoga on neuropsychological disorders have to be taken into consideration. Multiple investigations reporting beneficial effects of yoga on neuropsychological disorders were not precise in design, implementation, and analysis. There was considerable heterogeneity among the description of yoga interventions in different studies. Different yoga types and many disciplines within the practice have been conducted with various duration and frequency of training. Differences in yoga approaches and the use of different outcome measurements may explain why the outcome of yoga interventions often differed in patients with a common pathological circumstance.

Furthermore, many of these studies have several limitations, such as small sample sizes, short-term follow-up, confounding variables, and lack of appropriate controls. Heterogeneity of intervention procedures and poor qualities of the original investigations substantially influence the value of the meta-analyses that evaluated the effects of yoga on various disorders. Several studies evaluated the underlying mechanism of action of yoga on neuropsychological disorders. However, the exact mechanisms remain to be further elucidated.

Although yoga is a complex approach and difficult to standardize, it is crucial to distinctly describe the intervention procedures, both conceptually and operationally, and avoid excessive heterogeneity[226,227] to consider them as an integrative method in treatment plans for neuropsychological disorders[228]. Furthermore, accurate selection of populations and controls is of great importance to evaluate the potential benefit of yoga on patients with neuropsychological diseases.

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REVIEW

'Omics' of suicidal behaviour: A path to personalised psychiatry

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Abstract

Psychiatric disorders, including suicide, are complex disorders that are affected by many different risk factors. It has been estimated that genetic factors contribute up to 50% to suicide risk. As the candidate gene approach has not identified a gene or set of genes that can be defined as biomarkers for suicidal behaviour, much is expected from cutting edge technological approaches that can interrogate several hundred, or even millions, of biomarkers at a time. These include the '-omic' approaches, such as genomics, transcriptomics, epigenomics, proteomics and metabolomics. Indeed, these have revealed new candidate biomarkers associated with suicidal behaviour. The most interesting of these have been implicated in inflammation and immune responses, which have been revealed through different study approaches, from genome-wide single nucleotide studies and the micro-RNA transcriptome, to the proteome and metabolome. However, the massive amounts of data that are generated by the '-omic' technologies demand the use of powerful computational analysis, and also specifically trained personnel. In this regard, machine learning approaches are beginning to pave the way towards personalized psychiatry.

Key Words: Epigenomics; DNA methylation; Micro-RNA; Genome; Metabolome; Suicide

Core Tip: Suicide is major public health concern worldwide, and at the same time, it is preventable when timely measures are taken. The biological basis of suicidal behaviour is not a product of a single gene, transcript, protein or metabolite; rather, it is represented by intertwined cellular mechanisms, cell types and tissue changes, and based on numerous molecular pathways. The '-omic' technologies might represent the missing link between the current state of psychiatry and future personalised approaches, through the combination of -omics-derived information and the diagnostic process. However, first we need precise, specific and validated biomarkers.

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INTRODUCTION

The International Human Genome Sequencing Consortium published the first draft of the human genome in 2001[1,2]. It was completed in 2003, and it provides information on the human genome structure, organization and variation, as well as on the functions of the complete set of human genes. This determination of the 'blueprint' of the human being represented a major breakthrough for biological and medical research, and importantly, it contributed to the development of contemporary technologies for whole-genome studies[3]. Since then, the expectations in the field of molecular genetics of human diseases have been high for the tackling of the basic causes of numerous polygenic and multifactorial diseases. This also applies to psychiatric disorders and suicidal behaviour.

In the era of the continuing evolution of personalised and precision medicine, data on a patient's genetic background represent the foundation for further decisions on their disease diagnosis, treatment and monitoring, and also for disease prevention[4]. A better understanding of the roles of genetic variations in health and disease would benefit greatly in psychiatry, as psychiatric clinical evaluation currently relies on the clinical interview alone.

Suicidal behaviour

Suicidal behaviour is one of the major global public-health concerns, as every year it accounts for more than 800000 deaths worldwide. In other words, suicides account for 50% of all violent deaths in men, and 71% in women[5]. Suicidal behaviour includes suicide attempts and completed suicides, and its ethology is complex. Many different factors contribute and shape suicidal behaviour, ranging from, but not limited to, biological (genetic, epigenetic), psychological (personality traits), clinical (psychiatric disorders), social and environmental factors[6]. The multifactorial nature of suicidal behaviour demands simultaneous inclusion of many different aspects to deepen our understanding of this phenomena.

The first clues for genetic implications in suicidal behaviour were based on family, twin and adoption studies, and the heritability of suicidal behaviour was estimated to be from 38% to 55% of all attempted and completed suicides[7]. A family history of suicidal behaviour has been recognized as biological, and as a psychological risk factor for suicidal behaviour, independent of psychopathology. This has been supported by small studies[8-12] as well as by a large population study[13]. Impulsive-aggressive behaviour is considered as an endophenotype for suicide, and its familial transmission has been associated with elevated suicide risk in families[14,15]. Twin and adoption studies have provided useful contributions for further estimate of the genetic *vs* environmental factors. Monozygotic twins have shown higher suicide risks than dizygotic twins[13,16], while in studies of suicidal behaviour and adoption, the biological parents had similar effects on suicides in their offspring in non-adopted and adopted situations[17,18].

Rise of the -omics

Initially, the search for genetic biomarkers of suicidal behaviour was based on a candidate gene approach, which was mainly oriented towards neurotransmitter systems, with stress on the serotonergic system. The reason for this stemmed from neurobiological studies that determined the potential characteristics of suicidal behaviour on different body fluids (*e.g.*, blood, cerebrospinal fluid) and *post-mortem* brain. These studies investigated the roles of the serotonergic, noradrenergic and dopaminergic neurotransmitter systems in suicide, as well as signal transduction pathways and cellular morphology[19].

The first genetic studies of suicidal behaviour showed that two genes involved in the serotonergic pathway appear to be involved in suicide vulnerability: Those for tryptophan hydroxylase 1 and serotonin transporter[20]. However, none of the many studies on candidate gene approaches that followed have provided an answer for the genetic variations that lead to suicidal behaviour. From studies on psychiatric disorders, it became apparent that as in other complex diseases, the genetic contri-

bution to such disorders is polygenic–it arises through numerous variants from an extensive number of loci, each of which has small effect on the ultimate disease risk [21]. This caused the shift from a hypothesis-driven approach towards the hypothesis-free approach, to search for novel candidate genes and variants.

With the more recent technological advances applied to the human genome across different populations, tenths of millions of genetic variants have been found. It has been shown that typically the human genome differs across 4.1 to 5.0 million sites from the reference human genome. The majority of these differences (99.9%) are single nucleotide polymorphisms (SNPs) and short insertions and deletions[22]. Genome-wide association studies (GWAS) have thus emerged, with the use of microarray approaches that can interrogate hundreds of thousands of SNPs.

As suicidal behaviour is also particularly affected by environmental factors, such as early-life adverse events, studies on the epigenetic background have begun to increase over the last decade. DNA methylation studies are the most numerous, and a substantial part of the 28 million CpG dinucleotide DNA methylation sites are now being interrogated through microarray and sequencing approaches[23].

USE OF -OMICS IN RESEARCH INTO SUICIDAL BEHAVIOUR

Large genetics-based studies of suicidal behaviour currently show great diversity for the phenotypes under study, and as suicidal behaviour varies in terms of the degree of lethality and suicidal intent, it is expected that these variables will have an impact on biomarkers. Therefore, studies on completed suicides, as the most homogenous phenotype, might reduce this variability[24]. However, due to limited access to *post-mortem* samples from suicide victims, these studies are relatively few. Therefore, studies other than gen-'omic' have more frequently focused on different suicidal behaviours, as well as suicidal thoughts and ideation. Frequently, suicidal behaviour is included only as an additional phenotype in what are primarily psychiatric disorder studies, which will sometimes obscure any clear genetic contributions to suicidal behaviour *per se*. Additionally, comparisons of the data obtained are often hindered due to variabilities in study design, which range from large population-based studies, to a two-step training and testing sample design, to small case-control studies of only a handful of patients. Despite this apparent diversity and the frequent lack of power to detect small effect sizes, these studies have still contributed importantly to a better understanding of the molecular-biological mechanisms underlying suicidal behaviour.

Genomics

Only a handful of GWAS have analysed suicide as the primary phenotype[25-29] (Table 1). One of the most unique study designs included more than 4500 DNA samples from consecutive individuals who died by suicide in the state of Utah. These samples were linked to the population database, through which they identified 43 extended families (7–9 generations) with significantly elevated risk for completed suicides. This thus increased the power to identify genomic regions with high-risk variants for suicide, and at the same time reduced the shared environment effects. Out of 207 target genes identified for suicide, 18 were implicated in inflammation and immune functions, which supported previous studies on associations between inflammation and the aetiology of suicide[25,30]. In the second part of this study, they performed follow-up on the identified target regions in an independent population-based analysis, again on completed suicides, and identified four genes: *SP110*, *AGBL2*, *SUCLA2*, and *APH1B*; however, these should be further sequenced to obtain the potential segregating risk variants[25]. A GWAS on a consortium of three different samples did not reveal any SNPs with genome-wide significance ($P < 1.0 \times 10^{-8}$), but still the pathway analysis of the results identified associations with "Cellular Assembly and Organisation", "Nervous System Development and Function", "Cell Death and Survival", "Immunological Disease", "Infectious Disease" and "Inflammatory Response", all of which have been previously shown to be abnormal in suicidal behaviour[26]. In a far smaller study, again, GWAS did not reveal any significant results, but the validation of the GWAS results with a gene expression study identified a cluster of genes involved in neuroimmune function[27].

The most comprehensive study was carried out through a large United Kingdom biobank for a general population cohort that included over 500000 people, and it covered four suicidality phenotypes that were defined as the categories of "thoughts that life was not worth living", "ever contemplated self-harm or suicide", "acts of deliberate self-harm not including attempted suicide", "attempted suicide" and "no

Table 1 Genome-wide association studies and completed suicide

Type of -omic	Tissue	Number of samples	Main results	Ref.
Illumina Infinium PsychArray platform v 1.0 (approximately 555000 markers)	Blood	216 suicide cases from extended families	*SP110* (rs181058279), *AGBL2* (rs76215382), *SUCLA2* (rs121908538), *APH1B* (rs745918508)	Coon *et al* [25], 2020
llumina Omni1-Quad Beadchip (1014770 markers)	Not stated	577 suicide attempters and suicides, 1233 non-attempter psychiatric and healthy controls	SNPs in *STK3*, *ADAMTS14*, *PSME2*, and *TBX20* genes	Galfalvy *et al* [26], 2015
Affimetrix GeneChip Mapping 50K Xba Array (58900 markers)	Brain tissue	68 suicides, 31 non-suicide deaths	58 SNPs in or near 19 known genes	Galfalvy *et al* [27], 2013
Illumina HumanOmniExpress (733202 markers) and HumanOmniExpressExome BeadChips (273000 markers)	Not stated	Approximately 746 suicides and 14049 non-suicide controls	No genome-wide significant SNP; *GTF2IRD1* locus suggested as associated with age at completed suicide	Otsuka *et al* [28], 2019
Affymetrix United Kingdom BiLEVE Axiom (807411 markers) or the Affymetrix United Kingdom Biobank Axiom (825927 markers) arrays	Blood	> 500000 subjects of different suicide phenotypes and non-suicidal controls	Significant loci for suicidality on chromosomes 9 (*ZCCHC7*), 11 (*CNTN5*) and 13 (rs7989250); genetic correlations between suicidality and depression	Strawbridge *et al*[31], 2019
Illumina Infinium PsychArray platform (593260 markers), Illumina HumanOmniExpress (733202 markers) and HumanOmniExpressExome BeadChips (273000 markers)	Blood	3413 suicides, 14810 controls	Two genome-wide significant loci involving six SNPs: rs34399104, rs35518298, rs34053895, rs66828456, rs35502061, and rs35256367. Additional 52 variants (mapping to 22 genes) with nominal significance	Docherty *et al* [29], 2020

suicidality" controls. A "completed suicides" sub-group was also identified based on death certificates. Generally, a polygenic risk score was observed, but the genetic contributions to different suicidality phenotypes implicated distinct genetic contributions to these categories[31].

Another population based study was performed through an extensive DNA bank of suicide deaths that were merged with medical records and sociodemographic data. This was the first study on completed suicide with sufficient power for a GWAS. Two genome-wide significant loci were identified on chromosomes 13 and 15 that were associated with suicide, and the significant heritability based on the SNPs was estimated to be as high as 25%[29], compared to the heritability of a previous population-based study on suicidality, of 7.6%[31]. The only GWAS on an East Asian population for suicide showed the SNP-based heritability to be 35% to 48%, which again confirmed the polygenic nature of the suicide risk[28].

Several other GWAS have been carried out on other suicidal behaviour phenotypes, rather than completed suicide, and they have most often been studied in association with psychiatric disorders. However, due to the variability of the study designs and the lack of in-depth annotation of the significant variations determined with more comprehensive gene function descriptions, any integration of the results is still missing[32].

Epigenomics

Epigenetics is a rapidly developing field that connects environmental and genetic factors. The term epigenetic regulation broadly covers DNA methylation, histone posttranslational modifications, and regulation by non-coding RNAs[33]. As there is some discussion as to whether non-coding RNAs are truly an epigenetic modification (they show regulation at a post-transcriptional gene expression level), they will be further discussed in the scope of transcriptomics.

DNA methylation is by far the most extensively studied epigenetic modification of suicidal behaviour using candidate gene and -omics approaches. An overview of epigenomic studies that have focused on DNA methylation and suicidal behaviour is given in Table 2. There are multiple approaches to analyse DNA methylation on a genome-wide scale, including whole genome bisulphite sequencing and microarray and antibody-based approaches; these can again make it hard to directly compare studies[34]. The results defined a complex picture of the association of DNA methylation and suicidal behaviour, which included the involvement of differences in cognitive functions[35], cell cycle and cell-cell signalling[36,37], regulation of gene transcription and expression[38], glutamate signalling[39], cell structural integrity and nervous system regulation[40], and neurodevelopment and polyamine metabolism [41].

Table 2 Overview of epigenomic studies that have examined suicidal behaviour

Type of -omic	Tissue	Number of samples	Main results	Ref.
Agilent 400K promoter tiling microarrays	Dentate gyrus	46 suicide completers and 16 comparison subjects	Significantly differential methylation of 366 promoters in suicide victims (273 hypermethylated and 93 hypomethylated)	Labonté *et al* [35], 2013
Illumina Infinium Human Methylation 27 BeadChip	Orbitoprefrontal cortex	25 depressed suicide cases and 28 non-psychiatric sudden death controls	Significantly increased DNA methylation in suicide victims	Haghighi *et al* [36], 2014
Illumina Human Methylation 450 BeadChip	Prefrontal cortex	23 suicide and 35 non-suicide	Significant altered methylation at four CpGs (*ATP8A1*, *SKA2*, *LOC153328* and *KCNAB2* in suicide victims	Guintivano *et al* [37], 2014
Illumina Human Methylation 450 BeadChip	Prefrontal cortex	Six suicide, six non-suicide	Significantly decreased level of methylation in suicide victims	Schneider *et al* [38], 2015
Illumina 450 K Infinium microarray	Prefrontal cortex	22 suicide completers and 28 control subjects	Significantly differential methylation of 454 CpGs in suicide completers	Kozlenkov *et al* [47], 2017
Methylation binding domain-2 (MBD2) sequencing	Prefrontal cortex	22 suicide cases and 17 controls	Significantly decreased methylation in suicide victims, with 115 differentially methylated regions	Nagy *et al*[39], 2015
Reduced-representation bisulphite sequencing	Prefrontal cortex and hippocampus	Nine suicide victims and nine controls	Significantly decreased methylation of 63 and 2406 CpGs and increased methylation of 43 and 328 CpGs in prefrontal cortex and hippocampus, respectively	Kouter *et al*[40], 2019
Illumina Infinium Human Methylation 450K BeadChip	Prefrontal cortex	21 suicides and six non-suicides	Significant correlation of 22 CpGs with gene expression in suicide victims	Cabrera-Mendoza *et al* [41], 2020

Finally here, few studies on epigenetic regulation have so far been carried out that have investigated histones and their posttranslational modification. Most of these have focused on targeting selected genes (*e.g.*, H3K27me3 and TrkB[42]; H3K27me3/H3K4-me3 and polyamine system genes[43,44], H3K9me3 and astrocyte connectivity[45]), with limited success. Misztak *et al*[46] (2020) reported a significant increase in H3K27me2 and decrease in H3K9/14ac in the hippocampus and frontal cortex of suicide victims, which might result in lowered brain-derived neurotrophic factor (BDNF) protein levels[46].

Transcriptomics

Gene transcription can be affected by various biological responses that have tight temporal regulation, which can range from very short (milliseconds) to long-lasting (days) effects[47,48]. Initially, studies used microarray-based approaches to study transcriptomics. As hybridisation-based microarrays have some limitations (*e.g.*, they only allow detection of transcripts complimentary to oligonucleotides bound to the array, and they can cause cross-hybridisation), focus has shifted to sequencing-based methods[49]. Additional advantages of sequencing are the possibility to detect alternative splicing, which is especially common in the brain, and the possibility for qualitative analysis[50].

An overview of transcriptomic studies that have examined suicidal behaviour is given in Table 3. The term transcriptomics refers to the study of all of the coding (*i.e.*, producing a code for a protein output) and non-coding (*i.e.*, providing additional regulatory mechanisms) RNA. As the field of non-coding RNAs is particularly diverse, we will focus on micro-RNAs (miRNA) only. The transcriptome of a given cell often exhibits high tissue specificity, which might be why studies have generally focused on transcriptome analysis of the brain. For suicide victims, changes in mRNA expression have been observed for many processes and pathways, which have included cell–cell communication, signal transduction, cell proliferation, development of the central nervous system[51,52], myelination[53] and microglial functions[54]. Changes have also often been observed for neurotransmission [*e.g.*, glutamatergic and gamma-aminobutyric acid (GABA)ergic signalling[53,55]] and for immune system responses and inflammation[52,54,56].

The search for miRNAs that might be used as biomarkers has not been successful yet, although various miRNAs have been identified as differentially expressed in suicide victims. However, such indications have often not been reproduced in other studies. For example, two studies identified miR-330-3p as differently expressed in suicide victims, with one reporting down-regulation in the prefrontal cortex[57], and

Table 3 Overview of transcriptomic studies that have examined suicidal behaviour

Type of -omic	Tissue	Number of samples	Main results	Ref.
U133A Oligonucleotide DNA Microarrays	Prefrontal cortex	19 depressed–suicide victims and 19 controls	No significant results	Sibille *et al* [105], 2004
Illumina Sentrix HumanRef-8 Expression BeadChips	Orbitofrontal cortex	11 suicide victims and ten controls	Significant downregulation of 59 genes and upregulation of 65 genes in suicide victims	Thalmeier *et al*[51], 2008
Human Genome U133 Set (HG-U133 A and B) microarray	Prefrontal cortex	16 depressed suicides, eight non suicides and 13 controls	Significantly altered expression of 267 genes, associated with cell cycle control and cell division, myelination, ATP biosynthesis and GABAergic neurotransmission in suicide victims	Klempan *et al*[53], 2009
HG-U133AB chipset	17 brain areas (amygdala, hippocampus, nucleus accumbens and 14 Brodmann areas)	26 suicide cases and 13 controls	Altogether over 4000 differentially expressed genes, association with cell communication and synaptic transmission in suicide victims	Sequeira *et al*[55], 2009
RNA-seq	Prefrontal cortex	21 major depressive disorder suicides, 9 MDD non-suicides and 29 controls	Significantly altered expression of 35 genes in suicide victims, association with microglial and immune system functions, and angiogenesis	Pantazatos *et al*[54], 2017
RNA-seq	Hippocampus	17 MDD suicide victims and 23 control subjects	Significant change in expression of 26 genes in depressed suicide victims, association with inflammation and chromatin regulation	Mahajan *et al*[56], 2018
RNA-seqc	Insula	52 mood disorder suicide victims and 45 non-mood disorder controls	Significant downregulation of 20 genes associated with inflammation response, protein- protein interaction, neurodegeneration, neurodevelopmental and upregulation of 5 genes, associated with intracellular protein transport, inflammation, apoptosis regulation and embryonic development in mood disorder suicide victims	Jabbi *et al* [52], 2020
RNA-seq	Prefrontal cortex	17 depressed suicide victims and 17 controls	Significant change in cell-type specific expression in depressed suicide victims	Nagy *et al* [60], 2020
TLDA based miRNA profiler	Prefrontal cortex	18 antidepressant-free MDD suicide victims and 17 controls	Significant downregulation of 21 miRNAs in suicide victims, miRNAs associated with nuclear proteins, transmembrane and signalling proteins	Smalheiser *et al*[106], 2012
LNA-based miRNA profiler	Prefrontal cortex	Four suicide victims and 4 controls	Significant upregulation of a single miRNA, targeting TrkB-T1, observed in low TrkB-T1 expression suicide victims	Maussion *et al*[107], 2012
TLDA-based miRNA profiler	Prefrontal cortex	18 suicide victims and 40 control subjects (all mood disorder)	Significant downregulation of 6 miRNAs and upregulation of 2 miRNAs in suicide victims	Smalheiser *et al*[57], 2014
Small RNA-seq	Prefrontal cortex	Nine suicide victims with depression, nine suicide victims and nine controls	No significant results	Pantazatos *et al*[54], 2017
TLDA-based miRNA profiler	*Locus coeruleus*	Nine suicide victims with depression and 11 controls	Significant upregulation of 10 miRNAs and downregulation of 3 miRNAs in suicide victims. Identified miRNAs are targeting multiple genes that were previously associated with psychiatric disorders	Roy *et al* [58], 2017

the other reporting up-regulation in the *locus coeruleus*[58]; this again indicates the potential importance of tissue specificity.

Recently, focus has been shifting from whole tissue homogenates towards single-cell transcriptome analysis, to better define the complexity of the brain structure and its cellular composition. In doing so, large differences have been seen between subtypes of brain cell populations[59]. Nagy *et al*[60] (2020) analysed the nuclei of the prefrontal cortex in depressed suicide victims, and they identified 26 distinct cell types. The most notable changes were in the deep layer of excitatory neurons and immature oligodendrocyte precursor cells. More specifically, there was association with fibroblast growth factor signalling, steroid hormone receptor cycling, immune function, and cytoskeletal regulation[60].

Proteomics

The proteome is defined as the complete set of proteins that are expressed by a cell or tissue type, or an organism, under specific conditions, which includes proteins that

result from alternative gene splicing, and posttranslational modifications of proteins [61]. The proteome can thus provide us with a snapshot view of the key players in many cellular processes. Compared to transcriptomics, proteomics has the advantage of providing additional information on RNA–protein translation, protein localisation, protein posttranslational modification, protein localisation, speed of protein production and degradation, and interactions with other proteins[62].

Compared to previously described -omics studies, large-scale studies of proteins are not as common when it comes to suicidal behaviour. An overview of proteomic studies that have examined suicidal behaviour is given in Table 4. Usually, protein samples are first separated (*e.g.*, two-dimensional gel electrophoresis to separate proteins based on molecular weight and isoelectric point), with mass spectrometry used to identify a protein of interest[63].

Various tissue samples have been used to date to study the proteomics of suicidal behaviour, including the prefrontal cortex[64-66], amygdala[65] and cerebellum[67]. Studies have also examined cerebrospinal fluid[68,69] and plasma[70,71], as although these are still invasive, they represent more easily accessible sources of tissue.

A reoccurring pattern can be observed, that is similar to the other -omics studies described above. Here, too, there are connections with many of the previously mentioned cell functions and pathways, with indications of association with glial function, neurodegeneration, oxidative stress, neuronal injury[64], the cytoskeleton, synaptic functions[65], coagulation and inflammation[70], decreased glucose utilisation[69], altered cholesterol metabolism in deliberate self-harm[71], transport functions and cell communication in schizophrenia suicide victims[67], the GABA receptor signalling pathway, and pathways related to other neurotransmitters in mood disorder suicide victims (*e.g.*, serotonin receptor signalling, melatonin signalling, CREB signalling in neurons, dopamine receptor signalling)[66].

Additionally, Cabello-Arreola *et al*[66] (2020) reported a reduction in the protein coded by *KCNQ3* (potassium voltage-gated channel subfamily Q member 3) in suicide victims. This protein serves as a building block for the M-channel, a slow working potassium channel that is involved in the regulation of neuron excitability, which has previously been associated with epilepsy, attention deficit hyperactivity disorder, and psychiatric disorders[72].

Suicidal behaviour is often presented as a comorbidity that is accompanied by other psychiatric disorders that have their own specific aetiologies. A study by Vidal-Domènech *et al*[67] (2020) demonstrated this problem. After comparison of cerebellum protein expression of suicide victims with schizophrenia and healthy controls, 99 proteins were identified as significantly altered. During the further validation of three proteins in a larger group of people, including non-schizophrenia suicide victims, only one of these remained associated with suicidal behaviour. This opens the question of whether the 99 proteins identified indicated associations with schizophrenia, suicidal behaviour, or both[67]. Similar considerations should be taken when interpreting other studies, including with patients with identified psychiatric or other disorders.

Metabolomics

Although the most pronounced changes in suicidal behaviour take place in the brain, the access to the brain itself is generally only through *post-mortem* studies. Finding biomarkers for suicidal behaviour that can be repeatedly and easily monitored in real time is therefore aimed at peripheral tissues, like cerebrospinal fluid, platelets, serum and urine, among others, where the intermediate or end products of metabolism can be measured. Among the first clues for metabolites as potential biomarkers for suicidal behaviour was the finding of Asberg *et al*[73] (1976). In the cerebrospinal fluid of depressed suicide attempters they reported that low levels of 5-hydroxyindoalacetic acid (a metabolite of serotonin degradation) were associated with more attempted suicides and with more violent means, compared to patients with high levels of 5-hydroxyindoalacetic acid[73].

An advanced study of metabolites in large numbers is defined as metabolomics. The patterns of metabolic intermediates can be used to determine dysfunctionalities in metabolic pathways, which can be linked to symptomatic presentation[74]. Studies of metabolomics and suicidal behaviour alone have not been performed yet, and have instead been incorporated into studies of psychiatric disorders, and most commonly, depression.

In a multicentre study on the severity of depression and suicidal ideation, plasma metabolites and a machine learning approach were used to build a model to discriminate between depressive patients without and with suicidal ideation. In this study, positive correlation between citrate and suicidal ideation was seen, while negative correlation was seen for kynurenine pathway metabolites (especially

Table 4 Overview of proteomic studies examining suicidal behaviour

Type of -omic	Tissue	Number of samples	Main results	Ref.
2D gel electrophoresis	Cerebrospinal fluid	Seven suicide attempter and seven non-attempters	Significantly altered level of a single protein in suicide attempters. Due to limited amount of material the protein could not be identified	Brunner *et al* [68], 2005
2D gel electrophoresis and MALDI TOF MS	Prefrontal cortex	17 suicide victims and 9 controls	Significantly altered levels of three protein: An isoform of the common astroglia marker glial fibrillary acidic protein (GFAP), manganese superoxide dismutase (SOD2) and α crystallin chain B (CRYAB)	Schlicht *et al* [64], 2007
DIGE qTOF tandem MS	Prefrontal cortex and amygdala	Six suicide victims and six controls	59 significantly altered protein levels in the cortex and 11 significantly altered proteins in the amygdala. Level of nine proteins were significantly altered in both brain regions, but with varying direction of change (either increased or decreased in suicide victims), suggesting the global change in the brain, yet highlighting the importance of tissue specificity	Kékesi *et al*[65], 2012
2D gel electrophoresis and-MALDI-TOF MS	Plasma	12 suicide attempters, 12 MDD patients and 12 controls	Significant change in 45 protein, enabling the differentiation between MDD patients exhibiting suicidal behaviour and non-suicidal MDD patients	Yang *et al*[70], 2016
HPLC and Ion Trap MS	Cerebrospinal fluid	Two suicide victims and two controls	69 proteins with significant change in suicide victims, association with dysregulation of glucose metabolism and oxidative stress response.	Semancikova *et al*[69], 2018
2D-gel electrophoresis and MALDI MS	Plasma	10 self-harm subjects and 18 controls	Downregulation of apolipoprotein A-IV (Apo A-IV) in deliberate self-harm subjects.	Mathew *et al* [71], 2019
Liquid chromatography and tandem MS	Cerebellum	Four suicide victims and four controls	99 significantly altered proteins in schizophrenia suicide victims, association with transport function and cell communication. Vacuolar-type proton pump ATPase (VPP1) further validated and associated with suicidal behaviour.	Vidal-Domènech *et al*[67], 2020
ESI-MS/MS	Dorsolateral prefrontal cortex	Five suicide victims and five controls	33 proteins with significant change in expression (24 decreased and nine increased in the suicide group). Biggest change observed in reduction in protein coded by *KCNQ3* (potassium voltage-gated channel subfamily Q member 3) in mood disorder suicide victims.	Cabello-Arreola *et al*[66], 2020

kynurenine and 3-hydroxykynurenine). Using only citrate and kynurenine, an algorithm for suicidal ideation grade was built[75]. This is of particular interest, as previous studies have associated the tryptophan-kynurenine pathway with brain inflammation and microglial activation, and more recently with suicide[76,77]. In another study of suicidal ideation that was performed on depressed antepartum women, significant inverse associations with suicidal ideation were shown for the neurotransmitter precursors for serotonin and dopamine: 5-hydroxytryptophan and phenylalanine, respectively[78]. Here, again the microglia activation hypothesis might serve as an explanatory mechanism, as it has been linked to alterations in tryptophan signalling and suicidal ideation[77,78]. Of interest, among the metabolomic studies there was also one on cerebrospinal fluid and the serum metabolome. This included treatment-refractory depressed patients, for whom cerebral folate deficiency was shown, although their serum folate levels were normal. In these cases, the metabolomic analysis revealed this reason for the lack of treatment response, which would not have been identified through any other conventional clinical, diagnostic or therapeutic approaches. Administration of folic acid reduced the symptoms of depression, and also the suicidal ideation[74].

Although studies of the metabolome and mental disorders are still in their infancy, these results show great potential for their use, particularly when common treatment approaches do not achieve satisfactory effects.

BUILDING THE BRIDGE BETWEEN PERSONALISED MEDICINE AND PSYCHIATRY

Throughout this review, we have presented the large body of work that has investigated suicidal behaviour, which has ranged from the genome all the way to the metabolome, thus demonstrating further the complexity of suicidal behaviour. A

biological basis of suicidal behaviour can therefore not be determined by any single gene, transcript, protein or metabolite, as it is the final sum of intertwined cellular mechanisms, cell types and tissue changes.

In these current times of the coronavirus disease 2019 (COVID-19) pandemic, the importance of novel approaches to diagnosis and treatment of people with psychiatric disorders is probably greater than ever. An important advance has been the increased use of telepsychiatry, which uses audiovideo technology to enable live interactions, which can be combined with previously prepared materials to provide the needed counselling, monitoring and therapy[79]. However, when it comes to tailoring the approach to the individual and the use of biological markers to diagnose or monitor treatments, great challenges still remain[80]. Psychiatry remains a field of medicine that is heavily dependent on arbitrary determined thresholds of standards, manuals and questionnaires to diagnose and monitor a patient. Not knowing the definitive cause of complex disorders prevents healthcare personnel from treating each patient in terms of his or her full needs. By personalising the care of people with suicidal behaviour and other psychiatric disorders, psychotherapy and drug treatments will improve from the current estimate of 50% success[81,82].

Personalised psychotherapy and pharmacogenomics

Suicidal behaviour and psychiatric disorders are often associated, but they are not exclusively bound together. While some studies have shown that the majority of suicide victims are, or could be, diagnosed with additional psychiatric disorders, it is estimated that only around 5% to 8% of people with psychiatric disorders will exhibit suicidal behaviour[83]. Thus, more suitable drugs and prescriptions would help a large segment of people with suicidal behaviour (as well as the non-suicidal patients).

Pharmacogenomics is a novel field that is studying the genetic basis of drug metabolism and response. The way we metabolise a drug can be greatly influenced by genetic variations, in terms of genes that code for enzymes, drug transporters and other proteins involved in drug metabolism[84]. The most commonly used phenotype classification system divides patients into subgroups of ultrarapid metabolisers, rapid metabolisers, normal metabolisers, intermediate metabolisers, and poor metabolisers [85].

The suitable choice of psychopharmaceuticals and their dosing is often a long process, with patients reporting side effects before the correct doses and drug combinations can be achieved[86]. Multiple enzymes are associated with differences in drug metabolism, with CYP2D6 and CYP2C19 being the most promising in the field of psychiatry. These both belong to the cytochrome P450 superfamily of enzymes that are responsible for drug metabolism. Based on the Pharmacogenomics Knowledgebase (PharmGKB) database, there are currently 17 antidepressants and 10 antipsychotics on the market. These have medical agency approved guidelines and the labels recommend genetic testing for CYP2D6 and CYP2C19. They then offer either selection or dosage recommendations based on the individual metabolic status[86].

While some studies have shown the association of other genetic variants with pharmacodynamics [*e.g.*, *SLC6A4, COMT, BDNF*; as detailed in a review by Lett *et al* [87] (2016)], recent guidelines from the International Society of Psychiatric Genetics do not support their use for prescribing psychiatric medications[86].

Despite its limitations (*i.e.*, test result interpretation, cost, high turnaround time, bias through focusing on European ancestry, population allele frequencies) pharmacogenomics has shown great potential, and might therefore be effective and safer for drug prescribing, such that they can be tailored to the personal genetic makeup of the patient[86,88].

Use of artificial intelligence

These -omic-based studies can provide us with large amounts of data. Artificial intelligence is an approach that is beginning to be increasingly used in various fields of medicine, including psychiatry[89]. Through the use of artificial intelligence, computer models can more easily analyse these large datasets, and more importantly, artificial intelligence can lead to predictions of the risk of an event or disease, based on previously analysed data. To date, artificial intelligence has been used in research into suicidal behaviour that has ranged from analysis of social media texts[90] and health records[91], to analysis of the previously described -omics approaches.

Machine learning algorithms have been successfully used to determine whether a person belongs in the group of suicide attempters or non-attempters with 67% accuracy; this was based on only three SNPs: In *HTR1E* (5-hydroxytryptamine receptor 1E); *GABRP* (g-aminobutyric acid type A receptor subunit Pi); and *ACTN2* (actinin α2) [92]. Based on gene expression and DNA methylation, Bhak *et al*[93] (2019)

successfully differentiated between suicide attempters and patients with major depressive disorder with 92.6% accuracy, and between suicide attempters and control subject with 86.7% accuracy[93]. Similarly, metabolic profiles can be used to try and differentiate between people. A study by Setoyama *et al*[75] (2016) associated the kynurenine pathway metabolites and citrate with suicidal ideation, which allowed determination of the patients without and with suicidal ideation[75].

An interesting study was reported by Just *et al*[94] (2017), where they used functional magnetic resonance imaging to provide an insightful view of the differences of concept understanding. By measuring the changes in brain activity when presented with words or concepts, the locations and intensity of the responses differed between people with suicidal ideation and the control group; this model differentiated between these two groups with 91% accuracy[94].

Although artificial intelligence comes with several limitations, such as the need for large amounts of unbiased data, precise model development, and technical abilities, it appears to hold promise of better treatment possibilities of individuals. Artificial intelligence should provide better understanding and detection of suicidal behaviour and suicidal ideation, aid in therapy progression and treatment planning, and help with patient monitoring and stratification[95].

Challenges of personalised medicine

Psychiatric disorders are highly heterogeneous, with complex biological underpinning, paired with additional cultural, social and environmental factors[96]. Bragazzi[96] (2013) proposed the use of "psychiatome" to combine the interactions of all of the -omics involved in the development of the psychiatric state of a person. This covers genes, transcription and protein networks, along with brain anatomy, and should incorporate the concept of '5P' medicine: personalised, participatory, predictive, preventive and psycho-cognitive[96]. These -omics might represent part of the missing link between the current state of psychiatry and future personalised approaches, through the addition of -omics-derived information to the diagnostic process. However, for this we need precise, specific and validated biomarkers, which have not yet been identified. Additional limitations of personalized medicine in psychiatry include the question of stigma (*e.g.*, effects on the general population, patients and public health policy makers), ethical aspects (*e.g.*, conflicts of interest, informed consent of patients, data protection), cost-effectiveness and need for additional skillsets for healthcare providers[97].

By including -omics-based data in the diagnostic process, psychiatric disorders can be viewed as spectrum disorders, instead of the current binary "disease or health" approach that is proposed by psychiatric manuals[98]. Here, the end goal is not to reject the classical definition and the diagnostics and care of psychiatric disorders, but to compliment these with better understanding of each patient group[99].

CONCLUSION

Suicide is devastating, but at the same time it is preventable if timely measures are taken. Therefore, understanding the biological background of suicide is important, to help develop clinically applicable tools for its detection. However, like in many other cases of complex diseases, we are only just beginning to uncover the biological clues for its development.

Candidate gene approaches and GWAS still lack the identification of any common gene or variant. None of the most researched genes in suicidal behaviour, the serotonergic genes, have been replicated in any GWAS on suicidal behaviour[100]. The replication of results is affected by significant sample differences (*e.g.*, demographic characteristics, primary diagnosis, suicidal behaviour/ideation phenotype) and methodological approaches (*e.g.*, candidate genes, GWAS) across studies. Microarrays are being gradually supplemented and replaced with novel sequencing approaches that can produce faster and cheaper information, which will lead to the generation of more medically useful information, like whole exome sequencing. However, in the case of mental health, we are still far away from any molecular-based tool that is useful for clinical prediction. Only single studies on suicide and whole exome sequencing are currently available[101], and although several hundred thousand SNPs and insertions/deletions have been identified, currently these data provide 'only' a resource for further laborious in-depth analysis to find further biologically meaningful information.

In recent years biomarker research has started to uncover the intriguing roles of extracellular vesicles. These small vesicles are excreted by virtually all cells, and they are involved in cellular communication, as they can travel over short or long distances. Their crossing of the blood–brain barrier gives them particular value in research into the central nervous system, as extracellular vesicles are defined by their origin and their cargo (*e.g.*, proteins, DNA, RNA). This opens new potential for peripheral markers for brain disorders[102]. In the field of metal disorders, only a few studies have been performed, while their involvement in research into suicidal behaviour is currently still untouched[103]. Determination of the origin, number and content of extracellular vesicles, can provide an important contribution to our understanding of brain function in a state of severe stress, such as inflammation or an immune response, both already associated with suicidal behaviour. As the current COVID-19 pandemic represents a significantly increased risk of sociological risk factors for suicidal behaviour, the disease itself triggers inflammation and extremely strong immune responses with a cytokine storm, which can promote increased risk of psychiatric disorders, chronic trauma and stress, which in turn will increase suicide and suicidal behaviour[104]. From this point of view, this represents a unique opportunity to perform molecular-genetic studies on suicidal behaviour using cutting-edge technology.

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MINIREVIEWS

Environmental pollution with psychiatric drugs

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Abstract

Among all contaminants of emerging interest, drugs are the ones that give rise to the greatest concern. Any of the multiple stages of the drug's life cycle (production, consumption and waste management) is a possible entry point to the different environmental matrices. Psychiatric drugs have received special attention because of two reasons. First, their use is increasing. Second, many of them act on phylogenetically highly conserved neuroendocrine systems, so they have the potential to affect many non-target organisms. Currently, wastewater is considered the most important source of drugs to the environment. Furthermore, the currently available wastewater treatment plants are not specifically prepared to remove drugs, so they reach practically all environmental matrices, even tap

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water. As drugs are designed to produce pharmacological effects at low concentrations, they are capable of producing ecotoxicological effects on microorganisms, flora and fauna, even on human health. It has also been observed that certain antidepressants and antipsychotics can bioaccumulate along the food chain. Drug pollution is a complicated and diffuse problem characterized by scientific uncertainties, a large number of stakeholders with different values and interests, and enormous complexity. Possible solutions consist on acting at source, using medicines more rationally, eco-prescribing or prescribing greener drugs, designing pharmaceuticals that are more readily biodegraded, educating both health professionals and citizens, and improving coordination and collaboration between environmental and healthcare sciences. Besides, end of pipe measures like improving or developing new purification systems (biological, physical, chemical, combination) that eliminate these residues efficiently and at a sustainable cost should be a priority. Here, we describe and discuss the main aspects of drug pollution, highlighting the specific issues of psychiatric drugs.

Key Words: Antipsychotics; Pharmaceuticals in the environment; Drug pollution; Antidepressants; Wastewater; Ecotoxicity

Core Tip: Psychiatric drugs have received special attention as contaminants of emerging interest because of two reasons: First, their use is increasing. Second, many act on phylogenetically conserved neuroendocrine systems, potentially affecting many non-target organisms. Drug pollution is a complicated problem involving many stakeholders with different values and interests. Solutions can be applied at source, using medicines more rationally, prescribing greener drugs or designing pharmaceuticals that are more biodegradable. Besides, end of pipe measures, *e.g.*, developing new purification systems will also be crucial. Finally, educating both health professionals and citizens, and collaboration between environmental and healthcare sciences is going to be essential.

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INTRODUCTION

Toxic problems caused by chemicals, such as aromatic compounds, polychlorinated biphenyls, heavy metals, pesticides, *etc.*, are well known. However, concern regarding the so-called "pollutants of emerging interest" is increasing, with pharmaceuticals causing the greatest concern. Pharmaceutical products have two important characteristics that are driving this preoccupation: Firstly, they produce pharmacological effects at low concentrations, such as those found in the environment. Secondly, they are designed with stability in mind, so they are more likely to reach and interact with their target molecules.

THE PROBLEM OF ENVIRONMENTAL POLLUTION WITH PHARMACEUTICALS

Publications in scientific journals regarding the presence of pharmaceutical products in the environment has grown exponentially since the end of the 1990s, due to improvements in analytical techniques allowing for the detection of lower concentrations of drugs in different matrices[1]. Currently available information regarding the presence of pharmaceuticals in the environment and their consequences is simply

overwhelming.

A recent study estimated that approximately 4000 different pharmacologically active substances are currently being administered globally, including: Prescription drugs for human use, over-the-counter drugs, and veterinary drugs[2]. Global drug use continues to grow, with an estimate of 4.5 trillion doses consumed in 2020[3]. The trend will probably continue for the following reasons[2]: The age and life expectancy of populations has increased; economies are growing, especially emerging economies, so the capacity and expectations to treat aging and chronic diseases increase; intensification of livestock and aquaculture practices to meet demand; the design of new pharmaceutical products; climate change, which will aggravate existing diseases (both communicable and non-communicable).

Psychiatric drugs have received particular attention above other therapeutic classes for two main reasons: Their widespread use and their potential to provoke ecotoxicological damage. Some authors believe the current situation due to the Coronavirus disease 2019 pandemic may lead to an increase use of certain psychiatric drugs, like anxiolytics or antidepressants[4].

Life cycle of drugs

The liberation, absorption, distribution, metabolism, excretion (LADME) scheme showing the curse of drugs in the human organism is still shown in universities across the world. Drugs are first released, then absorbed, distributed, metabolized, and finally excreted outside. But in this anthropocentric scheme, little or no attention is paid to drugs and metabolites once they are excreted outside the organism (Figure 1).

Of course, drugs and their metabolites do not disappear after flushing the toilet, but rather reach the environment in different amounts depending on the proportion metabolized in the body. It has been estimated that the percentage of unchanged drug excreted in feces and urine is between 30% and 90% on average[5].

Any of the multiple stages that make up the life cycle of the drug: production, consumption and waste management; is a possible entry point to the different environmental matrices.

In any case, currently the most important source is considered to be wastewater, which includes wastewater of domestic, hospital, industrial and of agricultural or livestock origin. Pollution due to industrial waste disposal was not considered a major factor until recently. Contemporary research shows, however, that certain production factories can cause environmental pollution at levels well above what was previously thought[6]. For example, very high venlafaxine concentrations were found in a wastewater treatment plant (WWTP) that received the discharge of a large industrial plant near Jerusalem, in Israel[7].

But pharmaceutical products can reach the aquatic environment by other routes, including, for example: aquaculture, runoff water from the agricultural sector, through the removal of sewage sludge (especially when used as fertilizer in agriculture), or leaching to groundwater after rain. Likewise, the presence of pharmaceuticals has to be considered when re-using wastewater in agriculture, a practice that is expected to increase in the near future[8].

The current purification systems: WWTPs

Currently available WWTPs are not specifically designed to remove drugs. Some of them are eliminated, but others remain unchanged and are discharged with the effluents. As an example, a study carried out in the United Kingdom in 2018 estimated that in 13% of the WWTPs available in that country, the effluent contained potentially dangerous concentrations of drugs such as ethynylestradiol, diclofenac, propranolol, macrolide antibiotics and fluoxetine[9]. Sometimes, paradoxically, the drug concentration in the effluent of the WWTP can be even higher than that in the influent. This is due to the microorganisms in charge of the biological (secondary) treatment of wastewater may be in charge of metabolizing the conjugates with glucuronic acid, so that the drug returns to its original form[5]. This is the case with carbamazepine, amitriptyline, lamotrigine, doxepine, citalopram, among many other pharmaceuticals [10]. Besides, a study estimated that up to 70% of all wastewater does not receive treatment before being discharged, so the situation in developing countries is probably even worse[11,12].

Presence of drugs in environmental matrices

Residues of multiple types of drugs (about 700) have been detected in different environmental compartments mainly in wastewater, surface and groundwater, but also in soil, air and biota, even in the tap water that we drink[13]. In the specific case of

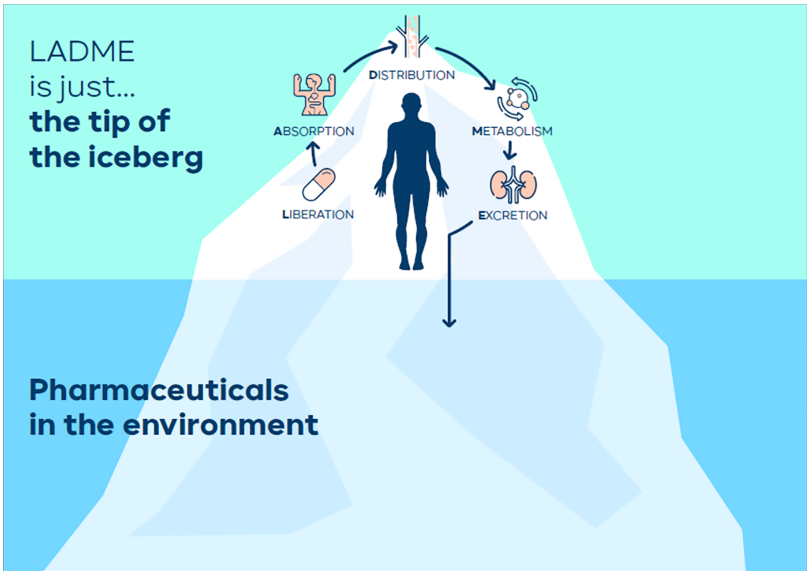

Figure 1 The liberation, absorption, distribution, metabolism, excretion scheme is just the tip of the iceberg. LADME: Liberation, absorption, distribution, metabolism, excretion.

psychiatric drugs, there are complete books reviewing their presence in the environment[14]. Carbamazepine has even been considered as a marker for wastewater influenced water bodies due to its omnipresence[15].

For a greater detail of all the drugs detected in any environmental matrix, the free database of the German Environment Agency can be consulted, which maintains an exhaustive registry of all published studies, available from: https://www.umweltbundesamt.de/dokument/database-pharmaceuticals-in-the-environment-excel.

Furthermore, once they have reached the environment, parent drugs (or metabolites) continue to transform and continue to undergo complex metabolic processes by different organisms as well as by different physicochemical mechanisms (photo-degradation, adsorption to solids, *etc.*), leading to "transformation compounds". For example, Trawiński *et al*[16] reviewed the photodegradation process of psychotropic drugs. Some substances can remain unchanged in the environment for decades, *i.e.*, are very persistent. This is the case of oxazepam, which has remained unchanged at the bottom of Swedish lakes for more than 30 years[17].

Ecotoxicological effects of psychiatric drugs

Toxic effects of drugs in the environment can go far beyond growth, mortality or reproduction. For example, psychoactive drugs can affect organism behaviour and fitness, altering population dynamics[18-21]. The therapeutic targets and the physiological systems in which drugs act are not exclusive to human beings. Many of these structures and signaling pathways are highly conserved phylogenetically, and are present in many living organisms[22]. For example, multiple behavioral tests (such as anxiety, fear and stress) for experimental drugs intended for human use are performed on fish[23]. Fish share many of the neurotransmitter and signaling pathways with us. In fact, biogenic monoamines (serotonin, dopamine, norepinephrine, *etc.*) are found in vertebrates and invertebrates, including amphibians, fish, insects and echinoderms[24,25]. These substances are so ancient from an evolutionary point of view that they are present in organisms outside the animal kingdom. For example, acetylcholine is present in fungi and bacteria[26] and serotonin in plants[27]. Fluoxetine has shown to induce behavioral changes in crickets[28]. Fish also become constipated in the presence of the antipsychotic clozapine[29], plants accumulate benzodiazepines that could act on their GABAergic system[30], or sertraline affects sedimentary nitrification processes by altering the microbial trophic chain[31].

Castillo-Zacarías *et al*[32] have recently reviewed available literature about the presence and effects of antidepressants on the environment. We have also shown that the role of antipsychotic drugs as environmental pollutants has probably been underrated so far[33].

In short, the psychoactive drugs that we use and excrete into the environment can have pharmacological effects in different non-target organisms. However, the extent of exposure and subsequent effects remains unknown for many taxa and ecosystems[34]

(Table 1).

Effects of drug pollution on human health

The effect of drug pollution on human health is still relatively little studied. A WHO report published in 2012 concluded that drug concentrations in tap water should not pose any health problems[35]. These findings were confirmed in a recent study carried out in China[36]. However, the presence of drugs in the environment could be a problem for the most vulnerable groups of patients (*e.g.*, allergic[5]). Although there is no evidence of short-term effects on human health, uncertainties remain, in particular concerning long-term exposure (chronic exposure) to a mixture of pollutants[5]. The possible routes of exposure are, mainly, consumption of drinking water, vegetables and tubers, meat, fish, shellfish and dairy products[5].

Probably the best known example of the deleterious effect of drug pollution on human health is that of the increase in bacteria with resistance to antibiotics, which is currently recognized as the biggest public health problem worldwide. In this sense, we consider that the "One Health" approach or philosophy, which considers that human health is closely interrelated with environmental health, is essential[37]. Nevertheless, we believe that it is necessary to extend this approach to all therapeutic groups including psychiatric drugs, not only antibiotics[38,39].

Some authors have suggested that psychoactive drugs present in the environment may potentially be associated with human neuropsychiatric disorders such as autism, Alzheimer's disease and schizophrenia, since they are able to cross the maternal barriers affecting the development of the embryonic brain[40].

Bioaccumulation

Recent studies suggest that certain drugs bioaccumulate in non-target organisms through the food web, reaching tissue concentrations much higher than those found in the environment. For example, a study carried out in five Australian rivers found that platypuses and brown trouts bioaccumulate 66 of the 80 drugs studied due to their insectivorous diet. First, the larvae of riparian insect's bioaccumulated certain drugs present in surface waters, and subsequently, these drugs can pass to the animals that eat them. Surprisingly, the researchers estimated that, in the case of antidepressants, platypus might be exposed to amounts up to half the daily doses used in humans[41]. (Table 1).

A recent work studied the presence of more than 90 drugs pertaining to 23 different drug classes in blood plasma of wild European fish in three different European countries. For some drugs, measured fish plasma concentrations were above human therapeutic plasma concentrations. Indeed, three of the four drugs that showed a moderate or a high risk of inducing toxic effects on fish were antipsychotics: *i.e.*, risperidone, flupentixol and haloperidol[42].

An excellent review of the bioaccumulation of pharmaceuticals (including psychiatric drugs) in aquatic fish and invertebrates was published by Miller *et al*[43]. Besides, this bioaccumulation process is not exclusively restricted to the aquatic environment. A study carried out in the Doñana National Park, Spain, showed that dung beetles accumulate the antiparasitic ivermectin used in livestock in their tissues. Ivermectin, with recognized insecticidal activity, is toxic to beetles that are in charge of processing manure, in such a way that the properties of the soil are altered[44]. In addition, some studies suggest certain psychiatric drugs like carbamazepine and fluoxetine might bioaccumulate in terrestrial organisms (earthworms) depending on the properties of the soil and the physico-chemical characteristics of the drug[45].

We still understand little about what is happening ... although highly hypothetical, what if insectivorous bats were accumulating drugs in their tissues? What consequences could this have on the appearance of new zoonosis[46]?

Environmental impact risk reports from the European Medicines Agency

Since October 2005, the European Medicines Agency has required the laboratories holding the marketing authorization to assess the environmental impact of medicines [47] (ERA: Environmental risk assessment). Despite this significant progress, this report is not considered during the benefit-risk balance in drug evaluation, even if it shows potential risks for the environment. For example, the ERA of the recently marketed antidepressant vortioxetine[48] recognizes that this drug is "potentially harmful to the environment". Something similar occurs with the antipsychotic asenapine[49], for which the ERA recognizes that it is a potential endocrine disruptor. Despite this, both drugs have been marketed without any restrictions.

Table 1 Examples of the presence of certain psychiatric drugs in the environment and ecotoxicological effects on organisms

Therapeutic class	Drug	Non-target organism	Ecotoxicological effects	Ref.
Antiepileptics	Carbamazepine	Ryegrass (*Lolium perenne*)	Accumulation in plants tissues	Carter *et al*[83], 2014
Antidepressants	Various	Platypus (*Ornithorhynchus anatinus*), Brown Trout (*Salmo trutta*)	Half of human daily dose, insectivorous diet. Effects?	Richmond *et al*[41], 2018
	Sertraline	River sediment microorganisms	Sedimentary nitrification processes by altering the microbial trophic chain	Li *et al*[31], 2020
	Fluoxetine	Cricket (*Gryllus campestris)*	Behaviour disturbance	Abey-Lee *et al*[28], 2018
		Starling (*Sturnus vulgaris*)	Reduced female attractiveness	Whitlock *et al*[84], 2018
Benzodiazepines	Various	Beet (*Beta vulgaris*)	Phitotoxicity	Carter *et al*[30], 2018
	Oxazepam	European perch (*Perca fluviatilis*)	Behaviour and feeding rate disturbance	Brodin *et al*[85], 2013
Antipsychotics	Clozapine	Zebra fish (*Danio rerio*)	Constipation	de Alvarenga *et al* [29], 2017
	Risperidone	Zebra fish (*Danio rerio*)	Alteration of antipredatory behavior, transgenerational effect	Kalichak *et al*[86], 2019
	Various	Chub (*Squalius cephalus*)	Fish plasma concentrations > Human plasma therapeutic concentrations	Cerveny *et al*[42], 2020

At the moment, and contrary to what happens for certain medicinal products for veterinary use, the environmental impact is not taken into account in the benefit/risk balance of the evaluation of medicinal products for human use, which is based solely on criteria of efficacy and safety. We believe that this may change in the future, as we gain knowledge on the environmental risks of medicines[38]. In addition, another aspect to consider is that all drugs marketed before that date (October 30, 2005) are exempt from submitting this environmental impact report in the renewal of their marketing authorization, so the information available about many of the drugs currently used is scarce or non-existent. For some drugs, such as fluoxetine, an ERA is published many decades after its authorization[50]. Another aspect is that current ecotoxicological tests demanded by the EMA do not include behavioral tests. Some authors propose updating the demanded tests in order to incorporate these kind of ecotoxicological tests[21]. Currently, the regulation of ERAs for medicines for human use is under review. It seems that some changes will occur, specifically in terms of bioaccumulation and fundamentally endocrine disruptors[51]. However, the legislation involved in Europe is varied, abundant, complex and not always easy to understand by non-experts in the field[52]. Another important issue is that legislation differs between countries, or is, directly, non-existent[53]. On the other hand, there are veterinary drugs used in pets, for which the environmental impact assessment is not considered in the benefit/risk balance either. There are authors who consider that this should change, taking into account the toxicity of some of the substances used and the increasing number of pets in our environment[54,55].

POSSIBLE SOLUTIONS

The study of the problem of drug pollution is among the priority lines of research of the main organizations dedicated to the protection of public and environmental health, such as the WHO and the European Commission. In this regard, it is worth highlighting the publication of the "Strategic approach of the European Union in the field of pharmaceutical products in the environment" by the European authorities, probably the front-runners in the field[56].

The contamination of the environment with pharmaceutical products is a complicated and diffuse problem that entails scientific uncertainties, a large number of stakeholders with different values and interests, and great complexity. This is probably why the Dutch government has classified it as a "wicked problem" (a

problem that is difficult or impossible to solve given that it presents incomplete, contradictory and changing requirements that are generally difficult to recognize). In their comprehensive strategy to face the problem, they have established that all agents involved in the complex life cycle of the drug should participate in the solution[57].

It is more than likely that in the future, as the detection of drugs and ecotoxicological studies progress, many drugs will end up being a priority in legislative matters, and that maximum concentration of certain drugs in wastewater may be established. We believe that we are on the verge of a revolution in the field of psychopharmacology[38].

At source measures

Before trying to improve the elimination processes of drugs once they reach the WWTP and the environment, it is probably reasonable to act at source. Considering that drugs have offered, and continue to offer, an unquestionable benefit to the health of humanity, great care must be taken not to restrict access to those drugs that are necessary. Here are some ideas that could help improve the problem.

Rational use of the drug, eco-prescription, or "green prescription"

The "Rational use of medicines" is a term coined by WHO experts more than 30 years ago, in 1985[58]. To date, the rational use of medicine has been defined as "patients receive the appropriate medication for their clinical needs, in the doses corresponding to their individual requirements, for an adequate period of time and at the lowest possible cost for them and for the community". This term has served as a conceptual framework of undoubted value to promote actions and strategies that have improved the health of countless patients, avoiding excesses in the use of medications, polypharmacy, *etc.* However, we believe that the term requires an update, so that the "One Health´s philosophy, which tries to achieve optimal health for people, animals and our environment taking into account the existing interrelations, is considered[59]. Currently this philosophy is already applied, but fundamentally to antimicrobials. We believe that broadening the approach is necessary. Reducing the inappropriate consumption of drugs will reduce their entry into ecosystems, improving people's health and that of the environment[60].

Christian Daughton, head of the American Environment Agency, now retired, proposed more than 5 years ago the term "eco-prescription", or "green prescription". Ultimately, it means that the prescriber should consider the characteristics and environmental behavior of drugs when prescribing them[10]. This is definitely going to be challenging. For example, oxazepam (not available in some countries such as Spain, but a common metabolite of numerous benzodiazepines commonly used in our setting), is considered a good choice for the elderly due to its adequate pharmacokinetic profile, since it is not eliminated by oxidative metabolism and is excreted unchanged in urine. However, it is a known to cause of potential toxic effects in fish, and can accumulate for decades without biodegrading. From an environmental point of view, substances that are metabolized to inactive metabolites prior to elimination may be preferable[10]. We believe that incorporating environmental criteria in the use of medicines is essential, and it may become a true revolution in pharmacotherapeutics [38].

Another interesting classification of drugs is the one proposed by the Swedish Environmental Research Institute. It is one of the few available classifications of drugs according to their environmental characteristics. It is an initiative of the Stockholm City Council, driven by the pharmaceutical industry. Each drug receives three scores, each of which can take a value from 0 to 3: one on its persistence in the environment (P); another on bioaccumulation (B) and another on toxicity (T). The overall score is the sum of the points obtained for each item[61].

Prescribers may incorporate this information when using drugs in individual patients. The "Wise List" (*Kloka Listan)*, is so far, the only multifaceted approach incorporating environmental aspects to recommend drugs in ambulatory care[62]. The chain approach of the Dutch Government also incorporates a "psychotropic task force" in order to reduce psychotropics in water[57]. We believe further research is urgently needed in this crucial area.

The design of more biodegradable and sustainable drug: "Green design"

An attractive idea for the future is to design greener and more biodegradable drugs; i: e: "benign by design" concept[63]. Although there are already some examples of the development of more "environmentally friendly" drugs, such as glufosfamide[64] and green drug delivery systems[65], no psychoactive drugs has been designed to be more biodegradable.

Furthermore, a holistic approach should be considered when evaluating the environmental impact of medicines, and other constituent parts of medicines ought to be taken into account apart from active pharmaceutical ingredients. We believe there is room for improvement in this specific area. For example, inhaled loxapine, a recently marketed antipsychotic for the treatment of agitation, requires a lithium battery for each dose administered. Another example would be Abilify Mycite®, in which an electronic circuit is excreted with each capsule administered[38].

Education

Until now, healthcare professionals who are in charge of prescribing, administering and dispensing drugs have paid little attention to the problem of drug contamination, which has been preferentially addressed by biologists, chemists and other professional profiles such as environmentalists. We firmly believe that this concern cannot be ignored anymore in the schools of Medicine, Pharmacy and Nursing[66]. Recent studies carried out in China have shown that awareness of the problem in both pharmacists[67] and prescribers[72] has a wide room for improvement. As proposed in the European Commission strategy[56], we believe that general education for both health professionals and citizens is a key element in the fight against drug pollution.

Improved waste management, responsible consumption

The incorrect management of pharmaceutical waste is one of the routes of entry of medicines into the environment. Studies indicate that up approximately 33% of patients do not use all the medicines dispensed, which generates a waste of health resources and possible environmental contamination[2]. The generalization of the adoption of refund schemes such as SIGRE, implemented in Spain, will be another key element. This is especially important in countries where waste management is not working well and where inappropriate drug disposal can be expected, such as regions form the Middle East, Asian and African countries[69]. Optimizing package sizes and extending drug expiration dates where possible will allow drugs that are still safe to use from being unnecessarily discarded. The idea of reusing drugs has also been proposed. In this regard, a survey conducted in the United Kingdom found that more than half of those surveyed would welcome the reuse of medicines in the future[70]. Although it is not legally accepted in many countries, it could help reduce the amount of unused medicine accumulation, a fact that can lead to overuse or incorrect use of medicines or also to incorrect disposal. However, obviously, considering security issues is mandatory if such policies are going to be implemented.

From a regulatory perspective, the European Parliament suggests that "eco-labeling" of pharmaceutical products with a high risk for the environment should be explored (Figure 2), as is already done with other products in the market[71].

Legislation

As knowledge about the environmental impact of pharmaceuticals keeps mounting up, ERAs need to update accordingly to improve our capability of correctly assessing the risk posed. It is interesting to highlight that last year, venlafaxine and desvenlafaxine were considered as suitable for inclusion in the next "Watch List" (WL): under the European Union Water Framework Directive[72]. These antidepressants are the first psychoactive drugs ever to be included in such a list[73].

End of pipe measures

Apart from implementing at source measures, it is essential to address the problem of waste already generated. Taking into account the growing consumption of drugs at a global level, the research and development of new purification systems (biological, physico-chemical) that eliminate these residues efficiently and at a sustainable cost should be a priority.

Improvement of WWTPs

The design of purification systems requires prior knowledge of the physical-chemical characteristics of the effluent wastewater and of the concentration of the main eliminated drugs, especially those that represent a greater risk for the environment.

For example, in order to optimize costs, various authors propose eliminating drugs at the hospital wastewater effluent instead of treating the total amount of water reaching WWTPs, since hospitals are the main consumers of certain types of pharmaceuticals (some cytostatics, broad-spectrum antibiotics, iodine contrasts). There are already interesting initiatives such as the one implemented at the Herlev Hospital in Copenhagen, Denmark, where improved treatment of hospital wastewater is

Figure 2 Will we see drugs with eco-label?

performed on-site to effectively remove all drugs before they reach the municipal WWTP[74].

Anther strategy is that carried out by Switzerland, a country in which all treatment plants from a certain size are going to be improved (through tertiary treatment with ozone and activated carbon) to effectively eliminate drugs and other emerging contaminants, at an approximate cost of 1 billion euros[75]. However, this strategy is probably not sustainable or applicable to most countries. On the other hand, ozonation can oxidize drugs producing new transformation products with poor known ecotoxicological effects[76].

New methods that improve the performance of WWTPs in the elimination of drugs continue to be studied and sought. A curious method is the use of xylophagous fungi (*white rot fungi*) of which the species most used to date is *Trametes versicolor*. These fungi, in charge of degrading soil organic matter in nature, possess enzymes, called "laccases" with the capacity to oxidize a wide spectrum of organic substances, including drugs[77].

Eco-pharmacovigilance, environmental pharmacovigilance

In the 1960s, the use of thalidomide was used for the treatment of nausea and vomiting in pregnant women. Later, the drug proved to be teratogenic, producing thousands of newborns malformations. This disaster gave rise to the modern pharmacovigilance systems currently in place. Since the ecological disaster produced by diclofenac in the Indian subcontinent, various authors have asked to create a new discipline, *i.e.*, "Eco-pharmacovigilance" or "environmental pharmacovigilance"[78]. This discipline will dedicate to "monitor" the environmental impact of drugs[79]. Will be ever witness a market withdrawal of an antidepressant or an antipsychotic, or any other drug, because of environmental factors in the future? May be.

Phytoremediation

From the point of view of environmental drug contamination, the accumulation of drugs by plants can be harmful (in the case of agriculture) or beneficial, if done on purpose. Phytoremediation is a technology that uses plants and the associated microorganisms of the rhizosphere (zone of interaction between plant roots and soil microorganisms) to eliminate, transform or contain toxic chemicals located in soils, sediments, groundwater and surface waters, among others. Different species of plants have been used for the treatment or removal of a variety of pollutants such as oil, chlorinated solvents, pesticides, metals, radionuclides, explosives and pharmaceuticals [80]. The design of constructed wetlands, a technique than can be employed for the removal of pharmaceuticals from wastewater, has received particular attention[81]. It is interesting to verify that the detoxification mechanisms used by plants, are sometimes surprisingly similar to those of mammals, as in the case of glutathione conjugation of paracetamol in the *Brassica juncea* plant[82].

CONCLUSION

So far, the problem of drug pollution has been largely ignored by healthcare professionals and academics. However, if the problem is to be dealt with effectively, an interdisciplinary approach will be necessary, allowing integration of the knowledge of the different agents involved[38].

In conclusion, drug pollution with psychiatric drugs is a problem of emerging concern. This complex problem involves many stakeholders with different values and interests. Solutions can be implemented at source, before drugs reach the environment: using medicines more rationally, prescribing greener drugs, or designing pharmaceuticals that are more easily biodegradable. Besides, end of pipe measures, such as the development of new, sustainable purification systems will also be crucial. Finally, educating both health professionals and citizens, and collaboration between environmental and healthcare sciences is going to be essential.

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MINIREVIEWS

Connecting brain and body: Transdiagnostic relevance of connective tissue variants to neuropsychiatric symptom expression

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Abstract

The mind is embodied; thoughts and feelings interact with states of physiological arousal and physical integrity of the body. In this context, there is mounting evidence for an association between psychiatric presentations and the expression variant connective tissue, commonly recognised as joint hypermobility. Joint hypermobility is common, frequently under-recognised, significantly impacts quality of life, and can exist in isolation or as the hallmark of hypermobility spectrum disorders (encompassing joint hypermobility syndrome and hypermobile Ehlers-Danlos syndrome). In this narrative review, we appraise the current evidence linking psychiatric disorders across the lifespan, beginning with the relatively well-established connection with anxiety, to hypermobility. We next consider emerging associations with affective illnesses, eating disorders, alongside less well researched links with personality disorders, substance misuse and psychosis. We then review related findings relevant to neurodevelopmental disorders and stress-sensitive medical conditions. With growing understanding of mind-body interactions, we discuss potential aetiopathogenetic contributions of dysautonomia, aberrant interoceptive processing, immune dysregulation and proprioceptive impairments in the context of psychosocial stressors and genetic predisposition. We examine clinical implications of these evolving findings, calling for increased awareness amongst healthcare professionals of the transdiagnostic nature of hypermobility and related disorders. A role for early screening and detection of hypermobility in those presenting with mental health and somatic symptoms is further highlighted, with a view to facilitate preventative approaches alongside longer-term holistic management strategies. Finally, suggestions are offered for directions of future scientific exploration which may be key to further delineating fundamental mind-body-brain interactions.

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Core tip: The association between vulnerability to psychological or psychiatric symptoms and hypermobile joints may initially appear counterintuitive to many clinicians. However, a relationship with anxiety is consistently confirmed across multiple studies worldwide. In this narrative review, we appraise increasing evidence linking neuropsychiatric presentations to hypermobility across the lifespan, including emerging links to neurodevelopmental disorders and stress-sensitive medical conditions. We discuss pertinent mechanistic insights in the context of growing understanding of mind-body interactions. We offer direction for future research and highlight implications for clinical practice, notably roles of timely screening and detection alongside longer-term holistic management strategies.

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INTRODUCTION

There is a rapidly growing body of evidence showing a curious excess of psychiatric burden among individuals with joint hypermobility. Common constitutional variants of connective tissue often present as joint hypermobility, reflecting increased laxity of ligaments and extended movement of joints beyond typically 'normal' limits (otherwise described as joint hyperlaxity, being double-jointed)[1]. Internationally, joint hypermobility is found in up to 20% of the general population, and is influenced by age, sex and ethnicity; hypermobility is more frequent in children, with higher prevalence in women, and Asian and African populations[2]. Hypermobility is also highly heritable, and has been proposed to be an autosomal dominant trait with incomplete penetrance, variable expressivity and influenced by sex[3]. The epidemiological characterisation is influenced by clinical definitions and assessment tools; the 9-point Beighton score is used most frequently to assess hypermobility in both clinical and research settings, although other methods include the Hospital del Mar criteria [4], and self-administered hypermobility questionnaires.

Hypermobility is a descriptive term and might exist as an asymptomatic and isolated feature. However, neuropsychiatric symptoms are among extra-articular manifestations that frequently accompany more widespread musculoskeletal symptoms that typically co-occur with hypermobility. In these cases, hypermobility appears as one feature of a multisystemic disorder[3]. This complexity is reflected in the current debate concerning terminology and classification: A consensus group in 2017 introduced the concept of hypermobility spectrum disorders (HSD); encompassing a continuum including hypermobile Ehlers-Danlos syndrome' (hEDS, previously EDS-HT), joint hypermobility syndrome [JHS, previously diagnosed according to the Brighton Criteria – Revised (1998)][5] and symptomatic hypermobility not fulfilling stricter criteria for other associated syndromes[6]. Diagnostic classification remains a contentious area, particularly since reliable genetic tests or physiological markers for HSD are presently lacking, so diagnosis relies solely on clinical criteria[6]. Hypermobility may also signal the presence of other heritable disorders of connective tissue including Marfan syndrome, osteogenesis imperfecta and Ehlers-Danlos syndromes which have a more clearly defined genetic basis[7]. Here, we review literature across a broad terminology referring to joint hypermobility and related syndromes.

Joint hypermobility is frequently under-recognised[3] and has a significant impact on quality of life across all age-groups[8,9]. Anxiety symptoms and disorders have a well-established link with hypermobility, yet growing evidence also now points

towards associations across psychiatric diagnoses, notably with affective illnesses, increasingly with neurodevelopmental disorders and with stress-sensitive medical conditions, including fibromyalgia, myelo-encephalomyelitis/chronic fatigue syndrome (ME/CFS) and irritable bowel syndrome (IBS). Awareness of these relationships are important to enhance understanding of early risk factors to allow screening and timely intervention for vulnerable individuals. The value of such a strategy is illustrated by a recent longitudinal study, which demonstrated that hypermobile children at age 14 years were more likely to suffer from anxiety and depression by age 18 years[10]. Increasing clinicians' awareness of the multisystemic features associated with hypermobility, especially psychiatric morbidity, will enable appropriate detection, diagnosis, and preventative intervention and can shape the implementation of effective longer-term holistic management strategies.

This paper presents a comprehensive narrative review of existent clinical knowledge and empirical evidence regarding the association of hypermobility with psychopathology. We also present a broad perspective on this expression of body-brain-mind interactions, including current mechanistic understanding, and we highlight implications for clinical practice and directions of future research.

LITERATURE SEARCH

This is a narrative review based on a comprehensive search of online databases (including MEDLINE, Embase and PsychInfo). Search terms included were 'hypermobility' and 'joint laxity' combined with each diagnostic category. This search comprised studies published from 1980 to 2021. Reference lists of identified papers were further scrutinised for additional relevant articles.

RESULTS

Anxiety

The expression of anxiety in the context of joint hypermobility was first recognised in the late 1980s. Subsequent research has repeatedly demonstrated this association, which has been the subject of several substantive reviews (for example[11]). Anxiety disorders are the most prevalent set of psychiatric illnesses[12], and hypermobility is most strongly linked to the expression of panic disorder and agoraphobia[13]. Moreover, state anxiety is a transdiagnostic symptom that is pervasive across distinct psychiatric disorders; even in non-clinical populations, hypermobility predicts elevated levels of trait and state anxiety, without necessarily reaching formal thresholds for anxiety disorder[14]. This pattern has been observed in the elderly[15] and in children, including both clinical[16,17] and non-clinical cohorts[18].

Affective disorders

Hypermobility is becoming a recognised vulnerability factor for affective disorders, particularly depression, especially if comorbid anxiety is present[19,20]. Patients with clinically significant hypermobility (*i.e.*, HSD/hEDS) demonstrate higher rates of depressive disorders (for example[21]), recently summarised in a meta-analysis[13] although there some inconsistencies within the literature[22]. A population-wide study, using Swedish national registries, observed a heightened risk of depression and increased rates of attempted suicide among hypermobile (EDS and HSD) individuals and their siblings[23]. Hypermobility is also associated with elevated self-report depressive symptoms in non-clinical populations[24]. There are a number of reasons why hypermobility may be linked to depression, and in many cases it is unclear whether studies have effectively controlled for anxiety, which could act as an explanatory mediator between hypermobility and depression, since these two conditions are highly comorbid. Other potential mediating factors common to both HSD/hEDS and depression include chronic pain, fatigue or impaired sleep[25].

An increased risk of bipolar affective disorder (BPAD) is also reported in individuals with ESD/HSD (relative risk, RR = 2.7)[23]. In this study, no difference in rates of schizophrenia were observed between people with and without hypermobility. Similarly, hypermobility is over-represented in patients with BPAD diagnosis attending a psychiatric outpatient setting[26]. However, further detailed studies are lacking, and the potential mediating role of other conditions, such as attention deficit hyperactivity disorder (ADHD; see below), are as yet unexplored.

Thus the link between hypermobility and BPAD remains preliminary.

Eating disorders

There are several case series and reports that describe the co-occurrence of EDS and eating disorders (reviewed in[27]). Elevated rates of hypermobility occur in both psychiatric outpatients with eating disorders[27] and in hospitalised in-patients with anorexia nervosa[28], who experienced excess gastrointestinal symptoms, orthostatic intolerance and fatigue (symptoms common to HSD/hEDS). A higher lifetime prevalence of eating disorder was also demonstrated in students with non-clinical hypermobility[29]. However, large and comprehensive epidemiological studies investigating this proposed link are lacking.

Mechanistically however, a proposed model of the relationship between eating disorders and HSD/hEDS recognises the contribution of both articular (such as temporo-mandibular disorders) and extra-articular features (including gastrointestinal problems, smell and taste abnormalities, dental problems, oral mucosal fragility) to difficult or painful eating, which reinforce dysregulated eating behaviour and associated weight loss[27,29]. Thus HSD/hEDS can plausibly contribute to, mask or even be misdiagnosed as an eating disorder.

Psychosis

The link between hypermobility and schizophrenia-type psychosis remains much less apparent than that seen in relation to anxiety, affective and eating disorders. One case-control study reported similar prevalence of HSD/hEDS in patients with schizophrenia and controls[30], a finding that was confirmed in a population matched cohort study[23]. Even in psychiatric outpatients, schizophrenia was reported to be negatively associated with hypermobility[26]. Nevertheless, hypermobility is implicated as a clinical marker for co-morbid anxiety in schizophrenia: Patients with comorbid hypermobility and schizophrenia express elevated rates of panic/agoraphobia disorder, exacerbating positive psychotic symptoms[31].

Personality disorder

Only one case-control study to date has investigated personality disorder in hypermobility, revealing elevated prevalence of personality disorder in JHS (RR = 5.8), especially of the obsessive-compulsive (anankastic) subtype[21]. It was speculated that that joint instability and associated imprecision of proprioception might underlie compensatory over-controlling behaviours (in the context of anxiety), and even that unrecognised JHS can contribute to perfectionism. However, rates of hypermobility were reported elsewhere to be no different in psychiatric outpatients with or without personality disorder[26]. While a number of possible putative mechanisms might link hypermobility to personality disorder (including anxious temperament and/or neurodevelopmental conditions including as ADHD), these findings should be interpreted cautiously, as there is an obvious need for large and well powered studies.

Addictions/substance misuse

Studies investigating addiction and substance misuse in the context of hypermobility are sparse. Early findings of elevated hypermobility scores in female chronic alcoholic patients[32] have not been replicated since. One longitudinal study revealed significantly higher prevalence of at-risk drinkers and smokers in young females with hypermobility compared to controls[33]. It is possible that alcohol and tobacco use could be overused to cope with chronic pain and anxiety (or indeed to self-medicate against ADHD symptoms, see below) and further studies should evaluate and control for these variables.

Neurodevelopmental disorders

In recent years, several authors have highlighted a relationship between hypermobility and neurodevelopmental disorders, notably autism (autistic spectrum disorders, ASD), ADHD and developmental coordination disorder (DCD)[34,35]. Interest in tic disorder (Tourette syndrome) and hypermobility is also growing. Hypermobility is frequently co-morbid with neurodevelopmental disorders and may contribute to the accompanying physical behavioural and cognitive symptoms that encompass motor difficulties, sleep and feeding problems, sensory hypersensitivities, behavioural hyperactivity, inattention, dysexecutive issues, speech and language problems and social deficits. Neurodevelopmental disorders most often present in school age children, and thus may precede or overshadow recognition of comorbid HSD/hEDS [35]. Nevertheless, these two clinical entities retain their association through into

adulthood[26,36]. Interestingly, however, subclinical expression of neurodevelopmental (ADHD, ASD or DCD) traits in the general population are not strongly associated with hypermobility, suggesting that the expression of this association is limited to clinical populations[37].

Autism: Evidence for an overlap between hypermobility and autism is growing. Initially described in case reports (reviewed in[38]), excess hypermobility has since been demonstrated in children with ASD (average age 4 years) in a case-control study [39], although differences in passive muscular tonicity may be a confound[40]. At a population-level, elevated rates of ASD is apparent in individuals with EDS/JHS and their siblings[23]. Both ASD and HSD/hEDS are considered heritable spectrum disorders that appear in infancy and share clinical presentations that include motor and coordination difficulties, sensory hypersensitivity/hyperalgesia, autonomic dysfunction, proprioceptive impairments and sleep disorders[34]. This has led to the suggestion that EDS/HSD might be considered as a subtype of ASD[34].

Furthermore, there has been longstanding recognition of the positive association between ASD and heritable disorders of connective tissue including Marfan's syndrome[41] and osteogenesis imperfecta[42]. ASD is known to be associated with several genetic causes, the most common being Fragile X syndrome (caused by mutations in *FMR1* gene). Up to half of patients with Fragile X syndrome are hypermobile. Soft skin, scoliosis and flat feet are common, providing further evidence for variant of collagen or related connective tissue[43]: The gene *FMR1* negatively regulates protein translation, which theoretically could cause downstream effects on collagen formation[43]. More broadly, across monogenic genetic syndromes strongly associated with both ASD and hypermobility, and known genetic causes of EDS subtypes, analyses of gene interactions reveal extensive gene clustering that might represent a biological mechanisms for the observed clinical overlap[34].

ADHD: Increasing clinical awareness of the co-occurrence of ADHD and hypermobility was confirmed by two case-control studies[44,45] and a population based cohort study[23], which also demonstrated higher rates of ADHD in siblings of children with HSD/hEDS diagnosis. Co-occurrence of ADHD and HSD/hEDS is also seen in adults[36,46].

DCD: According to DSM-5[47], EDS/JHS is included both as a differential diagnosis and as a potential comorbidity of DCD (previously termed developmental dyspraxia) in acknowledgement of the functional and clinical similarities[48]. High rates of symptoms related to HSD/hEDS are found among patients with DCD diagnosis, including pain and autonomic dysfunction, and there are significant commonalities in their motor features[48].

In children with HSD/hEDS diagnoses, high rates of clumsiness, impaired coordination and dyspraxia are observed[49], and up to 55% meet DCD criteria[50,51]. Similarly, 46%-64% of children with DCD are hypermobile[52,53], the exact figure depending on appropriate use of age appropriate Beighton score cut-offs[51].

Developmental tic disorder (Tourette syndrome): Despite emergent evidence describing hypermobility in ASD, ADHD and DCD, data concerning neurodevelopmental tic disorders (such as Tourette's syndrome) are remarkably lacking. To our knowledge, no current data have assessed this relationship in children. The first work in adults found elevated prevalence (38%) of hypermobility amongst 24 adults with Tourette syndrome[36]. Interestingly, these individuals had a high comorbidity of obsessive-compulsive disorder diagnoses (37.5%), another condition which is yet to be investigated with respect to hypermobility.

Stress medical sensitive conditions

Fibromyalgia and ME/CFS: Fibromyalgia and ME/CFS are both common overlapping disorders characterised by chronic pain, fatigue, sleep disturbance, cognitive complaints, gastrointestinal disturbance and affective problems.

There is further overlap of symptomatology and clinical findings with HSD/hEDS [54]. High rates of hypermobility are present in patients with fibromyalgia both as adults[55] and children[56], and in patients with ME/CFS, again both in adults[57] and children[58]. Hypermobility is specifically linked to the expression of pain and fatigue in these patients[59]. Conversely, the majority of EDS patients suffer from marked fatigue[60]. In fact, many patients with HSD/hEDS meet Fukada criteria for diagnosis of CFS[50], and hence it is argued that an assessment for hypermobility/variant connective tissues should be an integral part of a thorough evaluation of ME/CFS[61].

IBS and functional gastrointestinal disorders: Gastrointestinal symptoms (including nausea, abdominal pain, bloating, constipation and diarrhoea) are commonly experienced by patients with HSD/hEDS diagnosis[62]. Objectively, gastrointestinal dysmotility is observed[63] and is predicted by the symptoms and signs of dysautonomia, notably the occurrence of postural tachycardia syndrome (PoTS). Interestingly, psychiatric disorders, especially mood and somatoform disorders, occur at higher rates in patients with HSD/hEDS who experience gastrointestinal dysfunction and associated abdominal pain[64].

The prevalence of hypermobility appears to be greater in patients with IBS or gastrointestinal symptoms (especially functional dyspepsia) when compared to healthy controls[65]. This represents a subgroup (even variant phenotype) of patients who experience primary gastrointestinal problems with co-existing HSD/hEDS, who also demonstrate high comorbidity with chronic pain and fibromyalgia. These patients show increased somatisation score, urinary autonomic (symptom) score and reduced pain-related quality of life[66]. High rates of hypermobility are particularly observed in patients with constipation-predominant IBS[67], consistent with perturbation of colonic sensorimotor biomechanics consequent upon variant connective tissue.

However, while in adults the association between hypermobility and functional gastrointestinal disorders appears relatively robust, in children there is increasing evidence that the prevalence of hypermobility is similar for children with IBS, functional abdominal pain or functional constipation, and for healthy controls[68-70]. Intriguingly, this suggests that, in hypermobile individuals, IBS and functional GI symptoms may develop later in life perhaps interacting with hormonal or other maturational changes that impact connective tissue compliance.

Other associated stress-sensitive medical conditions: There are reports demonstrating that HSD/hEDS is also associated with increased risk of migraine (in females)[71], and with chronic regional pain syndrome[72], chronic myofascial pelvic pain[73], and stress incontinence[74].

DISCUSSION

The 'biopsychosocial approach' in psychiatry acknowledges the contribution of interconnected and interacting influences on the development and maintenance of psychiatric symptoms and diagnoses, including biological vulnerabilities, psychological factors and dynamic social context. The associations highlighted within this review, linking psychiatric symptoms and conditions to constitutional differences in connective tissue (apparent, in part, as joint hypermobility), likely depend on multiple mechanisms, which may differ between disorders. Hypothetically, joint hypermobility may represent a non-specific signature of a general mechanism linking variant connective tissue to psychological vulnerability, manifesting in a continuum across neurodevelopmental and psychiatric disorders. Alternatively, a pre-existing pathological process (as yet undiscovered) could predispose to both psychopathology and hypermobility in parallel *via* independent actions on the musculoskeletal and central nervous systems (Figure 1).

Psychosocial factors

Through lived experience, the presence of hypermobility from early childhood may directly underpin the development of psychiatric disorders. Excluding neurodevelopmental conditions, this makes temporal sense: The presence and consequences of hypermobility in childhood precedes the typically later emergence of psychiatric disorders in adolescence and adulthood. When symptomatic from a young age, the daily challenges of living with physical risks and difficulties associated with HDS/hEDS (including chronic pain and disability, threat of injury secondary to connective tissue fragility, restriction of social and physical activities and associated stigma) contribute to psychiatric vulnerability, avoidant behaviours and the development of anxiety and depressive symptoms[75].

Correspondingly, intense fear of pain and subsequent pain-avoidant strategies that limit movement (kinesiophobia) are common in HSD/hEDS[76]. These increase the likelihood of deconditioning and symptom progression, thereby furthering physical and psychological disability. In addition, problematic hypermobility is typically under-recognised and diagnostic delay is common[3]. Consequently, patients may experience frustration if their complaints are trivialised by healthcare professionals, adding to suffering and exclusion[75]. High anxiety and distress may drive

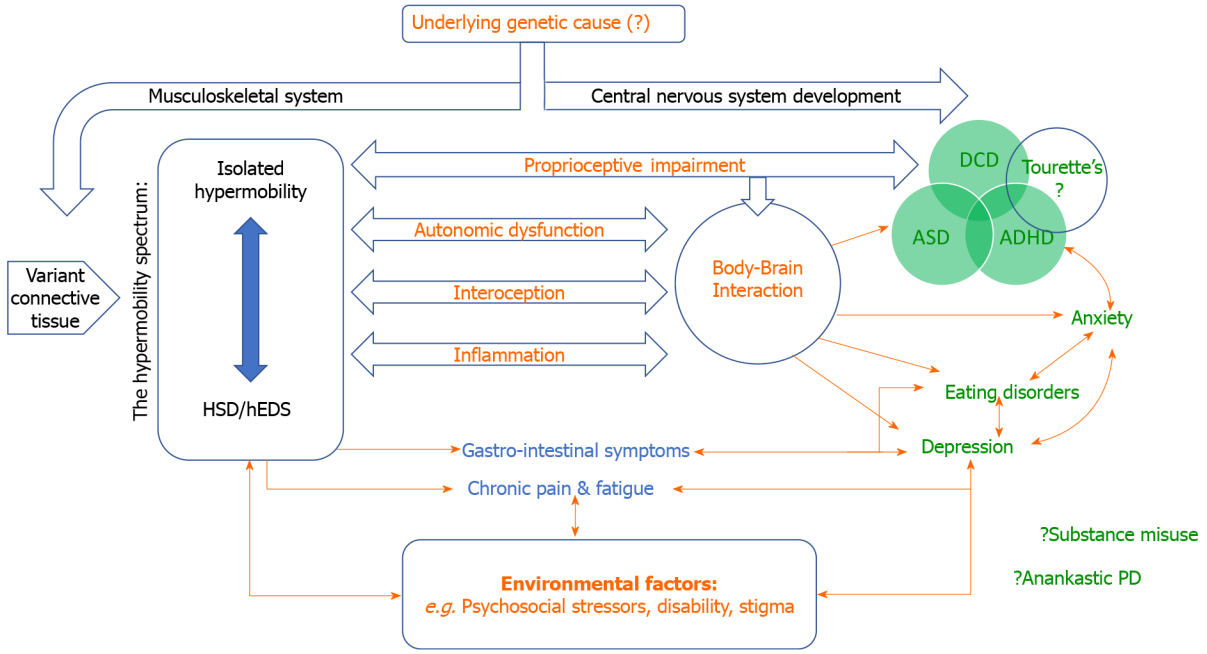

Figure 1 Diagram illustrating possible pathways for the aetiopathogenesis of psychiatric disorders in joint hypermobility. Orange text: Putative mechanisms; Blue text: Symptoms related to Hypermobility Spectrum Disorders/hypermobile Ehlers-Danlos Syndrome; Green text: Psychiatric and neurodevelopmental disorders. ASD: Autism spectrum disorder; ADHD: Attention deficit hyperactivity disorder; DCD: Developmental coordination disorder; PD: Personality disorder.

maladaptive behaviours including tobacco/alcohol use and disordered eating[33], and the psychosocial complexity surrounding hypermobility is associated with poorer quality of life in both adults[8] and children[9]. In hEDS patients, the psychological expression of high anxiety interacts with more severe fatigue and depressive symptoms, pain catastrophising, somatosensory amplification, to predict poorer social functioning and worse general health[20].

The bidirectional interaction between pain and psychological ill-health is widely recognised; chronic pain influences psychiatric symptoms including depression and anxiety, while low mood and negative emotions increase and maintain the experience of pain[77]. In this context, psychiatric disorders in HSD/hEDS may be secondary to pain symptoms rather than a primary or parallel manifestation. Hypermobility is a risk factor for chronic widespread pain[78], and hypermobile individuals exhibit sensory hypersensitivity to nociceptive stimuli[79] and secondary central sensitisation [80]. In fact, the presence of pain, rather than the degree hypermobility, is associated with the expression of psychiatric symptoms in EDS patients[81]. Similarly, the experience of pain and gastrointestinal dysfunction, rather than connective tissue features *per se*, is associated with higher rates of psychiatric disorders (especially mood and somatoform conditions) in HSD/hEDS patients[64].

Genetic factors

The relationship with pain is more nuanced; rates of psychiatric disorder are higher for HSD/hEDS than for other chronic pain conditions[13]. Thus, psychosocial theories fail to explain the full extent of all associations between hypermobility and psychopathological distress. This is particularly evident when considering neurodevelopmental disorders and in individuals with seemingly expressing sub-syndromic and isolated hypermobility. Instead, alternate theories propose that a common set of pathological mechanisms fundamentally predispose to the expression of both hypermobility and psychopathological symptoms (for example, as genetic pleiotropy).

There is interesting evidence from animals: Hypermobility is linked to exaggerated reactivity of behavioural/emotional arousal and excitability in dogs[82]. This finding suggests that the link between joint hypermobility and the affective control of bodily arousal is a universal transdiagnostic trait in mammals, influencing the expression of anxiety and behavioural responses. Moreover, such findings argue against conscious awareness and social implications of living with physical symptoms as a primary driver for the raised levels of psychopathology associated with hypermobility.

Genetic and/or early environmental influences are suggested by the increased risk of psychiatric disorders observed in the (unaffected) first-degree relatives of HSD/hEDS patients[23]. However, unlike other heritable disorders of connective tissue and EDS subtypes, genetic origins for HSD/hEDS remain poorly understood[3]. Previous identification of a genetic anomaly common to both anxiety and hypermobility, a duplication within chromosome 15, failed confirmation in subsequent studies[83]. A promising link has been noted between EDS and the gene TNXb (6p21.33), encoding the extracellular matrix glycoprotein *Tenascin-XB*, which is directly involved in connective tissue structure[84]. This molecule was recently identified as integral in enteric motor neurons and influencing nociceptive sensory neurons[85] and is expressed in the brain, suggesting further roles within the central nervous system. The extracellular matrix plays a critical role in both variant connective tissue and central nervous system development, and so alterations could predispose to abnormalities across central and peripheral systems[86].

Autonomic dysregulation and interoception

HSD/hEDS frequently co-occurs with autonomic dysfunction commonly experienced as symptoms of orthostatic intolerance and, in severe cases, PoTS[87]. The diagnosis of PoTS focuses on the characteristic elevation of heart rate during postural change and accompanying orthostatic intolerance[88]. The widespread presence of variant connective tissue is implicated as one potential physiological mechanism for the overlap between HSD/hEDS and dysautonomia. Within blood vessels, more compliant connective tissue may cause abnormal vascular reactivity, notably increased venous pooling on standing, which reduces venous return. Heart rate acceleration and a secondary hyperadrenergic state would thus result[87].

There is significant phenomenological overlap between symptoms of anxiety and panic and the symptoms of autonomic disfunction in orthostatic intolerance and PoTS: Physical symptoms include palpitations, breathlessness and dizziness[88], and these themselves could trigger and amplify anxiety states or be misperceived or diagnosed as panic attacks. Enhanced bodily awareness (described below) may be both a consequence and maintaining factor for such experiences, since altered autonomic reactivity will influence emotional state and vulnerability to psychiatric disorders[89]. Autonomic dysfunction is also demonstrable in children with neurodevelopmental conditions linked to hypermobility, notably ASD[90] and ADHD[91]. Again, there is symptomatic overlap between PoTS and ASD in both affective symptoms and sensory sensitivities[34]. The causal relationship between altered autonomic function and neurodevelopmental phenotypes remains unclear but evidence for an interactive association continues to grow.

Interoception refers to the afferent signalling to brain of changes in the internal physiological state of the body, and the perception of these changes. Interoceptive signals therefore represent the sensory limb of autonomic control loops (*e.g.*, the baroreflex), yet also reach perceptual awareness as physiological feelings including palpitations, nausea and arousal. In this way, interoceptive signals can guide motivation behaviour and are fundamental components of emotional feeling states. Central interoceptive representation and/or misinterpretation of dysregulated peripheral autonomic function may underpin the generation of a range of symptoms associated with hypermobility[92]. Dysregulated interoceptive processes are implicated in the expression of specific psychiatric symptoms, particularly anxiety [92]. Hypermobile individuals demonstrate enhanced subjective sensitivity to internal bodily sensations[93] and in more objective measures of detecting interoceptive signals. These differences are shown to mediate the relationship between state anxiety and hypermobility[94] and offer a potential treatment target for intervention.

Neuroimaging studies in hypermobile individuals reveal structural[93] and functional brain differences[94] notably within brain systems critical to emotional processing and anxiety[95], including regions such as insular cortex, that are also specifically implicated in interoceptive representation[94]. However, much of this work has been conducted in sub-clinical cohorts. While findings endorse a potential autonomic/interoceptive basis to vulnerability to anxiety and other neuropsychiatric symptoms, further work is needed to map these relationships in patients with psychiatric disorders in the context of hypermobility and to dissect levels of putative interoceptive dysfunction.

Immune dysregulation

Extensive bi-directional communication exists between the brain and the immune system and, increasingly, immune mechanisms are implicated in the pathogenesis of psychiatric disorders[96]. A specific association appears to exist between immune

system and hypermobility: Mast cell related disorders (giving allergy-like symptoms often across multiple organ systems) are commonly reported in patients with EDS/hEDS, highlighting a deep interrelationship between connective tissue and immune function occurring across genetic, molecular and physiological levels[97]. The concurrent expression of connective tissue impairments and immune dysfunction is speculated to influence vulnerability to psychiatric disorders. This may extend to neurodevelopmental disorders[34], as recent evidence highlights immune dysregulation in ASD[98].

Proprioceptive abnormalities

Abnormal proprioception is observed in both hypermobility and neurodevelopmental disorders and may account for their association[38]. Symptoms of both are present from early in childhood and appear highly heritable. Impaired proprioception particularly affects the lower limbs of children and adults with HSD/hEDS[99] and often leads to issues with coordination, balance, clumsiness and motor problems. Poor proprioception may directly account for the relationship between hypermobility and DCD[100]. Moreover, it is speculated that maintaining motor competences despite impaired proprioceptive function may overload executive functions and compete for attentional resources. This may in turn reinforce inattention in ADHD[101], and could further impact the timely acquisition of social and communication skills, thereby exacerbating ASD traits[34].

Implications for practice

We echo other authors calling for widened awareness of the diverse manifestations of hypermobility, particularly in psychiatry[34]. A recently proposed 'neuroconnective phenotype' model usefully describes the symptom profiles often expressed by people with hypermobility, including behavioural, psychopathological, somatic symptoms, somatosensory symptoms and somatic illness[11]. Considering the evidence presented here, we recommend vigilance for potentially overlooked mental health symptoms within the plethora of difficulties faced by patients living with HSD/hEDS. These should be part of a holistic clinical formulation that can enable appropriate psychoeducation, referral to mental health services, prompt diagnosis and access to optimal treatments.

Alongside this, we recommend screening for hypermobility, particularly in those presenting with neurodevelopmental disorders, but also in other mental health presentations, notably of panic and anxiety, in the context of physical symptoms, since articular and extra-articular features are often present[102] (Table 1). Simple screening using a 5-point questionnaire can detect hypermobility with high sensitivity and specificity[1] (Table 2). Early assessment can prompt referral to specialist services and thus reduce delayed or misdiagnosis of HSD/hEDS. It also widens opportunities for early intervention to prevent progression of psychological as well as physical symptoms throughout the lifespan.

Currently, there no specific guidelines for the psychological or pharmacological management of psychiatric conditions in patients with HSD/hEDS. Nevertheless, considering the complex difficulties faced by these patients, we recommend multidisciplinary management across mental and physical health professionals, including early involvement of physiotherapy to facilitate improvement of proprioception and bodily awareness[19].

Limitations

One considerable limitation in evaluating the growing evidence base describing the association between joint hypermobility and psychiatric disorder is the variable use of assessment tools to measure hypermobility. Specific genetic tests or biomarkers do not exist. The use of assorted self-report questionnaires and distinct clinical assessment scales is liable to subjective interpretation and observer dependence, limiting reliability. Furthermore, the application of age-dependent cut-off scores remains controversial. Our review has considered articles covering the whole spectrum of hypermobility and related disorders yet highlights the need for further disentangling research.

Nevertheless, individuals with higher anxiety and more severe symptoms are more likely to seek medical attention, join patient support associations and participate in research studies, even among 'non-clinical' populations. Those recruited may be experiencing higher distress, and hence introduce sampling bias. Published studies may therefore overlook (and over-pathologise) the spectrum of hypermobility presentations.

Table 1 Indications prompting screening for hypermobility spectrum disorders/hypermobile Ehlers-Danlos syndrome amongst patients presenting to mental health services (adapted from Ross and Grahame 2011[102])

	Extra-articular features	Articular features
In children and adolescents	Prolonged fatigue or tiring easily	Joint dislocations/subluxations (including congenital hip dislocation)
	Poor motor coordination or 'clumsiness' (such as poor ball catching and poor handwriting)	Recurrent ankle sprains
	Chronic widespread pain or 'growing pains'	
	Delayed walking, with bottom shuffling instead of crawling	
In adults	Prolonged unexplained fatigue (including ME/CFS)	Recurrent joint dislocations
	Chronic widespread pain, particularly if unresponsive to analgesia (including fibromyalgia)	Multiple soft tissue injuries/rheumatisms
	Functional gastrointestinal disorders (such as IBS, functional dyspepsia, constipation)	Premature osteoarthritis
	Autonomic dysfunction (such as orthostatic intolerance or PoTS)	Persistent or recurrent joint pains
	Progressive loss of mobility secondary to pain or pain-avoidance strategies	
	Laxity in supporting tissues (such as hernias, varicose veins, pelvic floor dysfunction)	
	Soft/hyperextensible skin, unexplained striae, easy bruising	

ME/CFS: Myelo-encephalomyelitis/chronic fatigue syndrome; IBS: Irritable bowels syndrome; PoTS: Postural tachycardia syndrome.

Table 2 Five-point screening questionnaire for detecting hypermobility (from Hakim and Grahame 2003[1])

1 Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2 Can you now (or could you ever) bend your thumb to touch your forearm?
3 As a child, did you amuse your friends by contorting your body into strange shapes OR could you do the splits?
4 As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
5 Do you consider yourself 'double-jointed'?
Answering yes to two or more questions suggests hypermobility with sensitivity 80%-85% and specificity 80%-90%

Future research

There is strong evidence linking the expression of mental health disorders to hypermobility as a signature of variant connective tissue. However, future research is needed to investigate the genetic, neural and psychophysiological mechanisms for such mind-body interactions. Longitudinal studies are needed to better identify which hypermobility individuals develop psychiatric symptoms or diagnoses to delineate contributions of precipitating, perpetuating, and preventative factors and map how these progress with time. Such fresh insights offer the potential for the implementation of early preventative strategies in at-risk individuals, minimising complications in later life.

We argue that variant connective tissue contributes to the pathogenesis of mental health disorders: This likely represents an 'endophenotype'; a measurable component along the pathway between phenotype and disease, an important emerging concept in neuropsychiatric research[103]. In this respect, hypermobility is clearly heritable, and presents with excess relative risk in relatives[23]. In addition, its role has biological plausibility, is not state dependent, and is easily testable. However, there remains much to understand, not least how hypermobility is connected with candidate genes. In this context, across psychiatric disorders the presence of hypermobility could represent a phenotypic subgroup of patients[103]. Hypermobility may also act as a clinical marker for specific target symptoms *e.g.*, anxiety[16], as demonstrated in hypermobile patients with schizophrenia[31] or for sensory hypersensitivities, *e.g.*, to olfactory stimuli in patients with panic disorder[104].

More research is also needed to determine if this patient subset responds differently to treatment, allowing for a 'personalised medicine' approach. For example, a dietary intervention (low FODMAP) for irritable bowel syndrome is reportedly more effective in hypermobile compared to non-hypermobile patients[105]. Dysfunctional coping strategies are associated with hypermobility[33], so psychological approaches addressing these could prove beneficial. Anecdotally, sensitivity to unwanted drug side-effects is high in this group. The first randomised controlled trial of a targeted non-pharmacological therapy for anxiety in the context of hypermobility is currently ongoing, comparing modified interoceptive training to standard supportive treatment in individuals with hypermobility and anxiety[106].

CONCLUSION

In conclusion, alongside the well-known link between hypermobility and anxiety, recognition of which has expanded across age groups, there is growing evidence of associations with depression, eating disorders, neurodevelopmental conditions and stress-sensitive medical conditions. There remains a paucity of evidence for links with schizophrenia and addictions. We recommend clinicians across different specialities are aware of the transdiagnostic nature of HSD/hEDS, which may present with both primary and secondary difficulties in psychological and physical domains. In particular, professionals encountering patients with mental health difficulties should consider the prospect of underlying hypermobility as a potential influence on neuropsychiatric symptom progression in this subgroup of patients.

While hypermobility and psychopathological attributes are conventionally considered distinct, their association affirms the pervasive interplay of mind, brain and body. Perceptions, emotions, cognitions and behaviours are dynamically coupled to the state of the body through both unconscious and conscious mechanisms[89]. Further investigation of the psychophysiological, cellular, molecular and genetic underpinnings of the link between hypermobility and psychiatric disorders may provide clinically relevant insights to improve recognition, identify treatment targets, and plan holistic management strategies across the lifespan that combine both psychiatric and somatic approaches.

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MINIREVIEWS

Psychiatric sequelae in COVID-19 survivors: A narrative review

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Abstract

In December 2019, a novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was initially reported in Wuhan, China. Previous epidemics including SARS and middle east respiratory syndrome raises concern that COVID-19 infection may pose a significant threat to the mental health of affected individuals. Studies and reviews have shown the acute psychiatric manifestations in COVID-19 patients, although long term psychiatric sequelae are predicted, there are only few review studies about the long term psychiatry outcome in COVID-19 survivors. Clinically significant post-traumatic stress disorder, anxiety, and/or depression among COVID-19 survivors during 14-90 d were observed following the diagnosis. Risk of anxiety or depression were higher in patients with more severe illness at 6 mo follow-up, early convalescence, and at 1 mo follow-up. Diagnosis of COVID-19 Led to more first diagnoses and relapses of psychiatric illness during the first 14-90 d after COVID-19 diagnosis. The possible underlying mechanisms of psychiatric sequelae in COVID-19 infection are neurotropism, immune response to SARS-CoV-2, hypothalamo-pituitary-adrenal axis hyperactivity, disrupted neuronal circuits in several brain regions, increased stress levels, neuroinflammation, and neuronal death. This study will review the psychiatric sequelae in previous coronavirus pandemics, current studies, risk factors, and thorough explanation on patho-physiology of the psychiatric sequalae in COVID-19 survivors.

Key Words: Psychiatrics sequelae; Mental disorders; COVID-19; SARS-CoV-2

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Core Tip: Studies and reviews have shown the acute psychiatric manifestations in coronavirus disease 2019 (COVID-19) patients, and although long term psychiatric sequelae are predicted, there are only few review studies about the long-term psychiatry outcome in COVID-19 survivors. Clinically significant post-traumatic stress disorder, anxiety, and/or depression among COVID-19 survivors during 14-90 d following the diagnosis. Risk of anxiety or depression were higher in patients with more severe illness at 6 mo follow-up, early convalescence, and at 1 mo follow-up. Diagnosis of COVID-19 Led to more first diagnoses and relapses of psychiatric illness during the first 14-90 d after COVID-19 diagnosis.

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INTRODUCTION

In December 2019, a novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was initially reported in Wuhan, China. This disease has caused a national outbreak of severe pneumonia in China and spread worldwide rapidly. On January 30th, 2020, the World Health Organization (WHO) declared the outbreak to be a Public Health Emergency of International Concern[1]. As of February 5th, 2021, there have been 103989900 confirmed cases of COVID-19, including 2260259 deaths, globally[2]. Previous published meta-analysis studies have identified several comorbidities[3-7], home medications[8,9], and laboratory values[10,11] which are associated with severe outcomes and the risk of dying from COVID-19.

Based on previous epidemics experiences, including SARS and middle east respiratory syndrome (MERS), it is recognized that COVID-19 infection may pose a significant threat to the mental health of affected individuals[12]. Studies have reported psychiatric symptoms in SARS survivors, including post-traumatic stress disorder (PTSD), depression, panic disorder, and obsessive-compulsive disorder at 1 to 50 mo follow up[13-15].

Previously published systematic review and meta-analysis studies have shown that the prevalence of psychological consequences of those inflicted or suspected of COVID-19, health care workers, and the general population is 26% (95%CI: 21-32). Pooled prevalence for symptoms of PTSD was 33% (0–86), anxiety 28% (21-36), stress 27% (14-43), and depression 22% (13-33)[16]. Although psychiatric sequelae are predicted, there are only a few studies about the long-term psychiatry outcome in COVID-19 survivors.

The pandemic itself is a significant psychological stressor in addition to its enormous impact on social and economic sectors worldwide. Isolation and small social networks during quarantine period limit access to external supports[17].

Beside the pandemic-associated psychological distress, there are several arguments that may explain the association between COVID-19 and psychological symptoms as its sequelae. Hereby, we review the current evidence regarding the characteristics of psychiatric sequelae from COVID-19 and the mechanism of how COVID-19 infection affects the communication between endocrine, immune, and central nervous systems, resulting in psychiatric sequelae in COVID-19 survivors (Figure 1).

PSYCHIATRIC SEQUELAE IN PREVOUS CORONAVIRUS PANDEMICS

Past pandemics have demonstrated that diverse types of neuropsychiatric symptoms, such as encephalopathy, mood changes, psychosis, neuromuscular dysfunction, or demyelinating processes, may accompany acute viral infection, or may follow infection by weeks, months, or longer in recovered patients[18].

A meta-analysis study conducted by Rogers *et al*[19] showed that the prevalence of PTSD in the post-illness stage among patients admitted to hospital for SARS or MERS

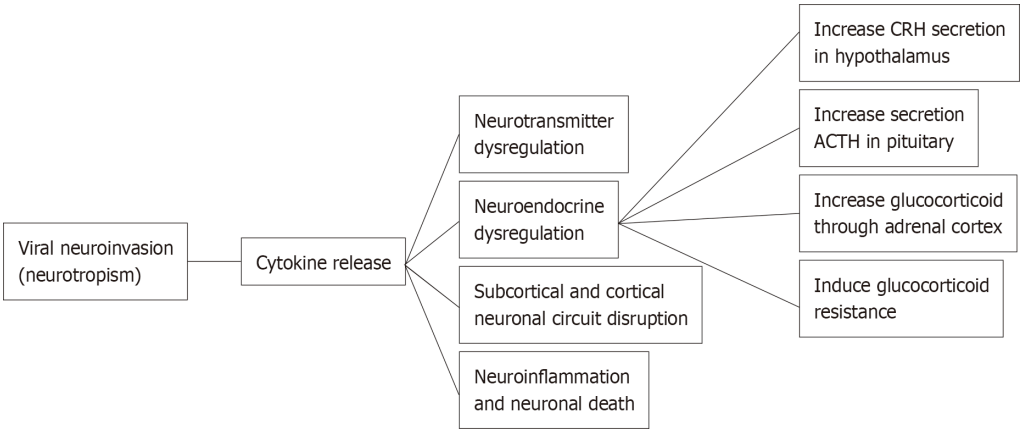

Figure 1 Mechanisms of psychiatric sequelae in coronavirus disease 2019 survivors. ACTH: Adrenocorticotropic hormone; CRH: Corticotropin-releasing hormone.

was 32.2% (95%CI 23.7–42.0; 121 of 402 cases from 4 studies), while the prevalence of depression was 14.9% (12.1–18.2; 77 of 517 cases from 5 studies), and that of anxiety disorders was 14.8% (11.1–19.4; 42 of 284 cases from 3 studies). 446 (76.9%; 95%CI 68.1–84.6) of 580 patients from 6 studies had returned to work at a mean follow-up time of 35.3 mo (SD 40.1).

Survivors of SARS-CoV-1 were clinically diagnosed with PTSD (54.5%), depression (39%), pain disorder (36.4%), panic disorder (32.5%), and obsessive compulsive disorder (15.6%) at 31 to 50 mo post-infection, a dramatic increase from their pre-infection prevalence of any psychiatric diagnoses which is only 3%[15]. Fatigue, myalgia, depression and poor sleep were seen in a cohort of 22 patients and a post-SARS syndrome, similar to fibromyalgia or post viral chronic fatigue syndrome, was suggested, possibly as a result of the psychological trauma or neurological involvement of SARS[20]. SARS has been since described as a mental health catastrophe as a result of the psychological impact on survivors, especially in Health Care Workers, including anxiety, depression, psychosis and high rates of PTSD[21]. After a mean post-SARS duration of 39 mo, 181 subjects underwent interviews with SCID-II for assessment of any psychiatric morbidity. The commonest disorders were major depressive disorder, post-traumatic stress disorder, somatoform pain disorder, and panic disorder[22].

One study showed that at 12 mo post-MERS 27% of survivors had depression and 42% had PTSD, which improved at 18 mo but was still a problem in 17% and 27% of survivors respectively[23]. At 4-6 mo after release from isolation, anxiety symptoms were observed in 3.0% (95%CI: 2.2%-3.9%). Feelings of anger were present in 6.4% (95%CI: 5.2%-7.6%)[24].

Severance *et al*[25] also found the increased prevalence of antibodies against 4 HCoV strains in patients with a recent psychotic episode compared to non-psychiatric controls, suggesting a possible relationship between CoV infections and psychosis, which may also occur in SARS-CoV-2. Seropositivity for coronaviruses associated with suicide and psychosis persisting 1 year after SARS[26].

CURRENT STUDIES ON PSYCHIATRIC SEQUELAE IN COVID-19 SURVIVORS

Recent ambi-directional cohort study of 1733 of COVID-19 survivors in Wuhan found that risk of anxiety or depression were higher in patients with more severe illness at 6 mo follow-up. Patients showed an odds ratio OR 0.88 (0.66–1.17; $P = 0.37$) for scale 4 (requiring supplemental oxygen) *vs* scale 3 (not requiring supplemental oxygen) and OR 1.77 (1.05–2.97; $P < 0.05$) for scale 5–6 (requiring HFNC, NIV, or IMV) *vs* scale 3 for anxiety or depression. Sleep difficulties (26%, 437 of 1655) were one of the most common symptoms reported[27].

Current studies reported clinically significant PTSD, anxiety, and/or depression among COVID-19 survivors during 14-90 d were observed following the diagnosis[28-32], early convalescence[33], and at 1 mo follow-up[34]. PTSD was the most common condition reported, with female gender, past traumatic events, protracted symptoms,

stigmatization, and a negative view on the COVID-19 pandemic as the predictors of symptoms severity ($P < 0.05$)[28]. Older survivors experienced less severe PTSD and anxiety symptoms than younger ones ($P = 0.04$ and $P = 0.045$, respectively). Older age had a significant inverse association with the severity of emotional symptoms of depression ($P < 0.001$)[33].

One retrospective case control cohort studies of 62354 COVID-19 cases in the USA found that diagnosis of COVID-19 Led to more first diagnoses and relapses of psychiatric illness during the first 14-90 d after COVID-19 diagnosis compared control health events (HRs between 1.58 and 2.24, all $P < 0.0001$). At 90 d, the estimated probability of having newly diagnosed psychiatric illness after COVID-19 diagnosis was 5.8% (95%CI: 5.2-6.4) compared with 2.5%-3.4% of patients in the comparison cohorts. The most frequent psychiatric diagnosis was anxiety disorder (HRs 1.59–2.62, all $P < 0.0001$). The probability of a first diagnosis of mood and psychotic disorder was 2% (95%CI: 1.7-2.4) and 0.1% (95%CI: 0.08-0.2), respectively. The rate of first or relapsed psychotic disorder diagnosis after COVID-19 diagnosis was 0.9% (95%CI: 0.8-1.1). The probability of a first diagnosis of insomnia was 1.9% (95%CI: 1.6-2.2; HRs 1.85-3.29, all $P < 0.0001$). The probability of being diagnosed with dementia was increased after a diagnosis of COVID-19 among patients older than 65 years the risk was 1.6% (95%CI 1.2-2.1; HRs 1.89-3.18). COVID-19 patients admitted to hospital have higher risk of psychiatric sequelae than patients not requiring admission (HR 1.40, 95%CI: 1.06-1.85; $P = 0.019$)[30].

RISK FACTORS

Psychiatric outcomes of COVID-19 patients are affected by several biological factors (*e.g.*, obese, older age, pregnancy) and external psychosocial stressors (*e.g.*, social isolation, financial stress). Associated with systemic inflammation and impaired immunity, obesity not only can increase vulnerability for COVID-19 infection, but also constitutes an important risk factor for the development or worsening of psychiatric disorders[32].

Aging is related to cytokine imbalances, which are high levels of pro-inflammatory cytokines, low levels of anti-inflammatory cytokines and decrease in T-cell-mediated function[33]. These changes in elderly may be associated with higher susceptibility to viral diseases and neuropsychiatric disturbances, such as cognitive impairments[34].

Female COVID-19 survivors are at higher risk for developing psychiatric symptoms [27,30,31]. Maternal immune activation in early stages of fetus development is another important risk factor for developing neuropsychiatric disturbances, such as autism spectrum disorder[35]. The presence of family members or close relatives infected was significantly related to anxiety and depression ($P < 0.001$)[30]. Patients with a positive previous psychiatric diagnosis showed a significant increase in psychiatric symptoms measures[29,31].

Recent studies among COVID-19 patients found greater occurrence of depressive and anxiety disorders in people who are in quarantine, front-line workers or among family members of affected patients[36]. This finding suggested psychological stressors, such as social isolation, psychological impact of a severe and potentially fatal illness, concerns about infecting others, and stigma can lead to psychological consequences[31,36]. Loneliness has been associated with several psychiatric disorders, such as depression, anxiety, and suicide behavior[37]. In addition, it has been shown that lonely people present several immune dysregulations, such as upregulated expression of pro-inflammatory cytokine genes[38]. Studies with animal models have provided important clues on the neurobiological and the behavioral consequences of social isolation. In rodents, the stress of social isolation leads to changes in several neurotransmitter systems (*e.g.*, dopaminergic, adrenergic, serotonergic, gabaergic, glutamatergic, nitrergic, and opioid systems). The social isolation stress can also lead to hyperactivity of the hypothalamo-pituitary-adrenal (HPA) axis through an increase in corticosterone production and release in rodents [39].

Financial problems may enhance the impact of social isolation on mental health during quarantine[40]. Studies showed that a worse socioeconomic status is directly related to higher systemic levels of inflammatory markers such as interleukin (IL)-6 and C-reactive protein[41].

PATHOPHYSIOLOGY

The underlying mechanisms of psychiatric sequelae in COVID-19 infection are still unknown and in need further investigation. However, the relationship between COVID-19 severity and psychiatric outcome, albeit modest, might represent a dose-response relationship, suggesting that the association might be mediated by biological factors directly related to the virus (*e.g.*, immune system, viral load)[29] (Figure 1 and Table 1).

Neurotropism

Coronaviruses, including SARS-CoV-2 also invade the central nervous system. There is evidence of SARS-CoV-2 neurotropism based on clinical, pathological, and molecular studies. SARS-CoV-2 invades epithelial cells by binding to ACE2 on the cell membrane which is also expressed in the brain, both in neurons and glia. There are several routes for viral neuroinvasion, including trans-synaptic transfer across infected neurons in splanchnic nerves, entry *via* the olfactory nerve, infection of vascular endothelium, leukocyte migration across the blood-brain barrier (BBB), and/or a conjunctival route[42].

Immune response to SARS-CoV-2

COVID-19 infection triggers a local immune response, recruiting macrophages and monocytes that release cytokines and induce T and B cell responses. In most people, this adaptive immune response is capable of resolving the infection. However, in some individuals, a dysfunctional immune response occurs which may cause severe lung damage and multiple organ failure through catalyzing enzymes such as proteases and toxic free radicals. These processes may damage immune residue in brain neural circuits among COVID-19 patients[43].

High levels of IL-1β, IL-6, interferon-γ, CXCL10, and CCL2 were observed in COVID-19 patients, suggesting an activation of T-helper-1 cell function. Moreover, unlike in SARS and MERS, elevated levels of T-helper-2 cell-secreted cytokines (such as IL-4 and IL-10) were found in COVID-19 patients[44]. Persistent with these findings, emerging evidence found that COVID-19 infection can induce a cytokine release syndrome as a part of host's innate immune, commonly observed in cytopathic virus infections[45]. Soluble cytokines that reach the brain have significant effects on multiple neurotransmitters, including dopamine, serotonin, norepinephrine and glutamate through impact on their synthesis, release, and reuptake[46]. Changes in the metabolism of neurotransmitters contributed to the pathophysiology of various psychiatric disorders, such as depression, anxiety, and PTSD[47,48]. Pro-inflammatory cytokines increase oxidative stress which damages cellular membranes and reduce the expression of excitatory amino acid transporters that are necessary to end glutamatergic signaling that results in elevated glutamate levels[42]. Hence, the immune activation hypothesis which has been postulated for many psychiatric disorders may be a relevant mechanism for mental health issues in COVID-19 survivors[18] (Figure 1).

HPA axis hyperactivity

Since communication occurs between the endocrine, immune, and central nervous system, the activation of inflammatory responses may affect neuroendocrine processes, and vice versa. During COVID-19 infection, pro-inflammatory cytokines are released by immune cells present in the periphery (*e.g.*, macrophages, T and NK cells) and/or in the brain (microglia). High levels cytokines can affect neuroendocrine axis and activate the HPA axis at three different levels: increasing the secretion of the corticotropin-releasing hormone in the hypothalamus, the secretion of adrenocorticotropic hormone in the pituitary, and release of glucocorticoids (*e.g.*, cortisol) through the adrenal cortex[49]. Inflammatory cytokines and their signaling pathways including MAPK, NF-kappa B, signal transducers and activators of transcription and cyclooxygenase have been found to inhibit glucocorticoid receptor (GR) function by acting on its translocation or on GR-mediated gene transcription, thus inducing glucocorticoid resistance that results in dysfunction in the negative feedback between the HPA axis and the immune system.

HPA axis hyperactivity is one of the characteristic features of major depression (MD). Some studies have suggested that glucocorticoids also contribute to the hippocampal atrophy found in patients with MD[50]. Rates of insomnia diagnosis were also markedly elevated, in agreement with predictions that circadian disturbances will follow COVID-19 infection. The HPA axis plays important roles in modulating sleep. Therefore, dysregulation of the HPA axis at any level can disrupt

Table 1 Comparison of psychiatric sequelae in severe acute respiratory syndrome, middle east respiratory syndrome, and coronavirus disease 2019 survivors

Psychiatric sequelae	SARS	MERS	COVID-19	Ref.
Post-traumatic stress disorder	√	√	√	[15,21-23,28,29]
Pain disorder	√	-	-	[15,21]
Panic disorder	√	√	√	[15,21,22,24,27-29]
Depression	√	√	√	[20-23,27-29]
Sleep problems	√	-	√	[20,27,29]
Psychosis	√	-	-	[21]
Dementia	-	-	√	[29]

COVID-19: Coronavirus disease 2019; MERS: Middle east respiratory syndrome; SARS: Severe acute respiratory syndrome.

sleep[51].

Disrupted neuronal circuits in several brain regions

Findings from neuroimaging studies indicate that inflammatory cytokines impact the function of subcortical and cortical neuronal circuits in the brain, especially the basal ganglia and dorsal anterior cingulate cortex, leading to significant changes in motor activity and motivation as well as anxiety, arousal and alarm. Chronic activation of this innate behavioral and immune response may contribute to the development of depression and anxiety disorders in vulnerable individuals. Other brain regions including amygdala, hippocampus, insula, dorsolateral prefrontal cortex and subgenual anterior cingulate cortex are also involved[46].

Increased stress levels

Increased stress levels and worries during pandemic are also the major contributing factors to clinical insomnia[52]. Worry provokes cognitive arousal and may therefore disturb sleep cycle. Reduced physical fatigue and exposure to the sun, as well as increased use of electronic devices may also affect sleep homeostasis. A study showed increased prevalence of insomnia in women compared with men, suggesting that they are more prone to develop stress-related disorders such as post-traumatic stress disorder and anxiety disorders[53]. Sleep disturbances are involved in PTSD development and maintenance[54].

Neuroinflammation and neuronal death

SARS-CoV-2 infection triggers a massive release of inflammation signals leading to BBB dysfunction, injury to astrocytes, activation of microglia and astrocytes resulting in neuroinflammation and neuronal death. Immune response and excessive inflammation in COVID-19 may also speed up the progression of brain inflammatory neurodegeneration. An early report found that one in three individuals with COVID-19 had dysexecutive syndrome at the time of hospital discharge. SARS-CoV-2 can infect endothelial cells leading to further damage of the vasculatures. The resulting hypoperfusion may disrupt energy substrates needed for maintaining neuronal networks thereby accelerating cognitive decline. Damage to limbic and cortical regions could cause retrograde and anterograde amnesia[42].

CONCLUSION

Studies above identified COVID-19 survivors at high risk for psychological problems. Good social support and a number of simple attitudes or activities should be done to prevent psychiatric sequelae in COVID-19 survivors, such as strengthen bonds with other people through social media, think and talk positively, sleep properly, balance diet, regular daily routine, relaxation exercise and other healthy lifestyle measures[49,55]. Music therapy can also be a relevant and simple strategy to improve mental health. A meta-analysis study showed music can modulate cytokine levels (including reducing IL-6 levels), as well as neuroendocrine-immune responses triggered by

physical stress caused by viral infection[56]. In addition, music interferes positively in the immune system when subjected to acute stress, regulating the function of IL-6 and the HPA axis[57]. On the other hand, substance use, eating too much fast food, excessive online activity, excessive watching television, and trusting fake news should be avoided[58].

We suggested that all COVID-19 survivors should be screened for stress disorder, anxiety, and depression regularly to identify those with psychological distress for timely intervention; particularly those with the positive predictive factors (female, prior psychiatric diagnosis, presence of infected family members). Previous studies found that psychiatric sequelae occurred months after the acute infection, therefore the need for sustained follow-up beyond documenting acute stress levels, is important and urgent. Strategies aiming at minimizing mental problems during not only the acute phase of infection but also recovery phase must be designed. Since poorer mental health can be associated with shorter life expectancy and higher economic burden, political and health authorities should be aware of the mental health of COVID-19 survivors[59-61].

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MINIREVIEWS

Metabotropic glutamate receptors and nitric oxide in dopaminergic neurotoxicity

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Abstract

Dopaminergic neurotoxicity is characterized by damage and death of dopaminergic neurons. Parkinson's disease (PD) is a neurodegenerative disorder that primarily involves the loss of dopaminergic neurons in the substantia nigra. Therefore, the study of the mechanisms, as well as the search for new targets for the prevention and treatment of neurodegenerative diseases, is an important focus of modern neuroscience. PD is primarily caused by dysfunction of dopaminergic neurons; however, other neurotransmitter systems are also involved. Research reports have indicated that the glutamatergic system is involved in different pathological conditions, including dopaminergic neurotoxicity. Over the last two decades, the important functional interplay between dopaminergic and glutamatergic systems has stimulated interest in the possible role of metabotropic glutamate receptors (mGluRs) in the development of extrapyramidal disorders. However, the specific mechanisms driving these processes are presently unclear. The participation of the universal neuronal messenger nitric oxide (NO) in the mechanisms of dopaminergic neurotoxicity has attracted increased attention. The current paper aims to review the involvement of mGluRs and the contribution of NO to dopaminergic neurotoxicity. More precisely, we focused on studies conducted on the rotenone-induced PD model. This review is also an outline of our own results obtained using the method of electron paramagnetic resonance, which allows quantitation of NO radicals in brain structures.

Key Words: Dopaminergic neurotoxicity; Metabotropic glutamate receptors; Nitric oxide; Rotenone; Parkinson's disease

Core Tip: Dopaminergic neurotoxicity is characterized by damage and death of

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dopaminergic neurons. Chronic systemic exposure to rotenone (an inhibitor of mitochondrial complex I and a commonly used pesticide) induced dopaminergic degeneration and reproduced many features of human Parkinson's disease in rats. The current paper aims to review the involvement of metabotropic glutamate receptors and the contribution nitric oxide to dopaminergic neurotoxicity.

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INTRODUCTION

The dopaminergic system is a part of the brain that plays a key role in the control of locomotor activity, stress reactions, aggressive behavior, and mechanisms of the formation of dependence in humans and animals[1,2]. Dopaminergic neurotoxicity is characterized by damage and death of dopaminergic neurons. The contribution of dopaminergic neurotoxicity to the pathogenesis of several disorders of the central nervous system (CNS), such as Parkinson's disease (PD)[3,4], Tourette syndrome[5], drug abuse[6,7], and schizophrenia[8,9], has been postulated. Currently, neurodegenerative diseases are a major cause of disability around the world. PD is the second-leading cause of neurodegenerative disorder after Alzheimer's disease (AD)[4]. PD is manifested primarily by movement disturbances. Mental health disorders are also a serious nonmotor feature of PD[10,11]. Thus, psychotic symptoms are not uncommon among individuals with PD, with a prevalence rate of approximately 25%-30%[12,13]. In this regard, the study of mechanisms, as well as the search for ways to prevent and treat PD, is not only an important medical problem but also a social problem[14].

A growing body of evidence has demonstrated that glutamatergic neurotransmission plays an important role in the mechanisms of dopaminergic brain damage[15,16]. Previous studies have shown that modulation of metabotropic glutamate receptors (mGluRs) may be considered a more promising way to alter the activity of the brain glutamatergic system than direct action on ionotropic glutamate receptors of the N-methyl-D-aspartate and amino-methyl-phosphonic acid subtypes[17]. However, the neurochemical and neuropsychological effects of mGluRs on dopaminergic neurotoxicity remain poorly understood.

The association between the neurotransmitter function of glutamate and the formation of neuronal messenger nitric oxide (NO) has received increased attention in recent years. NO is considered to be the first representative of a novel family of signaling molecules with neurotransmitter properties[18,19]. NO is a labile free radical that is involved in many physiological processes[20]. It is assumed that together with some important physiological functions in the CNS, NO can have either neuroprotective or neurotoxic actions, depending on its redox state[21]. There are growing numbers of studies concerning the involvement of NO in the mechanisms of dopaminergic neurotoxicity[22-24]. Measurement of NO is technically difficult due to its rapid chemical reactions with a wide range of molecules, such as free radicals, metals, thiols, *etc*[25]. Thus, accurate detection and quantification are critical to understanding health and disease[26]. Most of the NO measurement techniques in the literature are indirect[27,28]. In our work, we used the direct electron paramagnetic resonance (EPR) method, which allows us to estimate the generation of NO radicals directly in brain tissue[29-31]. The current paper aims to review the involvement of mGluRs and the contribution of NO to dopaminergic neurotoxicity. More precisely, we focused on studies conducted on the rotenone-induced Parkinson's disease model. This review is also an outline of our own results obtained using the EPR method, which allows quantitation of NO radicals in brain structures.

MODELS OF DOPAMINERGIC NEUROTOXICITY

The use of animal models to study neurological diseases associated with dopaminergic neurotoxicity allows for in-depth study of their neuropathophysiology[32,33]. Patholo-

gically, the hallmark of idiopathic PD is the loss of dopaminergic neurons in the substantia nigra (SN). However, in the absence of nigral involvement, noncatecholaminergic neurons are also affected[34]. Agents that selectively damage or disrupt catecholaminergic systems, such as reserpine, methamphetamine (METH), 6-hydroxydopamine (6-OHDA), and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), have been used to develop PD models of PD[35,36]. Based on experimental and clinical evidence, PD was the first neurological disease to be modeled and subsequently treated with neurotransmitter replacement therapy[35]. Recent studies have shown that nigrostriatal dopamine degeneration can be induced *via* overexpression of α-synuclein using viral vectors or transgenic techniques. In addition, protein aggregation pathology can be triggered by inoculating preformed fibrils of α-synuclein in the SN or the striatum[37,38]. Transgenic animals that overexpress α-synuclein were used to study the role of this protein in dopaminergic degeneration[39,40]. Nevertheless, although transgenic models offer insight into the causes of the pathogenesis of PD or Lewy body (LB)-like formation, the lack of sequential loss of neurons in the SNc remains a major limitation for these models[40]. Conversely, toxin-based models recreate selective nigrostriatal cell death and show extensive motor dysfunction. However, these toxin models do not reproduce the extranigral degeneration that also occurs as part of the disease and lack the pathological hallmark of LB inclusions[39,41]. Betarbet *et al*[42] reported that chronic, systemic introduction of rotenone, an inhibitor of mitochondrial complex I, accurately replicates many aspects of the pathology of PD. Additionally, in rotenone-treated animals, α-synuclein-and polyubiquitin-positive aggregates were observed in dopamine neurons of the SN[43,44]. The advantages of this model include a slow and specific loss of DA neurons. The disadvantages of the model include the duration of drug administration, as well as sometimes high animal mortality[36]. Currently, several modifications of rotenone-induced Parkinson's disease models have been created. These modifications are different in the mode of administration as well as in the dosage and duration of treatment with rotenone[44-46]. The fact that rotenone is still widely used in agriculture as a pesticide increases the relevance of studying this model[47-49]. However, while the behavioral effects of rotenone administration are well characterized, the mechanisms of rotenone action are still poorly understood.

MGLURS IN MODELS OF DOPAMINERGIC NEUROTOXICITY

A significant number of studies have revealed that the excitotoxicity of glutamate contributes to the development of dopaminergic neurotoxicity[50-52]. It has been reported that various neurotoxic agents, including rotenone and METH, can severely damage both ionotropic and metabotropic glutamate receptors, which leads to the progression of toxic effects[53]. An important functional interplay between the dopaminergic and glutamatergic systems has stimulated the consideration of mGluRs as potential therapeutic targets in PD[54-56]. Eight mGluRs (GRM1 to GRM8) have been identified and divided into three groups based on their sequence similarity and pharmacology[57,58]. All mGluRs are family C G-protein-coupled receptors that participate in the modulation of synaptic transmission and neuronal excitability throughout the CNS[59]. Studies have shown that mGluR-mediated mechanisms have been implicated in both neuroprotection and neurotoxicity. The involvement of mGluRs in the control of movement, spatial and olfactory memory and nociception has been demonstrated[57,60,61]. Studies have shown the antiparkinsonian potential of mGluR modulation in groups I, II and III in experimental MPTP and 6-OHDA models of PD[56,62]. It has been reported that group I mGluR antagonism and groups II and III mGluR activation improve some motor symptoms of PD by regulating excitatory and inhibitory transmission in the basal ganglia[55]. However, the mechanism by which these mGluR ligands may alleviate the symptoms of parkinsonism in animal models is largely unknown.

Involvement of mGluRs in neurotoxicity induced by rotenone

Because the rotenone model of PD has attracted much attention, we searched the PubMed and Google Scholar databases for articles concerning the effect of mGluR on the rotenone model of neurotoxicity. In the end, by consensus, primary articles were selected as relevant to our goals (Table 1). Thus, it has been reported that the application of a group III mGluR agonist (L-AP-4) significantly reduced the toxicity of rotenone in a culture of TH+ midbrain neurons[63]. The authors hypothesized that activation of group III mGluR decreases the selective toxicity of rotenone to dopamine

Table 1 Main findings on metabotropic glutamate receptors involvement in rotenone-induced neurotoxicity

Ref.	Object of study	mGluR type	Ligand
Luo *et al*[67], 2019	Cell culture; rats	mGluR5	Antagonist MPEP
Bai *et al*[66], 2018	Cell culture	mGluR5	Agonist CHPG; antagonist MPEP
Xia *et al*[65], 2015	Cell culture, rats	mGluR5	Antagonist MPEP
Bashkatova *et al*[69], 2012	Rats	mGluR5	Antagonist MPEP
Sun *et al*[64], 2012	Cell culture, rats	Group I mGluR	Agonist DHPG
Zhu *et al*[68], 2012	Cell culture, rats	mGluR5	Antagonist MPEP
Alam *et al*[70], 2009	Rats	mGluR5	Antagonist MPEP
Jiang *et al*[63], 2006	Cell culture	Group III mGluR	Agonist L-AP-4

mGluR: Metabotropic glutamate receptors; MPEP: 2-methyl-6-(phenylethynyl) pyridine; CHPG: (RS)-2-chloro-5-hydroxyphenylglycine; DHPG: (S)-3,5-dihydroxyphenylglycine.

neurons by activating the MAP kinase pathway to stabilize microtubules[63]. In contrast, activation of group I mGluRs enhances rotenone-induced toxicity in MN9D cells[64]. The modulation of the mGluR5 type in rotenone-induced PD models has attracted much attention from researchers. Pharmacological inhibition of mGluR5 has beneficial anti-akinetic effects in animal models of PD; however, the mechanism by which these antagonists alleviate PD symptoms is largely unknown[65]. Previous studies have shown that downregulation of mGluR5 promotes cell apoptosis in a model of rotenone-induced cellular PD. Moreover, conditioned media derived from rotenone-treated dopaminergic MN9D neuronal cells have been found to enhance the production of reactive oxygen species (ROS), which can be further attenuated by an mGlu5 agonist[66]. The selective mGluR5 antagonist 2-methyl-6-(phenylethynyl) pyridine (MPEP) prevented rotenone-induced DNA damage in MN9D dopaminergic neurons through a mechanism involving ROS-related mitochondrial dysfunction[65]. It has been demonstrated that mGluR5 expression is decreased in a time- and dose-dependent manner in rotenone-treated MN9D cells[67]. It has been reported that oxidized extracellular cysteine/cystine redox potential plays a role in mGluR5 activity in the rotenone rat model of PD[68]. In our studies, MPEP (3 mg/kg) reduced the intensity of catalepsy in rats after long-lasting administration of rotenone at a dose of 1.5 mg/kg[69]. We observed that the mGluR5 antagonist partially prevented the increase in NO generation evoked by rotenone[69]. In another study, it was shown that the behavioral effects of MPEP (2.5 mg/kg) were less pronounced in rats receiving a higher dose of rotenone (2.5 mg/kg) following the same duration of neurotoxin administration[70]. It has been reported that coadministration of MPEP with rotenone reduces the descent latency in the grid test at day 60 but does not block the decrease in DA and serotonin levels induced by treatment with this neurotoxin[70]. Thus, the behavioral effects of mGluR5 were notably dependent on the dose of rotenone administered. The above findings indicate that mGluR5 inhibition produces an inhibitory effect on ROS and NO activity[65,66,69]. In summary, an analysis of the literature data supports the notion that antagonists of mGluR5 are considered promising targets for the treatment of pathological conditions induced by dopaminergic neurotoxicity.

INVOLVEMENT OF NO IN DOPAMINERGIC NEUROTOXICITY

NO as neuronal messenger

Currently, mitochondrial dysfunction is thought to be associated with NO pathways in glutamate neurotoxicity[71]. NO is a gaseous chemical messenger that modulates many functions of the nervous system, including the release of neurotransmitters, interneuronal communication, synaptic plasticity, receptor state, and intracellular signal transduction[20,72]. The role of NO as a biological mediator is primarily determined by its physical and chemical properties. NO is generated by the enzyme NO synthase (NOS), which is widely distributed in the brain[19,73]. One of the possible mechanisms of the neurotoxic effect of NO may be the reaction of NO with

ROS, leading to the formation of a highly toxic product peroxynitrite[24,74,75]. The short half-life of the NO radical is 2-5 s[20]. There are several indirect methods for determining NO and its products/metabolites in biological fluids and tissues. One of the most frequently used indirect methods for the determination of NO is the measurement of nitrite and nitrate by spectroscopy using the Griess reagent[27]. Another well-known method for indirect measurement of NO is the quantitative determination of 3-nitrotyrosine (a product of tyrosine nitration)[76]. The applicability of these indirect methods seems to be problematic. Quantitative determination of nitrites by the Griess method is falsified in the presence of reducing agents as well as thiol groups[77]. These data are consistent with our opinion that only direct methods may be used for reliable determination of NO levels. One of the most accurate and correct ways to measure these data is through use of the EPR method[26,31,78,79].

Participation of no in dopaminergic neurotoxicity

Recent reports claim that NO is involved in neurotoxicity elicited by dopaminergic neurotoxins[24,74,79]. Over the past two decades, significant advances have been made in improving knowledge about the role of NO in the mechanisms of PD pathogenesis[21,80,81]. Thus, in brains from victims of PD, a nitrosyl species, identified as nitrosyl hemoglobin, has been observed in the SN[82]. Previous studies have shown that neurotoxic agents such as MPTP[83], 6-OHDA[84] or METH[74] induce a significant increase in the production of 3-nitrotyrosine in the striatum. The protective effect of neuronal NOS inhibitors has been demonstrated in the MPTP neurotoxicity model in mice[85].

Involvement of no in neurotoxicity induced by rotenone

NO is cytotoxic, partly due to its effects on mitochondria[86]. Research reports have shown that NO is involved in rotenone-induced neurotoxicity (Table 2). However, the detailed mechanisms of this process are not well understood. Our data indicate that following a single injection of rotenone (1.5 mg/kg), the levels of NO in all studied brain areas were indistinguishable from those in control animals[78]. The data obtained correspond with the results of other authors. Thus, acute administration of rotenone at a significantly higher dose (15 mg/kg) did not affect the level of hydroxyl radical generation[87]. The NO level reached its maximum in dopaminergic structures, the prefrontal cortex, and the NAc 60 d after administration of rotenone[78]. We observed a more than 2-fold elevation in NO generation in all studied brain structures of rats only after repeated injections of rotenone[78]. These results are consistent with other studies investigating NO metabolites/products in the brains of rats treated with rotenone (Table 2). Thus, a significant increase (by 200.0%) in the concentration of nitrite determined by the spectrophotometric method was observed[88]. Authors suggest that overproduction of NO may be associated with Snitrosylation or nitration of certain important proteins[88]. It was reported that the production of 3-nitrotyrosine in the brains of rats treated with rotenone for 40 d increased significantly[76]. In recent years, several studies have investigated the potential neuroprotective properties of various plant extracts[89-91], polyphenolic agents[92] and flavonoids[93] in a rotenone model of PD. The authors measured the level of nitrites as a marker of neurotoxicity in the dopaminergic brain structures of animals after long-lasting administration of rotenone (Table 2). The above studies indicate that the content of NO and its metabolites in the brain is currently considered one of the markers of rotenone-induced neurotoxicity.

In our opinion, it seems to be critical to study the dynamics of NO changes in various brain structures during long-term administration of rotenone. This issue is practically not studied. Our results demonstrated a significant enhancement of NO generation in the NAc after 20 d of treatment with rotenone, while the NO level was not elevated yet in the frontal cortex[78]. These data may indicate that dopaminergic neurons in the NAc may be intrinsically susceptible to oxidative damage compared to other neurons. Taken together, our results, as well as literature data, allow us to conclude that rotenone can produce a neurotoxic effect and cause an increased production of free radicals, including NO, only with long-lasting chronic administration. This, in turn, confirms the assumption that the cascade of biochemical reactions causing the development of neurotoxic processes can be triggered only after repeated injections of rotenone[35,78,87,94]. In summary, the data obtained indicate prospects for further research on the interaction of dopaminergic, mGluR and NO systems in rotenone models of PD to search for and study the mechanism of action of substances with neuroprotective properties (Figure 1).

Table 2 Main finding on the determination of nitric oxide and its products/metabolites in the rotenone model of neurotoxicity

Ref.	Dose of rotenone	Duration	NO or its products/metabolites	Method of NO determination
Kumar *et al*[91], 2021	2.0 mg/kg	28	Nitrite	Spectrophotometry
Parkhe *et al*[92], 2020	2.0 mg/kg	21	Nitrite	Spectrophotometry
Sharma *et al*[93], 2020	2.0 mg/kg	28	Nitrite	Spectrophotometry
Sun *et al*[80], 2019	1.5 mg/kg	28	Nitrate/nitrite	NO assay kit
Jayaraj *et al*[90], 2019	1.5 mg/kg	28	Nitrite	Spectrophotometry
Abdel-Salam *et al*[89], 2017	1.5 mg/kg × 3	7	Nitrite	Spectrophotometry
Javed *et al*[86], 2016	2.5 mg/kg	28	Nitrite	Spectrophotometry
Xiong *et al*[88], 2015	1.5 mg/kg	6	Nitrite	Spectrophotometry
Tapias *et al*[23], 2014	3.0 mg/kg	Individually[1]	3-NT (3-nitrotyrosine)	Immunofluorescence
Bashkatova *et al*[69], 2012	1.5 mg/kg	60	NO (Nitroxyl radical)	EPR
Bashkatova *et al*[78], 2004	1.5 mg/kg	60	NO (Nitroxyl radical)	EPR
He *et al*[76], 2003	2 mg/kg × 3	40	3-NT (3-nitrotyrosine)	HPLC

[1]Tissue collection was carried out when each individual animal had reached endpoint (when the behavioral phenotype became debilitating, *i.e.*, when akynesia, rigidity, and postural instability were manifested)[23]. NO: Nitric oxide; EPR: Electron paramagnetic resonance; HPLC: High performance liquid chromatography.

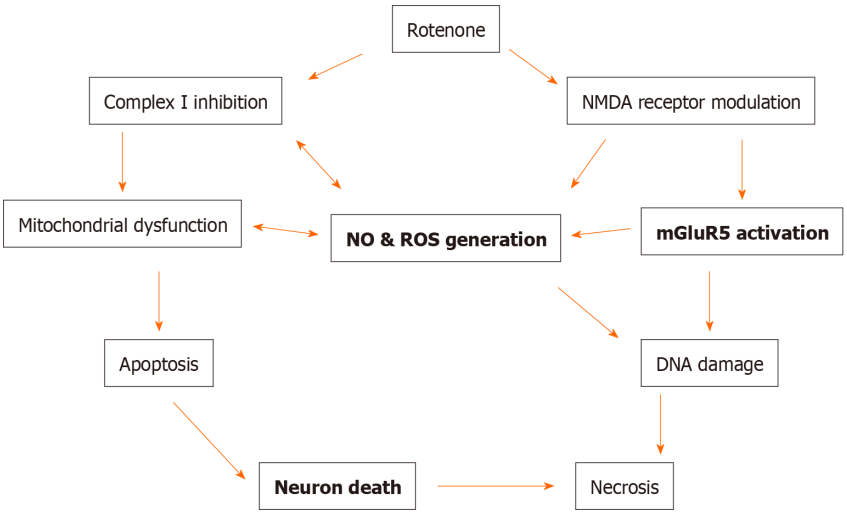

Figure 1 Proposed scheme for the involvement of nitric oxide and metabotropic glutamate receptor subtype 5 in rotenone-induced dopaminergic neurotoxicity. It is now generally accepted that rotenone in low doses of rotenone specifically binds complex I and induces mitochondrial dysfunction. The action of rotenone can be mediated by an increase in the N-methyl-D-aspartate current, which leads to the activation of metabotropic glutamate receptor subtype 5. Complex I, in combination with excitation of glutamate receptors, induces the generation of reactive oxygen species and nitric oxide. In summary, these key cellular events induce progressive death of dopaminergic neurons in the substantia nigra pars compacta *via* apoptosis and necrosis. It is important to note that at each stage, the action of rotenone becomes regionally limited so that inhibition of complex I ultimately lead to highly selective degeneration and loss of dopaminergic neurons of the nigrostriatal pathway. NO: Nitric oxide; ROS: Reactive oxygen species.

CONCLUSION

This review summarizes several newly discovered mechanisms of dopaminergic neurotoxicity (Figure 1). Current treatments for PD are mainly the administration of dopaminergic drugs. However, dopaminergic drugs are only symptomatic treatments and are limited by several side effects. Understanding the pathogenetic mechanisms of the onset and development of PD is of great clinical importance. Recent studies on drug development have focused on emerging new molecular mechanisms, including modulation of mGluRs and NO formation. Despite the growing number of studies demonstrating the positive effect of some mGluR ligands on motor symptomatology in PD models, there are still no drugs in clinical practice targeting mGluRs to restore

neurological disorders of PD. Treatment with NO scavengers/NOS inhibitors may be another potential neuroprotective strategy for diseases associated with dopaminergic neurotoxicity. In addition, our preliminary results and literature data suggest that an increase in the formation of NO radicals in some brain structures may precede the onset of behavioral disorders in rats treated with rotenone. Therefore, finding a possible correlation between the generation of NO radicals and the onset of neurological disturbances during long-term application of rotenone can be an important step in understanding the pathogenesis of rotenone-induced neurotoxicity We can assume that in the future, the determination of NO generation may become a test for the early diagnosis of PD in patients who do not yet have specific symptoms of the disease.

Additionally, long-term application and widespread use of synthetic insecticides have resulted in the accumulation of their residues in food, milk, water, and soil and have adverse health effects for humans[95]. Although all natural insecticides are not completely safe, it seems necessary to phase out the use of rotenone pesticides in agriculture and replace them with natural ("organic") pesticides with maximum safety.

In summary, alternative treatment strategies beyond dopaminergic drugs might be a major topic of future PD therapy. In conclusion, the findings demonstrate that modulation of mGluR and NO formation suggests the possibility of developing new treatment strategies for PD.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Factors causing a relapse of major depressive disorders following successful electroconvulsive therapy: A retrospective cohort study

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Abstract

BACKGROUND

Electroconvulsive therapy (ECT) is used to treat major depressive disorder (MDD). Relapse is often observed even after successful ECT, followed by adequate pharmaceutical treatment for MDD.

AIM

To investigate the diagnostic factors and treatment strategies associated with depression relapse.

METHODS

We analyzed the relationships between relapse, the diagnostic change from MDD to bipolar disorder (BP), and treatment after the initial ECT. We performed a 3-year retrospective study of the prognoses of 85 patients of the Shiga University of Medical Science Hospital. The relative risk of relapse of depressive symptoms was

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calculated based on the diagnostic change from MDD to BP. A receiver operating characteristic (ROC) curve was generated to evaluate the predictive accuracy of diagnostic changes from MDD to BP based on the duration between the first course of ECT and the relapse of depressive symptoms.

RESULTS

Eighty-five patients initially diagnosed with MDD and successfully treated with ECT were enrolled in the study. Compared with the MDD participants, more BP patients experienced relapses and required continuation and/or maintenance ECT to maintain remission (65.6% *vs* 15.1%, $P < 0.001$; relative risk = 4.35, 95%CI: 2.19-8.63, $P < 0.001$). Twenty-nine patients experienced relapses during the three-year follow-up. In 21 (72.4%, 21/29) patients with relapse, the diagnosis was changed from MDD to BP. The duration from the first course of ECT to relapse was shorter for the BP patients than for the MDD patients (9.63 ± 10.4 mo *vs* 3.38 ± 3.77 mo, $P = 0.022$); for most patients, the interval was less than one month. The relative risk of depressive symptoms based on diagnostic changes was 4.35 (95% confidence interval: 2.19–8.63, $P < 0.001$), and the area under the ROC curve for detecting diagnostic changes based on relapse duration was 0.756 (95%CI: 0.562-0.895, $P = 0.007$).

CONCLUSION

It may be beneficial to suspect BP and change the treatment strategy from MDD to BP for patients experiencing an early relapse.

Key Words: Electroconvulsive therapy; Major depressive disorder; Bipolar disorder; Antidepressant; Prognosis; Relapse

Core Tip: Patients who are diagnosed with major depressive disorder (MDD) but repeatedly relapse after electroconvulsive therapy (ECT) and require continuation and/or maintenance electroconvulsive therapy (C/M-ECT) may be in the depressive phase of bipolar disorder (BP). Rather than repeating C/M-ECT alone, even without obvious manic symptoms, the treatment for MDD may have to be revised to that for BP for patients who relapse within one month.

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INTRODUCTION

Treatment options for major depressive disorder (MDD) resistant to pharmaceutical therapy are extremely limited[1]. Currently, electroconvulsive therapy (ECT) is the most promising therapeutic modality for MDD, including drug-resistant depression[2,3]. The efficacy of ECT is reportedly 50%–60% for drug-resistant depression, irrespective of the presence of psychotic features[4]. However, most ECT-treated patients who continue pharmacotherapy experience relapse within 6 mo after receiving adequate ECT[5,6].

Thus, some maintenance therapies after adequate ECT are usually utilized to prevent relapse if the initial therapy results in the complete remission of depression. It has been reported that maintenance therapy with a combination of lithium and an antidepressant is more effective than antidepressants alone[7,8]. Moreover, cumulative evidence suggests that continuation and/or maintenance ECT (C/M-ECT) combined with pharmacotherapy maintains a significantly higher remission rate several months after the initial ECT[9,10]. Recent reviews and meta-analyses have recommended

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C/M-ECT combined with pharmacotherapy for MDD[11,12].

However, it remains unclear whether the recommended therapeutic strategy obscures the potential risk of a future manic episode since both ECT and mood stabilizers, such as lithium, are effective for both depressive and manic symptoms. A considerable proportion of patients with bipolar disorder (BP) are misdiagnosed with MDD at their first visit[13-15] because their episodes emerge as depression more often than mania.

Several studies have reported a diagnostic change from MDD to BP during the treatment of MDD[14-18]. However, the prognosis of antidepressant-resistant depressive patients after remission using ECT has not been systematically investigated. Therefore, we hypothesized that remission of depression after ECT followed by a relapse, even after receiving an antidepressant-based maintenance therapy without any mood stabilizers, is indicative of BP. To test our hypothesis, we conducted a retrospective cohort study involving a 3-year follow-up of patients who experienced remission of depression after undergoing ECT at our hospital.

MATERIALS AND METHODS

Participants

We recruited patients who were admitted to the Department of Psychiatry at the Shiga University of Medical Science Hospital and had their first ECT between January 2009 and December 2011.

Diagnoses of inpatients in the psychiatry department, based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[19], were routinely made by the consensus of multiple psychiatrists who are members of the Japanese Board of Psychiatry at weekly conferences. Decisions to change the diagnosis of manic/hypomanic episodes from MDD to BP were also made during the conferences. We included patients who were initially diagnosed with MDD (n = 112) without any other mental or neurological disorders (Figure 1). Patients who were initially diagnosed as BP or with BP mixed episodes were not included in this study.

Definitions of remission and relapse

We defined successful remission after ECT as follows: (1) The patient no longer conformed to the diagnostic criteria for MDD; (2) the Hamilton Depression Scale 21-Item (HAMD-21)[20] score improved by ≥ 60% since admission; and (3) the patient was discharged and resumed normal activity at home.

Relapse was defined as the reappearance of five or more symptoms of the diagnostic criteria for MDD.

Criterion for changing diagnosis

When there was a manic/hypomanic episode meeting the DSM-IV-Text Revision (DSM-IV-TR)[19] criteria during the follow-up, the diagnosis was changed to BP. BP I and II were diagnosed when the patients had manic and hypomanic episodes, respectively. Diagnostic changes and changes in treatment strategy from MDD to BP among inpatients were made within one week after the first manic/hypomanic episodes were observed. Manic/hypomanic episodes of outpatients were determined when manic/hypomanic symptoms persisted for at least more than a couple of days. Moreover, when other psychotic and epileptic symptoms were dominant and met the DSM-IV-TR[19] diagnostic criteria, the diagnosis was changed to schizophrenia and epilepsy, respectively.

The patients were typically treated with antidepressants according to the American Psychiatric Association (APA) guidelines[4]. ECT was carefully applied according to the APA Practice Guideline[4] and the National Institute for Health and Care Excellence (NICE) guidelines in the United Kingdom[21]. At least one of the following criteria was met for the administration of ECT to patients with MDD: (1) The patients did not experience remission despite receiving a sufficient dose of two or more antidepressants (drug resistance); (2) The patients had serious suicidal thoughts; and (3) It was difficult to administer pharmacotherapy, such as when patients were unable to take food and oral medications due to psychomotor retardation or hypobulia.

We excluded patients who failed to achieve remission after the first ECT (n = 11) and those who were diagnosed with schizophrenia (n = 3), epilepsy (n = 1), chronic pain (n = 2), or Alzheimer's disease (n = 4) during the follow-up. We could not follow up 6 patients for the duration after the first ECT, as they moved out (Figure 1).

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Eighty-five participants, with a significant improvement in depressive symptoms and remission after the first successful course of ECT, were naturally observed. Depression severity and psychosocial dysfunction were assessed using the HAMD-21 [20] and the Global Assessment of Functioning scale (GAF) of the DSM-IV-TR[19]. The duration of the follow-up observation was set to 36 mo after remission was achieved with the first course of ECT. Anxiety symptoms were not included in this study, which were not included in the diagnostic criteria for MDD in the DSM-IV-TR.

The study was conducted according to the guidelines of the Declaration of Helsinki. Written informed consent was not obtained because of the retrospective nature of the study. We displayed the study protocol on the hospital's website and outpatient units of the hospital. The participants were offered the opportunity to opt out of the study. The study protocol was approved by the Shiga University of Medical Science Ethics Committee (27-178) and registered in the UMIN-CTR (UMIN000030458).

We obtained patient data from the medical records: Age, sex, number, and date of ECT, HAMD-21, GAF, diagnosis, onset of disease, medication, psychotic features, and depressive symptoms. These were all essential medical data for ECT and were cross-checked with the doctors in charge. No missing data were included in the study.

Group classification

The participants were retrospectively classified into four groups based on their clinical course (Figure 1). Four groups were included and analyzed in this study.

Groups A and B

Fifty-six participants who did not experience a relapse of depressive symptoms after the first course of ECT were classified as A and B. The patients were treated with pharmacotherapy based on their respective diagnoses.

Group A included 45 participants with MDD; 40 remained in remission with treatment with a continuous single antidepressant, and five remained in remission with the concomitant use of lithium and some antidepressants.

Group B included eleven participants with BP, whose diagnoses changed from MDD to BP based on the manic/hypomanic symptoms during their first course of ECT or during subsequent maintenance therapy with antidepressants. Six and five of them were diagnosed with BP I and BP II, respectively. The maintenance therapy was continued after ECT, and the antidepressant treatments were discontinued. All patients in group B were maintained in remission with mood stabilizers.

Groups C and D

Twenty-nine participants who experienced relapses of depressive symptoms after the first course of ECT were classified as C and D. All patients achieved remission after the second course of ECT and were switched to C/M-ECT with antidepressants.

Group C included eight participants with MDD: five experienced a repeated relapse of depressive symptoms and were maintained in remission with SSRIs or SNRIs; two experienced relapse and were maintained in remission on a tricyclic antidepressant and aripiprazole; and one experienced relapse but was maintained in remission on an antidepressant with lithium after C/M-ECT was discontinued.

Group D included twenty-one participants with BP whose diagnoses changed from MDD to BP because they had manic/hypomanic symptoms during C/M-ECT with antidepressants, which persisted after treatment was discontinued. Two and nineteen of them were diagnosed with BP I and BP II, respectively. Patients in this group were maintained in remission with mood stabilizers without C/M-ECT.

ECT procedures

ECT was performed using a THYMATRON SYSTEM IV ECT instrument (Somatics LLC, Lake Bluff, IL, USA). Procedures for anesthesia and the determination of seizure adequacy followed a standardized clinical protocol that was consistent with the current standards of care[3]. Anesthesia for the procedure included intravenous thiamylal (1.0 -1.5 mg/kg) and succinylcholine (1 mg/kg). The participants were pre-oxygenated and manually ventilated using a valve mask and 100% oxygen after they showed adequate muscle relaxation. The electrodes were placed bilaterally on the forehead. The electrical dose for the short-term course of ECT was estimated using the ''half age method.'' The median number of ECT sessions was 8.47 ± 3.72. The same energy required for short-term treatment was used for the second course of ECT and C/M-ECT. For the short-term course, the participants received two or three weekly sessions until remission.

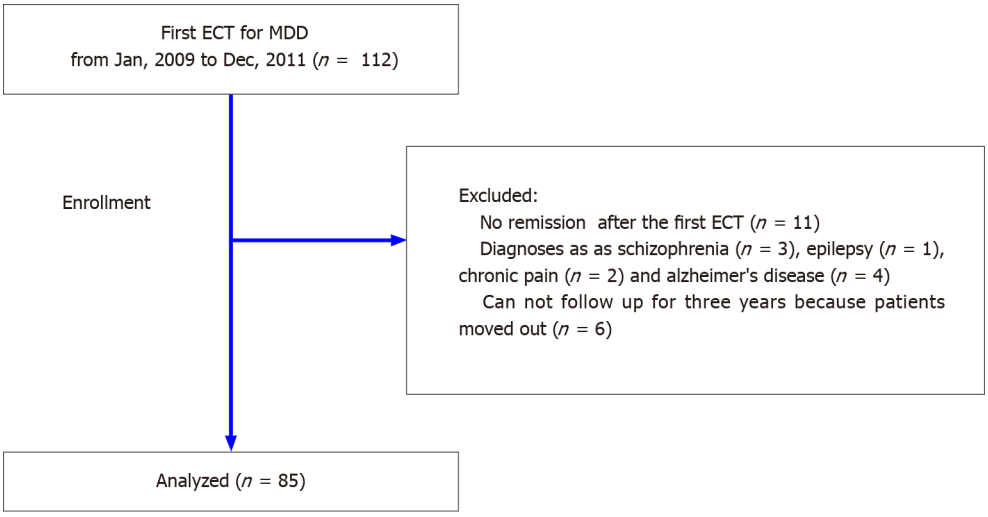

Figure 1 Flow diagram of the participants. ECT: Electroconvulsive therapy; MDD: Major depressive disorder.

Follow-up regimens

Pharmaceutical maintenance therapy was administered to all participants following the first course of ECT. Tricyclic antidepressants (TCAs) were preferentially selected for the maintenance treatment of all participants with MDD if they were tolerable. Sackeim *et al*[22] reported that nortriptyline increases remission compared to venlafaxine when concomitantly administered with ECT in patients with MDD. Venlafaxine was not available in Japan during the study period. Fifty-two participants primarily received TCAs, and 41 received selective serotonin or norepinephrine reuptake inhibitors (SSRI/SNRIs). All antidepressants were prescribed in doses equivalent to 150 mg of imipramine, which satisfied the maximum allowable dose.

When 29 of the participants experienced a relapse, a second course of ECT was administered, and remission was achieved. Subsequently, the treatment was changed to C/M-ECT with antidepressants. If no relapse was observed, the intervals for the C/M-ECTs gradually increased from one to six months.

We terminated C/M-ECT when remission was maintained for more than 6 mo or new-onset psychiatric symptoms (*e.g.*, mood-incongruent delusions) were dominant.

Statistical analyses

The clinical characteristics are presented as mean ± SD. We performed a chi-square test or *t*-test to investigate any intergroup differences in the following items as needed: (1) Demographic data (sex, age at onset, and disease duration until the first ECT session); (2) Admission data (HAMD-21 score during admission, GAF score, the presence of psychotic features, and the number of ECT performed during the first course); (3) Discharge data (HAMD-21 score during discharge, GAF score, and type of antidepressants for maintenance therapy); and (4) Post-discharge data (the period of relapse to C/M-ECT and the diagnosis 36 mo after the final ECT).

The relative risk (RR) and 95%CIs of the relapses of depressive symptoms were calculated according to the diagnostic changes from MDD to BP during the three-year follow-up. Receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic accuracy of predicting diagnostic changes from MDD to BP from the duration between the first course of ECT and relapse of depressive symptoms. We used the MedCalc Software Ver. 19.7.2 (Ostend, Belgium) for statistical analyses. Statistical significance was set at $P < 0.05$. For the sensitivity analysis, we performed a non-parametric analysis (Mann-Whitney test).

Sample and power analyses were performed using G*Power 3.1.9.7 (University of Kiel, Germany). Kellner *et al*[23] reported that the average duration of relapse was 9.1 ± 7 wk after ECT. We determined to use the same sample size and SDs for the MDD and BP groups, and hypothesized that the mean difference in the relapse durations of 9 wk may be clinically significant. We used $\alpha = 0.05$, power = 0.80, mean difference = 9, and SD = 7 for the sample size estimation. In this study, we estimated the need for a sample size of 22.

The statistical methods used in this study were reviewed by Prof. Hiromu Kutsumi and Mr. Shoji Momokawa from the Center for Clinical Research and Advanced Medicine, Shiga University of Medical Science.

RESULTS

Characteristics of the participants

This study included 85 participants aged 56.0 ± 17.0 years; 31.8% of them were males (n = 27) (Table 1, Figure 1). The average initial depressive episode started at the age of 51.7 ± 17.4 years, and the first ECT was administered after 53.1 ± 83.2 mo. All participants were followed up for 36 mo. Depression was recovered by the first ECT with scores of HAMD-21 (from 22.3 ± 13.8 to 7.13 ± 5.03, P < 0.001) and GAF (from 32.9 ± 15.5 to 66.6 ± 7.70, P < 0.001).

The MDD participants included patients whose diagnosis was not changed during the three-year follow-up for the initial ECT (groups A and C in Figure 2).

The BP participants included patients whose diagnosis was changed from MDD to BP during the three-year follow-up for initial ECT (groups B and D in Figure 2).

MDD with remission participants included patients who experienced relapses of depressive episodes after the first course of ECT, who maintained remission with MDD treatment (groups C).

BP with remission participants included patients whose diagnoses were changed from MDD to BP because of manic/hypomanic symptoms during C/M-ECT with antidepressants (group D). Subjects in this group experienced relapses of depressive symptoms after the first course of ECT with antidepressants, but they maintained remission with BP treatment.

Three subjects without relapse were excluded from this study. The diagnoses of two subjects (one male and one female) were changed to schizophrenia due to psychotic episodes. The diagnosis of another man was changed to epileptic psychosis because of his past convulsive seizure episodes with psychotic features.

Seven subjects with relapse were also excluded from the study. Four subjects (two women and two men) had their diagnoses changed to concomitant MDD and Alzheimer's dementia due to their consistent mnemonic impairments; two males had their diagnoses changed to concomitant MDD and chronic pain, and another male had his diagnosis changed to schizophrenia.

Diagnostic group-specific characteristics (MDD vs BP)

We compared the demographic data of the participants whose MDD diagnosis did not change during the three-year follow-up (Groups A and C) and those whose diagnosis was changed to BP (Groups B and D). There were no significant differences between the two groups related to sex, age, age of onset, and HAMD-21/GAF scores during admission or discharge (Table 1). However, the duration from the onset of depression to the first ECT was significantly shorter in the MDD participants (Groups A and C) than in the BP participants (Groups B and D) (33.5 ± 48.1 *vs* 85.8 ± 114.9%, P = 0.009), while psychotic features were more prominent in the MDD participants (43.4% *vs* 21.9%, P = 0.046).

The MDD and BP participants with remission (Group C *vs* D) had similar demographic data, except for the duration from the first course of ECT to relapse (Table 1).

Diagnostic change due to manic/hypomanic episodes

Of the 85 participants, 32 (37.6%) had their diagnosis changed to BP because of manic/hypomanic episodes experienced after remission after the first ECT or during the C/M-ECT period (Groups B and D; Figure 2).

Higher risk of relapse among patients with diagnostic changes than those without

We observed a significantly higher risk of relapse in the diagnostic change groups (Groups B and D) than in the unchanged groups (Groups A and C) (RR = 4.35, 95%CI: 2.19-8.63, P <0.001). A higher percentage of relapses was found in participants whose diagnosis was changed from MDD to BP (65.6%: Group D/Groups B + D) than in those whose diagnosis was MDD (15.1%: Group C/Groups A + C) (P <0.001) (Figure 2). In addition, the types of antidepressants (SSRI/SNRI or TCA) for maintenance therapy were similar among the groups (Groups A, B, C, and D) (chi-square test, P = 0.77).

Period until relapse

We investigated the duration from the first course of ECT to the relapse of depressive symptoms in the patients with MDD and BP (groups C and D). The relapse was significantly earlier in the group with a change in the diagnosis to BP (Group D) than in the group without any diagnostic changes (Group C). (t-test, P = 0.022; Figure 3). As

Table 1 Characteristics of the participants

Variables	Total	MDD patients	BP patients	*P* values	MDD with remission	BP with remission	*P* values
n	85	53	32		8	21	
Male, n (%)	27 (31.8)	16 (30.2)	11 (34.4)	0.690	2 (25.0)	7 (33.3)	0.670
Age, yr	56.0 ± 17.0	56.6 ± 17.6	55.0 ± 16.1	0.676	55.0 ± 21.3	51.9 ± 14.9	0.656
Onset age, yr	51.7 ± 17.4	53.7 ± 18.3	48.5 ± 15.3	0.179	51.4 ± 23.3	47.0 ± 13.2	0.527
Duration from onset to first ECT, mo	53.1 ± 83.2	33.5 ± 48.1	85.8 ± 115	0.009	36.9 ± 37.9	67.1 ± 86.1	0.385
Psychotic features, *n* (%)	30 (35.3)	23 (43.4)	7 (21.9)	0.046	3 (37.5)	5 (23.8)	0.469
HAMD-21 on admission	22.3 ± 13.8	24.4 ± 15.1	18.9 ± 10.9	0.079	26.4 ± 11.0	19.1 ± 10.2	0.103
HAMD-21 on discharge	7.13 ± 5.03	6.77 ± 4.14	7.72 ± 6.26	0.008	8.75 ± 4.59	6.90 ± 5.43	0.403
GAF on admission	32.9 ± 15.5	31.0 ± 16.0	36.0 ± 14.5	0.150	37.9 ± 9.88	39.0 ± 16.0	0.861
GAF on discharge	66.6 ± 7.70	66.4 ± 7.52	67.0 ± 8.08	0.720	66.5 ± 9.07	69.2 ± 5.97	0.348
Duration from first ECT to relapse, mo					9.63 ± 10.4	3.38 ± 3.77	0.022

Results showed as mean ± SD. MDD: Major depressive disorder; BP: Bipolar disorder; ECT: Electroconvulsive therapy; HAMD-21: Hamilton Depression Scale; GAF: Global Assessment of Functioning Scale.

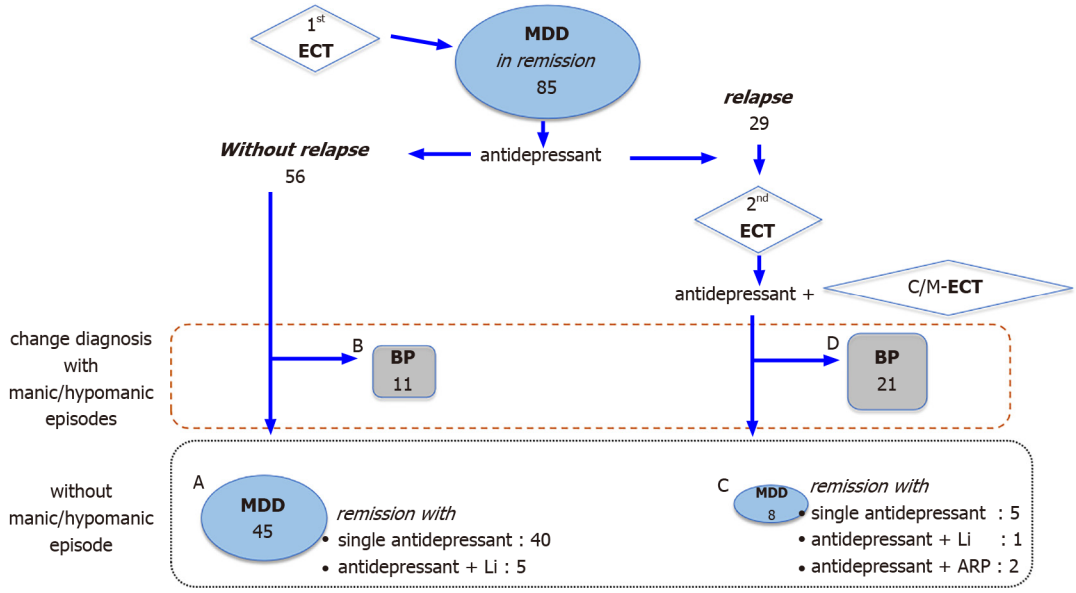

Figure 2 Changes in the treatment and diagnosis based on the relapse and manic/hypomanic episodes after remission after the first electroconvulsive therapy. Relapses were characterized by five or more of the diagnostic criteria for major depressive disorder. Patients in groups A and B did not experience relapse after the first course of electroconvulsive therapy (ECT). Patients in groups C and D experienced a relapse after the first course of ECT. When there was a manic/hypomanic episode during the follow-up, the diagnosis was changed from major depressive disorder to bipolar disorder. ECT: Electroconvulsive therapy; MDD: Major depressive disorder; BP: Bipolar disorder; Li: Lithium; ARP: Aripiprazole.

a sensitivity analysis, we performed a non-parametric analysis (Mann-Whitney test) on duration from the first course of ECT to relapse between patients with MDD and BP (groups C and D), and we had a similar finding with a *P* value of 0.034.

To determine the predictive value of the duration until relapse for BP, we performed an ROC analysis (Figure 4). Of the patients who experienced a relapse of depressive symptoms within 3 mo, 75% had BP, whereas 61.9% of those who remained relapse-free for at least 3 mo had MDD.

A period of less than 1 mo to relapse demonstrated a sensitivity of 38.1% (95%CI: 18.1%-61.6%), specificity of 100% (95%CI: 63.1%-100%), and the area under the ROC curve of 0.756 (95%CI: 0.562-0.895) (P = 0.007), which indicated a moderately

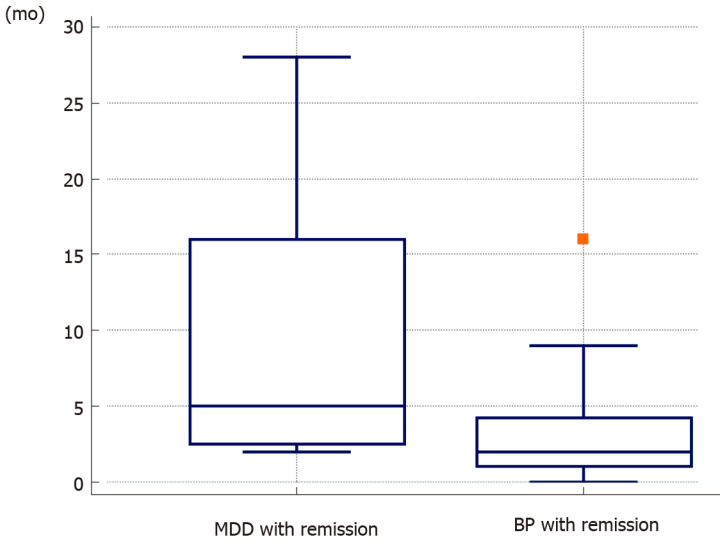

Figure 3 Period to relapse in the continuation and/or maintenance electroconvulsive therapy group. The box-and-whisker plot displays the statistical summary of the variables. The central box shows values from the lower to the upper quartiles. The middle line represents median values. The horizontal line extends from the minimum to the maximum value, excluding the outliers, which are displayed as separate points. The BP participants in group D experienced relapse significantly earlier than the major depressive disorder participants in group C.

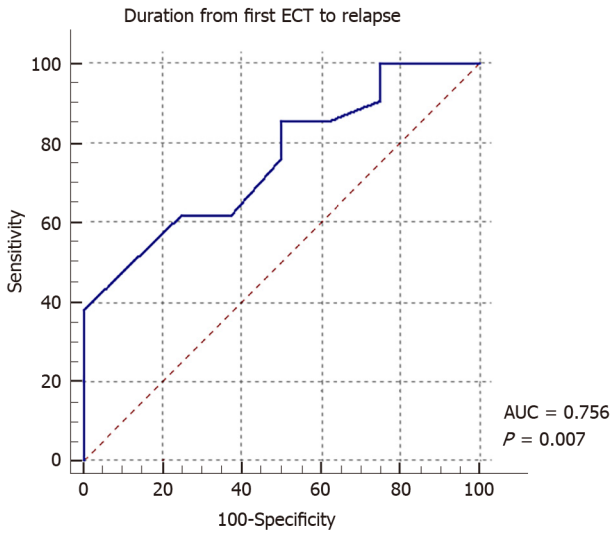

Figure 4 Receiver operating characteristic analysis for determining the accuracy of the diagnosis based on the duration of the period until relapse. Receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic accuracy of predicting diagnostic changes from major depressive disorder to Bipolar disorder from the duration between the first course of electroconvulsive therapy and relapse of depressive symptoms. The area under the ROC curve to for detecting diagnostic changes by based on relapse duration was 0.756 (95%CI: 0.562-0.895, $P = 0.007$).

predictive of the diagnostic change from MDD to BP.

DISCUSSION

Patients with BP are more likely to experience relapses after ECT

We investigated the prognosis of 85 participants who were initially diagnosed with MDD, underwent ECT, and experienced remission over 3 years to identify the effect of subsequent maintenance pharmacotherapy on patients with MDD. Our results indicate that 29 participants experienced a relapse despite maintenance therapy with antidepressants after their first course of ECT and subsequently required C/M-ECT. Twenty-one participants (group D) had their diagnosis changed to BP. Therefore, BP was overlooked when potential BP patients who had depressive episodes were diagnosed with MDD, underwent ECT, and were treated with antidepressants.

Patients with BP are more likely to experience a relapse during maintenance therapy with antidepressants[24,25]. This may be a major reason for drug resistance and necessitates repeated C/M-ECT.

There are no established guidelines for the management of ECT–induced mania, and there is little evidence to guide clinicians beyond case reports and clinical experience[26]. A case report by Lee *et al*[27] described ECT-induced mania treated by aborting ECT and adding a mood stabilizer. Another case report by Thomas *et al*[26] described ECT-induced mania treated with repeated ECT alone. In this study, we aborted ECT and used mood stabilizers to treat ECT–induced mania.

Generally, a large proportion of patients with BP-associated depression may be misdiagnosed with MDD and initially treated with antidepressants alone. Regardless of treatment resistance, their diagnoses changed from MDD to BP during treatment [14-18]. In agreement with this, we found that the proportion of participants whose diagnosis was changed from MDD to BP during the maintenance treatment was similar to or higher than those reported in previous studies, although those studies involved smaller samples or reported shorter follow-ups than the current study[14-18]. To our knowledge, this is the first report to date that focuses on the possibility that patients with MDD, for which ECT is repeatedly indicated, may experience the depressive phase of BP. When patients have never experienced manic/hypomanic episodes, they cannot be diagnosed with BP; therefore, they remain diagnosed with MDD and are treated with maintenance antidepressant therapy until a first manic/hypomanic episode occurs.

Predictors of conversion to BP include the prevalence of psychotic depression[28]. Psychotic features were not prevalent among patients diagnosed with BP in this study, which may be related to the relatively old age of the patient group in this study (51.7 ± 17.4 years).

Requirements of augmentation pharmacotherapy as a potential predictor for future BP diagnosis

Of the 53 participants (groups A and C) who were ultimately diagnosed with MDD, 45 (84.9%) remained in remission with a single antidepressant, irrespective of the type of antidepressant (TCA or SSRI/SNRI). Although antidepressant-antipsychotic cotreatment is known to be effective in treating psychotic depression[29], there are no established guidelines for the management of MDD manifesting with psychotic symptoms after ECT.

In groups A and C, only five participants in group A and three participants in group C required lithium or aripiprazole augmentation to maintain remission (15.1%: (5 + 3)/(45 + 8)), whereas 45 participants maintained remission using a single antidepressant without requiring the use of lithium [84.9%: (40 + 5)/(45 + 8)]. Sackeim *et al*[7] (2001) indicated that the concomitant use of lithium was more effective than the use of nortriptyline alone in maintaining remission after ECT in patients with MDD. Likewise, aripiprazole has also been reported as a popular augmentation agent for the treatment of depression[30]. Although we considered the possibility that lithium augmentation could obscure the actual diagnosis, the results indicated that BP was more common in the relapse group.

A recent observational study reported no significant difference in the relapse ratio between MDD and BP after receiving ECT during a one-year follow-up[31]. However, valproate maintenance pharmacotherapy for MDD was associated with a lower risk of relapse than valproate treatment (multivariate analysis, hazard ratio: 0.091; $P = 0.022$).

In the current study, a large proportion (84.9%, 45/53) of patients with MDD remained in remission for three years with only a single antidepressant. Thus, an adequate dose of antidepressant monotherapy can maintain remission with good tolerability if the diagnosis of MDD is accurate.

These results indicate the importance of the initial diagnosis of MDD. Moreover, relapse that occurs during antidepressant maintenance therapy seems to be a major predictor of later changes in BP diagnosis.

Average time to relapse after administration of initial ECT

Relapse occurred significantly earlier in patients with BP than in those with MDD after the first course of ECT, indicating that BP depression is difficult to prevent through the pharmacological action of antidepressants. Paradoxically, a large proportion of MDD patients could maintain remission with a single antidepressant for at least 3 years if remission was achieved by ECT. A time threshold of one month until relapse may be a good predictor of BP diagnosis.

Although a large proportion of BP patients requires treatment with mood stabilizers to maintain remission, all patients who recovered from depression after ECT were treated with antidepressants. This may explain the earlier relapse in BP patients in the current study. The time-to-relapse may be a good indicator for predicting the prospective occurrence of manic/hypomanic episodes. Early and repetitive relapses of depressive symptoms may be an adequate milestone for predicting BP and for changing treatment strategies for maintaining remission[32].

Limitations

A major limitation of this study is that it was a naturalistic and retrospective cohort study based in a clinical setting. Diagnosis was based on the consensus of multiple psychiatrists, and the Structured Clinical Interview for DSM Disorders[33] was not performed in this study. Scales for BP, such as the Mood Disorder Questionnaire[34] and Bipolar Spectrum Diagnostic Scale [35], were not used. Although a family history of BP is one of the predictors of conversion to BP[28], a family history of BP was not analyzed.

Furthermore, the number of patients was relatively small from a single perspective, which could be a generalization bias. Retrospective clinical investigations could not perfectly exclude the ambiguity of diagnosis, because clinical diversity and flexibility are often required for the optimal treatment of patients. Comprehensive judgments are required for past clinical history and current agonizing symptoms for diagnosis such as mixed states, among others, for a diagnostic change. However, this study strictly adheres to a therapeutic strategy for maintaining remission using a single antidepressant. Thus, the current results ensure novelty in detecting the margin of antidepressant maintenance therapy for drug-resistant depressive patients achieving remission by ECT. With such limitations, our study suggests that C/M-ECT is commonly required for patients initially diagnosed with MDD, and the diagnosis was subsequently changed to BP. Patients diagnosed with MDD who are unable to continue using antidepressants after remission with ECT and relapse and require C/M-ECT may have BP. C/M-ECT with an antidepressant plus lithium prevents both BP and MDD relapses; however, it may have several side effects and lead to a lost opportunity for validating the diagnosis for remission.

CONCLUSION

Appropriate withdrawal from C/M-ECT and multiple dosing regimens contribute to improvements in the quality of life of patients and the suppression of medical and social welfare costs. It may be reasonable that changes from the treatment of MDD to BP can be considered for patients who experience a relapse within one month after the course of ECT, even if they do not have a manic/hypomanic episode. The development of a method to predict manic/hypomanic episodes can prevent the exacerbation of MDD and overtreatment to maintain the remission of MDD after the initial ECT.

ARTICLE HIGHLIGHTS

Research background

Certain proportions of depressed patients relapse after electroconvulsive therapy (ECT), and it is important to explore ways to maintain remission.

Research motivation

Since 2001, when Sackeim reported on the addition of lithium to antidepressants for maintenance treatment after ECT, only symptomatic measures, such as continuation of continuation and/or maintenance ECT (C/M-ECT) have been proposed, and there have been no new findings leading to a fundamental solution for more than 20 years.

Research objectives

The objective of our study was to investigate the diagnostic factors and treatment strategies associated with the relapse of depression.

Research methods

We analyzed the relationships between relapse, the diagnostic change from major depressive disorder (MDD) to bipolar disorder (BP), and treatment strategies after the initial administration of ECT. We performed a 3-year retrospective cohort study on the prognosis of 85 patients at the Shiga University of Medical Science Hospital. The relative risk of relapse of depressive symptoms was calculated based on the diagnostic changes from MDD to BP. A receiver operating characteristic (ROC) curve was generated to evaluate the accuracy of predicting diagnostic changes from MDD to BP based on the duration between the first course of ECT and the relapse of depressive symptoms.

Research results

Compared with the MDD participants, a greater proportion of BP participants experienced relapse and required continuation and/or maintenance ECT for maintaining remission. The duration from the first course of ECT to relapse was shorter for the BP than the MDD patients.

Research conclusions

Instead of repeating treatment for MDD, such as C/M-ECT with antidepressants without definitive evidence of resolution, patients who relapse after ECT and maintenance with antidepressants may benefit from changing the maintenance treatment after remission with C/M-ECT to the treatment for BP depression, which includes mood stabilizers without antidepressants.

Research perspectives

It is also necessary to develop a method for predicting the occurrence of manic episodes to prevent the exacerbation of MDD, as well as overtreatment for maintaining the remission of severe MDD after initial ECT.

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ORIGINAL ARTICLE

Retrospective Study

Determinants of mechanical restraint in an acute psychiatric care unit

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Abstract

BACKGROUND

Despite numerous attempts to reduce the use of mechanical restraint (MR), this technique continues to be widely applied in many acute psychiatric care settings. In order to reduce MR, a better understanding of the variables associated with its use and duration in different clinical environments is essential.

AIM

To determine the proportion of patients subjected to MR and the duration thereof in two acute care psychiatric units; and to identify the variables associated with the use and duration of MR.

METHODS

Descriptive study of all patients admitted to the acute psychiatric units at the Parc de Salut Mar (Barcelona, Spain) in the year 2018. The number and percentage of

this study was not necessary given the nature of the study.

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patients subjected to MR, as well as the duration of each episode were assessed. The following data were also registered: sociodemographic characteristics, psychiatric diagnosis, and presence of cultural and/or language barriers. Multivariate analyses were performed to assess determinants of MR and its duration.

RESULTS

Of the 464 patients, 119 (25.6%) required MR, with a median of 16.4 h per MR. Two factors - a diagnosis of psychotic disorder [Odds ratios (OR) = 0.22; 95%CI: 0.06-0.62; *P* = 0.005] and the presence of a language barrier (OR = 2.13; 95%CI: 1.2-3.7; *P* = 0.007) - were associated with a significantly higher risk of MR. Male sex was associated with a longer duration of MR (B = -19.03; 95%CI: -38.06-0.008; *P* = 0.05).

CONCLUSION

The presence of a language barrier and a psychotic disorder diagnosis are associated with a significantly higher risk of MR. Furthermore, male sex is associated with a longer duration of MR. Individualized restraint protocols that include the required tools are necessary to ultimately limit the use of mechanical restraint.

Key Words: Mechanical restraint; Prolonged restraint; Determining factors; Psychiatric acute unit

Core Tip: The purpose of this descriptive study was to determine the proportion of patients subjected to mechanical restraint (MR) and the duration thereof in two acute care psychiatric units. Secondly, to identify the variables associated with the use and duration of MR. The most important highlights show that the MR remains frequent and with a median duration of more than 16 h. The diagnosis of psychotic disorder and the presence of a language barrier were associated with a significantly higher risk of MR. Furthermore, male sex was associated with a longer duration of MR.

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INTRODUCTION

Mechanical restraint (MR) is defined as the immobilization of a person through the application of mechanical devices that cannot be easily controlled or removed to prevent free movement of their body[1] . The use of MR in hospitalized psychiatric patients remains controversial, in part due to the numerous ethical, legal and clinical questions associated with this practice[2].

In clinical practice, MR is considered an emergency procedure for patients exhibiting potentially dangerous behaviour associated with psychiatric illnesses who have failed to respond to less restrictive interventions (principle of proportionality)[2,3]. In addition to protecting the patient from himself, MR also serves to ensure the safety of healthcare personnel and others, and/or to prevent damage to buildings and physical objects[4]. The application of MR must be carefully considered given that it deprives the individual of their freedom[5] and is also often accompanied by mandatory drug restraint (medication administered against the explicit will of the patient)[6]. In this sense, MR has been associated with physical and psychological sequelae[3,7] in patients[8] and staff[9].

Many efforts have been made to reduce the use of MR and restrictive measures in general, as evidenced by the numerous legal, ethical, and clinical regulations and/or recommendations that have been developed[10,11]. Nevertheless, MR remains widely used in acute psychiatric care settings throughout Europe, although with marked international variation[12]. According to the European Evaluation of Coercion in Psychiatry and Harmonization of Best Clinical Practice[12], which evaluated and compared the use of restrictive measures in inpatient psychiatric centres in 10 European countries, the percentage of patients subjected to MR in those countries varied widely, ranging from 15% to 55% depending on the country (37% in Spain). This variability is highly influenced by legal, social, and cultural factors[13]. However, given that substantial variation has also been observed within countries, it seems clear that other factors play an important role in the use of MR[9]. The application of MR may also be influenced by variables related to the patient, the staff or the ward. According to some studies, the main determinants for MR are patient-related, including sociodemographic characteristics (age, sex, ethnicity, and employment, housing, and educational status)[14,15] or directly related to the mental disorder (*e.g.*, diagnosis, symptom severity, level of aggression, and recurrence of hospitalization) [15]. Nevertheless, there is some disagreement among these studies with regards to these determinants.

Few studies have evaluated the characteristics and determinants of the duration of MR episodes in psychiatry. Moreover, it is not known whether the reasons for the use of MR are related to the duration. In addition, epidemiological data show that the duration of MR varies greatly, ranging from 4.5 to 1182 h in one study[10].

The available data suggest that there are large differences in the proportion of patients subjected to MR and in the duration of restraint episodes, but the reasons for these discrepancies are still not clear. Given the consequences associated with the use of MR, it is essential to ascertain the underlying mechanisms that lead to MR and prolonged episodes, in order to develop strategies to minimize both the use and duration of MR.

In this context, the objective of the present study was to determine the proportion of patients subjected to mechanical restraint and the duration of these episodes in two acute psychiatric care units in our hospital system. We also aimed to identify the determinants of MR and their duration.

MATERIALS AND METHODS

This was a descriptive study involving a sample of patients admitted to two acute psychiatry hospitalization units (Hospital del Mar and the Dr. Emili Mira Center) at the Parc de Salut Mar (PSMar) in Barcelona from January 1, 2018 to December 31, 2018. The project was approved by the ethics committee at the PSMar (CEIC PSMAR).

Assessment

We determined the percentage of patients admitted to these centres in the year 2018 who were subjected to MR and the duration of these episodes. For the analysis, we considered only the first episode of MR. For patients readmitted during the study period, only the first admission was included.

The following cases were excluded from the analysis: abdominal MR in a bed or chair due to risk of falls, gait instability, or risk of removing life support systems. All data related to the MR episodes were consecutively registered, according to institutional restraint protocols, by staff members (nurses and/or psychiatrists), and incorporated into the patients' medical records. The date and time of day of the incident were recorded. However, some cases were registered several hours after the episode. Since the computer system does not permit any changes in the time or date, we reviewed the medical records of all restrained patients to verify the exact time and duration of the episode. During this review, we also determined whether a language barrier was present. Age, sex, psychiatric diagnoses, and place of birth at the time of restraint were obtained from the medical records. We checked the place of birth to differentiate between non-native and native-born patients in order to include this as a study variable (*i.e.*, potential cultural barrier). The diagnoses were recorded according to the ICD-10 classification and classified into four groups: (1) psychotic disorders (all types of schizophrenia, schizoaffective disorders, manic disorders, and bipolar disorders in manic phase); (2) depressive disorders (including bipolar disorders in depressive phase); (3) substance abuse disorders (SAD); and (4) other mental disorders (anxiety disorders, obsessive compulsive disorders, borderline personality disorders,

Alzheimer's, dementia, anorexia nervosa, among others).

Statistical analysis

Data were analyzed using the IBM-SPSS statistical software, v. 20.0 for Mac. The Kolmogorv-Smirnov test was applied to assess the distribution normality of the variables. Two variables - age and hours of restraint - were not normally distributed. Consequently, we performed a logarithmic transformation, but the distribution remained non-normal. Thus, the raw scores for these variables were used in subsequent analyses.

Univariate analyses were performed to assess differences between those patients who underwent MR and those who did not. The χ^2 test was used to compare the categorical data (sex, diagnosis, language barrier, and cultural barrier). The Mann-Whitney *U* test was performed to assess the role of age (non-normal distribution).

A binary logistic regression analysis was carried out using the "ENTER" method to examine the factors independently associated with MR. In this analysis, MR was the dependent variable and the independent variables were sex, age, diagnosis, and language barrier. For the multivariate analyses, we omitted the cultural barrier due to collinearity problems. The reference diagnostic group was "psychotic disorders".

Another univariate analysis was performed to determine the effect of the various study variables on hours of MR. Spearman's correlation was performed for quantitative variables, the Kruskal-Wallis test for categorical variables with more than one category, and the Mann-Whitney *U* test for categorical variables with two categories. Next, a multiple linear regression analysis was performed ("ENTER" method) to determine the variables independently associated with hours of restraint. In that analysis, the dependent variable was hours of restraint while the independent variables were sex, age, diagnosis, and language barrier.

RESULTS

A total of 474 patients were hospitalized during the study period. Of these, 129 required MR. Ten cases were excluded from the study because MR was applied due to the risk of falls or to start vital system support. Thus, the final sample consisted of 464 patients, 119 of whom were subjected to MR. The sample characteristics are described in Table 1, together with the results of the univariate analysis for MR.

On the univariate analysis, the median age in the MR group was significantly lower than in the non-MR group: ($P = 0.005$; $Z = 2.80$). Patients with a language barrier ($P < 0.0001$; $\chi^2 = 15.06$) or cultural barrier ($P = 0.005$; $\chi^2 = 7.76$) were more likely to be physically restrained than native-born patients. Finally, the diagnostic category was significantly associated with the use of MR ($P < 0.0001$; $\chi^2 = 18.41$) (Table 1).

On the binary logistic regression, the presence of a language barrier was associated with a significant higher risk of MR [Odds radio (OR) = 2.13; 95%CI: 1.2-3.7; $P = 0.007$] and the diagnosis was also a significant determinant of MR. Patients diagnosed with depressive disorder (OR = 0.22; 95%CI: 0.06-0.62; $P = 0.005$) and "other" diagnoses (OR = 0.46; 95%CI: 0.23- 0.93; $P = 0.03$) were significantly less likely to be subjected to MR compared to patients diagnosed with psychotic disorder (Table 2).

Hours of mechanical restraint

The median number of hours of restrain per episode was 16.4 (IQR: 7.98-29.27; $Z = 2.959$). The results of the univariate analysis for hours of MR are shown in Table 3. The univariate analysis showed a significant association between sex and hours of restrain ($P = 0.004$; $Z = -2.856$).

On the multiple linear regression analysis, the only variable significantly associated with hours of restraint was sex, which was longer in men (B = -19.03; 95%CI: -38.06-0.008; $P = 0.05$; $f^2 = 0.03$) (Table 4).

DISCUSSION

The aim of the present study was to determine the proportion of patients subjected to MR and the duration of each episode at our institution during the year 2018. We also sought to identify the main factors associated with the use and duration of MR. During the study period, 25.6% of patients were subjected to MR, with a median duration of 16.4 hours per episode. After controlling for possible confounding factors, the determ-

Table 1 Demographic and clinical characteristics of the study sample according to use of mechanical restraint (univariate analysis), *n* (%)

	n (%)	Without MR	With MR	*Z*, χ^2	*P* value
Age (Median/IQR)	42 (30-53)	44 (31-56)	39 (28-48)	(Z) 2.801	0.005
Sex				1.124	0.289
Male	234 (50.4)	169 (72.2)	65 (27.8)		
Female	230 (49.6)	176 (76.5)	54 (23.5)		
Diagnosis				18.414	0.000
Psychotic disorder	318 (68.5)	219 (68.9)	99 (31.1)		
Depressive disorder	55 (11.9)	51 (92.7)	4 (7.3)		
SAD	21 (4.5)	16 (76.2)	5 (23.8)		
Others	70 (15.1)	59 (84.3)	11 (15.7)		
Language barrier				15.058	0.000
No	388 (83.6)	302 (77.8)	86 (22.2)		
Yes	76 (16.4)	43 (56.6)	33 (43.4)		
Cultural barrier				7.756	0.005
No	313 (67.5)	245 (78.3)	68 (21.7)		
Yes	151 (32.5)	100 (66.2)	51 (33.8)		

IQR: Interquartile range; SAD: Substance abuse disorders.

Table 2 Binary logistic regression analysis

	Beta	SE	*P* value	OR	95%CI for OR	
					Low	High
Age	-0.011	0.008	0.181	0.989	0.973	1.005
Sex	-0.032	0.229	0.889	0.969	0.619	1.516
Diagnosis			0.008			
Depressive disorder	-1.526	0.545	0.005	0.217	0.075	0.633
SAD	-0.427	0.535	0.425	0.652	0.229	1.861
Others	-0.776	0.358	0.030	0.460	0.228	0.928
Language barrier	0.758	0.281	0.007	2.133	1.229	3.702
Constant	-0.501	0.394	0.204	0.606		

OR: Odds ratio; SAD: Substance abuse disorders.

inants of MR were diagnosis (higher risk in patients with a diagnosis of psychotic disorder) and the presence of a language barrier. Furthermore, male gender was the only variable associated with prolonged MR. The proportion of patients who required MR - approximately one out of every four patients admitted to acute care - was similar to the rates reported in other studies, such as the 24% rate reported in a study carried out in Italy[12] and the 28.8% rate in another study in Spain[16]. However, studies conducted in other regions[10,17-20] have reported substantially lower rates of MR (from 1%-8%), probably because other methods (in addition to mechanical and pharmacological restraint) are used in those regions, such as isolation and, in some cases, the patient is allowed to select the restrictive measure. These differences may also be at least partially attributable to different cultural contexts and regulations governing hospitalization of psychiatric patients and the use of MR. Furthermore, given that high intra-country variability has also been observed in many studies, other

Table 3 Basic demographic and clinical characteristics of the study sample according to median hours of restraint (univariate analysis)

	n (%)	Restraint duration		Statistical	
		Median	IQR	Z, χ^2	*P* value
Age				(*r*) 0.027	0.768
Sex				(Z) - 2.856	0.004
Male	65 (54.6)	19.28	11.30-34.13		
Female	54 (45.4)	12.61	6.53-20.03		
Diagnosis				(χ^2) 6.488	0.090
Psychotic disorder	99 (83.2)	17.48	9.13-29.75		
Depressive disorder	4 (3.4)	5.05	2.92-7.86		
SAD	5 (4.2)	11.77	7.98-18.37		
Others	11 (9.2)	13.10	8.88-28.92		
Language barrier				(Z) - 0.819	0.413
No	86 (72.3)	15.68	7.98-29.27		
Yes	33 (27.7)	18.70	9.70-24.57		

IQR: Interquartile range; Z: Statistical value of *U* of Mann-Whitney; *r*: Spearman's statistical value; SAD: Substance abuse disorders.

Table 4 Multiple linear regression analysis

	B	SE	Beta	*t*	*P* value	95% CI for B	
						Low	High
Age	0.252	0.319	0.080	0.792	0.430	-0.379	0.884
Sex	-19.028	9.601	-0.214	-1.982	0.050	-38.063	0.008
Diagnosis							
Depressive disorder	-24.739	25.780	-0.101	-0.960	0.339	-75.850	26.372
SAD	-11.822	21.032	-0.054	-0.562	0.575	-53.520	29.875
Others	8.074	15.317	0.053	0.527	0.599	-22.294	38.442
Language barrier	-1.353	10.110	-0.014	-0.134	0.894	-21.397	18.691
Constant	30.248	20.105		1.505	0.135	-9.611	70.107

OR: Odds Ratio; SAD: Substance abuse disorders.

non-cultural factors, such as patient-related factors or the type of unit, may also help explain the differences.

After controlling for other variables, we found no association between age and MR. In line with our findings, several other studies have found no association between MR and age[20-23]; by contrast, several other studies have reported a significant association[9,13,17,24]. It is important to emphasize that most of the studies that found an association with age did not control for other variables (*e.g.*, diagnosis), whereas the studies that have reported no significant associations did control for other factors. Given that psychotic disorder is diagnosed more frequently in younger patients (relative to other diagnoses), we hypothesised that the key factor that determines the application of MR in younger patients could be the diagnosis rather than age.

Numerous studies have explored the influence of patient sex on MR, with most not finding any significant differences[15,18,21-23,25], in line with our findings. Nonetheless, some studies have reported an association between MR and male sex[17,20,24], although such findings may be due to the failure to control for other factors. In fact, the univariate analysis in two studies[21,22] revealed significant differences between men and women sex in terms of MR, but this difference was no longer significant after

controlling for other variables. This finding suggests that sex alone is not an independent predictor of MR, which may be more influenced by the psychiatric diagnosis or other variables.

In our study, the diagnosis was independently associated with MR. Specifically, patients diagnosed with a psychotic disorder had a significantly higher risk of MR, a finding that is consistent with multiple studies[12,17,22,26-28] and reviews[9,21]. That said, it is worth noting that several studies have not found any association between psychotic disorder and MR[13,23,29]. Different cultural contexts and the grouping of different psychiatric diagnoses in these studies could help to explain the discrepancies between those studies and ours.

Another factor associated with MR in our study was the presence of a language barrier. Although we initially differentiated between language and cultural barriers (due to the inclusion of non-native patients without a language barrier), we ultimately decided to omit the variable "cultural barrier" due to problems of collinearity, thus including only "language barrier" in the multivariate analysis. Other studies have found that being an immigrant (without specifying the presence of a language barrier or not) is a determinant of MR[25,30,31]. A study conducted in Spain in 2010 found that patients classified as immigrants had a significantly higher MR rate than paired Spanish-born hospitalized patients (81% *vs* 31%, respectively)[32]. In a study conducted in Italy, immigrant patients were more likely to require physical restraint than Italian-born patients[30]. A two-year retrospective analysis[25] found a 21.6% MR rate among patients with an immigration history compared with 12.9% of Norwegian-born patients. However, other studies have not found any differences between immigrants and native-born patients[33]. Communication problems derived from cultural and language differences between professionals and patients could lead to less successful interventions in risk situations.

The median duration of restraint in our study was 16.4 h, which is higher than some other studies[29,34]. This difference could be due the availability of other measures (*e.g.*, isolation) in those other studies/regions. Male sex was the only determining factor of restraint duration, a finding that is consistent with other reports[26,34]. Along these lines, it is worth highlighting a study carried out to assess the emotional reactions of staff to violent behaviour in psychiatric hospitalized patients. Interestingly, that study found that men and women provoked different reactions among staff members[35], suggesting that women may be perceived to be less threatening than men, which may partially explain why they are less likely to require prolonged MR.

Limitations

This study has several limitations. The first limitation is the retrospective study design, which did not allow us to explore certain key aspects. For example, we were unable to perform a more detailed clinical assessment of patients prior to and during the restraint period. Another limitation is that we assessed only acute psychiatric patients, who tend to have more severe symptoms, with more frequent and longer lasting episodes of MR. Consequently, the finding reported here may not apply to chronic psychiatric settings.

CONCLUSION

Despite efforts to reduce or eliminate the use of mechanical restraint, the results of this study show that these procedures remain widely used in the acute care units at our hospital. Two variables - a diagnosis of psychotic disorder and the presence of a language barrier - were associated with a greater risk of MR. In addition, male sex was associated with longer restraint periods. It is important to identify the patients most likely to require MR or those likely to require longer duration of MR in order to develop specific protocols to further reduce the use of MR.

ARTICLE HIGHLIGHTS

Research background

The use of mechanical restraint (MR) in hospitalized psychiatric patients remains controversial due to the numerous ethical, legal, and clinical questions associated with this practice. Many efforts have been made to reduce the use of MR. Nevertheless, it remains widely used in acute psychiatric care settings throughout Europe.

Research motivation

It's essential to identify the patients most likely to require MR or those likely to require a more prolonged duration of MR.

Research objectives

The main objective is to determine the proportion of patients subjected to MR and the duration thereof in two acute care psychiatric units. Secondly, to identify the variables associated with the use and duration of MR.

Research methods

Descriptive study of all patients admitted to the acute psychiatric units at the Parc de Salut Mar. The number and percentage of patients subjected to MR and the duration of each episode were assessed. Multivariate analyses were performed to evaluate the determinants of MR and its course.

Research results

The results show that the use of MR is very frequent. The diagnosis of psychotic disorder and the presence of a language barrier were associated with a greater risk of MR. The male sex was associated with longer restraint periods

Research conclusions

Despite efforts to reduce or eliminate the use of MR, the results of this study show that these procedures remain widely used in the acute care units at our hospital. Its determining factors are the psychotic disorder and the language barrier. The factors of a prolonged MR is the male sex.

Research perspectives

It is important to develop specific protocols to further reduce the use of MR.

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ORIGINAL ARTICLE

Retrospective Study

What factors explain anger and mental health during the COVID-19 pandemic? The case of Israeli society

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Abstract

BACKGROUND

What factors affected the levels of anger and emotional distress experienced during the coronavirus disease 2019 (COVID-19) pandemic? We hypothesized that (1) sociodemographic factors and resiliency factors would partially explain psychological distress and anger, with stronger resiliency associated with lower levels of distress and anger; (2) women would report more trust in national leadership, as well as more psychological problems; (3) individuals of low socioeconomic status would report less resiliency, less trust in national leadership, and greater distress than individuals of higher socioeconomic status; and (4) hope would mediate the relationships between the other resiliency factors and both anger and distress.

AIM

To explore whether community resilience, hope, and trust in leaders were associated with lower levels of anger and emotional distress during the COVID-19 pandemic.

METHODS

For this observational study, data were gathered in Israel during the second wave of the COVID-19 pandemic, just before the Jewish New Year (mid-September 2020), as a second lockdown was announced. Data were gathered from 636 Israeli adults, who were recruited by the Midgam research panel. The participants filled out self-reported questionnaires including one on state anger, the Brief Symptom Inventory as a measure of mental-health problems (*i.e.*, somatization, depression, and anxiety), and questionnaires about trust in the state's leaders, community resilience (CCRAM), and hope as measures of coping resources and resiliency. *t*-

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tests were used to explore differences between men and women and between those of lower and higher socioeconomic status. A hierarchical multiple regression analysis was then used to examine whether and how the sociodemographic and resiliency variables explained state anger and psychological distress. A Sobel test was used to evaluate the possible effects of hope on community resilience and trust in leadership in the context of both distress and anger.

RESULTS
Our results revealed differences between women and men in terms of anger and mental-health problems, but not in terms of coping resources. Women reported higher levels of both anger and mental-health problems. Participants of lower socioeconomic status reported more mental-health problems, more anger, and greater trust in the state's leaders; whereas those of higher socioeconomic status reported greater hope. Furthermore, hierarchical multiple regression analyses revealed that the sociodemographic factors of gender, age, and socioeconomic status, as well as community resilience, trust in the state's leaders, and hope explained mental health with a total of 19% of the variance and anger with a total of 33% of the variance. The Sobel tests showed that hope mediated the relationships between community resilience and mental health ($z = 3.46$, $P < 0.001$), community resilience and anger ($z = 2.90$, $P < 0.01$), and trust in leaders and anger ($z = 3.26$, $P < 0.01$), but did not affect the relationship between trust in leaders and mental health ($z = 1.53$, $P > 0.05$).

CONCLUSION
Personal and communal factors affect psychological distress. Personal resilience is an important factor that should be strengthened throughout life. Trust in leadership is important for citizens' mental health.

Key Words: Community resilience; Hope; Trust in government; Anger; Mental health; Pandemic

Core Tip: The aim of this study was to explore whether community resilience, hope, and trust in leaders reduced anger and emotional distress during the coronavirus disease 2019 pandemic. Data were gathered from 636 Israeli adults. The participants filled out self-reported questionnaires including one on state anger, a measure of mental-health problems, and questionnaires about trust in the state's leaders, community resilience, and hope. Our results showed that personal and communal factors play significant roles in reducing psychological distress. This study confirms that personal resilience is an important factor that should be strengthened throughout life. Trust in leadership is important for citizen's mental health.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has led governments around the world to impose lockdowns, which have ranged in duration from several weeks to several months. In Israel, the first lockdown began in March 2020 and continued until May 2020. As the country exited that lockdown, citizens felt that normal life had returned and governmental orders to minimize gatherings were not enforced. Schools opened in early September, with students in isolated groups (capsules). By mid-September, a second wave had arrived and, just before the Jewish New Year, the

government announced a second lockdown, with restrictions that were more severe than those imposed during the first lockdown.

Against the backdrop of the second wave of the epidemic and the second lockdown, the present study aimed to explore communal resources and personal resources, community resilience, trust in the country's leaders, and hope as potential resiliency factors capable of reducing mental-health problems and feelings of anger during this difficult period. We wanted to examine the above-mentioned resiliency and emotional and psychological distress variables among Israeli adults. We compared women and men, as well as individuals of relatively high and low socioeconomic status, to try to understand which of the potential resiliency factors could explain mental-health problems and feelings of anger in this context.

Literature review

Community resiliency: It is important that studies of individuals during a collective crisis take into account the ecological context[1,2], such as different aspects of the communities in which individuals live. Community resilience includes community readiness and preparedness for such events, as well as social cohesion, social support, and social ties and commitments within the community[3-5]. Community resilience and wellness are derived from different capacities, which are dynamic and which must be strengthened and preserved. The current study is focused on the role of community resilience during a pandemic and its association with other resiliency factors in helping individuals to cope during times of epidemics and lockdowns.

Trust in the country's leaders

Faced with the great deal of uncertainty surrounding this novel coronavirus, the public has had to rely on various authorities, such as political leaders and governments, for information and guidance[6]. Trust or confidence in one's country's leaders might serve as an important factor protecting individuals from mental-health problems and feelings of anger during the COVID-19 pandemic.

Indeed, citizens' trust in governmental institutions has been crucial for fostering willing compliance with regulations designed to limit the COVID-19 pandemic[7]. Furthermore, citizens' trust in governmental leadership has helped countries to recover fairly well from the pandemic; countries whose citizens have greater trust in governmental figures and institutions have reported fewer health, psychological, and/or economic problems[8].

Hope

Hope for the future helps us to cope effectively with challenges. It helps individuals to view all of their options and to examine sources of personal strength, by relating to the future instead of focusing on the past[9]. Hope involves emotional elements of expectation, as well as cognition (including deduction) to pursue new ideas and solutions[10,11]. Some researchers have viewed hope as a positive attitude toward life and the ability to hold optimistic views[12-14]. Jacoby and Goldzweig[15] emphasized the emotional component of hope that exists alongside the cognitive component[15]. It is widely agreed that hope is an important resiliency factor that helps individuals to cope and that high levels of hope facilitate well-being in various stressful situations (*e.g.*,[16]).

Indeed, hope has been found to lead to positive outcomes even during a pandemic [17,18]. Thus, in this study, we explored and examined the global concept of hope as a resiliency factor that might aid in reducing mental-health problems and feelings of anger. This study was designed to explore the concept of hope as a potential mediator between community resilience or trust in leadership and mental-health outcomes.

Mental health and anger

Stress has cognitive, emotional, physical/somatic, and social aspects[19]. Research has shown that individuals who are exposed to stressful situations, including the COVID-19 pandemic and the lockdowns and curfews that were imposed in attempts to control that pandemic, tend to be especially vulnerable to developing mental-health problems and anger[20-23]. In summary, those who report higher hopes, stronger community resilience, and more trust also report fewer mental-health symptoms and lower levels of anger[16,24-26].

Gender: No significant gender differences have been found for hope or community resilience[27-29]. However, women have been found to express greater trust in government and leaders[30]. In general, women report more mental-health problems

and feelings of anger than men do and this has held true during the COVID-19 pandemic[31,32].

Age: Older individuals tend to express more community responsibility and resiliency and more trust than their younger counterparts[29,30]. Younger people tend to report higher levels of hope[33], as well as more mental-health problems[32,34].

Socio-economic status: Low socio-economic status (SES) has been found to be associated with lower levels of hope[35] and less confidence and trust in officials, systems, and governments[36]; whereas higher SES has been found to be associated with higher levels of hope[35]. Additionally, low-SES individuals tend to report more mental-health problems than their high-SES counterparts in various stressful situations, including the COVID-19 pandemic[37].

In accordance with the literature review and the aims of the study, several research questions and hypotheses were formulated: (1) Are there differences between men and women in terms of the study variables, namely, hope, trust in leaders, community resilience, mental-health problems, and anger? We expected to find that women report more trust in the country's leaders and more psychological problems (*e.g.*,[30,31]). We did not expect to find any gender differences in the various resiliency factors (*e.g.*,[29]); and (2) Are there differences between individuals of different socioeconomic levels in terms of the study variables, namely, hope, trust in leaders, community resilience, mental-health problems, and anger? Lower-SES individuals were expected to report weaker resiliency than their higher-SES counterparts[35] and to have less trust in their leaders[36]. We also expected that they would report higher levels of psychological distress[37].

To what extent do sociodemographic variables (*i.e.*, gender, age, and SES) and the resiliency factors of hope, community resilience, and trust in leaders explain psychological distress and feelings of anger? We expected that the various sociodemographic factors and the different resiliency variables would contribute to the explanations of both psychological distress and anger. We also expected that stronger resiliency factors would be associated with lower levels of psychological distress and lower levels of anger[16,24].

Does the personal resource of hope mediate the relationships between community resilience or trust in leaders and mental-health problems or feelings of anger? We expected that hope would mediate those relationships[38].

MATERIALS AND METHODS

Participants

Data were gathered from 636 Israeli adults aged 18-70 years old (mean ± SD: 37.14 ± 12.63). The sociodemographic data are presented in Table 1.

Procedure

All of the ethical guidelines applicable to this study were followed. The study was approved by the Human Subjects Ethics Committee of the Conflict Management and Resolution Program at Ben-Gurion University of the Negev (Approved Ethics Form No. 2020-008). Participants completed self-report questionnaires in mid-September 2020, just before the Jewish New Year, as a second lockdown was being announced and approximately six months after the start of the COVID-19 pandemic. The participants were recruited by the Midgam panel (https://www.midgampanel.com/) and were informed that the researchers were interested in their experiences. They were also informed that their participation was voluntary and anonymous and that they were free to withdraw their participation for any reason at any time during the questionnaire procedure.

Measures

Demographics: Participants were asked to report their gender, age, and SES. SES was measured by one question in which participants were presented with the average salary in Israel and asked whether they earned less than that amount or that amount or higher. They were also asked to report their marital status, whether they had any children, and their type of employment (*i.e.*, full-time, part-time, or not employed at all).

Table 1 Frequencies and prevalence of the various sociodemographic variables

Variable	*n*	Prevalence (%)
Gender		
Women	342	53.8
Men	294	46.2
Socioeconomic status		
Below average salary	397	56.6
Average/above average salary	239	34
Current work		
Full time	408	64.2
Part time	79	12.4
No work at all	149	23.4
Family status		
Single	202	31.8
Married	397	62.4
Divorced	35	5.5
Widowed	2	0.3
Children		
Yes	407	64
No	229	36

Conjoint community resilience assessment measure: We used the short version of this scale, which includes 10 items that are each scored on a 5-point Likert-type scale ranging from 1 (do not agree at all) to 5 (definitely agree). The scale is constructed to assess conjoint community resilience assessment measure and to facilitate the estimation of an overall community-resiliency score. It also detects the strength of five important constructs of community functioning following a disaster: Leadership, Collective Efficacy, Preparedness, Place Attachment, and Social Trust. Examples of items are: "I feel that I belong to the place where I live; I believe that my community has the ability to overcome a crisis." The Cronbach's alpha coefficient for the entire scale was $\alpha = 0.91$.

The Conjoint Community Resiliency Assessment Collaboration (CCRAC) is coordinated by Limor Aharonson-Daniel and Mooli Lahad[1]. Partners are: Bruria Adini, Miriam Billig, Orna Braun-Lewensohn, Daphna Canneti, Odeya Cohen, Paula Feder-Bubis, Avi Israeli, Shaul Kimhi, Dima Leykin, Sabina Lissitsa, Yochanan Peres, Carmit Rappaport, Avi Sender, Shifra Sagy, and Michal Shamai.

Trust in the nation's leaders: This questionnaire included six questions that were each answered on a scale of 1 (not at all) to 5 (very much). This questionnaire was designed specifically for the present study, to try to evaluate the extent to which the Israel public believed that its leaders were making the right decisions during the pandemic. Participants were asked to evaluate the government as a whole, minsters, and members of parliament, in terms of how much they each cared and worked for the citizens in the country. Examples of items: "You can trust the government; The government does not spend money on the right things; The government is attentive to the public; The members of the parliament are attentive to the public." The mean was computed and the reliability was $\alpha = 0.84$.

Hope[15]: We used the 18-item, short version of a hope questionnaire. Each item was scored on a Likert scale ranging from 1 (do not agree at all) to 4 (totally agree). The global scale of hope used for the current study is built out of three subscales: Interpersonal Hope, Intrapersonal Hope, and Transpersonal Hope. Examples of items: "I draw strength from the relationships in my life; At difficult times in my life, I trust that I will be able to get myself out of the difficult situations I face; I have faith, which

gives me a sense of comfort". In the present study, the mean of the 18 items was computed. The Cronbach's alpha coefficient was α = 0.91.

State anger[39]: This scale consists of six items related to different aspects of anger. The participants were asked to respond to the items using a 4-point Likert scale (1–almost never; 4–almost always). Examples of items: "I am angry; I want to scream at someone; I feel frustrated". The mean scores were used and the Cronbach's alpha coefficient was α = 0.89.

Brief Symptom Inventory[40]: We used the short version of this inventory, which is comprised of 18 items that are each rated on a 5-point Likert scale (0–not at all; 4–very much). This questionnaire examines three areas of psychological and psychiatric problems: somatization, depression, and anxiety; which can be combined into one scale, namely, the Global Severity Index. Examples of items: "To what extent have you felt faint or experienced dizziness? To what extent have you suffered from a feeling of stress? To what extent have you suffered from a feeling of depression?" The reliabilities of the short version of the questionnaire and its three subscales have been reported to be good[41]. The Cronbach's alpha coefficient for the Global Severity Index was α = 0.88.

Data analyses

First, *t*-tests for independent samples were computed to explore differences between men and women and between those of lower and higher SES, in terms of all of the study variables. Secondly, a hierarchical multiple regression analysis was conducted to evaluate the explanations of the two dependent variables, state anger and the Global Severity Index, by the sociodemographic, resiliency, and resource variables. Finally, we used a Sobel test to evaluate the possible effects of hope on community resilience and trust in leaders in the context of both mental-health problems and feelings of anger.

RESULTS

Differences were found between men and women, in terms of the outcome variables. The women suffered from more severe psychological problems and reported higher levels of state anger, confirming our hypothesis. No gender differences were found in terms of any of the coping resources. Results are presented in Table 2.

As for the hypothesis regarding SES, differences were found in terms of all of the variables, except for community resiliency. Those who belonged to the lower-SES group reported more trust in the country's leaders, greater anger, and more severe psychological distress; whereas those from the higher-SES group reported higher hopes. Results are presented in Table 3.

Our third hypothesis related to the explanation of the dependent variables state anger and Global Severity Index (psychological distress) by the various sociodemographic factors of SES, age, and gender, and the resiliency factors of community resilience, trust in leaders, and hope. The overall explanation of state anger by the various variables was 19%. Those variables explained 33% of the scores on the global severity index of psychological distress. The results (presented in Table 4) show that the sociodemographic variables played different roles in the explanations of state anger and psychological distress. Each of those variables played a significant role in the context of psychological distress, but only gender had a significant effect on anger. All of the resiliency factors played significant roles in explaining each of the two dependent variables.

Finally, a Sobel test was run to examine the variable of hope as potential mediator of the relationships between community resilience or trust in leaders and mental-health problems or feelings of anger. Our results show that hope mediated the relationships between community resilience and mental health ($z = 3.46$, $P < 0.001$), community resilience and anger ($z = 2.90$, $P < 0.01$), and trust in leaders and anger ($z = 3.26$, $P < 0.01$), but did not affect the relationship between trust in leaders and mental health ($z = 1.53$, $P > 0.05$). Thus, it seems that, overall, the individual resiliency factor of hope was the most important factor protecting individuals from mental-health problems and feelings of anger during this pandemic.

Table 2 Differences between men and women in terms of the main variables

	Women, *n* = 324	Men, *n* = 281	*t*
CCRAM (1-5)	3.23 ± 0.97	3.16 ± 0.84	0.94
Trust in leaders (1-5)	2.14 ± 0.85	2.15 ± 0.90	-0.11
Hope (1-4)	3.21 ± 0.55	3.17 ± 0.53	0.63
State anger (1-4)	1.97 ± 0.71	1.81 ± 0.70	2.68[b]
Global severity index (0-2)	1.01 ± 0.87	0.68 ± 0.62	5.56[c]

[b]$P < 0.01$.

[c]$P < 0.001$. Date is presented as mean ± SD. CCRAM: Conjoint community resilience assessment measure.

Table 3 Differences between the socio-economic status groups in terms of the main variables

	Low SES, *n* = 378	Average/high SES, *n* = 227	*t*
CCRAM (1-5)	3.18 ± 0.95	3.23 ± 0.86	-0.58
Trust in leaders (1-5)	2.23 ± 0.88	2.01 ± 0.85	2.98[b]
Hope (1-4)	3.15 ± 0.56	3.26 ± 0.49	-2.33[a]
State anger (1-4)	1.94 ± 0.72	1.82 ± 0.71	2.08[a]
Global severity index (0-2)	0.97 ± 0.81	0.67 ± 0.70	4.65[c]

[a]$P < 0.05$.

[b]$P < 0.01$.

[c]$P < 0.001$. Date is presented as mean ± SD. SES: Socio-economic status; CCRAM: Conjoint community resilience assessment measure.

DISCUSSION

The aim of this study was to examine Israeli adults' resiliency factors against the backdrop of a second lockdown during the COVID-19 pandemic. In our study, the women reported more psychological distress than the men. This is similar to the findings of other studies of different stressful situations around the world (*e.g.*,[31]). It remains unclear whether women feel that they have more social permission to report distress or whether they objectively feel more distress. In accordance with our hypothesis, women also reported higher levels of anger. It could be that the traditional roles of women in terms of home maintenance and child care, as well the fact that more women than men lost their jobs during this period[42] put an extra burden on women during the COVID-19 pandemic and, as a result, they felt more anger. No gender differences were found for any of the examined resiliency factors. However, trust in the country's leaders was low for both men and women, indicating that the Israeli public did not think that the prime minister, the government, and the members of parliament were taking good care of the public and pursuing their welfare during the difficult, prolonged situation of the pandemic.

The second research question related to differences between individuals with average/high and low SES, in terms of the different study variables. Most of the study's results confirm the results of other studies, such as low-SES individuals reporting more mental-health problems[37] and lower levels of resiliency factors, such as hope, among low-SES populations[35]. However, although all of the participants reported low levels of trust in the country's leaders, our finding that lower-SES individuals reported higher levels of trust in the country's leaders contradicts previous studies[36]. It should be noted that, in Israel, a majority of supporters of the government during the time of the study were members of low-SES groups, namely, people who live in the periphery of the country, those with traditional beliefs, and Ultra-Orthodox Jews. These individuals had supported that government and the then-prime minister for more than a decade[43]. Moreover, they had maintained that support despite criticism from numerous directions regarding the performance of the country's political leaders during this pandemic.

Table 4 Results of hierarchical multiple-regression analysis predicting state anger and psychological distress, as measured by the global severity index

	State anger			GSI		
	R^2	β	*t*	R^2	β	*t*
Step 1	0.02			0.11		
SES		-0.06	-1.35		-0.11	-2.62[b]
Age		-0.06	-1.42		-0.21	-5.11[c]
Gender		-0.10	-2.40[a]		-0.20	-4.96[c]
Step 2	0.06			0.08		
SES		-0.06	-1.34		-0.10	-2.38[b]
Age		-0.04	-1.09		-0.19	-4.87[c]
Gender		-0.11	-2.73[b]		-0.21	-5.50[c]
CCRAM		-0.24	-6.05[c]		-0.28	-7.62[c]
Step 3	0.04			0.01		
SES		-0.08	-1.97[a]		-0.11	-2.96[b]
Age		-0.06	-1.34		-0.19	-5.00[c]
Gender		-0.10	-2.63[b]		-0.20	-5.43[c]
CCRAM		-0.18	-4.53[c]		-0.26	-6.72[c]
Trust in leaders		-0.22	-5.33[c]		-0.09	-2.36[a]
Step 4	0.07			0.13		
SES		-0.05	-1.33		-0.08	-2.16[a]
Age		-0.05	-1.30		-0.18	-5.24[c]
Gender		-0.11	-3.02[b]		-0.22	-6.25[c]
CCRAM		-0.08	-2.03[a]		-0.13	-3.47[b]
Trust in leaders		-0.19	-4.85[c]		-0.06	-1.55
Hope		-0.29	-7.33[c]		-0.38	-10.40[c]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$. GSI: Global severity index; CCRAM: Conjoint community resilience assessment measure; SES: Socio-economic status.

Our main results relate to community resiliency, trust in leaders, and hope, which significantly explained both psychological distress and anger. These results continue a line of studies that have stressed the importance of communal[24] and personal[17] resiliency factors for helping individuals to cope with various ongoing stressful situations, including the current pandemic. In this study, the communal factor was found to be an important protective factor. Local leaders, such as mayors and local council heads, who created different activities to benefit their residents in the fields of education, sports, culture, *etc.* strengthened their residents' resiliency and thereby contributed to their residents' well-being without relying on the national leaders to do so. An additional novel aspect of this study is the introduction of another potential resiliency factor, namely, trust in the country's leaders, which was found to protect and aid in reducing stress and anger. Indeed, this factor was significantly associated with stress and anger. Greater trust was associated with lower levels of distress and fewer feelings of anger. This could be explained by the fact that when one trusts his/her leaders, she/he can be confident that the public is being taken care of and that decisions are being made in the public interest.

Our last question related to the mediating role of hope in the relationships between community resilience or trust in the country's leaders and psychological distress or anger. Hope did indeed mediate these relationships. Hope proved to be the most important and significant factor in reducing stress and anger. As noted in other studies, hope helps individuals to cope well, facilitates well-being, and leads to

positive outcomes in various stressful situations, including a pandemic (*e.g.*,[16-18]).

Study limitations

Information about participants' experiences during the COVID-19 pandemic was provided only by the participants themselves and, therefore, the collected data are subjective. In addition, because we lack baseline information about the rates of psychological distress and resiliency factors among the surveyed individuals prior to the study period, we cannot with certainty ascribe the outcomes solely to the impact of the examined stressful situation.

Strengths

The importance of this study lies in the fact that it is a field study conducted during a stressful situation, which provided a natural laboratory for the investigation of human behavior[44]. Future studies should employ a longitudinal design to examine the nature and direction of the observed relationships, such as the impact of one variable on another.

CONCLUSION

The current study aimed to explore personal and communal resiliency factors, as factors that might reduce anger and emotional distress during the chronic-stress situation of the COVID-19 pandemic. It seems that both personal and communal factors play significant roles in reducing psychological distress. Therefore, it is important for communal leaders to play significant roles in this type of situation. They should play active roles during crises, including epidemics. This study continues a line of studies that have claimed that personal resilience is an important factor that should be strengthened throughout life. Finally, trust in the country's leaders is important for its citizens, not only for their obedience to published guidelines, but also for their mental health and, therefore, leaders around the world should act to facilitate and strengthen such trust. These findings could also be beneficial and useful for counselors and other mental-health professionals.

ARTICLE HIGHLIGHTS

Research background

We aimed to examine community resilience, hope, and trust in leaders as potential contributors with lower levels of anger and emotional distress during the coronavirus disease 2019 (COVID-19) pandemic.

Research motivation

To understand in what ways personal and communal factors as well as trust in leaders affect psychological distress of citizens during health pandemic.

Research objectives

(1) To assess sociodemographic factors and resiliency factors as explanatory factors of psychological distress and anger, with stronger resiliency associated with lower levels of distress and anger; (2) To examine gender differences on trust in national leadership and psychological problems; (3) To examine differences between individuals from socioeconomic status on resiliency, trust in national leadership, and distress; and (4) To explore the mediating role of hope in the relationships between resiliency factors and anger and distress.

Research methods

Data were gathered from 636 Israeli adults. The participants filled out self-reported questionnaires. *t*-tests and hierarchical multiple regression analysis were used to examine the various research questions.

Research results

Differences between women and men were revealed on anger and mental-health problems, but not in terms of coping resources. Individuals of lower socioeconomic status reported more mental-health problems, more anger, and greater trust in the

state's leaders; whereas those of higher socioeconomic status reported greater hope. The sociodemographic factors of gender, age, and socioeconomic status, as well as community resilience, trust in the state's leaders, and hope explained mental health with a total of 19% of the variance and anger with a total of 33% of the variance.

Research conclusions

Personal and communal factors affect psychological distress. Personal resilience is an important factor that should be strengthened throughout life. Trust in leadership is important for citizens' mental health.

Research perspectives

Trust in the country's leaders is important for its citizens, not only for their obedience to published guidelines, but also for their mental health and, therefore, leaders around the world should act to facilitate and strengthen such trust. These findings could also be beneficial and useful for counselors and other mental-health professionals.

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SYSTEMATIC REVIEWS

Measures of empathy in children and adolescents: A systematic review of questionnaires

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Abstract

BACKGROUND

Empathy has long been considered a multidimensional construct, encompassing cognitive, affective and behavioral domains. Deficits in empathic competences in early childhood contribute to psychopathology, and have been variably implicated in several clinical conditions, such as autism spectrum disorders (ASD) and conduct disorders.

AIM

To identify and describe empirically validated questionnaires assessing empathy in children and adolescents and to provide a summary of related theoretical perspectives on empathy definitional issues.

METHODS

A systematic review of the literature was conducted. Three bibliographic databases were searched. A total of 47 studies were selected for final analysis and 16 distinct measures were identified and described.

RESULTS

Questionable to excellent levels of internal consistency were observed, while few studies assessed test–retest reliability. Although construct definitions only partially overlapped, affective and cognitive domains of empathy were the commonest internal factors that were often separately evaluated. New facets of the construct (*i.e.*, somatic empathy and sympathy) and specific clinical populations (*i.e.*, ASD) could be specifically addressed through more recent instruments.

CONCLUSION

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The combination of different assessment methods is recommended in order to foresee further improvements in this field and try to overcome the problem of limited convergence with more objective measures.

Key Words: Empathy; Assessment; Child; Adolescent; Autistic disorder; Conduct disorder

Core tip: Measures of empathy in children and adolescents constitute useful clinical tools for evaluating impairments in empathic competences and social skills within neurodevelopmental disorders and psychiatric conditions. However, the choice of the instrument to use should clearly vary, depending on the setting and the object of study. The present review could be useful to clinicians and researchers to allow a direct comparison of the available measures and identify strengths and limitations of each one depending on different purposes.

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INTRODUCTION

In the 19th century, the term *Einfühlung* (*ein*- 'into' + *Fühlung* 'feeling') was first coined by Vischer to mean humans' spontaneous projection of psychic feelings into people and things they perceive[1]. Later, the term empathy (from Greek empatheia: *em*- 'in' + *pathos* 'feeling') was suggested by Titchener as a process of humanizing objects and feeling ourselves into them[2]. Psychoanalysis from its beginning was attracted by the concept, viewed as the process of "feeling in the guise" of another person to better understand how therapy works[3]. Since then, many other disciplines of psychology demonstrated a broad interest in empathy[4], and the construct has proved itself as highly relevant to psychiatric research and clinical practice with patients affected by autism spectrum disorders (ASD) or psychopathy[5].

The acquisition of empathy is considered an essential component of moral development, and empirical relationships between many forms of prosocial behavior and empathy have been demonstrated. Indeed, empathy plays an important role in the development of social competence[6]. Adolescents with higher levels of trait empathy exhibit more prosocial and altruistic behavior, whereas adolescents with lower levels of empathy have been shown to be more aggressive. Deficits in empathic competences in early childhood contribute to psychopathology later in life, and have been implicated in the development of antisocial behaviors, bullying, aggression, sexual offending, and serious violent crime. Iindividuals who share and comprehend another's distress, which occurs as a result of their own aggressive or antisocial behavior, may be less inclined to continue with this behavior or act in an antisocial or aggressive manner in the future[6]. Reduced empathy is also observed in children with conduct disorder (CD) and callous–unemotional traits[7-9]. However, few studies have distinguished between proactive and reactive aggression; the former of which may be more strongly associated to low empathy levels, thus often resulting in a nonsignificant relationship between empathy and overall aggression.

Empathy deficits have also been implicated in several other neurodevelopmental disorders, among which autism is one of the most studied. The so-called extreme male brain theory of autism[10,11] proposes that individuals with ASD show reduced empathy and perform worse on empathy-related tasks that normally give rise to female superiority, especially reflecting a specific cognitive empathy impairment. Additionally, novel hypotheses that imply empathy deficits in different mental disorders have emerged in the last decade. Among such conditions, attention deficit and hyperactivity disorder[12-15] and anorexia nervosa[16-18] revealed empathic defects by means of both self- and parent-reported questionnaires.

Despite its relevance, the construct of empathy has posed noteworthy definitional issues that are still under debate. For instance, eight different conceptualizations of empathy have been reported by Batson[19]. Empathy has been first identified as a primarily affective phenomenon, referring to the immediate experience of the emotions of another person[20]. A definition of empathy, as a primarily cognitive construct, has been subsequently proposed, referring to the intellectual understanding of another's experience[21]. However, since the initial differentiation of its instinctive and intellectualized facets in the 18th and 19th centuries, empathy has been considered a complex multidimensional concept, including both cognitive and affective facets, or manifesting either in the cognitive or the affective domain, depending on the situation [22]. Indeed, empathy has been conceptualized as a superordinate category with subclasses of phenomena sharing the same mechanism, including emotional contagion, sympathy, cognitive empathy, helping behavior, and empathic perspective taking[23,24]. Decety and Jackson[25] identified four subjectively experienced components of empathy, *i.e.*, affective sharing, self-awareness, perspective taking, and emotion regulation. A 3D model has also been proposed, including the affective response, the cognitive processing, and the conscious decision making to undertake an empathic or prosocial action[26].

Although empirical literature has not always consistently distinguished between these subtypes of empathy, neurobiological research has indeed suggested that these components reflect independent processes and are governed by separate brain systems [27]. Prefrontal circuits are believed to facilitate empathic responses through enhancing working memory and improving the ability to assess likely outcomes[23]. In addition, anterior insula and anterior cingulate cortex are activated during the empathic experience of others' pain, while the medial dorsal and orbitofrontal cortex and the right temporoparietal junction are activated by empathy appraisals[27]. Converging evidence from several studies shows that the inferior frontal gyrus and the inferior parietal lobule are necessary for affective empathy, while the ventromedial prefrontal cortex, temporoparietal junction, and the medial temporal lobe are key regions for cognitive empathy[28]. Intriguingly, correlates of empathy subtypes have been measured using several physiological measures, such as electromyography (EMG), somatosensory event-related potentials, and transcranial-magnetic-stimulation-induced motor-evoked potentials[29].

Several approaches have been used to measure empathy, with the first instruments dating back to the 1940s, *e.g.*, Dymond's Scale for the Measurement of Empathic Ability[30]. From the 1980s, physiological measurements, such as skin conductance and heart rate, were increasingly being used and, later, empathy measurement has been influenced by the development of social–cognitive neuroscience. Empathy measures have been previously generally reviewed elsewhere[22,31,32]. In particular, Neumann *et al*[33] provided a brief and succinct review of empathy measures, distinguishing behavioral measures (including reactions to strips or picture stimuli), neurophysiological approaches (*e.g.*, functional magnetic resonance imaging, facial EMG, electroencephalography and evoked related potentials) and self-report questionnaires. Among the last category, the authors included eight measures, of which only three were validated in children and adolescents [Feeling and Thinking (F&T) scale, Basic Empathy Scale (BES), Griffith empathy measure (GEM)]; further, one behavioral measure (Kids' Empathetic Development Scale) was specifically intended to be administered to children.

Miller and Eisenberg[34] first systematically reviewed studies correlating empathy and behavior in children and adolescents, subdividing them by the mode of assessing empathy. They identified four methods traditionally used to assess empathy in children. These include picture and/or story methods, in which probands respond to hypothetical stories; experimental induction procedures, designed to elicit empathic responses; facial affect and/or gestural reactions to others' emotions, as depicted in films or picture stimuli; and self-, parent- or teacher-report questionnaires. Each of these methods has advantages and disadvantages[35]. While most real-life social and interpersonal situations are complex and dynamic, and involve multiple players, most test scenarios rely on very simple two-person interactions. Moreover, infants and young children respond to others' emotions before developing the ability to express or define an emotion lexicon[34]. Laboratory-based stimuli are expensive, relatively invasive, and not suited for large community studies and clinical diagnostic settings. Facial and gestural responses to empathy-inducing stimuli, as well as physiological measures, also tend to be complicated, usually involving special equipment and time-consuming data processing and analysis. Even though these types of data are relatively independent of social desirability, young children may react to the physiological equipment. In addition, Problems also arise with these measures when

trying to disentangle or distinguish between physiological responses for empathy, sympathy and distress, as there is little observable physiological distinction between them[36,37].

There are substantial problems with using self-report questionnaires of empathy in children[33]. Indeed, young children lack the cognitive and verbal abilities to report on internal states. For older children, their reports of affective empathy and their scores on picture/story indices still do not converge with their prosocial behavior and are heavily affected by demand characteristics. Nonetheless, self-report can be a vital tool for some research questions, with responses reflecting attitudes and likely behavior. The inclusion of a social desirability assessment is also recommended, as children have a tendency to provide socially acceptable answers to please others, which is a major general limitation of self-administered questionnaires, so it would be advisable to complement the evaluation of the construct with other measures and informants[35]. Parent or teacher surveys are relatively unbiased and more cost- and time-efficient, especially when studying young children[35]. Anyway, self- or others-reported questionnaires remain the most common method for structured assessment of the behavioral correlates of empathy both in adults and in children and adolescents. While multimethod approaches are clearly favored in basic research, such approaches are not fully applicable to the clinical context, where both timing and setting often limit the extent of more thorough investigation. In fact, rating scales and questionnaires are essential to clinical evaluation for therapeutic and research purposes.

Clinicians and researchers in the neurodevelopmental field still lack a comprehensive overview of validated questionnaires for measuring empathy. Indeed, a systematic review of studies validating questionnaires that clinically evaluate empathy deficits in the pediatric population was published in French in 2016[38]. However, it was limited to the adolescent population (age 12–18 years) and to the period from January 2002 to December 2012, and it was mainly aimed at assessing the clinical features of empathy deficits. Only three validated instruments, namely the BES, the GEM and the Interpersonal reactivity index (IRI), were selected and described. Given the apparent lack of exhaustive and thorough reviews on the topic, published in English, we conducted an updated systematic review of the existing literature on questionnaires assessing empathy validated in children and adolescents. The main goal of our search was to identify the available measures of empathy, and to define how reliable and valid they are. As a consequence, we decided to restrain our search to studies aimed at validating empathy questionnaires (EQ). Psychometric validation of multiple-item scales is an integral and essential part of data analysis, to allow a direct comparison of distinct measures used to assess the same construct. Nevertheless, applied research often do not include psychometric evaluations of the tools, which results in the common use of measures with insufficient proof of validity and reliability and raises concerns on their applicability[39]. Thus, including studies that did not provide a psychometric validation of the used empathy measures would have had little meaning in the present systematic review, whose scope was, among the others, to compare the robustness of each tool. Moreover, since we were interested in identifying the definitions of the construct and the components on which each measurement was based, we provided measures structure comparison with a summary of related theoretical perspectives on empathy definitional issues which are relevant to neurodevelopmental disorders.

MATERIALS AND METHODS

Search

A systematic review of the literature was conducted and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to describe procedures and results[40]. PubMed, Scopus and Web of Science bibliographic database were searched from their date of inception to February 2019. Reference lists of included studies were also carefully searched for relevant citations. The research team discussed and reviewed the results of an initial scoping search. We developed a strategy using four groups of search terms. These were: empathy OR empathic (group 1) AND questionnaire OR measure OR measurement OR scale (group 2) AND child OR children OR adolescent OR youth (group 3) AND validity OR validation (group 4). In summary, the strategy was to include all relevant abstracts relating to groups 1–4. Terms were adapted as necessary for each database. Results were downloaded into Mendeley software. The search included reviews and original studies. If a previous review was found, we searched the reference list to identify and

retrieve the primary studies.

Eligibility criteria

Studies were included if they met the following criteria: Study design: studies aimed at presenting or validating original questionnaires of the psychological construct of empathy, validating their adaptations to other samples or translations into different languages, or further evaluating psychometric properties of these measures.

Comparison: No restriction for comparison groups was applied.

Participants: Children, adolescents and/or young people under 21 years old.

Definition: Any definition of the empathy term was accepted.

Measures: Any questionnaire assessing empathy, including paper-and-pencil or computer-administered measures.

Studies were excluded if they met at least one of the following criteria: (1) the study was not aimed at validating a measure (*e.g.*, assessing a clinical cohort or comparing it with a control population by means of a specific measure); (2) the study was aimed at validating a measure other than a questionnaire (*e.g.*, picture-based tasks or experimental procedures); (3) the validated questionnaire was intended to assess a related psychological construct other than empathy (*e.g.*, social skills, aggressive behaviors, callous–unemotional traits) or to provide diagnostic measures for psychopathy and antisocial personality, ASD and Asperger syndrome, social anxiety; (4) the validated questionnaire was not intended to primarily assess empathy but more general related constructs that only marginally included empathy-related subscales (these measures will be considered in the Discussion); (5) the validation was performed on samples including adults or young adults aged ≥ 21 years; (6) the full-text article was written and published in a language other than English, French, Spanish or Italian (only these languages are well mastered by the authors); and (7) reviews (they will be considered in the Discussion).

Abstract screening

We retrieved 911 abstracts using our search strategy, and 285 were removed as duplicates. Ten additional records were identified through other sources (citations in reference lists of screened papers and reviews). Thus, 626 + 10 abstracts were screened. If a title appeared potentially eligible, but no abstract was available, the full-text article was retrieved. Two researchers (Sesso G and Brancati GE) scanned all titles and abstracts to identify relevant articles for full-text retrieval. Any disagreements were resolved by consensus.

Data collection process

For each study, data on participants and setting, country and language of validation, size, age and gender of the sample and relevant measurements were extracted from full-text papers. For each measure, full name and abbreviation of the scale, number of subscales and items, number of response points for Likert-type scales, identity of responders (self- or parent-reported), empathy definition on which they are based, and data on reliability and validity were also extracted. Finally, data on languages of translation, novel versions or adaptations, and psychometric properties were extracted from full-text papers that were not aimed at presenting or validating original measures.

Synthesis of results

The included studies were heterogeneous in terms of definition and measurement of empathy; hence, we report a narrative synthesis of the findings together with discussion of relevant theoretical background. For each assessment scale we identified psychometric properties from the correspondent paper or from the wider literature. In order to synthesize the articles, identified through our search, we partitioned the papers in four groups: those aimed at presenting or validating original questionnaires; those aimed at validating novel versions or adaptations; those aimed at validating their translations into different languages; and those aimed at further evaluating psychometric properties of validated measures. Original measures were also classified based on validation in infants, preschool children, children and/or adolescents, and as parent- or self-rated.

RESULTS

Study selection and excluded measures

The PRISMA flowchart (Figure 1) shows the process of identification and selection of papers. We excluded 572 records based solely on title or abstract. A total of 64 full-text articles were thoroughly assessed, of which 17 were excluded. The main reasons for exclusion were: the study was aimed at validating a measure other than a questionnaire (n = 4); the validation was performed on samples including adults or young adults ≥ 21 years old (n = 10); or the full-text article was written in a language other than English, French, Spanish or Italian (n = 3).

We excluded measures intended to assess psychological constructs such as aggressive behavior and callous–unemotional traits, or to provide diagnostic clues for psychopathy and antisocial personality, which have been recently reviewed by Masi *et al*[41], and for ASD and Asperger syndrome, for which we refer to the broad available literature on the topic. We extended our search to the entire pediatric population, including infants, preschool children, school-age children and adolescents, but limited it to only paper-and-pencil or computer-administered questionnaires, both self- and parent-report (for instance, we excluded the Young Children's Empathy Measure[42] as it is a vignette-based interview).

Only full-text articles written and published in English, French, Spanish or Italian were retrieved, since these are the only languages that are sufficiently mastered by the authors to fully access the content of the papers. Unfortunately, the Media-Based Empathy Scale[43] was excluded, although being the only existing measure of empathy in the context of media use, since the full-text article was written in German, as well as the Child and Adolescent Forms of the KA–Sİ Empathic Tendency Scale[44, 45], a self-reported questionnaire with affective and cognitive empathy subscales, whose validating articles were published in Turkish.

We also excluded validated questionnaires that were not intended to primarily assess empathy, but more general related constructs (*e.g.*, social competences and emotion recognition) that only marginally included empathy-related subscales. Specifically, we did not consider in our final qualitative synthesis the following questionnaires: the Emotion Recognition Scale[46]; How I Think Questionnaire measuring cognitive distortions[47]; Interpersonal Gratitude Scale for Children[48]; Infant–Toddler Social and Emotional Assessment with its empathy factor[49]; Children's Behavior Questionnaire with its empathy subscale[50]; Multisource Assessment of Children Social Competence[51]; measure of adolescents' Prosocial Moral Reasoning[52]; Self-Compassion Scale[53]; Toronto Alexithymia Scale[54]; and Impulsiveness and Venturesomeness Scale with its empathy subscale[55]. Most of these measures include an empathy-related subscale or similar factors, which explore either the general construct of empathy or socially oriented behaviors and prosocial skills, without further defining the quality of such phenomenon. As we extensively discussed above, a finer description of empathy-related dimensions is among the main objectives of the questionnaires we selected in the present review, which is far from the scope of the above listed measures primarily intended to assess socioemotional and interpersonal aspects or related constructs.

For historical purposes, we should also mention the Hogan Empathy Scale[56], and the Questionnaire Measure of Emotional Empathy[57]; renowned early measures of empathy that were not used in current research and did not appear in our extensive search.

Study characteristics

Forty-seven primary studies were identified for final analysis, of which 16 were aimed at presenting or validating original questionnaires (Table 1). The sample size ranged from 109 to 2612, and the age range of participants included children and adolescents from 1 to 18 years; participants' gender varied from 46.3% to 100% male. Most study samples included healthy subjects recruited from communities, households, schools, centers and hospitals, except for one study performed only on antisocial convicts recruited from rehabilitation services, and two studies conducted also on patients, recruited from clinical centers, with conduct disorder and ASD, respectively, compared to healthy subjects.

Further characteristics of included studies aimed at validating novel versions or adaptations (n = 6) and translations into different languages (n = 19), or aimed at further evaluating psychometric properties of validated measures (n = 6), are shown in Table 2. Included studies were conducted in European, American and Asian countries, with translations into 11 languages (Basque, Bengali, Chinese, Dutch, French, Italian,

Table 1 Characteristics of included studies aimed at presenting or validating original questionnaires (*n* = 16)

Ref.	Measure	Country	Language	Setting	Participants	Sample size	Age, yr	Gender
Bryant[98], 1984	BEI	NA	English	NA	Healthy	128 + 163 + 73	7/10/14	NA
Litvack-Miller *et al*[99], 1997	IRI	Canada	English	Schools	Healthy	478	7-12	NA
Rey[63], 2003	SME	Colombia	Spanish	Schools (centers)	Healthy + CD	224 + 94	11-18	100/100
Garton *et al*[89], 2005	F&T	Australia	English	Schools	Healthy	413	8-10	53
Jolliffe and Farrington[6], 2006	BES	United Kingdom	English	Schools	Healthy	720	14.8 ± 0.48	50.8
Dadds *et al* [100], 2007	GEM	Australia	English	Schools	Healthy	2612	4-16	52.8
Funk *et al*[82], 2008	CEAQ	United States	English	Schools	Healthy	213	10-13	49.6
Sallquist *et al* [62], 2009	DPES	United States	English	Maternity hospital	Healthy	168	4.49 ± 0.07	52.9
Auyeung *et al* [64], 2009	EQ-C	United Kingdom	English	Schools (centers)	Healthy + ASD	1256 + 265	4-11	46.3/82.6
Rieffe *et al*[83], 2010	EQ	Netherlands	Dutch	Schools and centers	Healthy	109	1-5	47.7
Whitt and Howard[101], 2013	ES-PPI	United States	English	Rehab services	Antisocial	707	15.5 ± 1.2	87
Lopèz-Pèrez and Fernadèz [102], 2014	TECA	Spain	Spanish	NA	Healthy	670	10-16	NA
Vossen *et al*[88], 2015	AMES	Netherlands	Dutch	Households	Healthy	450	10-15	50
Wang and Wang[87], 2015	EToMS	China	Chinese	Schools	Healthy	189	3-6	50.8
Raine and Chen [29], 2017	CASES	United States	English	Community	Healthy	428	11-12	NA
Richaud *et al* [35], 2017	EQ	Argentina	Spanish	Schools	Healthy	479	9-12	46.3

Age is reported in years, as either mean ± SD or age range according to original available data; gender is reported as percentage of males. AMES: Adolescent Measure of Empathy and Sympathy; ASD: Autism spectrum disorder; BES: Basic Empathy Scale; BEI: Bryant's Empathy Index; CASES: Cognitive, Affective and Somatic Empathy Scales; CD: Conduct disorder; CEAQ: Children's Empathic Attitudes Questionnaire; DPES: Dispositional Positive Empathy Scale; EQ-C: Empathy Quotient for Children; EQ: Empathy Questionnaire; ES-PPI: Empathy Scale-Psychopathic Personality Inventory; EtoMS: Empathy and Theory of Mind Scale; F&T: Feeling and Thinking Scale; GEM: Griffith Empathy Measure; IRI: Interpersonal Reactivity Index; SME: Scale to Measure Empathy; TECA: Cognitive and Affective Empathy Scale (Test de Empatia Cognitiva y Afectiva); NA: not available.

Korean, Portuguese, Slovak, Spanish and Turkish). Adaptations included short versions of the original questionnaires and child parent-reported versions of adolescents self-reported measures. Most studies also evaluated the psychometric properties of the measurements, including validity and reliability. The sample size ranged from 51 to 2714.

Measures of empathy

A total of 16 measures were used to assess the construct of empathy in children and adolescents (Table 3). Further details on each measure are provided in Supplementary Materials.

Psychometric properties and validation samples

All measures consisted in Likert scales with number of items and responses varying for each questionnaire, mainly ranging between 12 and 30, with the Dispositional

Table 2 Included studies aimed at validating adaptations (*n* = 6, A) or translations of the included measures (*n* = 19, B), and assessing further psychometric properties (*n* = 6, C)

Ref.	Measure	Language	Sample size
(A) Adaptation studies			
Auyeung *et al*[95], 2012	EQ– adolescent version	English	1243
Bensalah *et al*[60], 2016	BES – child version	French	410
Merino-Soto and Grimaldo-Muchotrigo [103], 2015	BES – short version	Spanish	135
Overgaauw *et al*[59], 2017	EQ – CA version	Dutch	1250
Pechorro *et al*[104], 2018	BES – short version	Portuguese	543
Salas-Wright *et al*[105], 2013	BES – short version	Spanish	208
Sánchez-Pérez *et al*[58], 2014	BES – parent report	Spanish	364
(B) Translation studies			
Albiero *et al*[106], 2009	BES	Italian	665
Albiero *et al*[107], 2010	BES	Italian	1191
Čavojová *et al*[108], 2012	BES	Slovak	429
D'Ambrosio *et al*[109], 2009	BES	French	446
de Wied *et al*[110], 2007	BEI	Dutch	1978
del Barrio *et al*[111], 2004	BEI	Spanish	832
Geng *et al*[112], 2012	BES	Chinese	1524
Soroa *et al*[113], 201	TECA	Basque	504
Grazzani *et al*[114], 2017	EQ	Italian	304
Hawk *et al*[115], 2013	IRI	Dutch	501
Herrera-López *et al*[116], 201	BES	Spanish	747
Liu *et al*[117], 2018	CASES	Chinese	860
Lucas-Molina *et al*[118], 2018	EQ	Spanish	103
Pechorro *et al*[119], 2015	BES	Portuguese	221
Mestre-Escriva *et al*[120], 2004	IRI	Spanish	1285
Rudra *et al*[121], 2016	EQ-C	Bengali	51
Vilte *et al*[122], 2016	CEAQ	Spanish	297
You *et al*[123], 2018	BES	Korean	1524
Zengin *et al*[124], 2018	AMES	Turkish	212
(C) Psychometric Properties			
Anastácio *et al*[125], 2016	BES	Portuguese	1029
Carrasco Ortiz *et al*[126], 2011	IRI	Spanish	721
Holgado Tello *et al*[127], 2013	IRI	Spanish	721
Lasa Aristu *et al*[128], 2008	BEI	Spanish	2714
Lucas-Molina *et al*[129], 2016	BEI	Spanish	2050
Pechorro *et al*[72], 201	BES	Portuguese	377

AMES: Adolescent Measure of Empathy and Sympathy; BES: Basic Empathy Scale; BEI: Bryant's Empathy Index; CA: children and adolescents; CASES: Cognitive, Affective and Somatic Empathy Scales; CEAQ: Children's Empathic Attitudes Questionnaire; EQ: Empathy Questionnaire; EQ-C: Empathy Quotient for Children; IRI: Interpersonal Reactivity Index; TECA: Cognitive and Affective Empathy Scale (Test de Empatia Cognitiva y Afectiva).

Positive Empathy Scale (DPES) and the Empathy Scale derived from the Psychopathic Personality Inventory (ES-PPI) presenting a relatively low number of items,

Table 3 First validation of selected questionnaires (*n* = 16)

Name	Validation	Subscales	*n*	Response	Age	R	IC	Reliability	Criterion	Convergent /divergent
BEI	Bryant[98], 1984	None	22	1 (low) to 5 (high)	C, A	SR	α = 0.54 to 0.79	T-R: r = 0.74 to .83	NA	NA
IRI	Litvack-Miller *et al*[99], 1997	Fantasy; Perspective-taking; Empathic concern; Personal distress	28	0 (not well) to 4 (very well)	C	SR	NA	NA	NA	NA
SME	Rey[63], 2003	None	15	1 (never) to 4 (always)	A	SR	α = 0.78	NA	HC > CD: *P* = 0.008	NA
F&T	Garton *et al* [89], 2005	Affective; Cognitive	12	1 (not like me) to 5 (very like me)	C	SR	α = 0.54 to 0.69	NA	F > M	NA
BES	Jolliffe and Farrington[6], 2006	Affective; Cognitive	20	1 (agree) to 5 (disagree)	A	SR	α = 0.79 to 0.85	NA	F > M: *P* < 0.0001	IRI: r = 0.43 to 0.53; TAS: r = –0.20 to –0.17; SDS: r = –0.11 to 0.00
GEM	Dadds *et al* [100], 2007	Cognitive; Affective	23	–4 (disagree) to +4 (agree)	C, A	PR	α = 0.81 (tot); α = 0.62 to 0.83	IRR: r = 0.40 to 0.38; T-R: r = 0.69	F > M: *P* < 0.001	IQ: r = 0.30 (cogn); CAI-C: r = –0.12 to –0.31; CAI-N: r = 0.05 to 0.25; IRT: r = 0.30 to 0.56
CEAQ	Funk *et al*[82], 2008	None	16	No/Maybe/Yes	C	SR	α = 0.77	RPR = 0.75; RPSI = 1.75	F > M: *P* < 0.01	BEI: r = 0.57; SDQ-PS: r = 0.39; SDQ-CP: r = –0.17; CSDTC: r = 0.39
DPES	Sallquist *et al* [62], 2009	None	7	1 (really untrue) to 4 (really true)	P	PR	α = 0.81	NA	NA	ITSEA-E: r = 0.43; ITSEA-SC: r = 0.35; Task = 0.47
EQ-C	Auyeung *et al* [64], 2009	None	27	1 (disagree) to 4 (agree)	P, C, A	PR	α = 0.93	T-R: r = 0.86	HC-F > HC-M > ASD; *P* < 0.001	SQ-C: r = –0.13
EQ	Rieffe *et al* [83], 2010	Emotion contagion; Attention to others; Prosocial actions	20	1 (never) to 3 (often)	I, P	PR	α = 0.58 to 0.80	NA	NA	NA
ES-PPI	Whitt and Howard[101], 2013	None	5	1 (false) to 4 (true)	A	SR	α = 0.69	NA	NA	BSI-PS: r = 0.11 to 0.30; APSD: r = –0.18 to –0.08; MAYSI-2: r = 0.08 to 0.21
TECA	Lopèz-Pèrez	Perspective	30	1 (disagree) to 4	C, A	SR		NA	NA	NA

	and Fernadèz [102], 2014	taking; Emotion understanding; Personal distress; Empathic joy		(agree)						
AMES	Vossen *et al* [88], 2015	Affective; Cognitive; Sympathy	12	1 (never) to 5 (always)	C, A	SR	α = 0.75 to 0.86	T-R: r = 0.56 to 0.69	F > M; $P < 0.01$	IRI-EC: r = 0.29 to 0.63; IRI-PT: r = 0.21 to 0.45; PBS: r = 0.14 to 0.50; PA: r = –0.07 to -0.36
EToMS	Wang and Wang[87], 2015	Empathy; Nice ToM; Nasty ToM	16	1 (never) to 5 (always)	P	PR	α = 0.71 to 0.83	NA	F > M	WL-NiceToM: r = 0.21; SL-NastyToM: r = 0.33; FB: r = 0.27 (E) –0.28 (NiceToM)
CASES	Raine and Chen[29], 2017	Affective; Cognitive; Somatic	30	0 (rarely) to 2 (often)	C	SR	α = 0.63 to 0.91	NA	F > M	IQ: r > 0; RPAQ-R: r = –0.11; CBCL-Ext: r < 0; APSD: r = –0.12 to –0.39
EQ	Richaud *et al* [35], 2017	Emotion contagion; Self-other awareness; Perspective taking; Emotional regulation; Empathic action	15	1 (never) to 4 (always)	C	SR	ω = 0.70 to 0.76	NA	NA	PBS-C: r = 0.23 to 0.79; PBS-L: r = 0.21 to 0.49; IRI-PT: r = 0.32 to 0.37; PVAS: r = –0.18 to –0.31; EIS: r = –0.24

Validation refers to the original article in which the questionnaire was first validated. Construct refers to the original article in which the definition of the empathy construct for each questionnaire was provided; *n* refers to number of items. Response refers to the number of available Likert-scale responses for each item of the questionnaires. Age refers to the age range in which the original validation of the questionnaire was performed (*i.e.* infants, aged 1–3 years; preschool children aged 3–6 years; children aged 6–13 years; adolescents aged 13–18 years). R refers to type of report, either self- or parent-report. IC refers to internal consistency, measured by either Cronbach's alpha or McDonald's omega. Criterion and convergent/divergent refer to criterion and convergent/divergent validity, respectively. α: Cronbach's alpha; A: adolescents; AMES: Adolescent Measure of Empathy and Sympathy; APSD: Antisocial Personality Screening Device; ASD: autism spectrum disorder; BES: Basic Empathy Scale; BEI: Bryant's Empathy Index; BSI: Brief Symptom Inventory; C: children; CAI: Cruelty to Animals Inventory; CASES: Cognitive, Affective and Somatic Empathy Scales; CBCL: Child Behaviour Checklist; CD: conduct disorder; CEAQ: Children's Empathic Attitudes Questionnaire; CSDTC: Crandall Social Desirability Test for Children; DPES: Dispositional Positive Empathy Scale; EIS: Emotional Instability Scale; EmQue: Empathy Questionnaire; EQ: Empathy Questionnaire; EQ-C: Empathy Quotient for Children; ES-PPI: Empathy Scale-Psychopathic Personality Inventory; EToMS: Empathy and Theory of Mind Scale; F: females; FB: false belief; F&T: Feeling and Thinking Scale; GEM: Griffith Empathy Measure; HC: healthy controls; I: infants; IC: internal consistency; IQ: intelligence quotient; IRI: Interpersonal Reactivity Index; IRR: inter-rater reliability; IRT: Interpersonal Response Task; ITSEA: Infant-Toddler Social and Emotional Assessment; M: males; MAYSI: Massachusetts Youth Screening Instrument; NA: not available; P: preschool children; PA: physical aggression; PBS: Prosocial Behaviour Scale; PR: parent-report; PVAS: Physical and Verbal Aggression Scale; R: report; RPAQ: Reactive–Proactive Aggression Questionnaire; RPR: Rasch Person Reliability; RPSI: Rasch Person Separation Index; SDQ: Strengths and Difficulties Questionnaire; SDS: Social Desirability Scale; SL: strategic lie; SME: Scale to Measure Empathy; SQ-C: Systemising Quotient for Children; SR: self-report; TAS: Toronto Alexithymia Scale; TECA: Cognitive and Affective Empathy Scale (Test de Empatia Cognitiva y Afectiva); ToM: Theory of mind; T-R: Test-retest; WL: White lie; ω: McDonald's omega.

respectively including seven and five items. Reliability assessments (mainly using Cronbach's α) were available for most measures. Original validations of the measures showed questionable to excellent levels of internal consistency, with α values ranging from about 0.54 to 0.93. The lowest levels were found for the F&T and the Bryant's Empathy Index (BEI) questionnaires, while the Empathy Quotient for Children (EQ-C)

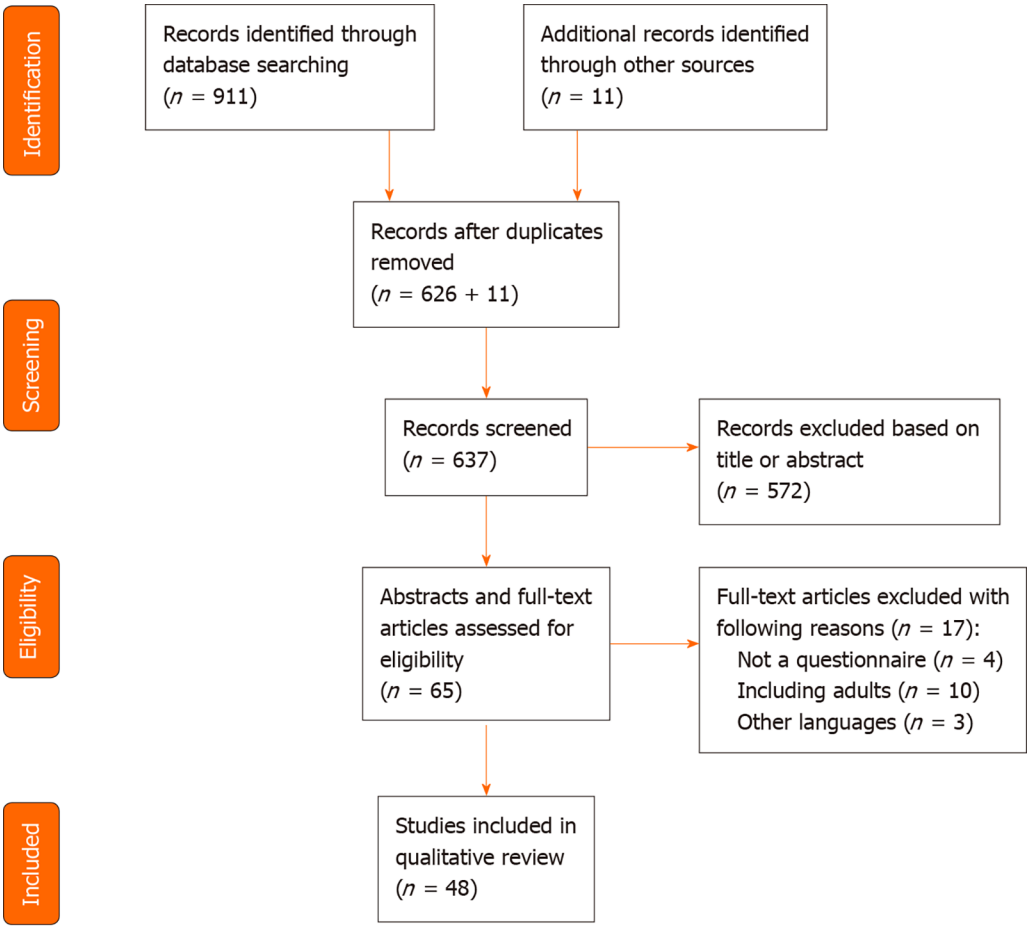

Figure 1 PRISMA flowchart. The process of identification and selection of papers according to PRISMA guidelines is shown in the flowchart. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

demonstrated the highest internal consistency. Test–retest and other reliability measures were uncommon. Good test–retest indexes were found for the BEI and EQ-C scales, while lower levels of reliability were identified for the GEM, Children's Empathic Attitudes Questionnaire (CEAQ) and Adolescents' Measure of Empathy and Sympathy (AMES). Several types of validity assessments were also available. Questionably, criterion validity was mainly based on the finding of higher empathic skills in women than in men. Additionally, the Scale to Measure Empathy (SME) was tested on patients with CD, who showed higher scores than healthy controls, whereas, in the EQ-C, typical individual scored the highest, followed by ASD children who scored the lowest. Convergent and divergent validity was tested by means of several measures, which can hardly allow direct comparisons of the validated questionnaires. Finally, it should be emphasized that, for the ES-PPI scale, content validity appeared questionable; indeed, all its five items could be easily interpreted as related to separation anxiety and interpersonal sensitivity.

As for the type of report, five measures were based on a parental report, while the other 11 were self-reported. Nonetheless, the BES questionnaire, originally developed as a self-report measure for adolescents[6], was also adapted in a parent-report form [58]. The Empathy and theory of mind scale (EToMS), EQ and DPES scales were specifically validated in infants and preschool children, while the SME, BES and ES-PPI measures were originally targeted to adolescents, although the EQ was also adapted for school-aged children and adolescents[59] and the BES for children[60]. No *a priori* restriction was applied to exclude teacher-reported questionnaires; however, no such measure was identified through our search. It is worthwhile noting that the GEM was also previously used for teacher report[61], as well as the abovementioned Infant-Toddler Social and Emotional Assessment questionnaire[62].

Noteworthy, the SME and the EQ-C were originally validated in clinical population of adolescents with CD[63] and children with ASD[64], respectively. In addition, the BEI and the IRI, two of the most widely used scales for empathy, already found a clinical application in the assessment of empathic skills in autism[65,66], conduct

disorders[12] and psychopathic traits[67-69]. Similarly, the GEM has already been used to examine empathy deficits in children with ASD[65], externalizing symptoms with aggressive behavior[61,70], and callous–unemotional traits[71], while the BES has been used in delinquents and institutionalized youths with conduct disorders[72-74]. Those latter three questionnaires also profit from many translations in several languages.

DISCUSSION

Constructs and dimensions: bipartite models

Six measures were monodimensional, while the other 10 appeared to be multidimensional, with variable internal factors. The commonest structure consisted in the combination of the two main components of empathy, namely the affective and cognitive subdivisions, which appear in the F&T, BES and GEM questionnaires. Indeed, most researchers agree on the multidimensionality of the construct of empathy which includes (at least) two main dissociable components[75]. Affective empathy refers to the response to the emotional displays of others, *e.g.*, their facial and vocal expressions and body movements, or to the verbal expression of stimuli with emotional valence[76]. It allows one to automatically relate to other people's emotional states, which is essential for the regulation of social interactions, coordinated activity, and cooperation toward shared goals[24]. Cognitive empathy, instead, refers to the capacity to comprehend another person's emotions, thus leading to the representation of the internal emotional experience of the other[24,76]. Based on the bipartite model of empathy, it has been hypothesized[5,77,78] that a deficit in a specific component relate to a specific neurobehavioral disorder; particularly, cognitive empathy would be specifically affected in ASD, while the affective domain would pertain conduct disorders, especially with callous–unemotional traits, and aggressive behaviors. In his fundamental paper, Blair[5] advocates that "fine cuts" between cognitive and emotional empathy are needed for a better understanding of amygdala dysfunction in psychopathy and autism. More speculatively, Smith[78] identified four main empathy disorders in abnormal developmental circumstances, predicting the existence of two empathy imbalance disorders and two general empathy disorders. The formers include the cognitive empathy deficit disorder (CEDD), consisting of low cognitive ability but high affective sensitivity, and the emotional empathy deficit disorder (EEDD), consisting of low affective sensitivity but high cognitive ability. The latter includes the general empathy deficit disorder (GEDD), consisting of low ability and low affective sensitivity, and the general empathy surfeit disorder (GESD), consisting of high cognitive ability and high affective sensitivity. Specifically, CEDD and EEDD respectively reflect the empathic profiles of autism and psychopathy, while GEDD and GESD that of schizoid personality and Williams syndrome. However, a meta-analysis [79] that confirmed the relationship between empathy deficits and criminal offending found a stronger effect for cognitive empathy deficits than for affective empathy. On the contrary, a review of affective empathy deficits in aggressive adolescents underlined the importance of this latter component of empathy[80]. Questionnaires, such as F&T, BES and GEM, that differentiate between these two components of empathy, could be best applied to the clinical assessment of such conditions in order to confirm or confute those hypotheses.

Hoffman's developmental model-based measures

Among bipartite measures, GEM was largely based on developmental stages of empathic skills proposed by Hoffman[75]. Similarly, both EQ and CEAQ were based on Hoffman's developmental model. While the former actually derives its three subscales from Hoffman's first stages of empathic responses development (*i.e.*, Emotion Contagion, Attention to Others' Feelings, Prosocial Actions), the latter has been validated according to the Rasch model and could thus be considered a unidimensional measure, where subjects and items are placed on the same metric scale: children can be, thus, placed along an "empathy development ruler" to quantify their likelihood of achieving different milestones.

Given its impact on empathy measures, Hoffman's developmental model merits further discussion. According to Hoffman[75], during development empathic responses progressively emerge to reach their final expression in adolescence. He distinguished four levels of empathy, which are believed to develop sequentially[20], although they are not mutually exclusive and, according to de Waal[24], follow one each other to build onto the former levels. the first level is labeled as global empathy or

emotion contagion and manifests itself as early as age 18–72 h and throughout the first year. At this level, newborns attend to others' emotions, although nonadaptively, since witnessing someone in distress may result in a similar affective response[81]. In other words, the theory assumes that humans are congenitally hardwired to automatically imitate and synchronize affective expressions, but infants cannot yet differentiate between self and other, which causes them to act as though what happened to the other person happened to them[20]. Furthermore, infants still have difficulties to control their level of arousal, and the ability for self-regulation is negatively associated with symptoms of emotion contagion[82]. The second level, that can be labeled as attention to others' feelings[83], starts after 1 year of age, and persists during the second year of life. At this level, self-other differentiation, perspective-taking, and emotional regulation gradually develop, and infants become aware that although they feel distressed, it is not oneself but someone else who is in actual danger or pain. Other people's emotions can be thus observed with less personal distress[82]. At the third level, by 2 years of age, concern for others may lead the child to react prosocially (prosocial actions)[83]. During the third year of life, children develop this capacity to intervene on behalf of others; this may take a variety of forms, including helping, sharing, and comforting. Later on, children acquire further social competences, that are frequently used as indicators of the development of a theory of mind (ToM), and progressively develop more effective helping strategies[20]. The fourth level in Hoffman's theory, that is empathy for another's life condition'[83], develops during late childhood. It refers to empathic responses, which are not only confined to the situation, but also with another's general level of distress or deprivation. This empathic level may motivate the child and adolescent to feel empathy for people who live in more unfavorable circumstances, and eventually support them by prosocial behaviors (*i.e.*, donating money to charity funds)[82].

Building on Hoffman's model, Decety and Jackson[25] developed a multidimensional model of empathy in children, on which EQ has been based. In particular, the attention to others' feelings stage proposed by Hoffman[20] is further split in the three components of self-awareness, perspective taking and emotion regulation. Self-awareness requires the child to simultaneously reflect on his feelings and suspend his own experience to evoke the thoughts and feelings of others. This skill is a prerequisite for perspective taking which requires the other to be perceived as different from oneself and yet to be put in one's place. Emotional regulation finally implies the ability for cognitive reappraisal of emotional stimuli in order to change one's own affect. Five subscales of EQ have been built accordingly, namely emotion contagion, self-awareness, perspective taking, emotional regulation and empathic action.

Constructs and dimensions: other multidimensional measures

More recent instruments address new facets of empathy, such as the somatic component, or related constructs, such as sympathy, which might integrate further complexity to the original bipartite model and provide new insights in the understanding of psychological faults in the aforementioned disorders. In particular, the AMES includes a sympathy subscale. While previous empathy scales equate affective empathy with sympathy (*e.g.*, IRI), this validated measure was purposefully intended to distinguish between empathy and sympathy. In this scale, the constructs of affective empathy, cognitive empathy and sympathy were respectively based on the definitions proposed by Mehrabian and Epstein[57] (experience of another person's emotion), Hogan[56] (understanding of another person's emotion) and Clark[84] (feeling concern or sorrow for another person's distress). Thus, affective empathy and sympathy are both conceived as emotional reactions to the perceived emotions of another person; however, in the case of empathy, the emotion is the same as the emotion of the other person (emotion congruence), whereas with sympathy, individuals experience feelings of concern and sorrow about distressful events in another person's life. A third dissociable component, somatic or motor empathy, as defined by Blair[76], can be identified using the Cognitive, Affective and Somatic Empathy Scale (CASES). According to Blair[76], somatic empathy occurs when the individual mirrors the motor responses of an observed actor, as described in the perception–action model of empathy[23]. Somatic empathy is thus conceptualized as more automatic than both affective and cognitive components and consists of a primitive form based on mirror neuron system. In other words, the perception of another person experiencing a specific emotion will elicit a motor act or a somatic body response[29]. Notably, the CASES has been recently applied to capture the multifaceted nature of empathy in the different forms of aggression[85]. In addition, affective, cognitive and somatic empathy could be further distinguished into positive and negative forms, based on CASES subscales[29]. As opposed to negative empathy,

positive empathy represents the expression of happiness or joy that results from comprehending another person's positive emotional state or condition. While CASES subscales could be subdivided in positive and negative components of empathy, Cognitive and Affective Empathy Scale (Test de Empatia Cognitiva y Afectiva; TECA) provide a specific subscale for Empathic Joy and DPES was primarily intended to assess positive empathy in children.

Finally, two facets of ToM, *i.e.*, nice and nasty ToM, are considered in the EToMS. ToM refers to the ability to represent the mental states of others[86]. Whether this concept overlaps with that of the cognitive empathy is still under debate. Indeed, both are perspective-taking capacities that are essential in maintaining a functional social relationship. ToM appears to concern the understanding of epistemic mental states such as knowledge and belief, as well as motivational mental states such as desire and emotion, and their consequences on people's behavior, thus possibly including in itself the concept of cognitive empathy[86]. Alternatively, ToM might be limited to the understanding of the intentionality implied by propositional attitudes, while empathy is linked to emotional connectedness and physiological arousal[87]. The distinction between these nice and nasty components captures the essence of the diverse nature of the social consequences of ToM depending on temperament and social goals. Nice ToM behaviors include cooperating, comforting, and considering feelings of others, while Nasty ToM behaviors include teasing, lying, cheating, and blaming.

Research and clinical applications

Given non-negligible differences in structure and validity between previously described instruments, the selection of questionnaires for research and clinical applications should be tailored to specific needs, depending on setting, goals and characteristics of the studied population.

Older scales, such as the BEI, IRI and BES, benefit from a longer tradition and a wider diffusion with respect to more recent instruments and are preferable in clinical settings. Importantly, the BEI and the IRI are self-report questionnaires validated in English for both children and adolescents and in Spanish for adolescents, while the BES has been validated in several European languages, but also in Chinese and Korean. It is noteworthy that the IRI has been used as reference measure for concurrent validity of four other questionnaires[35,83,88], including the BES[6]. In addition, the F&T has been developed as a modified version of the IRI[89]. Both the IRI and BES have been used in ADHD patients, with or without comorbid conditions such as ASD or disruptive behavior disorders[90]. In this context, they showed significant associations with executive functioning[90]. Interestingly, the IRI has also been used to unravel cognitive empathy deficits in adolescents with anorexia[17]. Several other associations between empathy and psychopathological dimensions, including psychopathy, conduct problems and internalizing symptoms such as anxiety and depression, have been revealed using BES in large samples of adolescent inpatients[91-93]. Finally, the BEI has been found to differentiate between children with conduct disorders and controls[68] and has been associated with conduct problems in children and adolescents with ADHD[13].

Despite their advantages, all these measures are self-reported, which may represent a major limitation when patients with ASD or disruptive behavior disorders are assessed. The GEM could represent a valuable option in this respect. Indeed, the GEM has been developed from the BEI as a parent-report scale for both children and adolescents. For instance, the GEM proved useful in differentiating adolescents with and without ASD, whose BEI scores did not differ[65], and children with and without disruptive behavior disorders based on teacher reports[94]. Importantly, the GEM significantly predicted proactive aggression after 1 year in a prospective study of 6- and 7-year-old children[61]. Another useful parent-report instrument, freely available in several languages, is the EQ-C, that has been validated in preschool children, children and adolescents with and without ASD[64,95]. Discrepancies between parent- and self-reports of empathy have been observed in ASD adolescents using this measure: patients were found to report more empathic features than their parents attributed to them[96]. Further to its focus on autistic traits, EQ-C has also been associated with peer-rated aggression in children[97]. More studies using EQ-C in non-ASD samples are, thus, justified.

Several among the other scales warrant further investigations. Some of the more recently developed instruments, for example, have the advantage to explore newer conceptualizations of interest in research settings. The AMES include a subscale dedicated to sympathy construct, while somatic empathy measurement could be specifically addressed only by CASES. Interestingly, the EQ strictly follows the developmental staging model proposed by Hoffman[20], while the CEAQ has been

validated according to the Rasch model and constitute a "developmental ruler" based on Hoffman's stages. Finally, the EQ, who is also based on Hoffman, is the only available instrument validated in infants, preschool children, children and adolescents.

CONCLUSION

Different measures of empathy have been developed and validated in children and adolescents. Even though construct definitions only partially overlap, affective and cognitive domains are commonly evaluated through separate subscales. Many of these instruments constitute extremely useful clinical tools for evaluating impairments in empathic competences and social skills within neurodevelopmental disorders and psychiatric conditions. However, the choice of the measure to use should clearly vary, depending on the setting and the object of study, and the combination of different assessment methods is recommended in order to foresee further improvements in this field and try to overcome the problem of limited convergence of rating scales with more objective measures. Finally, factor-analytic studies exploring the structure of empathy based on different questionnaires, combined with each other, are warranted, especially in the developmental age, in order to test different conceptualizations of empathy, and to unravel significant non-overlapping facets of the construct.

ARTICLE HIGHLIGHTS

Research background

Empathy deficits significantly contribute to developmental psychopathology. Questionnaires are the most used tools for the assessment of empathy both in adults and in children and adolescents.

Research motivation

No comprehensive overview of validated questionnaires for measuring empathy was available for clinicians and researchers in the neurodevelopmental field.

Research objectives

We aimed to identify and describe empirically validated questionnaires assessing empathy in children and adolescents and to provide a summary of related theoretical perspectives on empathy definitional issues.

Research methods

A systematic review of the literature was conducted according to PRISMA guidelines.

Research results

We identified and described 16 measures used to assess empathy in children and adolescents. Most measures were multidimensional. Several instruments were based on a bipartite model of empathy, with dissociable affective and cognitive components. Other tools were built on Hoffman's developmental model or included new facets, such as sympathy or somatic empathy.

Research conclusions

Different scales are suitable in varying research and clinical settings, depending on the object of study, the clinical population, the age range and the models of interest. The combination of different assessment methods is recommended.

Research perspectives

Future studies shall focus on directly comparing psychometric properties and factor-structure of different empathy questionnaires in multiple clinical and community samples.

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SYSTEMATIC REVIEWS

Neurofeedback for insomnia: Current state of research

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Abstract

BACKGROUND

Chronic insomnia affects about 6%-13% of the Canadian population. Although treatments already exist, they each have their own issues. Neurofeedback is a neuromodulation technique that specifically targets abnormal brain activity and is gaining attention as a possible insomnia treatment.

AIM

To review the latest studies pertaining to the use of neurofeedback in the treatment of insomnia.

METHODS

In this non-systematic review, only experimental studies assessing the effects of neurofeedback on patients with insomnia were targeted across four bibliographic databases.

RESULTS

A total of 12 studies were retained. All neurofeedback studies included in this study showed a clear improvement of subjective sleep. However, data concerning objective improvement are contradictory. Most studies regarding surface and z-score neurofeedback show that neurofeedback targeting the sensorimotor rhythm in the sensorimotor cortex may help improve subjective sleep. A placebo effect seems also to be present in some studies. Several limitations were present in each study.

CONCLUSION

While studies concerning neurofeedback as a treatment for insomnia are encouraging, many methodological barriers remain to be resolved to prove its efficacy unequivocally. More studies using robust design parameters, as well as the replication of existing studies, are necessary to support neurofeedback as an effective treatment for insomnia.

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Core Tip: Insomnia is a sleep disorder that is extremely prevalent in the general population. The current treatments offered tend to ignore the neurological marker of insomnia. Neurofeedback is a type of neurotherapy that is based on training one's electrical brain activity to treat multiple ailments including insomnia. In this review, we discuss the different studies that have been published in the last few years concerning the use of neurofeedback to treat insomnia and what needs to be improved in this domain of research.

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INTRODUCTION

Insomnia

Sleep difficulties are very common, with an estimated one-third of adults around the world being dissatisfied with their sleep[1]. Furthermore, approximately 6%-13% of the general population meets all criteria necessary for the diagnosis of insomnia disorder[1-4]. Insomnia is a sleep disorder characterized by a dissatisfaction with the quantity and/or quality of sleep[5]. This dissatisfaction must be associated with difficulty falling asleep, maintaining sleep and/or waking up early in the morning. These difficulties must be present at least 3 nights a week for the past 3 mo and must cause distress or impaired functioning[5].

Not only does insomnia causes distress, it is linked to multiple psychopathologies. In fact, there is a 40% co-occurrence between insomnia symptoms and mental illness [6]. Insomnia is also linked to multiple health problems, such respiratory and cardiac diseases[7]. Insomnia affects everyone differently, and the profile of individuals that suffer from it is very heterogeneous[8]. However, it is widely recognized that hyperarousal plays an important role in insomnia[9-12]. For example, insomnia is linked to an increased heart rate[13], increased facial muscle tension[14] and a higher rate of cortical activation[15]. According to Bonnet and Arand[16], insomnia is a hyperarousal disorder and its treatment should aim to decrease arousal.

Currently, there are two main types of treatment: Medication or cognitive behavioural therapy for insomnia (CBT-I)[17]. Medication has been shown as effective for treating insomnia, while its effects are mainly short-term[18]. Unfortunately, long-term use of medication causes undesirable side effects, such as cognitive and motor coordination problems, physical dependence and rebound insomnia[18,19].

Several studies support the effectiveness of CBT-I in reducing insomnia symptoms, such as wakefulness after sleep onset (WASO) and sleep efficiency (SE)[17,20,21]. However, there is a lack of research establishing that CBT-I leads to significant changes in sleep onset latency (SOL)[22]. It is also important to note that only 60% of individuals receiving CBT-I are considered good sleepers after treatment[23]. The literature showing that CBT-I is effective at decreasing hyperarousal is also quite scarce. In that regard, Altena *et al*[24] have shown a frontal hypoactivation after CBT-I, while Cervena *et al*[25] have shown an increase in slow waves and a slight decrease in beta activity after CBT-I.

While medication is recommended only as a short-term treatment for insomnia with non-equivocally lacking effectiveness in the long-term for treating insomnia[18], CBT-I focuses mainly on behaviors and cognition surrounding sleep[26]. Because hyperarousal has been identified as a predisposing and maintaining factor in insomnia disorder[27,28], it would be advisable to offer treatment, such as neurofeedback (NF), that aims to modulate hyperarousal and which could offer long-term benefits.

NF

NF is a sub-category of biofeedback, a technique where one learns to modulate bodily functions, such as heart rate, through feedback[29]. To do this, biofeedback uses various stimuli corresponding to one's physiological characteristics and presents them to the client (feedback). The client then uses this information to modify his/her physiological functioning[30]. In the case of NF, the physiological signals used and modulated are brainwaves.

NF is based on the principle of operative conditioning[31]. There are many different types of NF, but they all have in common the use of visual and/or auditory stimuli (video, music, *etc*.) as positive reinforcement presented when electroencephalographic (EEG) activity corresponds to the training goal. The withdrawal or modification of this stimulus is used as a negative punishment to inform the individual that his/her brain functioning is diverging from the training goal. With this basic principle, NF can both encourage and dissuade certain brainwaves[32].

The history of neurofeedback is strongly intertwined with that of sensorimotor rhythm, beginning with the studies of Sterman *et al*[33]. Their 1967's study, a precursor in neurofeedback research, led to the discovery of the sensorimotor rhythm (SMR), a brain state present only during periods of motor stillness. The aim of these studies was to reproduce the internal inhibition observed in Pavlov's previous studies, when presenting contradictory conditioned responses. Pavlov had observed that the modification of conditioned responses caused, in time, lethargy and even sleep in dogs. When they attempted to reproduce this effect with cats, they noticed that the suppression of a conditioned response, and thus of movement, was linked to a bursting rhythm localized at the sensorimotor cortex. This rhythm was thus named SMR (11-15 Hz)[34]. They reported that this EEG pattern strongly resembled the sleep spindles observed during sleep. In these studies, they also found that cats were able to induce this rhythm voluntarily. These cats then showed an increase in the density of sleep spindles as well as a reduction in sleep stage transitions and thus prolonged sleep[35].

Since then, research on neurofeedback as a treatment for sleep difficulties often focuses on the control of SMR. The frequencies associated with SMR vary between studies but they usually are around 12 to 15 Hz, sometimes including higher or lower frequencies. Some studies uses the inhibition of higher frequencies, such as high beta frequencies (20-35 Hz), to reduce alertness, whereas others enhance slower frequencies, from delta (less than 4 Hz) to alpha frequencies (8-12 Hz), to promote deep relaxation[36].

The various NF techniques can be divided into two broad categories: closed-loop NF and open-loop NF[37,38]. Open-loop NF aims at regulating EEG activity by using auditory and visual stimuli not representative of the EEG activity at that time. Rather, this type of NF aims at synchronizing brain activity to rhythmic external stimulus. Closed-loop NF, on the other hand, is based on real-time EEG activity to determine characteristics of the transmitted feedback (positive reinforcement or negative punishment)[39]. NF is not regulated by any governmental body. However, some organizations such as the Biofeedback Certification Institute of America and the International Society for Neurofeedback and Research offer guidelines for biofeedback training as well as certifications for clinicians. The list of NF techniques presented in the Results section is not exhaustive and refers only to those used by the studies included in this review.

MATERIALS AND METHODS

This review uses a non-systematic approach to give a general idea of the literature available in the field of NF. Articles were collected on four bibliographic databases: Psycnet, PubMed, Cochrane Central Register of Controlled Trials and Web of Science. For the bibliographic searches, the term "neurofeedback" was combined with the term "insomnia" for all categories with the "AND" operator. Synonyms and Medical Subject Headings for each term were combined with the "OR" operator.

Once articles were identified, those dealing directly with the use of NF for the treatment of insomnia were extracted. Studies focusing on insomnia treatment as a comorbid disorder were included, while those papers simply mentioning sleep difficulties, without any emphasis on it, were excluded. Only scientific articles and abstracts from experimental studies were used for this study. Case studies and retrospective studies were excluded. We included all sleep-related measures and outcomes. Results pertaining to other disorders are not discussed in this review since

our aim is to focus on the efficacy of NF as an insomnia treatment.

Overall, 12 articles were included in this study, including 6 on surface neurofeedback (NFS), 2 on z-score NF, 2 on open-loop NF, 1 on high-resolution, relational, resonance-based, electroencephalic mirroring (HIREEM) NF and 1 on Brain Music NF (see Figure 1 for the schematic of the bibliographical search).

RESULTS

NFS

NFS is a type of closed-loop NF that uses only two to four electrodes and targets a reduced number of cortical regions as well as a reduced number of brainwaves[40]. During NFS, the client will be presented with his/her own EEG activity, at a specific region, in the form of visual and/or auditory stimuli. The purpose of NFS is to increase/decrease specific frequencies at specific locations. Our review identified six studies using NF for the treatment of insomnia (see Table 1 for the study parameters and Table 2 for a summary of the results).

This study[41] used a counterbalance within-subject design with placebo to demonstrate whether NF can improve sleep and cognitive performance in individuals with insomnia. A single group of 24 participants with primary insomnia received 10 sessions of NF during which they had to increase the power of their SMR (12-15 Hz) at C3. They also received five placebo neurofeedback (PF) sessions where they trained the amplitude of non-SMR frequencies at random.

They found a significant increase in SMR power at C3 after NF sessions, with a non-significant increase at C4. No significant change was observed in SMR power across the PF sessions. They reported an increase in fast sleep spindles during non-rapid eye movement (referred to as NREM) but no change in slow sleep spindles. Sleep spindles are EEG waves of a frequency of 12 Hz (slow sleep spindles) to 14 Hz (fast sleep spindles) that are typical of NREM sleep, especially stage 2 sleep[42]. They are markers of the wake-sleep transition and have been theorized to play a role in learning and plasticity as well as in sleep protection by inhibiting sensory processing[43]. Slower sleep spindles have been found in sleep-maintenance insomnia and are linked to insufficient sleep pressure and thus difficulties maintaining sleep[44]. Accordingly, they observed a decrease in the number of awakenings and an increased duration of stage 3 following the NF sessions. The researchers also reported a decrease in subjective sleep complaints following NF and PF sessions, but it was not possible to determine whether this decrease was solely due to NF. On the other hand, physical quality of life improved regardless of the treatment offered, suggesting a placebo effect.

In conclusion, they found that it is possible for individuals with insomnia to increase SMR power, which allowed an objective modification of certain aspects of sleep architecture (N3, fast sleep spindles, number of awakenings). Thus, SMR NF in the sensorimotor cortex would improve sleep architecture, subjective sleep quality and physical quality of life. It is important to note that there is a strong chance that a placebo played a role in this study.

Schabus *et al*[45] tried to replicate their 2014 findings in a double-blind, placebo-controlled study. To do so, they used four groups: a primary insomnia group (INS: n = 16), an insomnia misperception group (MP: n = 9), a sleep control group (n = 26) and a NF control group (n = 12). The MP group was composed of individuals that met the subjective criteria for insomnia but not the objective criteria. The control groups were composed of healthy individuals. The INS and MP groups received 12 NF sessions (increase SMR) and 12 PF sessions (increase non-SMR frequencies at random) in reverse order. Polysomnographic (PSG) data were recorded before and after each condition (NF and PF) for the INS and MP group as well as an initial PSG for the sleep control group. The NF control group received only 12 NF sessions.

They found that participants had a higher SMR power after NF sessions than after PF sessions, suggesting the ability to self-regulate SMR frequencies. The MP group had higher SMR power following the NF sessions than the INS group. The NF control group also had an increase in SMR power, but that increase stabilized after one NF session. The MP group required four sessions and the INS group required six to achieve stabilization of the increase of SMR power. Contradictory to their 2014 study, no significant changes were found in sleep architecture following NF or PF sessions. The authors found that participants' subjective complaints were reduced following the NF as well as the PF sessions, regardless of group (INS/MP), with a larger decrease for participants who started with the NF sessions.

Table 1 Study parameters for surface neurofeedback

Ref.	Groups	Age/sex	Electrode placement	Protocol	Sessions	Control/sham condition
Schabus *et al*[45]	16 primary insomnia; 9 insomnia misperception; 26 sleep control; 12 NF control (criteria: PSG, PSQI, DSM-IV)	Insomnia group: 38.59 ± 11.18-year-old (range: 27- to 50-year-old) / 19 females and 6 males; Sleep control: 35.52 ± 10.63 (range: 24- to 47-year-old) / 19 females and 7 males; NF control: 26.67 ± 4.46 (range: 22- to 32-year-old) / 6 females and 6 males	C3	Enhance: SMR (12-15 Hz)	12 sessions NF 12 Sham (mixed); (2-4 sessions/wk); 8 5 min blocks/session	Enhance random frequencies (other than SMR rhythm) during present sessions (½ first; ½ second)
Schabus *et al*[41]	24 primary insomnia (criteria: PSQI, SIS-D)	34.83 ± 10.6 (range: 24- to 46-year-old) / 17 females and 7 males	C3	Enhance: SMR (12-15 Hz)	N/A	Enhance random frequencies (other than SMR rhythm) during preset sessions
Cortoos *et al*[46]	9 tele-NF; 8 tele-biofeedback; 12 controls	Tele-NF: 41.5-year-old / 3 females and 6 males; Tele-biofeedback: 43.8-year-old / 3 females and 5 males; Controls: 44.4-year-old/5 females and 7 males	Cz	Enhance: SMR (12-15 Hz); Inhibit: Theta (4-8 Hz) and high beta (20-30 Hz); Biofeedback: 50 Hz	18 sessions of 1 h (2-3 sessions/wk)	Control group
Arns *et al*[49]	51 ADHD (SMR: 27, TBR: 10, SMR + TBR: 14); 28 controls	ADHD: (range: 6- to 53-year-old) / 14 females and 37 males; Controls: (range: 21- to 64-year-old) / 15 females and 13 males	SMR: C3;Cz or C4; TBR: Fz; FCz or Cz	Enhance: SMR (12-15 Hz); TBR (20-25 Hz and 15-20 Hz)	29-31 sessions (2-3 sessions/wk); 8 5 min blocks/session	Control group
Sungwon[51]	14 participants; NF; CBT-I (criteria: ISI)	N/A	N/A	Inhibit: Beta	N/A	CBT-I
Shin[50]	4 mild insomnia (Registered at a sleep clinic)	34.8 ± 5.3-year-old/1 female and 3 males	N/A	Enhance: Theta and sigma; Inhibit: Beta	N/A	None

ADHD: Attention deficit hyperactivity disorder; CBT-I: Cognitive behavioral treatment for insomnia; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Fourth edition; NF: Neurofeedback; PSG: Polysomnography; PSQI: Pittsburgh Sleep Quality Index; SIS-D: Structured clinical interview for sleep disorders; SMR: Sensorimotor rhythm; TBR: Theta/Beta ratio.

The researchers therefore suggested that INS and MP participants were able to regulate SMR frequencies following the NF sessions and that this may lead to a decrease in the subjective symptoms of insomnia. However, the subjective effects reported by this study appear quite similar to those obtained with the placebo effect and were not associated with objective changes in PSG data.

In this 2010 study, Cortoos *et al*[46] investigated whether NF can reduce symptoms of primary insomnia using a pretest post-test design with control group. The study consisted of 17 participants with insomnia randomly distributed in two groups for: receipt of 18 NF sessions (n = 9) or receipt of 18 biofeedback sessions (BF; n = 8). A third group of 12 good sleepers was used as a control group to compare initial PSG data. PSG data were recorded for all participants at the beginning of the study and then at the end of the NF/BF sessions for the NF and BF groups.

The NF and BF sessions were ran at home and participants were responsible for electrodes' placement. The BF sessions consisted of relaxing the forehead muscles using information from an electromyogram. The NF group had to increase SMR (12-15 Hz) amplitude and reduce the amplitude of theta (4-8 Hz) and high beta (20-30 Hz) frequencies at Cz.

PSG data from both groups (BF; NF) showed a significant decrease in SOL and WASO. The BF group had a greater decrease in SOL (44.9%) than the NF group (39.7%), while the NF group showed a greater decrease in WASO (53.6%) than the BF group (13.2%). Both groups also had increased rapid eye movement (referred to as REM) duration. Only the NF group reported a significant increase in total sleep time (TST). The sleep diaries of the NF group also reported a significant decrease in SOL and WASO, and an increase in TST. The BF group only reported significant improvement in SE in their sleep diaries.

Cortoos *et al*[46] therefore concluded that NF allows for more significant sleep improvements, particularly TST, than biofeedback. Results of the BF group had a caveat since no participant reported abnormal forehead muscle tension or high somatic arousal compared to the control group, which can indicate that somatic

Table 2 Summary of the results on surface neurofeedback

Ref.	Sleep outcomes measurements	Results
Schabus *et al* [45]	Objective: PSG; EEG; Subjective: PSQI; WHOQLA; SSS	Significant effect for NF compared to PF: (1) Higher SMR-power directly after each session[b]; and (2) Higher spindle density for the fast spindle type (C3 only)[b]; Significant effect for NF and PF: (1) Reduction of subjective sleep complaints after 12 sessions[b]; and (2) Unspecific increase of physical quality of life[b]; Significant effect for INS compared to MP: (1) More wake time[b]; and (2) Less stage 2, stage 3 and REM[b]; Significant effect for MP compared to INS: Higher SMR-power after each session[b]
Schabus *et al* [41]	Subjective: PSQI, Sleep Diary, WHOQLA, WMS-R, BSI	Significant effect only for NF: (1) Increase of SMR activity at C3[a]; (2) Decrease of the number of awakenings[a]; and (3) Increase of stage 3[a]; Significant effect for NF and PF: (1) Reduction in subjective sleep complaints[b]; and (2) Increased physical quality of life[b]
Cortoos *et al* [46]	Objective: PSG; Subjective: Sleep diary	Significant effect only for NF: (1) Decrease of SOL[a] and WASO[a] (Sleep diaries)[a]; and (2) Increased TST[a] and SE[a] (Sleep diaries); Significant effect only for BF: Increase of SE[a] (Sleep diaries); Significant effect for NF and PF: (1) Decrease of SOL[a] and WASO[a] (PSG); and (2) Increase of REM sleep;
Arns *et al*[49]	Subjective: PSQI	Significant effect only for SMR: (1) Decrease of SOL[d]; (2) Decrease of SOL (40.1 min to 19.1 min)[b]; and (3) Correlation between the change in inattention and changes in PSQI[b] and SOL[b]; Significant effect for SMR + TBR: Decrease of SOL (25.8 min to 18.8 min)[a]
Sungwon[51]	Objective: EEG (resting state); Subjective: ISI, PSQI, DBAS	Significant effect only for NF: (1) Decrease of ISI[b]; (2) Changes in PSQI[a]; and (3) Decreased Beta power; Significant effect only for CBT-I: (1) Decrease of ISI[a]; (2) Changes in PSQI[a]; and (3) Decrease of DBAS[a]
Shin[50]	Objective: EEG	Significant effect only for NF: Decreased spectral power for theta[a]

[a]$P < 0.05$.
[b]$P < 0.01$, pre *vs* post.
[d]$P < 0.01$ pre-treatment *vs* mid-treatment.
BF: Biofeedback; BSI: Brief Symptom Inventory; DBAS: Dysfunctional Beliefs and Attitude about Sleep; EEG: Electroencephalography; INS: Primary insomnia; MP: Insomnia misperception; NF: Neurofeedback; PF: Placebo neurofeedback; PSG: Polysomnography; PSQI: Pittsburgh Sleep Quality Index; REM: Rapid eye movement; TBR: Theta/Beta ratio; SE: Sleep efficiency; SOL: Sleep onset latency; SMR: Sensorimotor rhythm; SSS: Stanford Sleepiness Scale; WASO: Wakefulness after sleep onset; WHOQLA: World Health Organization Quality of Life Assessment; WMS-R: Wechsler Memory Scale – Revised.

arousal was not an issue for the participants. It is also important to note that although sleep diaries in the NF group showed an overall improvement in sleep, there was no significant change in sleep diaries completed the day after the PSG recordings compared to those completed at home. This suggests a strong influence of the environment on the results, which is in accordance with sleep studies that have shown the effects of sleep laboratories on sleep parameters[47,48].

The purpose of this study[49] was to verify the presence of sleep difficulties in individuals with attention deficit disorder (ADHD) and to test the effects of SMR and theta/beta (TBR) NF on ADHD symptoms and the associated sleep difficulties. This study used an open-label design including a control group (n = 28) and an ADHD group (n = 51). The ADHD group was divided into three groups: a group (SMR) receiving NF sessions aimed at increasing SMR (n = 27), a group (TBR) aimed at increasing beta waves outside SMR frequencies (20-25 Hz, 15-20 Hz) and inhibiting theta waves (n = 10), and a last group receiving NF sessions combining SMR and TBR treatments (n = 9). The remaining five participants of the ADHD group were used as a control group for the initial measures. On average, participants received 30 NF sessions.

SMR and TBR NF significantly decreased SOL (SMR: 40-19 min; TBR: 26-19 min). SMR NF resulted in a rapid decrease in SOL between pre-treatment and mid-treatment measurements, followed by a plateau until the end of the sessions. TBR NF showed opposite results, *i.e.* a non-significant decrease for the first half of treatment and then a strong significant decrease during the second half. Strangely, they found that individuals who learned to increase their SMR during SMR NF sessions reported a smaller decrease in their Pittsburgh Sleep Quality Index (PSQI) score.

In this study[50], the researcher wished to quantify the effects of NF on the brain waves of individuals suffering from insomnia. To do so, he administered a randomized series of NF (increasing theta and sigma waves and decreasing beta waves) and placebo (PF) sessions.

By comparing the NF sessions to the PF sessions, Shin found a significant decrease in theta spectral power in the NF group. Mental slowness (delta to alpha ratio) increased slightly, but not significantly, during NF sessions. This study therefore suggests that individuals experience greater fatigue during NF sessions, which could

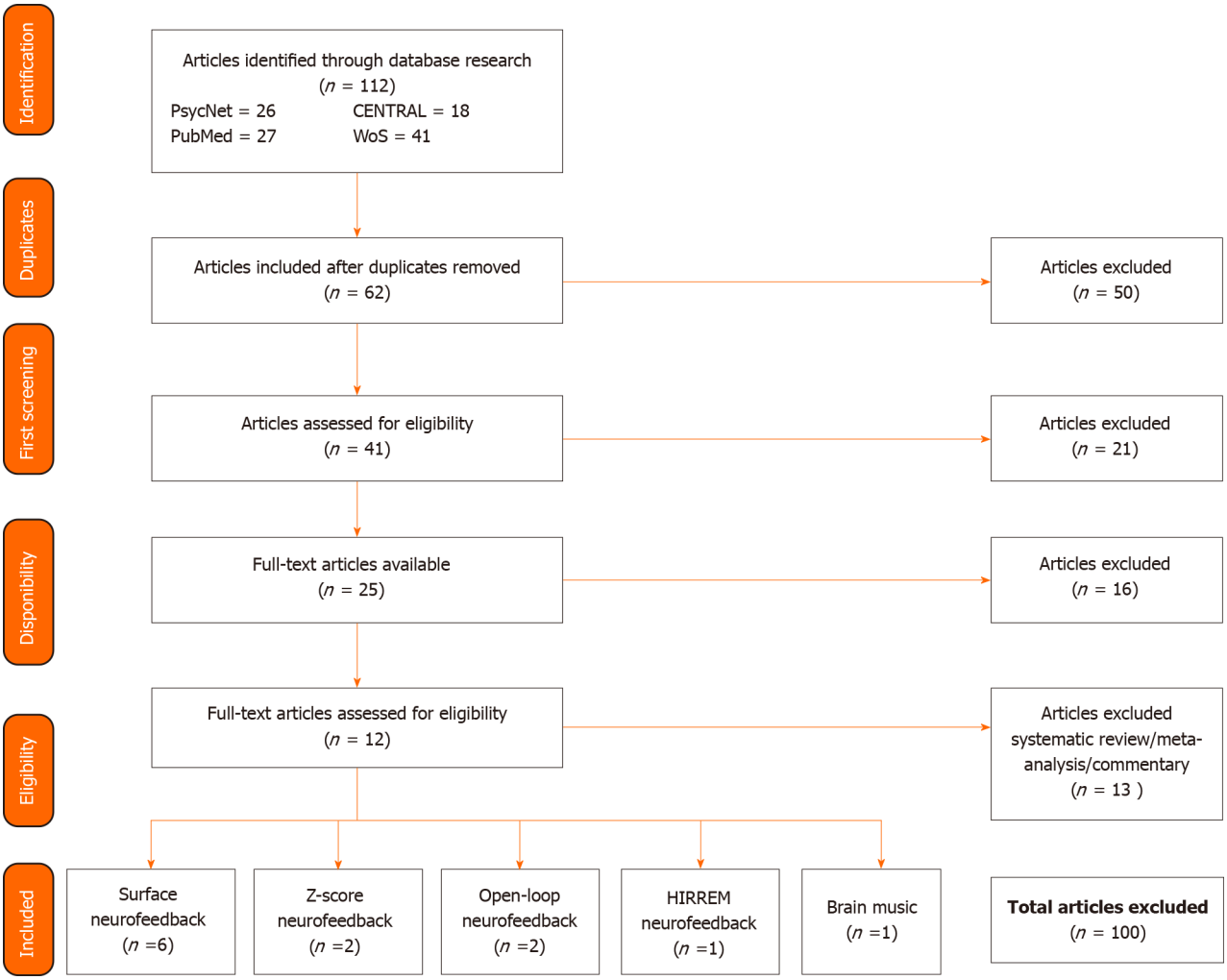

Figure 1 Summary of the bibliographical research. A total of 112 articles were extracted from four different databases. Fifty articles were excluded at first since they were duplicates. Twenty-one articles were excluded as they were not focused on neurofeedback as a treatment for insomnia. Sixteen articles were excluded since they were not available to study. Thirteen articles were then excluded as they were not experimental studies. A total of 100 articles were excluded. Twelve articles were included in this review. HIRREM: High-resolution, relational, resonance-based, electroencephalic mirroring; WoS: Web of Science.

explain sleep improvements by increasing sleep pressure and thus facilitating sleep onset.

In this abstract, Sungwon[51] verified whether NF is as effective as CBT-I in treating insomnia. A total of 14 participants were randomly assigned to two groups, one receiving NF sessions and one receiving CBT-I sessions. An EEG (resting state) was recorded before and after each condition.

Participants in both groups reported significantly lower Insomnia Severity Index (ISI) and PSQI scores following treatment. In contrast, only the CBT-I group reported a significant decrease of their Dysfunctional Belief and Attitudes about Sleep scores and only the NF group showed a significant decrease in beta potency. The author therefore concluded that both treatments are effective in reducing insomnia but each in its own way. NF reduces hyperarousal, while CBT-I reduces dysfunctional thoughts about sleep.

The majority of the studies aimed at increasing SMR in the sensorimotor cortex[41,45,46,49], and the number of sessions varied between 12 to 31 sessions at a minimum of two sessions per week. A total of four studies concerning NFS used a combination of objective and subjective measures[41,45,46,50]. All studies except one used subjective measures[50]. All of the studies using subjective measures reported a subjective improvement of sleep, such as SOL[46,49], WASO[41,46], TST[46] and subjective sleep complaints[41,45]. The results of objective measures were varied, but the recurrent finding was that EEG activity was changed after NF sessions, which suggests that the participants were capable of modulating their own EEG activity[41,45,50]. These results support the idea that modulation of EEG activity is possible and that it can reduce insomnia symptoms. However, a placebo effect was noted in the

Schabus[41,45]'s studies.

Z-score NF

Z-score NF (live z-score based training, LZT) is also part of the closed-loop NF family and is based on the same principles as NFS. The main difference is that the LZT is not based on the power spectral analysis of specific brain waves but on its comparison to the population average. To do this, EEG activity is compared in real time to a normative database that accounts for age, gender and handedness to provide a score (Z-score) representing the position of the client related to the population average[40, 52]. The purpose of LZT is to bring this score closer to the population average (Z = 0). This type of NF therefore aims to normalize brain activity at one or multiple cerebral regions. We included two studies in our literature review (see Tables 3 and 4).

The purpose of this study[53] was to determine whether two z-score NF protocols, one SMR protocol and one QEEG-guided and individualized protocol, can lead to a decrease in sleep and daytime dysfunction associated with insomnia. This pilot study used a randomized, parallel-group, single-blind experimental design.

All participants received a maximum of 15 sessions. They could stop sessions early when they felt that their insomnia had been successfully treated or when they were able to achieve normalization (Z-score < 0.5) of 80% of the trained variables for 80% of the training time. The SMR group had to increase, at Cz and C4, SMR frequencies (12-15 Hz) while inhibiting theta (4-8 Hz) and high beta (25-30 Hz) waves. Participants in this group also had to ensure that amplitudes and brain connectivity at the trained regions remained closed to the database average. Participants in the individualized protocol group were given a protocol tailored to their own brain activity, based on the four brain regions with the highest level of abnormal activity (highest z-score) identified during a quantitative EEG (QEEG). QEEG is the quantification of EEG data in order to compare it to databases or to highlight specific waveform components[54]. During training, the individualized protocol group had to normalize z-scores that deviated from the average of the database of delta, theta, alpha and beta waves amplitudes present in the four regions with the highest Z-score. They also had to normalize coherence, asymmetry and lag phase.

By the end of sessions, all participants had achieved the normalization of 80% of the trained variables for 80% of the training time. On average, participants achieved normalization of 88% of the variables for 80% of the training time (range: 80%-95%). On the other hand, no participant achieved complete normalization of all trained variables. Approximately 50% of participants were able to train closer to normal in their last session, with a Z-score of ± 1.5 on all variables. All but one participant of the SMR group managed to increase their SMR Z-score at Cz and C4, but there was no overall significant increase in SMR. For participants in the individualized protocol group, the proportion of abnormal z-scores was significantly lower after treatment for all brain regions, particularly for delta and beta waves. There was no significant difference between the different regions due to the individual aspect of their training protocols.

Following training, all participants reported an ISI score below the insomnia threshold (< 10) and 7 of the 8 participants reported a PSQI score below the insomnia threshold (< 5). The eighth participant had a PSQI score of 6. Half of the participants reported a decrease in WASO. Seven of the eight participants also reported an increase in TST. Six participants completed the 6-9 mo follow-up for the ISI. Five of the six participants remained below the threshold for insomnia, with three experiencing further sleep improvements in the following months. The sixth participant reported the same score as at their initial ISI.

In conclusion, the researchers reported that the SMR protocol achieved the same results as the individualized protocol in a simpler manner. They suggested that z-score NF is effective in the treatment of insomnia and that effects may last, or even improve, in the months following the end of treatment.

Information for this study[55] is taken from a brief abstract. The aim of this study was to observe the neurometric changes generated by 20 Z-score NF sessions. To do so, authors compared the initial and final QEEGs of 6 patients from the Nepsa clinic. A significant difference in the z-scores was found between the initial and final QEEGs, *i.e.* Z-scores out of range of the -1 to 1 average. Participants were also more likely to decrease the Z-score (normalization) than to increase it. Authors also reported a subjective improvement in patients' symptoms, who were asked to rate them on a visual scale. No information was given on the specific symptoms improved. Researchers therefore suggested that z-score NF allows normalization of EEG activity and the alleviation of insomnia symptoms.

Table 3 Study parameters for z-score neurofeedback

Ref.	Groups	Age/sex	Electrode placement	Protocol	Sessions	Sham condition
Hammer *et al*[53]	5 SMR; 3 IND	49.63-year-old / 5 females and 3 males	SMR: Cz and C4; IND: 4-channel (highest abnormal sites)	SMR: Increase SMR (12-15 Hz) and inhibit excessive theta (4-8 Hz) and high beta (25-30 Hz). Normalization at Cz/C4 (Amplitude, connectivity); IND: Normalization of amplitudes, coherence, asymmetry and phase lag with the highest Z-scores (> 1.96) at the 4-channels trained	Range: 9 to 15 sessions; (2 sessions/wk); 20 min/session	None
Perez-Elvira *et al* [55]	6 participants with insomnia and/or learning disorder	Range: 16- to 30-year-old	N/A	Normalization of the highest Z-score	20 sessions; (2 sessions/wk)	None

IND: Individualized protocols; SMR: Sensorimotor rhythm.

Table 4 Summary of the results on z-score neurofeedback

Ref.	Sleep outcomes measurements	Results
Hammer *et al*[53]	Objective: QEEG (Z-score); Subjective: PSQI, ISI	Significant effect only for SMR: Decrease z-score; Significant effect only for IND: Decreased proportion of abnormal z-scores at all 19 sites[b], especially for delta[b] and beta[b] bands; Significant effect for SMR and IND: (1) Decreased score for ISI[b], for PSQI[b]: All participants finished under the threshold for insomnia (ISI < 10; PSQI < 5, except 1 at 6); and (2) Increased TST[b]; Results of the 6-9 mo follow up: 5 out of 6 participants remained below the ISI threshold for insomnia; 3 of the 5 improved during the months following the end of the treatment
Perez-Elvira *et al* [55]	Objective: QEEG; Subjective: Visual analogue scale on their symptoms	Significant effect: (1) Significant difference of 5.70% between pre- and post-QEEGs; (2) More probable to normalize then to get further away from normalization[a]; and (3) Improvement of symptoms

[a]$P < 0.05$.

[b]$P < 0.01$ pre *vs* post.

IND: Individualized protocol; ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; QEEG: Quantitative Electroencephalogram; SE: Sleep efficiency; SMR: Sensorimotor rhythm; TST: Total sleep time.

Only two studies on Z-score NF were included in this review. Both of them found that participants were able to normalize their EEG activity in the NF sessions by reducing the proportion of abnormal z-scores. The number of sessions varied between nine and twenty sessions, at a rate of two per week. They all found a subjective improvement in sleep following the treatment. Only one study described the subjective improvement and the authors reported an increase of TST[53]. None of the studies used a placebo group. Both studies supported the idea that normalization of EEG activity was possible through z-score NF.

High-resolution, relational, resonance-based, electroencephalic mirroring

High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM) NF is a closed-loop NF technique aiming at improving neurodynamic self-regulation by presenting the brain with its own oscillatory pattern through auditory stimuli[56]. To do this, EEG activity is recorded at two locations (usually contralateral) on the scalp [57]. This activity is then translated into music based on the dominant frequency of the client's EEG activity. This creates a resonance between the music and the neural oscillations, thus encouraging self-regulation. A HIRREM session consists of several training protocols[56]. HIRREM NF thus aims at regulating the general oscillatory pattern. Only one study using this technique was used in this review (see Tables 5 and 6).

In their 2012 study, Tegeler *et al*[56] investigated whether HIRREM reduces insomnia symptoms. To do so, they used a randomized, unblinded, wait-list control, crossover, superiority study design. A first group (n = 10) received eight to twelve HIRREM sessions plus usual care, while a second group (n = 10) was placed on a wait-list control (usual care).

The researchers reported a significant drop of 10.3 points in ISI scores for participants following the HIRREM sessions, with 9 out of 10 participants in the HIRREM group now being just below the threshold (15 to 21) for moderate insomnia.

Table 5 Study parameters for high-resolution, relational, resonance-based, electroencephalic mirroring neurofeedback

Ref.	Groups	Age/sex	Electrode placement	Protocol	Sessions	Sham condition
Tegeler *et al*[56]	10 HUC; 9 UC (criteria: Clinical diagnosis (clinician referral and ISI)	HUC: 41.3 ± 17.5-year-old / 8 females and 2 males; UC: 49.5 ± 8.1-year-old / 6 females and 4 males	Two-channel, changes with each protocol	Each session comprises of 4-8 protocols	8-12 sessions of up to 90 min over 3 wk	None

HUC: HIRREM plus usual care; ISI: Insomnia Severity Index; UC: Usual care (wait-list).

Table 6 Summary of the results on high-resolution, relational, resonance-based, electroencephalic mirroring neurofeedback

Ref.	Sleep outcomes measurements	Results
Tegeler *et al* [56]	Subjective: ISI	Significant effects only for HUC: Decrease of ISI score[b]; Significant effect only for UC: Decrease of ISI score, once the treatment is received

[b]$P < 0.01$ pre *vs* post.

HUC: HIRREM plus usual care; ISI: Insomnia Severity Index; UC: Usual care (wait-list).

The wait-list group also reported a significant decrease in ISI scores, but only 6 out of 10 participants scored below the threshold for moderate insomnia (< 15) after receiving HIRREM sessions. ISI scores were stable for both groups 1 mo after the last HIRREM session. Finally, they appeared to have decreased in high-frequency brainwaves power (23-36 Hz) in temporal regions (T3/T4). A power decrease in high frequency brainwaves (23-36 Hz) in temporal regions (T3/T4) was also observed for all participants. However, no information was provided as to whether this decrease was statistically significant.

Open-loop audio-visual entrainment

Open-loop audiovisual training (AVE) is, as the name suggests, part of the open-loop NF category. It is designed to stimulate the cerebral cortex using goggles and headphones programmed to provide visual and auditory stimuli in the form of synchronous lights and auditory pulsations. Stimuli are constant, repetitive and delivered at a predetermined frequency to arouse the thalamus and the neo-cortex, where visual and auditory information will be respectively processed[38]. This stimulation is believed to synchronize neuronal activity between the thalamus and neo-cortex, which will subsequently spread to the rest of the cerebral cortex *via* thalamo-cortical-thalamic circuits[37,38]. A total of two articles using this technique were included in this review (see Tables 7 and 8).

In their study, Tang *et al*[37] used a pretest and post-test design to test the effectiveness of a daily 30-min AVE at bedtime for 1 mo in a group of 8 elderly people with chronic insomnia. Participants were required to use an AVE device. Sound stimuli gradually decreased from 8 Hz (theta/alpha), associated with a mental state of relaxed wakefulness, to 1 Hz (delta), which is usually associated with deeper sleep.

At the end of the month, researchers observed that 63% of participants no longer met the threshold for insomnia according to scores on the ISI (ISI ≤ 7). Although there was no significant pre/post difference in the overall ISI score, authors reported a significant improvement for daytime functioning and sleep quality. Clinical parameters reported in sleep diaries (SOL, TST, WASO) were not significantly different between subjects when compared across the five measurement periods (pre-treatment and subsequent 4 wkly sessions). However, the trend between weeks suggested that AVE effects appeared right in the first week and then stabilized.

As a follow-up to their 2015 study, Tang *et al*[58] recruited 19 seniors to test AVE NF on EEG activity during a 30-min session. To do so, they randomly assigned participants to two groups, AVE NF ($n = 9$) or placebo stimulation ($n = 7$). The placebo stimulation session consisted of a color changing dim light provided by goggles and a monotonous tone decreasing in frequency from 1 Hz to 0.2 Hz. The AVE group received flashing light (red and green spectrum) from goggles as well as auditory pulsations gradually changing from 10 Hz (alpha) to 2 Hz (delta). A QEEG (5 min, eyes closed, resting state) was recorded before and during both AVE and placebo

Table 7 Study parameters for open-loop audiovisual training neurofeedback

Ref.	Groups	Age/sex	Electrode placement	Protocol	Sessions	Sham condition
Tang *et al* [37]	8 chronic insomnia (criteria: ISI)	88 ± 8.7-year-old / 7 females and 1 male	N/A	Progressive reduction from 8 Hz to 1 Hz with flickering lights	30 sessions of 30 min (at bedtime) over 4 wk	None
Tang *et al* [58]	9 insomnia and chronic pain AVE; 7 insomnia and chronic pain Placebo (criteria: ISI)	AVE group: 67.2 ± 5.0-year-old / N/A; Placebo group: 69.6 ± 4.4-year-old / N/A	N/A	Progressive reduction from 10 Hz to 2 Hz with pulsing lights	1 session	Progressive reduction from 1 to 0.2 Hz with constant dim light changing in color

AVE: Open-loop audiovisual training; ISI: Insomnia Severity Index.

Table 8 Summary of the results for open-loop audiovisual training neurofeedback

Ref.	Sleep outcomes measurements	Results
Tang *et al* [37]	Subjective: ISI, PSQI, sleep diary	Significant effect: Decreased ISI score (15.6 ± 4.8 to 8.0 ± 6.4)[b]
Tang *et al* [58]	Objective: QEEG; Subjective: ISI, PSQI	Significant effect only for AVE: Increased delta frequencies' absolute power on all 19 EEG channels; Significant difference between AVE and placebo: Delta power at Cz

[b]$P < 0.01$ pre *vs* post.

ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; QEEG: Quantitative electroencephalogram.

sessions. Results were compared to a normative database taking into account age, gender and handedness.

At initial assessment, all participants had higher absolute power for high-beta (21-34 Hz) and gamma waves (35-45 Hz) than the database. After the experimental session, participants in the AVE group had a significant increase in the absolute power of delta waves on all 19 EEG channels, while participants of the placebo group had no significant EEG power change in any band frequency. Participants of the AVE group had higher delta power at Cz after the AVE sessions than the placebo group. Specific brain regions displaying a significant increase in delta power in the AVE group were central (Cz), fronto-parietal (*i.e.*, Fp) and occipital (*i.e.* O1 and O2) regions. According to the authors, this study showed that AVE NF allows for immediate changes in the EEG activity.

Both studies on AVE neurofeedback were conducted by Tang *et al*[58]'s research team. One study concerned the subjective improvement of sleep after 30 sessions and found that AVE neurofeedback led to a significant decrease of ISI scores. The second study concerned the objective effect of one session of AVE NF on brain activity. They found that participants presented increased delta frequencies, even when compared to a placebo group. This supports the idea that AVE NF can modulate EEG activity and improve insomnia symptoms.

Brain music

Brain Music NF is a type of open-loop NF that closely resembles HIRREM. This type of NF also uses musical compositions generated from one's brain activity. Music is created from various EEG parameters, such as frequency ratios of certain waves modifying octave selection, tempo, volume in the left or right ear, *etc.*[59]. Music tracks are built to correspond to two states of rest, one active and one calm, and to encourage brain functions associated with these mental states[60]. However, unlike HIRREM, the musical compositions are generated during an initial assessment, and the individual under training then listens to their own musical compositions at home, without being connected to an EEG. Thus, although the music reflects a specific brain state experienced by the individual in the past, it does not adapt to the individual's EEG fluctuations during a training session[60]. Very few papers regarding this technique were found, and only one met our inclusion criteria (see Tables 9 and 10).

DuRousseau *et al*[60] investigated whether a music-based NF treatment could improve sleep quality, mood and daytime functioning in policemen and firefighters

Table 9 Study parameters for brain music

Ref.	Groups	Age/sex	Electrode placement	Protocol	Sessions	Sham condition
DuRousseau *et al*[60]	15 OPS support; 20 first responders; 6 controls	Range 24- to 58-year-old / 13 females and 28 males	F3; F4; C3; C4	Brain Music (1-4 Hz up to 30 Hz)	N/A	Enhance random frequencies during preset sessions

OPS: Operational support; N/A: Not available.

Table 10 Summary of the results on brain music neurofeedback

Ref.	Sleep outcomes measurements	Results
DuRousseau *et al*[60]	Subjective: 128-questions homemade questionnaire	Significant effect for all groups (except control): Improved sleep quality[a]

[a]$P = 0.05$ pre *vs* post.

using a pre-test and post-test design with a control group. Participants were then given a copy of their personalized composition and had to listen to it during the day for 4 wk.

The study consisted of three groups: a group of individuals working in operational support of first responders ($n = 15$), a group of first responders ($n = 20$) and a control group of first responders ($n = 6$). Individuals in the control group were given the composition of another participant. Results are based on a 128-item questionnaire created by the group that focuses on mood, sleep quality, insomnia level, job performance and life satisfaction.

They found an improvement in sleep quality in 90% of participants (all groups combined) but more particularly in the two experimental groups. However, since the control group also reported improvements, it is possible that a placebo effect is present or that simply listening to music before falling asleep promotes sleep. Moreover, this study is based only on a subjective measure, the 128-item questionnaire. It is therefore difficult to estimate whether changes are really due to Brain Music training and not to a placebo effect.

A majority of studies included in this review were centered on closed-loop NF, precisely NFS[41,45,46,49-51] and Z-score NF[53,55]. They mostly used a protocol aimed at increasing SMR (12-15 Hz)[41,45,46,49,53].

All 10 studies using subjective measures reported subjective improvements in sleep [37,41,45,46,49,51,53,55,56,60]. The subjective sleep characteristics that most often appeared to be improved by NF, regardless of type, are SOL[46,49], WASO[45,46] and TST[46,53]. Another subjective improvement reported by studies is subjective complaints[41,45]. It should be noted that some studies[37,51,56,60] only reported changes in sleep using general questionnaires' scores (ISI, PSQI, *etc*.), without providing details on the specific sleep characteristics that had improved.

Only six out of twelve studies[41,45,46,50,55,58] used objective measures to verify sleep improvement. The objective results are very varied and do not reach a clear consensus. The PSG data were mostly used to verify sleep characteristics used in subjective measures such as TST, WASO, *etc*. Only a few studies used polysomnography to verify changes to sleep architecture. For example, Schabus *et al*[41] reported an increase in N3, whereas Cortoos *et al*[46] reported an increase of REM. The EEG data were mostly used to assess EEG activity right after the NF sessions. Most studies using objective measures reported a change in the brainwave-trained[41,45,50], supporting the idea that an individual is capable of regulating his/her own EEG activity. However, this change is not always sustained over time[41], which calls into question the idea of learning retention and its application in everyday life.

DISCUSSION

Results extracted from this review show that, although the use of NF seems encouraging for the treatment of insomnia, there are few studies in this field of research. Moreover, available studies often show methodological or clinical limits.

In general, NF appears to lead to improvements in sleep quality for individuals with insomnia, particularly SOL, WASO, TST, SE and subjective sleep complaints. In a few cases, improvements allowed participants to no longer meet the criteria for an insomnia diagnosis[53,56]. Studies on the objective effects of NF report conflicting results, so it is difficult to draw a clear conclusion. Still, most studies agree that objective measures of NF seem to confirm its ability to alter positively the electrical functioning of the brain during training, but it is unclear whether this effect persists in everyday life. It will be necessary for future studies to implement objective measures, such as EEG and PSG, to prove the efficacy of NF.

The most commonly used training protocol is aimed at increasing SMR oscillations in the sensorimotor cortex. The SMR is linked to a state of relaxed wakefulness as well as to NREM sleep[35,41]. The decrease in insomnia symptoms with the increase in SMR frequencies tend to support the hyperarousal model that postulates that individuals with insomnia present higher mental and physiological hyperarousal. For example, compared with good sleepers, individuals with insomnia generally present an increased power in fast EEG frequency bands during sleep[61]. By increasing SMR, NF counteracts for cortical hyperarousal associated with insomnia by attenuating the power of high-frequency EEG waves[41]. Some studies have used neuromodulation techniques, other than NF, that aim at reducing hyperarousal, such as transcranial magnetic stimulation, to treat insomnia, but the evidence remains scarce[62]. It would be interesting to verify the efficacy of NF for the treatment of other disorders that are characterized by hyperarousal such as post-traumatic stress disorder[63]. Such studies would provide additional support to the hypothesis that neuromodulation techniques, such as NF, reduce insomnia symptoms by decreasing cortical hyperarousal.

Common problems in NF studies

Although results of studies included in this review are encouraging for the future of NF in the treatment of insomnia, several impediments are present and obscure its effectiveness.

Lack of consensus and replication: First, there is a lack of consensus on the type of protocols to be used according to the different NF techniques. While trained brainwaves vary greatly between studies, guidelines for duration, frequency and number of sessions are necessary. For example, NF duration ranges from eight to thirty sessions at a rate of two to four sessions per week. However, some researchers suggest that up to 40 sessions of NFS and 10 sessions of LZT NF are necessary to change efficiently behavior and symptoms[64,65]. Therefore, without clear guidelines, it is challenging to replicate each study correctly. It is therefore essential for researchers to share clearly how their study was conducted and to be consistent in terms of training parameters. It is only then that researchers will be able to replicate other studies adequately.

Small sample size: NF studies generally have a small sample size. Whether this is because of the complexity of studies or the burden imposed upon participants during participation, larger sample size would be indicated to obtain reliable results that could then be generalized to the general population or the one under study. There is still undeniable advocacy towards the scientific community to run large-scale NF studies.

Insufficient placebo group: Studies with a pre-/post-test design without a placebo or even a control group are currently the standard in NF research. Studies using placebo groups often report a placebo effect that is sometimes equal to that of the one provided by NF. Reported placebo effects should be considered with caution because it is difficult to create a placebo treatment that can actually mislead participants without mistakenly producing neurophysiological neurological changes. For example, in the Schabus *et al*[41,45] studies, the placebo groups had to increase power in random EEG frequencies, other than those targeted by the experimental condition. Although these EEG frequencies were varied with each session to avoid long-term learning, it is difficult to argue that the placebo treatment was completely inactive. There is always the possibility of learning to modulate random EEG activity[66]. Since no alternative currently exists, the Schabus *et al*[41,45] studies represent the golden standard for placebo protocols. Understandably, to develop a truly inactive placebo treatment will require improvements to the ones currently used in research.

Possible bias: Sadly, only the study by Schabus *et al*[45] used a double-blind design. Although some studies are single-blind, it is difficult to ignore researchers' bias of their studies' outcomes, especially if participants are aware of the training condition. It

would therefore be crucial to use the double-blind design more often.

Limits

This review also has limitations. First, we focused on studies dealing with the treatment of insomnia. Studies using the general term of 'sleep difficulties' were not included and it would be interesting in the future to include these studies since favorable results with the use of NF were obtained. For example, NF was found to help reduce sleep difficulties in individuals that suffered from childhood obesity[67], seizures[68], fibromyalgia[69], stroke[70], traumatic brain injury[71], post-traumatic stress[71], *etc*. Second, our approach was a non-systematic one. It is possible that some studies have been discarded but would have contributed to our understanding of this encouraging treatment for insomnia.

CONCLUSION

Altogether, results of research using NF as a treatment for insomnia are encouraging with respect to subjective improvements in insomnia symptoms, specifically SOL, WASO and TST. The increase in SMR frequencies coupled with a decrease of insomnia symptoms, as seen in multiple studies, seem to support the hyperarousal model of insomnia. It will be interesting to study the efficacy of NF on other disorders characterized by hyperarousal, such as post-traumatic stress disorder, as a way to confirm if this technique reduces sleep difficulties by reducing cortical hyperarousal. However, multiple improvements are necessary in NF research beforehand to create reliable studies.

According to our literature review, there is an urgent need of double-blind controlled or placebo-controlled experimental design with larger sample sizes. Once this becomes usual in NF research, the replication of studies to strengthen NF's status as an alternative to traditional insomnia treatment will be possible.

ARTICLE HIGHLIGHTS

Research background

Insomnia is one of the most common sleep disorder among adults in Canada and the treatments currently available present some limits. Neurofeedback (NF) is a technique that could offer a new way to treat insomnia through the regulation of abnormal brain activity.

Research motivation

In the last few years, NF has been gaining attention in the research community. However, there are only a few studies in the field of insomnia and their methods and results vary greatly. It is important to offer a consensus as to what is missing and what is successful in NF research so that future researchers can build upon what has already been done.

Research objectives

The goal of this review was to summarize the research that has already been done concerning the use of NF in the treatment of insomnia. This summary includes the common results and methodologies used in NF research as well as the improvements that need to be implemented.

Research methods

Data from experimental studies pertaining to the use of NF as a treatment of insomnia was collected from four bibliographical database and analysed. A short summary containing the methods, the results and the conclusions for each study was provided as well as for each NF type. A general summary was presented for all the studies included in this review.

Research results

A total of 12 studies on 5 different types of NF were used in this review, including surface NF, z-score NF, open-loop NF, high-resolution relational resonance-based

electroencephalic mirroring NF and Brain Music NF. All the studies reported a clear improvement of subjective sleep, but there was no consensus concerning objective sleep. Many studies suggest that training the sensorimotor rhythm in the sensorimotor cortex improves subjective sleep. However, many studies also point out a possible placebo effect. The diversity of methods used across studies hinders on the ability to replicate NF studies and create robust studies.

Research conclusions

The findings of this study support the hyperarousal model of insomnia, by increasing sensorimotor rhythm frequencies to decrease insomnia symptoms. To verify this theory, further research should be conducted to study the efficacy of NF to treat other disorders that are characterized by hyperarousal. This review has also point out the limits that currently plague NF research such as small sample sizes, inexistent placebo group and double blind design.

Research perspectives

This review has brought to light the need for more double-blind controlled and placebo-controlled experimental design and bigger sample size to prove the efficacy of NF as a treatment of insomnia.

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