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THERAPEUTICS ADVANCES

Promoting recovery from severe mental illness: Implications from research on metacognition and metacognitive reflection and insight therapy

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Abstract

Research indicates that individuals with schizophrenia recover. Recovery, however means different things to different individuals and regardless of what kind of experiences define recovery, the individual diagnosed with the serious mental illness must feel ownership of their recovery. This raises the issue of how mental health services should systematically promote recovery. This paper explores the practical implications for research on metacognition in schizophrenia for this issue. First, we present the integrated model of metacognition, which defines metacognition as the spectrum of activities which allow individual to have available to themselves an integrated sense of self and others as they appraise and respond to the unique challenges they face. Second, we present research suggesting that many with schizophrenia experience deficits in metacognition and that those deficits

compromise individuals' abilities to manage their lives and mental health challenges. Third, we discuss a form of psychotherapy inspired by this research, Metacognitive Reflection and Insight Therapy which assists individuals to recapture the ability to form integrated ideas about themselves and others and so direct their own recovery. The need for recovery oriented interventions to focus on process and on patient's purposes, assess metacognition and consider the intersubjective contexts in which this occurres is discussed.

Key words: Schizophrenia; Rehabilitation; Self; Psychosis; Metacognition; Recovery; Psychotherapy; Social cognition

Core tip: Impairments in metacognitive processes challenge the abilities of individuals with schizophrenia to form and sustain an integrated sense of self and others. These deficits in metacognition compromise individuals' abilities to manage their lives and mental health challenges. Treatments which help individuals with schizophrenia recapture metacognitive abilities can assist those individuals to regain access to the kinds of integrated ideas about themselves and others which assists them to meaningfully direct their own recovery. Metacognitive Reflection and Insight Therapy is an example of this kind of treatment.

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INTRODUCTION

Serious mental illness, whether referring to schizophrenia spectrum disorders or psychosis more broadly, is by definition tied to a multitude of psychological and social challenges. Regardless of whether we are considering matters at the cellular level, larger brain structures, phenomenology, or complex social and environmental structures, individuals diagnosed with these conditions experience disruptions, which culminate in the interruption not only of their lives but also of the lives of their families, partners, friends, and others living in their communities.

For decades, these conditions were assumed to involve progressive decline and dysfunction. Individuals held out little hope for wellness and it was assumed that individuals diagnosed with these conditions could at best hope for stability. If operationalized, this seemed to consist only of freedom from acute distress and institutionalization[1]. Multiple levels of evidence, including careful long-term follow-up, qualitative and quantitative clinical research, and a multitude of first person accounts, however, have offered a very different picture. Taking an optimistic turn, this work has suggested that no matter how ill a person can be at a particular moment, individuals with serious mental illness can recover in a personally meaningful manner regardless of the limitations imposed upon an individual's life by the disorder[2].

These studies of outcome and recovery have also highlighted the complexity of the concept of recovery itself[3,4]. Among other things, it is clear that recovery can and does mean different things to different people[5]. Recovery, for some people, is mostly a matter of changes in objective phenomena. For example, to recover could mean that symptoms remit or that individuals attain certain psychosocial milestones, such as returning to work or school. Recovery can also involve a host of subjective experiences including attaining a self-appraised acceptable quality of life or reasonable sense of social rank. Recovery could mean no longer feeling tainted or different from others, or at a more subjective level, it could involve recapturing a cohesive sense of oneself as a valuable person in the world[6,7]. For many, these subjective and objective aspects of recovery are complementary and interact with each other[1,8]. Despite the complexity and individual variation of the concept of recovery, there do appear to be three things that are inevitably true about recovery: (1) It happens; (2) its meaning is contextualized; and (3) regardless of what kind of experiences define recovery, the person diagnosed with the serious mental illness must feel a sense of ownership of their recovery[2]. This is to say that the person diagnosed with mental illness must direct their own recovery. In this sense, recovery is a matter undertaken by an agent in the world[9]. Recovery consequently is not just "fixing" something or finding solutions for any number of dilemmas. Recovery requires individuals to make sense, in the moment and over time, of the experiences that surround mental illness. Sense and meaning has to be made of psychiatric and social challenges, changes in the person's own mind and body, the minds of others and about what is happening in the larger world. Meaning-making is necessary, both implicitly and explicitly, for decisions to be made about how to respond to challenges[2,10]. To sum up: Recovery from serious mental illness requires that the person diagnosed with the condition be an active agent in that process.

This knowledge is freeing but also adds extra responsibility for clinical care[11]. If recovery is possible, naturally it should be the goal of treatment. But given the different meanings recovery has and its requirement that the individual in treatment be in charge in some meaningful way, what is the clinician to do beyond offering general support and attending

to the other common factors of treatment? How can clinical care systematically promote something that differs from person to person and which has to be ultimately directed by the person with serious mental illness?

This paper explores how research on the integrative model of metacognition and related developments in individual psychotherapy may offer a partial answer to this question by offering a larger framework for thinking about how individuals form a sense of what recovery means to them and then how they should pursue it. The integrative model of metacognition frames metacognitive processes as a spectrum of activities that enable a sense of self and others to be available to individuals in the moment that can be used to understand and respond to life's challenges. Metacognition in the integrative model is, therefore, foundational for meaning making within a given moment, for a sense of agency and ultimately the ability to decide about the meaning of psychosocial challenges and the most effective response[7].

To explore how research on this model might help inform recovery oriented care, we will first offer a more nuanced definition of the integrative model of metacognition. We will then discuss a decade of quantitative research on the prevalence and psychosocial consequences of reductions in metacognitive capacity for adults with serious mental illness and detail the development of a specific integrative form of recovery-oriented individual psychotherapy inspired by this research. We will then suggest that this work suggests five general principles that could inform change in traditional practice in order to genuinely support recovery. Finally, we will discuss how these principles and implications of this research converge and diverge with other emerging approaches.

As an initial caveat, we think it is important to clarify two points regarding terminology. This paper will use the term schizophrenia. Many suggest the word schizophrenia is stigmatizing and questions whether there is a scientific basis for suggesting it is a medical entity. Recognizing this controversy, we will employ the word schizophrenia given that, in part, one of its later ancient Greek roots suggests the splitting or shattering of the mind, which seems a valid attempt to characterize fragmentation which those diagnosed with these conditions confront[12]. Second, when describing people engaged in treatment we use the word "patient." This also is a controversial term as many have found mental health care to be both stigmatizing and marginalizing. This has led to other terms being commonly used including consumers, experts by experience, service users, clients, and psychiatric survivors. We chose to use the word "patient" given its roots in Latin and Greek meaning "to suffer," believing again that this characterizes the often profound suffering individuals diagnosed with these conditions experience. We do reject any suggestion that wellness in the face of mental illness comes from being a passive recipient of care.

Metacognition

Original term: Metacognition was first used to describe the experience of having a cognition or thoughts about other cognitions. In education research it was used to examine how people are aware of their own learning and how that awareness is utilized[13]. The term was subsequently applied to other phenomena including self-regulation[14], the ability to monitor and correct reasoning and behavior[15], and to reflect upon memory[16] as well as to describe attentional biases or general interpersonal stances sometimes referred to as metacognitive beliefs[17].

Integrated model of metacognition: As metacognition has continued to be studied across a variety of disciplines including educational, developmental, neurocognitive, and abnormal psychology the term metacognition has emerged to take on many meanings[18]. In an effort to form an integrated model of metacognition we have proposed that metacognition is a spectrum of activities[19]. One end of that spectrum involves awareness of discrete mental experiences that can be distinguished from one another, such as a specific thought, certain feeling or a particular desire. At the other end of that spectrum is the integration of those discrete experiences into a larger complex sense of oneself and others[20]. These different ends of the spectrum continuously influence one another, as for any larger sense individuals have of themselves must account for discrete experience, while the meaning of a discrete experience is always influenced by a larger understanding of the individual having that experience.

In this model, metacognitive processes are what allows an integrated and cohesive sense of self and others to be available to an individual in a given moment[7]. When metacognitive processes are fully functional they allow individuals to engage effectively in a number of mental operations simultaneously and automatically. These include the ability to recognize and distinguish specific mental experiences, to perceive how those mental experiences are changing or not changing, to contrast those mental states with the demands of reality, to see how all of that is happening in a larger context, and to see how those concrete situations fit into a larger narrative of our lives and the lives of others. Metacognition thus allows individuals access to a sense of themselves (and of others) which is multifaceted and multidimensional, while also allowing for that sense of self and others to change responsively and adaptively as contexts change. Metacognition in the integrated model is not a form of disembodied cognition or set of calculations that exist in isolation. They are vital activities that enable individuals to respond to psychological and

social challenges and ultimately function as members of the human community[19].

For the purposes of thinking about recovery from serious mental illness, the integrative model suggests metacognitive processes have at least three distinguishing characteristics. First, metacognitive acts occur and evolve intersubjectively. The ideas individuals have of themselves or others, whether elemental and complex, are formed with others in mind, others who may be either present or implicitly imagined, such that those ideas can be shared with and acknowledged by other people[21-23].

Second, metacognitive processes can be differentiated from one another according to their focus. As Semerari *et al*[24] have described, there are four discernable objects or domains of metacognition which can be distinguished from one another. These include groups of metacognitive acts, which are focused on the self, others, one's larger community and the use of knowledge about self and others to respond to life's problems, or mastery.

Third, synthetic metacognitive processes are holistic in nature and involve a series of hierarchical steps. These steps are conceptualized, per domain, as a series of levels with each level incorporating something larger into what was incorporated into the step before it. For example, the fourth step of the metacognitive processes which are focused on the self adds and incorporates something new to what was incorporated in the third step allowing for a more complex sense of self to be available in the moment. A key implication of this is that for a given step to be operating successfully the step below it also has to be operating successfully. Consequently, once a step is not operating successfully then no higher step can operate in a fully successful manner given that those higher steps would necessarily be missing the information that was supposed to be provided by the more basic or lower step. This conceptual framework allows for individual differences in metacognitive capacity to be quantified and characterized as more or less functional on the basis of an identified level of metacognition which is not fully operational. Importantly, this is not to say that individuals with lesser metacognitive capacity have less experience of the self or others, but instead that their experience of self and others is less integrated or more fragmented. It is also not to imply a purely developmental model of metacognition, as individuals with lesser metacognitive abilities may have previously held these abilities but lost them for any number of different social, biological or psychological reasons[7] .

Measuring metacognition: The Metacognition Assessment Scale (MAS[24]) was one of the first scales that incorporated metacognition as a core construct to characterize how individuals form an evolving and multidimensional sense of self and others. The MAS offered multiple advances. First, it was explicitly interested in the psychological processes that go beyond momentary self-awareness and facilitate the emergence of a broader sense of self and others. It also operationally differentiated metacognitive acts based on their focus and allowed for the measurement of changes in how often particular metacognitive acts were being performed. This scale was adapted by Lysaker and colleagues[25], who transformed the original MAS into an ordinal scale referred to as Metacognition Assessment Scale Abbreviated (MAS-A). The MAS-A retained the original distinctions offered by Semerari *et al*[24] and so contained four scales: Self-reflectivity (S), Understanding other's minds (O), Decentration (D), and Mastery (M).

While the MAS was originally designed to detect the presence or proportion of times a metacognitive act could have been used *vs* was used within a psychotherapy session, the MAS-A is used to rate metacognitive capacity as it is manifest within an interview (*e.g.*, Indiana Psychiatric Illness Interview; IPII[25]) which provides opportunities for participants to reflect about their life and psychological challenges. Training for rating using the MAS-A consists of the completion of an established set of transcripts followed by supervision and the establishment of inter-rater reliability.

Concerning the content of the scale, the MAS-A, in contrast to the MAS, follows the integrated model of metacognition, and considers each item of each scale to reflect a more complex metacognitive act than the one before it. Each item describes a metacognitive act that requires the integration of a new kind of information that was not included in the previous item. Concretely then, a rater scores each item in the MAS-A as adequately functioning or attained ("1") if they judge the participant to be capable of performing that act or as not attained ("0") if they judge the participant to not be capable of performing that act and once a score of "0" is given for an item no further levels can be scored as attained. Thus, the scores from the MAS-A indicate participants' maximal level of metacognitive function, or the last level before their metacognitive processes were judged to fail to fully operate and so the scores on each MAS-A subscale allows for the degree of fragmentation (or lack of integration in a given metacognitive domain to be measured dimensionally.

Research on metacognition in schizophrenia: Research has found the MAS-A has fully acceptable psychometric properties[20] and assesses phenomenon which are distinct from the social cognition[26,27] as well as content specific metacognitive beliefs[28]. To date, research using this scale has addressed two broad research questions: (1) Are individuals with schizophrenia spectrum disorders more likely to experience disruptions in earlier or more basic aspects of metacognitive capacity; and (2) when disruptions occur at more basic levels of metacognitive function

are individuals more likely to experience greater levels of impairment in current and future function.

In response to the first question, research has revealed that individuals experiencing both first episode psychosis and prolonged schizophrenia experience significantly greater metacognitive deficits relative to others. Specifically, individuals with first episode psychosis and prolonged schizophrenia tend to experience disruptions in more basic levels of metacognitive capacity more often than individuals without any significant mental health concerns[26,28], minor anxiety and affective disorders[29] or with serious and prolonged non-psychiatric medical conditions[30]. Other mental health conditions have been found to involve metacognitive deficits including depression[31] substance use, borderline personality disorder[32,33], posttraumatic stress disorder[34], and bipolar disorder[28], though these deficits occur in less basic elemental levels than what is seen in schizophrenia spectrum disorders.

Concerning the relationship with function, disruptions observed in basic or more elemental levels of metacognition (referred to as more severe metacognitive deficits) have been found to predict generally poorer function[35]. This includes greater reductions in functional competence[36], reports of poorer subjective sense of recovery[37], a weaker therapeutic alliance in cognitive-behavior therapy[38], less reported ability to reject stigma[39], anhedonia in the absence of depression[40], a more sedentary life style[41], reduced awareness of negative changes in psychological and social function states[42] and lesser levels of behavior that is driven by internal rewards[43], all regardless of concurrent symptom severity. Individuals with schizophrenia spectrum disorders who experience disruptions in basic metacognitive function have also been found to be more likely to have future problems with vocational function[44], more likely to develop negative symptoms[45-47], and to experience reduced intrinsic motivation[48], regardless of baseline assessments of these phenomena.

Metacognitive reflection and insight therapy: An illustration of an emerging recovery-oriented treatment that targets metacognition in psychosis.

Application of metacognitive research to treatment: Inspired by both research on metacognition and emerging models of recovery, efforts commenced to develop a form of integrative psychotherapy that could promote recovery through stimulating metacognition. The core assumption was individuals with a more fragmented sense of self and others would struggle to make sense of psychiatric and social challenges and thus struggle to move toward recovery. Put another way, a treatment enabling the processes which allow individuals to form a more integrated sense of self and others (*i.e.* metacognition) would promote recovery. What was proposed then was a process oriented therapy referred to as Metacognitive Reflection and Insight Therapy (MERIT)[7], a therapy focused on enabling the metacognitive processes which would allow individuals diagnosed with schizophrenia spectrum disorders to determine what recovery meant to them, what steps they needed to take and to take charge of their own recovery.

As described elsewhere[7] this therapy was developed through a series of international conversations among clinicians with extensive experience providing long-term psychotherapy to individuals with serious mental illness. It was conceptualized as integrative in that it would describe principles that could be adapted by therapists from other perspectives in order to promote metacognition. These principles were explicitly described as core activities that offered patients maximal opportunity for the development of metacognition which should be present in any given psychotherapy session rather than a rigid set of activities to be carried out in a certain order. In this sense treatment does not approach metacognition as something someone has or does not have. Instead, MERIT approaches metacognition as something a person possesses to a varying degree and something they can further cultivate with time and practice.

Structure and principles of MERIT: The central assumption of MERIT is that patients can gain metacognitive capacity by practicing metacognitive acts within the flow of a psychotherapy session[7]. Following the integrative model of metacognition, it is assumed that as patients become able to perform a level of metacognitive acts, they will begin to be able to perform more complex metacognitive acts and consequently have a richer sense of self and others available to them as they seek to recover. Analogous to processes in physical therapy, patients could be expected over time to become able to perform more complex metacognitive acts, as physical therapy builds upon existing ability and stretches to the next level of function[49].

MERIT is grounded in several general principles including foremost that recovery from serious mental illness is expected, regardless of the severity of the mental health condition[7]. Consistent with the material presented above, MERIT also assumes patients must be active agents who direct their own recovery during all phases of illness and that this requires the rejection of stigma, as well as a non-hierarchical therapist-patient relationship in which the therapist's role is best understood as one of a co-participant or consultant. It is thus a therapy for any patient who consents and there are no particular preconditions before therapy can begin[7]. Importantly, MERIT is not intended as a replacement for other treatments but can be offered both on its own or in combination with other rehabilitative practices depending on unique patient needs and clinic resources.

In MERIT, eight elements should be present in any given session, each of which is assumed to uniquely assist adults with psychosis to recapture damaged, atrophied, or undeveloped metacognitive abilities. Each element describes a measurable activity that can occur regardless of the unique problem or dilemma a patient is experiencing or wanting to discuss in psychotherapy. The elements are conceptually and synergistically inter-related, but each can be considered and assessed independently[7].

The eight elements are divided into three classes. The first class includes what are referred to as content elements. These include four specific elements that call for the session to focus upon and discuss (E1) the patient's agenda, or wishes and needs in the moment, (E2) the patient's experience of the therapist's thoughts and feelings about the patient and his or her agenda, (E3) the patient's experience of life as revealed within specific and minimally abstract personal narrative episodes and (E4) the psychological challenges which emerge from the first three content elements. The second set of elements includes what are referred to as the process elements. The process elements include a discussion (E5) of the therapeutic relationship in which the patient is thinking about their sense of themselves and others and (E6) discussion of progress, including resultant changes in their minds and bodies. The final two elements are considered superordinate elements and call for reflections about (E7) self and others and (E8) mastery to be stimulated at a level consonant with the patient's metacognitive ability as assessed in the moment. In other words, efforts to meaningfully engage patients in conversations about their sense of themselves and others need to match the patient's metacognitive capacity.

Regarding treatment mechanisms, it is assumed that these elements will have the ability to enhance metacognitive capacity that will result in a more integrated sense of self and others becoming available to patients in the moment. This integrated and flexible understanding of self and others will then enhance the opportunities for more effective self-management culminating in recovery. An adherence scale has been developed which allows for assessment of whether a given session sufficiently conforms to the session guidelines and is available in the MERIT guidebook[7]. This adherence scale can be self-rated by therapists or by others in order to allow for fidelity to the MERIT procedures to be formally assessed between therapists.

Research evidence: Though still emerging as a treatment, research has indicated that MERIT can be delivered under routine conditions in natural clinical settings and that patients with severe mental illness will accept this treatment and demonstrate improvements in metacognition[50-53]. Exploring the first-person experience of MERIT, a qualitative study has examined the self-reported experience of patients who received at least one year of either MERIT or supportive psychotherapy[54]. This study found that MERIT, in contrast to supportive therapy, leads to improvements in sense of agency and the ability to tolerate and manage previously disabling levels of emotional distress. Studied at the level of individuals and their own unique needs, detailed case reports have indicated that participation in MERIT is associated with improvements in the unique goals patients set for themselves in both early and later phases of serious mental illness[10,55-61]. Concerning patients who deny they have a mental illness, Vohs and colleagues[53] randomly assigned adults with first episode psychosis with poor clinical insight to receive a 6-mo trial of MERIT *vs* treatment as usual. They found that the treatment completion rate for MERIT was 80% with statistically significant improvements in objective measures of awareness of illness without any concurrent increases in hopelessness or emotional distress.

Implications for developing and implementing recovery-oriented care in serious mental illness

At the outset of this paper we suggested that conventional treatment models for serious mental illness are challenged to account for three aspects of recovery: (1) Recovery is to be expected; (2) recovery means different things to different people; and (3) recovery must be self-directed to be meaningful. We then summarized research suggesting metacognitive deficits may hinder a person's abilities to form the kinds of complex ideas about self and others needed to direct one's own recovery effectively. We then offered an illustration of a form of integrative therapy, MERIT designed to target metacognition and promote a kind of recovery that is personally meaningful and self-directed. Consistent with the need for integrative approaches in the treatment of serious mental illness[62], MERIT offers principles which can be incorporated into different approaches in psychotherapy and hence does not require yet another new treatment approach unrelated to others[22,63].

Returning to the issue of how treatment can promote unique, individualized, and self-directed recovery, we would suggest this body of research on metacognition suggests at least five general principles that conventional treatments could potentially embrace.

Treatment must be process oriented: First, if treatment is to be concerned with how people understand their psychiatric and social challenges it has to begin with curiosity and inquiry about what patients think about those challenges. How does the patient experience challenges? How do they think about challenges now and how have they thought about challenges in the past? Thus, what therapy is trying to provoke or support is a process and not specific content such as accepting a fact. It is as much about how people think as what they think. Moreover,

that process is about making meaning of often complex and painful material.

This is not to say that content is irrelevant. Certain content may prove helpful for supporting the process of meaning making but those contents are likely different from patient to patient. Whereas one patient may find psychoeducation and support helpful, another may find it destructive and marginalizing. Some may find a particular skill based approach helpful, but others may experience that as useless or harmful. Content in fact should differ from person to person depending upon any number of individual differences in ages, gender, education, cultural background, trauma history, socio-economic status, talents, family history *etc*. Nevertheless, because understanding challenges involves making meaning and not the grasping of facts, treatment cannot be conceptualized as primarily following a curriculum seeking to "teach" patients to perform certain acts or "getting them" to think certain things. This require the clinicians to "give up" the knowing attitude[63] and let themselves be taken by surprise[64].

Treatment must be concerned with purposes beyond problems: Given that it is the meaning of challenges and the best response to them is at stake, a recovery-oriented approach also needs to be at least as focused on patients' purposes as it is on problems. In other words, it is vital for therapy to address not just what has gone wrong discretely, but what the patient is seeking, both in the moment and in recovery more broadly. Here the conventional assumption that the patient-clinician dyad should identify the problem and then the solution can be seen to risk undermining recovery and meaning making. For example, two patients could agree that they have the same problem, such as being anxious or hearing voices. Yet each may come to treatment and approach life with very different purposes. One patient may primarily want to avoid any future humiliation by keeping within the safety of the patient role and the other be primarily concerned only with finding a romantic partner. Clinician blindness to patient's purposes could then obviously derail the chances for joint meaning making.

Accordingly, an explicit requirement of recovery-oriented therapy seems likely to be that it involves direct and continuous discussions of patient's purposes and wishes, assuming that those wishes and purposes are likely to be complex. It is more likely than not that patients will have multiple purposes which may be contradictory, complementary or unrelated[65]. These purposes may be more or less in awareness and may change over time. In parallel, the purposes patients have for their therapists are also likely to be fluid and changing. Accordingly, an intervention which promoted the process of meaning making at one point might not at a later point and vice versa.

This is not to say that clinicians should unconditionally support any patient agenda. For example, patients may want to remain in the sick role, for the therapist to provide endless support, or to avoid guilt for neglecting real life responsibilities such as child support. What is essential is that what the patient is seeking is directly discussed and those discussions are employed in the service of understanding what the patient is facing and what he or she wants to do about that.

Process of recovery-oriented treatment is fundamentally intersubjective: The process of making meaning of challenges and purposes should be further understood as one that occurs between people. As noted above, individuals do not make meaning of themselves and their lives in isolation. Thus, the clinician has a clear role beyond blanket support or reassurance. In fact, supporting everything anyone thinks is never likely to be a successful strategy for promoting reflection.

What is necessary instead is an open and genuine dialogue which allows for disagreement but in which the clinician does not derail conversation by virtue of their power in the relationship. In this relationship, disagreement should not be confused as an expression of disrespect. Indeed, challenging individuals to think more deeply about their lives may be among the most respectful things human beings can offer one another.

The process promoted by recovery-oriented treatments should be conceptualized as taking place within the therapeutic intersubjective space, between the clinician and patient[63,66]. A deepening sense of self and others does not first occur in the mind of the therapist to then be shared with the patient. It is understanding that emerges from and within the encounter of unique persons. This allows for the therapeutic relationship to be a vehicle for a reflective dialogue.

Goals and outcomes will appear and change fluidly over time: Given that recovery-oriented treatment is concerned with meaning and purpose as well as the relationship within which it is taking shape, patients' goals within and outside of therapy are likely to evolve in ways that cannot be anticipated. It is likely that with more integrated ways of understanding oneself and others, or in the face of unexpected emotional pain, patients will find themselves with a different set of purposes and potentially very different goals. For example, a patient might originally seek to improve a relationship with an adult child but then suddenly on her own realize she needs to drive. This new goal may then shift the focus as he or she considers buying a car and learning to drive, despite that never having been a goal at any earlier part of treatment. Another patient may, with more awareness, suddenly take a more active role in thinking about medication he or she needs while another may decide it is time to try to manage his or her life without medication.

Interventions should match a patient's metacognitive capacity: Finally, if metacognitive

processes are what allow individuals to have an integrated sense of self and others, then interventions which seek to facilitate metacognitive capacity, need to continuously assess patients' level of metacognitive capacity and offer interventions that match that level of metacognitive capacity. Practically, asking a patient to question their own thoughts and perceptions is likely to only lead to frustration and misunderstanding rather than reflection if that patient is unable to see that their emotions and affects change over time and that their mental states are accordingly subjective and transitory.

This would require the assessment of metacognition and its responsiveness to changes within and between sessions. Certainly, the MAS-A is not the only means for assessing changes in metacognition but it does exist as a method of identifying points where metacognition fails to fully function and therefore the MAS-A can be used as a guide for intervention. The MAS-A further distinguishes metacognitive acts pertaining to the self, others, the community, and the use of that knowledge. This instrument has the benefit of responding to awareness of self and others as something more nuanced than a vague monolithic phenomenon. It allows clinicians to respond differently to patients based on clearly delineated levels of metacognitive capacity.

In this way recovery interventions may come to take on an usual character. Whereas most interventions tend to be considered in terms of high structure vs. low structure, the need to appraise metacognition and respond differently to individuals given their capacities in the moment give the clinician a highly structured task while the patient's task of making sense of what they face and need to do about it is clearly a highly unstructured task.

In summary, research suggests that many with schizophrenia experience deficits in metacognition, and that while these deficits are tied to poorer outcomes they may be the target of treatment leading to self-directed and personally meaningful recovery. In this paper we have suggested that this research offers some important directions for clinical interventions which could support recovery in serious mental illnesses such as schizophrenia. We have proposed this research suggest that these interventions need to be focused on process and on patient's purposes as well as the intersubjective context in which this is occurring. Further, these interventions need to allow for the fluid formation and evolution of goals while imposing on clinicians the highly structured task of assessing metacognitive capacity and responding accordingly to patients as they seek to make sense of what recovery means to them and how they should pursue it.

While these ideas may appear radical in some ways, it is worth noting that the metacognitive model of schizophrenia does not differ terribly from key features of Bleuler's[67] original model of schizophrenia which attributed the interruption of the lives in schizophrenia to disturbances in associative process or the ability to link ideas together *via* associative threads. The model of therapy inspired by this work, MERIT, shares this understanding with the practices of other contemporary approaches. For example, like Cognitive Behavior Therapy for Psychosis (CBT-P)[68], MERIT focuses on normalizing distressing experiences[69]. It also shares with mindfulness[70] and Acceptance Commitment Therapy[71,72] a focus on patients' relationship to their experience. MERIT and these therapies, sometimes called third wave Cognitive Behavior Therapy[73], seek to address matters that go beyond individual cognition and require curiosity about mental experience with the expectation that patients will have unique responses to psychological and social challenges[69]. MERIT, also like psychodynamic mentalization-based approaches, is interested in the ideas people form about one another in an explicitly intersubjective context. Like traditional humanistic practices[74,75] MERIT is concerned with self-actualization, agency, and understanding experience in the context of the human condition. Similar to skills based approaches to rehabilitation, MERIT is focused on real world outcomes, the rejection of stigma and the patient's movement beyond the sick role.

However, MERIT and treatments driven by its supporting research do diverge from these views. Unlike CBT-P, MERIT is expressly interested in understanding how individuals synthesize or integrate information, above and beyond particular beliefs considered in isolation. In contrast to the third wave of CBT, MERIT is explicitly concerned with joint reflection about self-experience in the moment, as it occurs in the relationship with the therapist and across patients' personal narratives[69]. Unlike ACT, MERIT is not concerned with abstractions about values but instead explores the larger complex web of meanings that span the course of an individual life. In contrast to mindfulness, MERIT is interested in patients' experiences as they occur in the mind in the moment, in response to the therapist's mind, and further asks about the meaning of those mental experiences in relation to one another, again in the context of a unique narratized life. MERIT also thinks about self-knowledge differently than other cognitive therapies. The self-knowledge that emerges from MERIT is not a knowledge of a true self or a matter of a more transparent perception of a self but instead the availability of a diverse self, which is able to respond to what is emerging at any point in a unique life[69]. In contrast to psychodynamic and mentalization based treatment[76], MERIT's use of the MAS-A to operationalize metacognition differentiates thoughts about the self, others, the community, and ability to use this knowledge to respond to life's challenges. Further differentiating MERIT from mentalization approaches is the assumption that difficulties in reflectivity can occur outside of the context of disturbed attachment and emotion dysregulation and have a bidirectional relationship with both constructs[77].

Concerning self-actualization and the development of agency, MERIT also moves beyond some of the classic humanistic approaches to psychotherapy[74,75], in that it proposes a method for scaffolding a complex and nuanced sense of self that could be actualized. Finally, the suggestions offered here are potentially at odds with rehabilitative skills based approaches which directly seek to "get" people to "do" particular things or to exercise certain skills that a clinician thinks are needed. Indeed, the work detailed above suggests that when those approaches take on the responsibility for deciding what patients need to think or do, that those approaches, regardless of how benevolent the clinician's intentions are, may do a significant disservice by reinforcing the patient's lack of agency and positioning them as stigmatized and not fully competent adults.

While considering the strengths and evidences of metacognitive approaches to recovery focused treatment such as the MERIT, limitations should be mentioned. Randomized controlled trials of MERIT are needed in a broad range of settings. Despite being an integrative psychotherapy, it is unclear how easily clinicians from different disciplines and with different backgrounds can make the adaptations we suggest. Methods for assessing treatment adherence exist but it remains to be determined how these affect therapists from different perspectives. It is also unclear how to make these adaptations in settings that do not allow extended contact with patients but instead offer only brief and intermittent contact, such as inpatient units. There is further need for replication and further study of both the methods for assessing metacognition and for delivering metacognitive therapies.

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MINIREVIEWS

Complex posttraumatic stress disorder: The need to consolidate a distinct clinical syndrome or to reevaluate features of psychiatric disorders following interpersonal trauma?

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Abstract

Complex posttraumatic stress disorder (Complex PTSD) has been recently proposed as a distinct clinical entity in the WHO International Classification of Diseases, 11th version, due to be published, two decades after its first initiation. It is described as an enhanced version of the current definition of PTSD, with clinical features of PTSD plus three additional clusters of symptoms namely emotional dysregulation, negative self-cognitions and interpersonal hardship, thus resembling the clinical features commonly encountered

in borderline personality disorder (BPD). Complex PTSD is related to complex trauma which is defined by its threatening and entrapping context, generally interpersonal in nature. In this manuscript, we review the current findings related to traumatic events predisposing the above-mentioned disorders as well as the biological correlates surrounding them, along with their clinical features. Furthermore, we suggest that besides the present distinct clinical diagnoses (PTSD; Complex PTSD; BPD), there is a cluster of these comorbid disorders, that follow a continuum of trauma and biological severity on a spectrum of common or similar clinical features and should be treated as such. More studies are needed to confirm or reject this hypothesis, particularly in clinical terms and how they correlate to clinical entities' biological background, endorsing a shift from the phenomenologically only classification of psychiatric disorders towards a more biologically validated classification.

Key words: Complex posttraumatic stress disorder; Posttraumatic stress disorder; Borderline personality disorder; Trauma; Complex trauma

Core tip: A cluster of complex posttraumatic stress disorder (PTSD), PTSD and borderline personality disorder that have in common a history of trauma, is proposed, as a clinical and biological continuum of symptom severity, to be classified together under trauma-related disorders instead of just distinct clinical diagnoses. Trauma depending on biological vulnerability and other precipitating risk factors is suggested that it can lead to either what we commonly diagnose as PTSD or to profound and permanent personality changes, with complex PTSD being an intermediate in terms of its clinical presentation and biological findings so far.

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INTRODUCTION

Complex posttraumatic stress disorder (Complex PTSD), has been originally proposed by Herman[1], as a clinical syndrome following precipitating traumatic events that are usually prolonged in duration and mainly of early life onset, especially of an interpersonal nature and more specifically consisting of traumatic events taking place during early life stages (*i.e.*, child abuse and neglect)[1].

In order to develop a new psychiatric diagnosis, it requires carrying a certain extent of validity as a distinct entity with a clinical utility[2], providing essential additions to already established diagnoses especially regarding biological aetiology, course and treatment options.

Several psychiatric disorders overlap in terms of symptomatology and there is a high comorbidity present to most, if not all, especially when precipitating factors are common or similar. Furthermore, until now, psychiatric diagnoses have been traditionally described as theoretical constructs, mostly to facilitate communication of professionals working in the field, with the exact psychopathological processes and biological background research only currently blooming. This also carries the question whether already established psychiatric diagnoses need to be re-evaluated and re-grouped following newly suggested research findings, aiming to offer more efficient treatment plans to patients in question.

It has been questioned[2,3] whether complex PTSD can form a distinct diagnosis, since its symptomatology often overlaps with several mental disorders following trauma, mainly with PTSD which is usually correlated to single event trauma as well as Axis II disorders, mainly borderline personality disorder (BPD). The latter besides the high comorbidity with complex PTSD[4], also shares some of the core symptoms described in complex PTSD especially related to impaired relationships with others, dissociative symptoms, impulsive or reckless behaviours, irritability and self-destructive behaviours.

Complex PTSD is defined by symptom clusters mainly resembling an enhanced PTSD, with symptoms such as shame, feeling permanently damaged and ineffective, feelings of threat, social withdrawal, despair, hostility, somatisation and a diversity from the previous personality. It also regularly presents with serious disturbances in self-organisation in the form of affective dysregulation, consciousness, self-perception with a negative self-concept and perception of the penetrator(s), often causing dysfunctional relations with others leading to interpersonal problems[1,5-7].

The aim of this paper is to review the until now research on complex PTSD and its correlation to other trauma-related mental disorders mainly PTSD and BPD, primarily regarding the diagnostic frame and biological correlates, in order to examine whether there is sufficient data to approve the need of establishing a distinct clinical mental syndrome or to address the need to reassess and expand the diagnostic criteria of trauma-related disorders to include clinical features of complex PTSD currently missing from the already confirmed clinical entities.

CLINICAL DESCRIPTIONS AND BIOLOGICAL CORRELATES OF COMPLEX PTSD, PRECIPITATING TRAUMATIC EVENTS AND CLINICAL DIVERGENCE FROM PTSD

Complex PTSD is already suggested as a distinct diagnostic entity, in the World Health Organization (WHO) International Classification of Diseases, 11th version, (ICD-11)[5], which is due to be published in 2018 and currently under review, classified under disorders specifically associated with stress. It is grouped together along with PTSD, prolonged grief disorder, adjustment disorder, reactive attachment disorder, disinhibited social engagement disorder and others. The disorders mentioned above are all associated with stress and exposure to distressing traumatic events. The clinical features following the stressful experience result in serious functional impairment regardless whether the traumatic event precipitating the disorder, falls under the normal range of life experiences (such as grief) or encompasses events of a menacing nature (*i.e.*, torture or abuse).

According to ICD-11[5], complex PTSD follows exposure to a traumatic event or a series of events of an extremely threatening nature most commonly prolonged, or repetitive and from which escape is usually impossible or strenuous[6].

Two decades ago when it was first proposed, precipitating traumatic events were described strictly as being prolonged in time usually taking place during early developmental stages (*i.e.*, childhood)[1]. The literature describing complex PTSD ever since, following its first initiation as a cluster of symptoms beyond classic PTSD, began to also include entrapping events taking place during adulthood[8] and argued against their prolonged nature *per se*, referring to single event traumas as well as repeated series of single complex trauma that could be so severe and catastrophic in nature leading to profound personal effects, such as personality modification, even after the conclusion of major developmental stages[9]. A recent study of Palic *et al*[10], argues of the complex PTSD association, not only with childhood trauma but with exposure to all forms of adulthood trauma, predominately having in common the interpersonal intensity of the stress induced and the severity of prolonged trauma exposure. Another study of va Dijke *et al*[11], correlated the presence of complex trauma in adulthood to complex PTSD symptomatology, specifically dissociation, suggesting a potential link to the dissociative subtype of PTSD.

Complex trauma, which summates a total of precipitating traumatic events to complex PTSD, is currently being described as a horrific, threatening, entrapping, deleterious and generally interpersonal traumatic event, such as prolonged domestic violence, childhood sexual or physical abuse, torture, genocide campaigns, slavery *etc*. along with the victim's inability to escape due to multiple constraints whether these are social, physical, psychological, environmental or other[12,13].

Complex PTSD includes most of the core symptoms of PTSD, specifically flashbacks (*i.e.*, re-experiencing the traumatic event), numbness and blunt emotion, avoidance and detachment from people, events and environmental triggers of the predisposing trauma as well as autonomic hyperarousal. Furthermore, due to the nature of the complex trauma experienced, it also includes affective dysregulation, adversely disrupted belief systems about oneself as being diminished and worthless, severe hardship in forming and maintaining meaningful relationships along with deep-rooted feelings of shame and guilt or failure[7]. Its distinct characteristics added upon PTSD symptomatology, often interfere to separate it from BPD (*i.e.*, affective dysregulation) and PTSD alone, which in cases with a chronic course will eventually transit to a lasting personality change[14].

Therefore it is speculated that prolonged exposure to complex trauma and/or chronic PTSD, would, therefore, lead to personality alterations that are often also seen clinically in complex PTSD patients (such as feelings of being permanently damaged and alienation), even when the traumatic experiences are taking place during adulthood[14]. It is speculated that complex trauma has to be present for a sufficient amount of time to cause a clinically evident diversion from the already established personality traits, towards traits that seem to either help the victim cope with trauma or as an expression of disintegration which might express as the dysregulation of emotion processing and self-organisation, two of the core symptoms added to the already established PTSD diagnostic criteria[10,15]. Complex trauma, especially childhood cumulative trauma and exposure to multiple or repeated forms of maltreatment, has been shown to affect multiple affective and interpersonal domains[12]. Also, chronic trauma is more strongly predictive of complex PTSD than PTSD alone, while complex PTSD is associated with a greater impairment in functioning[16].

Up to now, there is a lack of investigation of biological correlates to complex PTSD, referring to neuroimaging studies, autonomic and neurochemical measures and genetic predisposition[17]. The only data so far, consist of neuroimaging studies mainly in groups of child abuse-related subjects that mostly argue for the hippocampal dysfunction and decreased gray matter density observed, activation disturbances in the prefrontal cortex[18-20], as well as findings suggesting of more a severe neural imaging correlate in complex PTSD than those observed in PTSD patient studies, primarily involving brain areas related to emotional regulation and cognitive defects, symptoms that have been additionally added in

complex PTSD symptomatology *vs* PTSD[17]. Structural brain abnormalities in complex PTSD seem to be more extensive with brain activity after complex trauma being distinctive than the one seen in PTSD patients who had experienced only single trauma[21] with higher functional clinical impairment in complex PTSD independently described but confirming the biological results mentioned above[22,23].

The three additional clusters of symptoms beyond core PTSD symptoms refer to emotional regulation, negative self-concept and interpersonal relational dysfunction[24].

PTSD has been re-evaluated in DSM-5[15], adding a cluster D of PTSD symptoms including altering in mood and cognition following the traumatic experience, as well as the dissociative PTSD subtype (*i.e.*, depersonalisation and/or derealisation), a subtype that clinically resembles the cluster of symptoms that are commonly encountered in the complex PTSD[25]. A recent study of Powers *et al*[26] though, concluded that the ICD-11 Complex PTSD diagnosis is different than the DSM-5 PTSD diagnosis, in all clinical domains, showing more severe emotion regulation and dissociation, and more severe impairment in relational attachment, suggesting that they present two distinct constructs. More studies are needed to investigate the biological basis of complex PTSD as a clinical entity and its differences from trauma-induced disorders such as PTSD.

RE-CONCEPTUALISING BPD AS A COMPLEX TRAUMA SPECTRUM DISORDER

BPD is characterized by emotional dysregulation, oscillating between emotional inhibition and extreme emotional lability which has been often associated with prolonged childhood trauma[27], such as child abuse and neglect as well as adverse childhood experiences, present in a range within 30 to 90% of BPD patients[28-30]. Emotional dysregulation, an unstable sense of identity, difficulties in interpersonal relationships as core features of BPD[15] and precipitating complex interpersonal traumatic victimisation, a cluster of symptoms that overlaps with symptomatology described in complex PTSD, has led into a series of arguments whether BPD represents a comorbidity of trauma-related disorders or it actually duplicates complex PTSD, a clinical entity already introduced as a separate trauma-related diagnosis in ICD-11[31].

The WHO International Classification of Diseases, 11th version, (ICD-11), includes a slightly different spectrum of personality disorders classification, including BPD into a wider spectrum of the Emotionally Unstable Personality Disorder, carrying all of the characteristics that BPD has been known by, so far, but distinguishing two types; the impulsive type, defined by emotional instability and impulsiveness and the borderline type with an unstable sense of self and the environment, self-destructive tendencies and intense and unstable relations. Still again, while traumatic stress exposure is fundamental in Complex PTSD and has been added to its diagnostic criteria, it is not included in the definition of BPD, albeit the multiple references that trauma, especially during early life stages, plays a crucial role in the development of the borderline personality even if epigenetically added upon a temperamental vulnerability[32]. Especially childhood trauma such as, sexual and physical abuse, maladaptive parenting, neglect, and parental conflict has been correlated to BPD multiple times in literature as risk if not etiological factors[33].

The long-term stress response mechanism activation, mediated by the hypothalamic-pituitary-adrenal (HPA) axis, due to chronic stress exposure, can predispose to multiple stress-related psychiatric entities, including PTSD[34]. Stress early in life due to childhood trauma has been reported to result in an adjustment dysfunction of the HPA axis responsiveness upon stress states encountered, with patients with BPD. There seems to be an increased activation of the HPA axis[35,36], suggesting the association of the main stress regulating mechanism to childhood trauma and a biological correlation to the development of the borderline personality. Furthermore, several interacting neurotransmitter systems are shown to be affected in BPD[37,38], resulting to a disruption of emotional regulation and social interaction as well as cognitive impairments evident mainly in spatial memory, modulation of vigilance and negative emotional states mediated through the hippocampus and amygdala[39], symptomatology that is present in complex PTSD even in the lack of similar biological studies to support this, at least in terms of neuromodulation alterations in complex PTSD.

Additionally, neuroimaging studies on BPD, confirm the reduction in hippocampus and amygdala volumes as well as in the temporal lobes[39-42], while a recent study of Kreiser *et al*[43], found that BPD patients with a comorbid lifetime history of PTSD had smaller hippocampal volumes compared to the ones that didn't. Additionally, a study of Kuhlmann *et al*[44], correlated the history of trauma to BPD, showing a modification of grey matter at stress regulating centers, including the hippocampus, the amygdala, the anterior cingulate cortex and the hypothalamus.

Likewise, studies indicate that epigenetic changes upon the brain derived neurotrophic factor[45], which is a key mediator in brain plasticity, are associated to prolonged early stage trauma, contributing to the cognitive dysfunction which is often described in BPD patients[46,47].

Altogether, the similarities between studies concerning BPD and complex PTSD[17-20], in terms of the common underlying systems affected along with the clinical analogy in both disorders, both associated

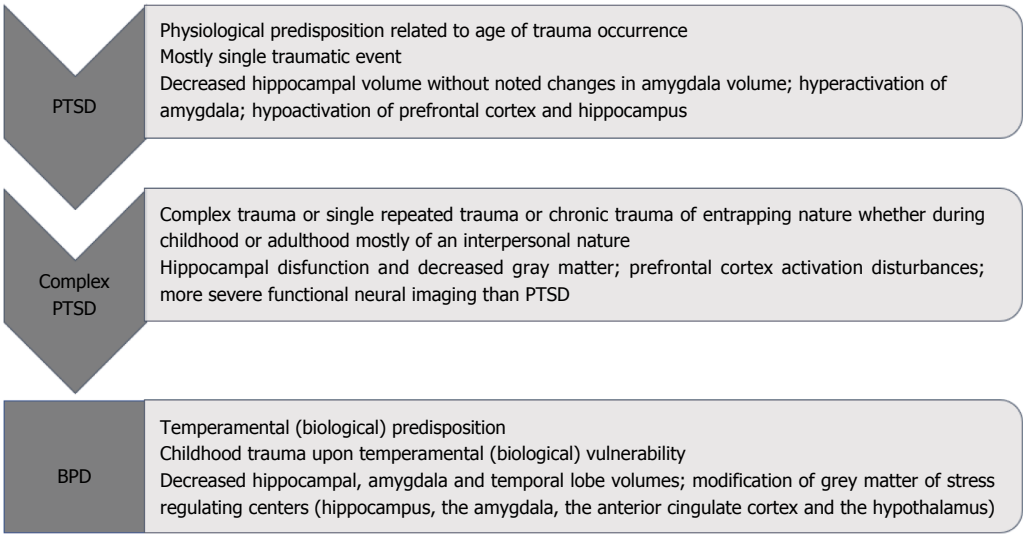

Figure 1 Proposed development of the clinical phenomenology based on trauma history and biological correlates. PTSD: Posttraumatic stress disorder; BPD: Borderline personality disorder.

to prolonged stress and trauma exposure, suggest the need to re-classify subgroups of patients with BPD, especially the ones that show comorbidity with PTSD, as possible cases of complex PTSD or, as it will be discussed below, added on a spectrum of trauma-related clinical entities carrying a similar biological background with complementary clinical expression.

CONCLUSION

The new proposed diagnosis of complex PTSD in ICD-11, re-conceptualises a previous ICD-10 diagnosis namely "enduring personality change after catastrophic experience", which carries characteristic clinical features of self-organisation dysfunction and exposure to multiple and chronic or repeated and entrapping, for the individual, traumatic events (*e.g.*, child abuse, domestic violence, imprisonment, torture). The ICD-11 complex PTSD shares three core symptom clusters of PTSD (re-experiencing, avoidance and sense of threat), adding three additional clusters of symptoms, specifically emotional dysregulation, negative self-concept and relational disturbances. Even if a clear personality change is not required for the diagnosis of complex PTSD, the sustainable and pervasive alteration in self-organisation, especially within the group of patients who have experienced long-lasting early life complex trauma, according to the authors, suggesting that a personality change is unavoidable, essentially while even chronic PTSD alone can lead to the change of personality eventually as it has been noted in the literature[14]. Therefore, complex PTSD, often clinically resembles a subtype of BPD.

There lies the question whether complex PTSD is a clearly defined distinct entity or a PTSD comorbid with BPD. The debate focuses mainly on the fact that even if both conditions share core symptoms, such as affect dysregulation and self-organization disturbances, BPD has been traditionally described by an unstable sense of self oscillating between highly positive and highly negative self-evaluation and a relational attachment style vacillating between idealizing and denigrating perceptions of others when complex PTSD on the other hand, is defined by a deeply negative sense of self and an avoidant attachment style that are stable in nature and follow complex trauma, something that is not described in the diagnostic criteria of BPD.

However, BPD seems to be a heterogeneous diagnostic category, which can include many subtypes of patients, such as patients with bipolar disorder, depression or other personality disorders such as narcissistic personality disorder, with an accurate clinical diagnosis being difficult under practical pressures posed upon physicians and the comorbidity present among the above mentioned disorders[48]. BPD clinical features do not seem to be stable over time, and this is suggested to be influenced by the underlying biological temperament[49,50], while the comorbidity with PTSD is common but not present in all of the BPD cases[51], therefore arguing for conceptualizing some of the BPD cases belonging to a trauma spectrum disorder instead[52].

Since the etiological background for most if not all psychiatric disorders, is not linear but instead it consists of many biological, psychological and social factors, interacting between each other and continuously adjusting, shifting and variating among individuals on top of brain plasticity and ever-changing circumstances, the authors suggest that the biological correlates of disorders appearing with similar phenomenology should be better investigated.

The different clinical profiles described in the most recent classification systems (Table 1) even if sharing many common clinical features, that surround PTSD, complex PTSD and BPD, are all associated with different levels of impairment and different risk

Table 1 Phenomenology of posttraumatic stress disorder, complex posttraumatic stress disorder and borderline personality disorder; DSM-5 clinical features and proposed criteria of ICD-11

	DSM - 5	ICD - 11
PTSD	Exposure to traumatic events; Intrusion symptoms; Persistent avoidance of stimuli; Negative alterations in cognitions and mood (dissociation, persistent negative beliefs of oneself, others or the world, distorted cognitions about the traumatic event, persistent negative emotional state, detachment from others, diminished interest or participation in previously enjoyed activities *etc.*); Alterations in arousal and reactivity; aggressive verbal and/or physical behaviour, reckless or self-destructive behaviour; depersonalisation or derealisation; Significant impairment in all areas of functioning	Exposure to an extremely threatening or horrific event or series of events; vivid intrusive memories, flashbacks, or nightmares, which are typically accompanied by strong and overwhelming emotions; avoidance of thoughts and memories, events, people, activities, situations reminiscent of the event(s); persistent perceptions of heightened current threat, hypervigilance or an enhanced startle reaction. Significant impairment in personal, family, social, educational, occupational or other important areas of functioning
Complex PTSD	Not included as a diagnostic entity	Exposure to an event(s) of an extremely threatening or horrific nature, most commonly prolonged or repetitive, from which escape is difficult or impossible; All diagnostic requirements for PTSD are and additionally: severe and pervasive affect dysregulation; persistent negative beliefs about oneself; deep-rooted feelings of shame, guilt or failure; persistent difficulties in sustaining relationships and in feeling close to others. Significant impairment in all areas of functioning
BPD	Pervasive pattern of instability of interpersonal relationships, self-image and affects and impulsivity; frantic efforts to avoid abandonment, unstable and intense interpersonal relations oscillating between idealisation and devaluation, unstable self-image or sense of self, self-harming behaviour, affective instability and marked reactivity of mood, chronic feelings of emptiness, poor anger management, transient paranoid ideation or severe dissociation	Emotionally unstable personality disorder, Borderline type: Maladaptive self and interpersonal functioning, affective instability, and maladaptive regulation strategies: Frantic efforts to avoid abandonment; unstable interpersonal relations (idealisation/devaluation); unstable self-image; impulsivity; self-damaging behaviours; marked reactivity of mood; chronic feelings of emptiness; anger management issues; dissociative symptoms

PTSD: Posttraumatic stress disorder; BPD: Borderline personality disorder.

factors mainly in the trauma history precipitating the phenomenology that finally occurs, which is evident in the neuroimaging findings of each disorder (Figure 1).

Since even chronic PTSD will eventually lead to personality modification, it is suggested that complex trauma exposure, even during adulthood, is a predisposing factor for complex PTSD occurring, which will, eventually, if relatively prolonged in time, lead to more severe personality changes often clinically similar to BPD. We suggest that the time of the traumatic events occurrence (*i.e.*, early developmental stages *vs* adulthood), their severity and context, their duration in time and whether they are of an entrapping and interpersonal nature, posed upon a genetically predisposed background will eventually progress into enduring or permanent personality modifications. Therefore, we suggest that within the heterogeneous group of cases classified as BPD, there is a subgroup that could be possibly classified under trauma-related disorders and be therapeutically treated as such.

Concluding, the authors suggest a continuum of clinical severity and symptoms' development in trauma-related disorders, within a spectrum of clinical features, biological background and precipitating trauma, from classic PTSD towards a subtype of BPD; especially concerning cases supposing a comorbidity with PTSD. We also suggest of complex PTSD being an "intermediate" in its phenomenological manifestation, with biological analogies seemingly supporting these hypotheses.

More studies are needed focusing on the biological background of complex PTSD and how this relates to its newly proposed clinical entity and how it correlates to the extended findings in the literature around the biology of PTSD and BPD. This is essential for examining the validity of it as a distinct and separated entity altogether or to confirm the hypothesis of a spectrum surrounding the disorders discussed above, at least within the range of cases having a history of trauma present.

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ORIGINAL ARTICLE

Clinical Practice Study

Repeatability of two-dimensional chemical shift imaging multivoxel proton magnetic resonance spectroscopy for measuring human cerebral choline-containing compounds

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Abstract

AIM

To investigate the repeatability of proton magnetic resonance spectroscopy in the *in vivo* measurement of human cerebral levels of choline-containing compounds (Cho).

METHODS

Two consecutive scans were carried out in six healthy resting subjects at a magnetic field strength of 1.5 T. On each occasion, neurospectroscopy data were collected from 64 voxels using the same 2D chemical shift imaging (CSI) sequence. The data were analyzed in the same way, using the same software, to obtain the values for each voxel of the ratio of Cho to creatine. The Wilcoxon related-samples signed-rank test, coefficient of variation (CV), repeatability coefficient (RC), and intraclass correlation coefficient (ICC) were used to assess the repeatability.

RESULTS

The CV ranged from 2.75% to 33.99%, while the

minimum RC was 5.68%. There was excellent reproducibility, as judged by significant ICC values, in 26 voxels. Just three voxels showed significant differences according to the Wilcoxon related-samples signed-rank test.

CONCLUSION

It is therefore concluded that when CSI multivoxel proton neurospectroscopy is used to measure cerebral choline-containing compounds at 1.5 T, the reproducibility is highly acceptable.

Key words: Cerebral metabolites; Chemical shift imaging; Choline; Neurospectroscopy; Neuropsychiatric disorders

Core tip: Proton neurospectroscopy is a powerful tool allowing the assessment of cerebral metabolites. As such, it is increasingly being introduced into the practice of psychiatry for the investigation of cerebral choline-containing compounds in patients, as well as being used as a research tool. However, it is important to establish the reproducibility of this sensitive technique. In the present study, we show that this technique (using 2D chemical shift imaging) gives a level of reproducibility that is highly acceptable. These results should further encourage the use of this technique, which, in principle, is available on all standard MRI scanners, in psychiatric practice.

Puri BK, Egan M, Wallis F, Jakeman P. Repeatability of two-dimensional chemical shift imaging multivoxel proton magnetic resonance spectroscopy for measuring human cerebral choline-containing compounds. *World J Psychiatr* 2018; 8(1): 20-26 Available from: URL: http://www.wjgnet.com/2220-3206/full/v8/i1/20.htm DOI: http://dx.doi.org/10.5498/wjp.v8.i1.20

INTRODUCTION

In vivo magnetic resonance proton spectroscopy studies of the human brain pose a technical challenge given that the water signal is four orders of magnitude greater than signals from metabolites of interest, and also because of the narrow range of the chemical shift, spin-spin coupling complicating the spectral pattern, and the higher scalp lipid signal compared with cerebral metabolite signals; nevertheless, choline-containing compounds (Cho) such as phosphoryl- and glycerophosphoryl-choline can be measured using this technique[1].

In contrast to the commonly used method of single-voxel spectroscopy (SVS), chemical shift imaging (CSI) is a multi-voxel technique. Thus, in neuroimaging, 2D-CSI has the distinct advantage over SVS of allowing larger areas of the brain to be studied during scanning, so that areas showing abnormal signals and also those appearing normal in structural magnetic resonance images can be included[2]. CSI can also be carried out in three dimensions, which should improve spatial resolution and the signal-to-noise ratio; however, 2D-CSI is more resistant to motion artefact, which can be a problem when scanning the brain, than 3D-CSI[3]. Furthermore, image quality is better with 2D-CSI compared with 3D-CSI at a usual magnetic field strength of 1.5 T or 3 T[4-6].

Choline is an alcohol which, in the human brain, is particularly abundant in phosphatidylcholine (in which it is attached, as a polar head group, *via* a phosphate group, to the Sn3 position of the glycerol backbone) membrane phospholipid molecules; Cho take part in membrane biosynthesis and breakdown[1]. Thus, measurement of Cho has clinical and research value. One example is in relation to chronic fatigue syndrome (also known as myalgic encephalomyelitis or systemic exertion intolerance disease), which is currently of unknown etiology. The first systematic proton neurospectroscopy study of this condition showed a significantly higher level of Cho in the occipital cortex in patients compared with matched healthy controls, and also loss of the spatial variation of Cho that is normally expected[7]. Given that such increased levels are associated with abnormal membrane phospholipid metabolism[8], this finding, which was essentially confirmed later by another group in respect of the basal ganglia[9], suggests that chronic fatigue syndrome/myalgic encephalomyelitis is associated with abnormal phospholipid metabolism in neuroglial membranes[1,7]. It has been suggested that this, in turn, might result from chronic viral infection[10]. Based on this Cho finding, a potential therapeutic approach to this difficult-to-treat disorder, involving long-chain polyunsaturated fatty acids, has been suggested[11,12]. A second example relates to dyslexia, which is another important neuropsychiatric disorder of unknown etiology, in which the first systematic proton neurospectroscopy study revealed decreased Cho in the left temporo-parietal lobe[13]. This finding could have resulted from reduced left temporo-parietal phospholipid metabolism[14], which would be consistent with the findings from the first systematic 31-phosphorus neurospectroscopy study of this disorder[15]. In turn, this has led to suggestions of potential therapeutic interventions[16].

2D-CSI may also be useful clinically in evaluating patients with acute onset of neuropsychiatric systemic lupus erythematosus[2]. Another important clinical use of 2D-CSI is in relation to grading gliomas when used in combination with diffusion kurtosis imaging and dynamic susceptibility-weighted contrast-enhanced MRI[17]. Indeed, in a brain histopathological study, it has been shown that 2D-CSI combined with perfusion MRI are associated with high sensibility and high specificity

in differentiating between glioblastoma multiforme and cerebral metastases and also in distinguishing between grade Ⅲ and grade Ⅳ gliomas[18]. It is therefore important to ascertain the reproducibility of 2D-CSI.

We present the results of the first study to investigate the repeatability of proton magnetic resonance spectroscopy 2D-CSI in the *in vivo* measurement of human cerebral levels of Cho at a magnetic field strength of 1.5 T.

MATERIALS AND METHODS

Study design

This study was a repeated-measures pilot study in six individuals. The study was approved by the Research Ethics Committee. All participants gave written informed consent. Immediately after undergoing MRI scanning (including 2D-CSI), each participant remained lying in the scanner and the scanning protocol, including the 2D-CSI, was repeated.

Volunteers

The cohort consisted of six healthy volunteers, three males and three females. Their mean age was 44.1 years (range 26 to 58 years).

MR spectroscopy

All measurements were carried out using a 1.5-T Siemens Symphony TIM (Total Imaging Matrix) scanner (Siemens Medical Systems, Erlangen, Germany) using a standard head matrix coil. Proton spectra were acquired using a 64-voxel 2D-CSI spin-echo spectroscopy sequence with TE = 30 ms, TR = 1500 ms, number of averages = 4, field of view = 160 mm × 160 mm, and thickness = 15 mm. Figure 1 shows the location of the voxels. Spectral analysis was carried out using the Siemens spectroscopy task card (Siemens Medical Systems, Erlangen, Germany). This automated software analysis was objective and clearly obviated the need for inter-observer analysis.

Statistical analysis

The main endpoint of this study was the ratio of Cho to creatine (Cr) for each voxel. The coefficient of variation (CV), repeatability coefficient (RC), and intraclass correlation coefficient (ICC) were used to assess the repeatability. The repeatability coefficient was calculated as 1.96 × (standard deviation of the mean difference between two measurements), after the method proposed by Bland and Altman as being more appropriate than the correlation coefficient when assessing the level of agreement between two methods of clinical measurement[19]. The CV was calculated as (the standard deviation of the mean difference between two measurements)/(the mean of all measurements) and was assessed in order to allow comparison of the results of the present study with those of previous studies of the reproducibility

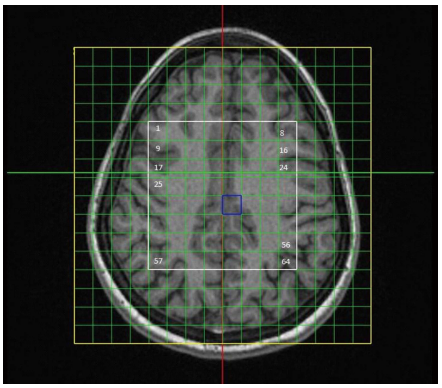

Figure 1 Location and numbering of voxels.

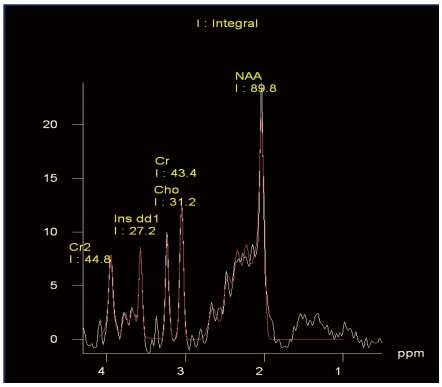

Figure 2 A fitted ^{1}H-MR spectrum.

of proton magnetic resonance (albeit without CSI). Differences between the results of the two scans were analyzed using the Wilcoxon related-samples signed-rank test (a repeated-measures nonparametric test). A *P*-value of less than 0.05 was taken to be statistically significant. Statistical tests were carried out using the software package IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, United States).

RESULTS

There were no technical difficulties in carrying out this study and all 2D-CSI proton neurospectroscopy data were included in the analyses. Figure 2 illustrates an example of a fitted spectrum from this study using the Siemens software.

The Wilcoxon related-samples signed-rank test results for all 64 voxels are shown in Table 1, using the voxel nomenclature given in Figure 1. Three voxels showed a significant difference between successive scans, namely voxels 3, 10 and 21.

The values of the mean CV, RC and ICC (together with corresponding *P* values) are given in Table 2. The CV ranged from 2.75% (voxel 3) to 33.99% (voxel 58). The minimum RC was 5.68% (voxel 3). Many of the ICC values were statistically significant, particularly for central and more caudal voxels, but also for some rostral voxels.

Table 1 Wilcoxon related-samples signed-rank test results

Voxel	Median Cho/Cr at first scan	Median Cho/Cr at second scan	Wilcoxon related-samples signed-rank test (*P* value)
1	0.681	0.624	0.345
2	0.825	0.836	0.917
3	0.897	0.924	0.046
4	0.819	0.785	0.917
5	0.822	0.812	0.753
6	0.998	1.060	0.917
7	0.868	0.902	0.600
8	0.661	0.708	0.463
9	0.751	0.579	0.075
10	0.878	0.799	0.028
11	0.970	1.043	0.173
12	0.793	0.860	0.173
13	0.822	0.765	0.600
14	0.993	0.989	0.753
15	0.923	0.894	0.600
16	0.714	0.682	0.463
17	0.760	0.644	0.249
18	0.947	0.855	0.116
19	1.027	1.045	0.345
20	0.751	0.828	0.173
21	0.898	0.816	0.046
22	1.063	1.056	0.173
23	0.942	1.022	0.917
24	0.728	0.747	0.116
25	0.713	0.705	0.249
26	0.941	0.984	0.917
27	0.940	0.961	0.345
28	0.808	0.831	0.753
29	0.853	0.851	0.600
30	1.030	1.083	0.600
31	0.991	0.929	0.249
32	0.709	0.696	0.173
33	0.660	0.660	0.600
34	0.892	0.922	0.345
35	0.948	0.905	0.917
36	0.732	0.718	0.600
37	0.750	0.724	0.345
38	1.032	0.904	0.173
39	0.982	0.946	0.345
40	0.700	0.744	0.116
41	0.627	0.597	0.917
42	0.866	0.854	0.249
43	0.871	0.793	0.600
44	0.591	0.595	0.600
45	0.573	0.584	0.753
46	0.793	0.875	0.600
47	0.903	0.940	0.249
48	0.563	0.686	0.075
49	0.571	0.575	0.463
50	0.779	0.817	0.345
51	0.740	0.777	0.116
52	0.539	0.533	0.463
53	0.546	0.500	0.463
54	0.767	0.752	0.463
55	0.812	0.838	0.046
56	0.530	0.583	0.345
57	0.498	0.507	0.917
58	0.692	0.715	0.463
59	0.607	0.683	0.463
60	0.466	0.472	0.173
61	0.569	0.451	0.173
62	0.825	0.677	0.753
63	0.638	0.639	0.753
64	0.530	0.625	0.600

Table 2 Mean coefficient of variation, repeatability coefficient, and intraclass correlation coefficient for all voxels

Voxel	Mean coefficient of variation	Repeatability coefficient	Intraclass correlation coefficient (*P* value)
1	0.080	0.159	0.492 (0.236)
2	0.057	0.194	0.866 (0.032)
3	0.028	0.057	0.982 (< 0.0001)
4	0.115	0.386	-1.877 (0.822)
5	0.101	0.260	-0.066 (0.523)
6	0.117	0.446	0.372 (0.335)
7	0.053	0.171	0.829 (0.046)
8	0.076	0.206	0.158 (0.429)
9	0.191	0.607	-0.233 (0.612)
10	0.049	0.113	0.901 (0.003)
11	0.071	0.191	0.702 (0.081)
12	0.091	0.225	0.509 (0.197)
13	0.076	0.213	0.724 (0.100)
14	0.078	0.233	0.696 (0.124)
15	0.089	0.277	0.735 (0.105)
16	0.091	0.236	-0.024 (0.509)
17	0.290	1.287	-3.314 (0.949)
18	0.095	0.226	0.811 (0.029)
19	0.058	0.226	0.816 (0.052)
20	0.058	0.137	0.370 (0.273)
21	0.058	0.106	0.569 (0.071)
22	0.064	0.214	0.780 (0.048)
23	0.055	0.238	0.941 (0.005)
24	0.258	6.467	0.152 (0.43)
25	0.192	0.305	0.866 (0.028)
26	0.044	0.129	0.974 (0.001)
27	0.062	0.205	0.833 (0.033)
28	0.087	0.242	0.652 (0.159)
29	0.059	0.170	0.749 (0.088)
30	0.061	0.205	0.851 (0.034)
31	0.046	0.114	0.983 (< 0.001)
32	0.093	0.174	0.907 (0.007)
33	0.126	0.244	0.872 (0.024)
34	0.057	0.146	0.829 (0.033)
35	0.066	0.230	0.793 (0.071)
36	0.063	0.151	0.883 (0.024)
37	0.036	0.079	0.960 (0.002)
38	0.096	0.314	0.397 (0.284)
39	0.087	0.269	-0.162 (0.584)
40	0.122	0.222	0.643 (0.116)
41	0.185	0.225	0.917 (0.011)
42	0.055	0.138	0.950 (0.002)
43	0.083	0.235	0.691 (0.132)
44	0.106	0.217	0.553 (0.216)
45	0.106	0.369	0.229 (0.397)
46	0.182	0.547	-0.256 (0.588)
47	0.054	0.136	0.942 (0.003)
48	0.175	0.274	-0.074 (0.555)
49	0.102	0.134	0.961 (0.002)
50	0.053	0.121	0.970 (0.001)
51	0.039	0.081	0.946 (0.001)
52	0.056	0.116	0.870 (0.03)
53	0.068	0.134	0.795 (0.064)
54	0.071	0.171	0.928 (0.007)
55	0.083	0.117	0.945 (0.001)
56	0.148	0.277	0.108 (0.448)
57	0.195	0.296	0.887 (0.022)
58	0.340	0.547	0.582 (0.188)
59	0.177	0.384	0.143 (0.43)
60	0.135	0.177	0.883 (0.011)
61	0.143	0.230	0.620 (0.135)
62	0.200	0.691	0.512 (0.253)
63	0.180	0.432	0.833 (0.046)
64	0.273	0.714	-0.957 (0.73)

DISCUSSION

There have been no previous studies of the repeatability of proton neurospectroscopy 2D-CSI in the *in vivo* measurement of human cerebral levels of Cho at a magnetic field strength of 1.5 T. Previous *in vivo* studies of the reproducibility of proton magnetic resonance spectroscopy measurements have used single voxel techniques and have reported "within day" CV values for human hepatic fat of between 0.3% and 8.5%[20-25]. Thus the results of the present study compare favorably with these reports, which is all the more impressive given that cerebral tissue is more heterogeneous than hepatic tissue. There have been few cerebral single-voxel proton reproducibility studies. Schirmer and Auer reported CVs for absolute human brain concentrations of the main metabolites Cho, Cr and N-acetylaspartate, ranging from 3.8% to 6.4%[26]; the present results compare very well with these.

Van Werven and colleagues reported a "within day" RC value for hepatic fat (using a single voxel technique at 3 T) of 0.4%. Again, the present result of a minimum voxel RC of over 5% compares very well this result. Twenty-six of the voxels in the present study had an ICC which was statistically significant, indicating a high level of agreement for these voxels.

Just three voxels had median Cho to Cr ratios which were different between scans. From Figure 1 it can be seen that these voxels (numbers 3, 10 and 21) have locations in sulcal regions of the brain. It is therefore possible that the poor reproducibility in these three voxels might be a function of "bleeding" in the neurospectroscopy data acquisition. Voxel "bleeding" refers to contamination with signals derived from any of the six adjacent voxels, and is an analogue of artifactual Gibbs ringing in structural MRI[27]. In the present case, the contaminating signals could have arisen from the low-signal sulcal spaces.

In conclusion, in this first study of its type, the reproducibility of proton magnetic resonance spectroscopy in the *in vivo* measurement of human cerebral levels of Cho at a field strength of 1.5 T using 2D-CSI has been found to be very acceptable. These findings should further encourage the use of this technique in psychiatric clinical practice as well as in research studies of neuropsychiatric disorders. Already, neurospectroscopy is proving helpful in studies of schizophrenia, major depressive disorder, forensic psychiatry (*e.g.*, posttraumatic stress disorder), chronic fatigue syndrome (myalgic encephalomyelitis or systemic exertion intolerance disease), and neuropsychiatric presentations in organic disorders, in which it has an important role to play in aiding diagnosis[16,28,29]. Given the present finding of a highly acceptable level of reproducibility of 2D-CSI, it would be appropriate in future to apply this technique to the follow-up of such patients, including monitoring their response to treatment.

ARTICLE HIGHLIGHTS

Research background

In vivo magnetic resonance proton spectroscopy studies of the brain can be used to measure Cho. In contrast to the commonly used method of SVS, CSI is a multi-voxel technique. Thus, compared with SVS, 2D-CSI allows larger areas of the brain to be studied, so that areas showing abnormal signals and also those appearing normal in structural MRI can be included. Compared with 3D-CSI, 2D-CSI is more resistant to motion artefact, which can be a problem when scanning the brain, and image quality is better at a usual clinical magnetic field strength of 1.5 T or 3 T.

Research motivation

Brain choline is particularly abundant in phosphatidylcholine membrane phospholipid molecules; Cho take part in membrane biosynthesis and breakdown. Thus, measurement of Cho has clinical and research value. For example, in chronic fatigue syndrome (also known as myalgic encephalomyelitis or systemic exertion intolerance disease), which is of unknown etiology, the first systematic proton neurospectroscopy study showed a significantly higher level of Cho in the occipital cortex in patients compared with matched healthy controls, and also loss of the spatial variation of Cho that is normally expected. This finding, which was essentially confirmed later by another group in respect of the basal ganglia, suggests that this disorder is associated with abnormal phospholipid metabolism in neuroglial membranes and has led to the suggestion of a potential therapeutic approach. A second example is dyslexia, also of unknown etiology, in which the first systematic proton neurospectroscopy study revealed decreased Cho in the left temporo-parietal lobe. This finding could have resulted from reduced left temporo-parietal phospholipid metabolism, which would be consistent with the findings from the first systematic 31-phosphorus neurospectroscopy study of dyslexia. In turn, this has led to suggestions of potential therapeutic interventions. 2D-CSI may also be useful clinically in evaluating patients with acute onset of neuropsychiatric symptoms. Another important clinical use of 2D-CSI is in relation to grading gliomas. It is therefore important to ascertain the reproducibility of 2D-CSI.

Research objective

The aim of this study was to investigate the repeatability of proton magnetic resonance spectroscopy 2D-CSI in the *in vivo* measurement of human cerebral levels of Cho.

Research methods

A repeated-measures study in six individuals was carried out using a 1.5-T Siemens Symphony TIM scanner and a standard head matrix coil. Proton spectra were acquired using a 64-voxel 2D-CSI spin-echo spectroscopy sequence. Spectral analysis was carried out using the Siemens spectroscopy task card. The main endpoint was the ratio of Cho to Cr for each voxel. The CV, RC, and ICC were used to assess the repeatability. There have been no previous studies of the repeatability of proton neurospectroscopy 2D-CSI in the *in vivo* measurement of human cerebral levels of Cho at a magnetic field strength of 1.5 T.

Research results

There was a minimum voxel RC of over 5%, which compared favorably with previous studies of the liver; the present results were all the more impressive given the much more heterogeneous nature of the brain compared with hepatic tissue. Twenty-six voxels had an ICC which was statistically significant, indicating a high level of agreement for these voxels. Just three voxels had median Cho to Cr ratios which were significantly different between scans. These three voxels were located in sulcal brain regions. Thus the poor reproducibility in these three voxels might be a function of "bleeding" in the neurospectroscopy data acquisition.

Research conclusions

In this first study of its type, the reproducibility of proton magnetic resonance spectroscopy in the *in vivo* measurement of human cerebral levels of Cho at a field strength of 1.5 T using 2D-CSI has been found to be very acceptable. Overall, the present findings should further encourage the use of this technique

in psychiatric clinical practice as well as in research studies of neuropsychiatric disorders.

Research perspectives

Overall, the results of this study are highly encouraging for the use of this technique in neuropsychiatric research and clinical practice. Further studies should be carried out to determine whether sulcal voxels should routinely be omitted from longitudinal comparison studies.

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ORIGINAL ARTICLE

Clinical Practice Study

Audit of physical health monitoring in children and adolescents receiving antipsychotics in neurodevelopmental clinics in Northumberland

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Abstract

AIM

To ascertain performance against the standards set by National Institute for Clinical Excellence (NICE) guidelines on physical health monitoring of thirty children and adolescents prescribed antipsychotics in neurodevelopmental clinics in Northumberland and identifying areas for improvement in practice.

METHODS

The audit involved a review of recorded documentation pertaining to physical health monitoring in patient electronic records pertaining to children and adolescents attending neurodevelopmental clinics in Northumberland prescribed antipsychotics. Clients were also contacted by telephone if relevant documentation could not be identified or retrieved to confirm the details. 32 case notes were perused of which 2 were excluded as they had refused to have venepuncture which was documented in the electronic records.

RESULTS

The overall audit results demonstrated partial compliance with NICE guidelines on physical health monitoring in children and adolescents prescribed antipsychotics. Bi-annual recording of height, weight, blood pressure, pulse rate and review of side effects

was completed in 100% of subjects. However, annual monitoring for blood tests including liver function, renal function full blood count as well as biannual monitoring of serum prolactin, serum lipid profile was completed only in 56% of subjects. Comparative baseline characteristics between the two groups (compliant and non-compliant with guidelines) found no differences based on any socio-demographic or clinical variables. However, the proportion of patients in the group compliant to guidelines was higher in the age group of 12-17 years as compared to < 12 years (70.58% *vs* 38.46%), though not statistically significant ($\chi^2 = 1.236$; $P = 0.24$).

CONCLUSION

Development of tailored and specific guidelines for physical health monitoring in children and adolescents prescribed antipsychotics taking into consideration clinical effectiveness and safety profile is likely to improve adherence rates.

Key words: Antipsychotic; Children; Physical health; Guidelines

Core tip: A number of clinical guidelines have been developed for physical health monitoring in children and adolescents on antipsychotics. However, none of them capture the intricacies and complexities involved in prescribing antipsychotics to children and adolescents, which is distinct from adults. The typically shorter duration of prescribing, lower doses used and lack of data on long term adverse effects with antipsychotics in this population have not been taken into account. This audit aimed to ascertain if physical health of children and adolescents attending neurodevelopmental clinics in Northumberland and prescribed antipsychotics followed National Institute for Clinical Excellence guidelines. The overall audit findings were partially compliant with the guidelines. Logistic and ethical challenges as well as lack of awareness about the guidelines could underpin these findings.

Gnanavel S, Hussain S. Audit of physical health monitoring in children and adolescents receiving antipsychotics in neurodevelopmental clinics in Northumberland. *World J Psychiatr* 2018; 8(1): 27-32 Available from: URL: http://www.wjgnet.com/2220-3206/full/v8/i1/27.htm DOI: http://dx.doi.org/10.5498/wjp.v8.i1.27

INTRODUCTION

Despite limited literature on long term effectiveness and side effects of antipsychotics in children and adolescents, antipsychotics are frequently used in this population in Europe and North America. In fact, recent trends of increased antipsychotic prescribing for this population has been well-documented. In a recent German nation-wide prescribing audit by health care insurers it was demonstrated that the rise in antipsychotic prescriptions was particularly marked among 10- to 14-year-olds (from 0.24% to 0.43%) and among 15- to 19-year-olds (from 0.34% to 0.54%)[1]. Psychosis, challenging behaviour in autism spectrum disorder (ASD) and Tourette's syndrome are the most common reasons for child and adolescent psychiatrists to prescribe antipsychotics. In addition, use of antipsychotics in other neurodevelopmental disorders like attention deficit hyperactivity disorder (ADHD) is not uncommon though "off-label" for this purpose[2]. In terms of symptom profiles targeted by antipsychotic use in this population, the most common indications were chronic behavioural disturbance with persistent aggression (34%), followed by agitation/anxiety (31%) and psychotic symptoms (31%) in a recent nation-wide audit of antipsychotic prescribing in children and adolescents in United Kingdom[3].

A survey of antipsychotic prescribing among child and adolescent psychiatrists in the United Kingdom found that over 95% had prescribed antipsychotics over a 12 mo period with the majority (almost 90%) choosing one of the second generation antipsychotics (SGAs)[4]. Risperidone followed by aripiprazole and olanzapine are the favoured antipsychotics in this population[4]. There is a relatively limited but gradually expanding evidence-base of randomised clinical trials to support antipsychotic prescribing in children and adolescents with non-psychotic illnesses. This includes management of challenging behaviour in ASD with risperidone; aripiprazole and risperidone for management of aggression with conduct disorder and learning disability[5-8].

It is to be noted that, children and adolescents are more sensitive to antipsychotic-related adverse effects than adults. This includes extrapyramidal side effects (EPS) with first generation antipsychotics (FGAs) and metabolic side -effects with SGA[9,10]. However, it is also worth noting that most literature relating to tolerability of antipsychotics in children and adolescents are based on the treatment of severe mental illnesses like psychotic disorders in typically short-term clinical trials lasting 6 to 12 wk. There is scant literature on the adverse effects associated with longer term prescribing of antipsychotics (the distal health outcomes as opposed to more proximal health outcomes) and more particularly, involving lower doses that are typically used in non-psychotic developmental disorders in children and adolescents. Possibly, as an extension to this, we do not know if these physical side effects are reversible, partially or completely with discontinuation of antipsychotics or are these irreversible side effects.

Individual antipsychotics (even within the same class) differ in terms of side effect profiles when prescribed to children and adolescents. For example, in this population, EPS are more common with haloperidol and high-

dose risperidone than with olanzapine. Weight gain is more common in olanzapine than with risperidone[10,11]. There is also some evidence for differential response to same medication based on age groups. For example, children and adolescents experience more weight gain on second generation antipsychotics than do adults[10]. However, most of the guidelines do not differentiate their physical health monitoring requirements, particularly in the maintenance phase between those on different antipsychotics or between different age groups. Also, first and second generation antipsychotics are different chemically and heterogeneous with respect to safety profile. Hence, having common monitoring requirement seems flawed, in practical terms.

The commonly followed guidelines for physical health monitoring in children and adolescents receiving antipsychotics include NICE (National institute for clinical excellence guidelines) (CG155); AACAP (American academy of child and adolescent psychiatry) - practice parameter for the use of atypical antipsychotic medications in children and adolescents; CAMESA - Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children and TRAAY (Treatment recommendations for the use of antipsychotics for aggressive youth) centre for the Advancement of Children's Mental Health[12-14]. The specificity of recommendations for ongoing monitoring for metabolic parameters varies, with some guidelines recommending "appropriate" monitoring while others identifying specific tests and pre-determined follow-up intervals.

The parameters specified in these guidelines include physical measurements like height, weight, blood pressure and pulse rate as well as those measured in laboratory with a blood sample like liver function test, renal function tests and blood glucose. Usually, there are specifications for monitoring parameters at baseline as well as during the maintenance phase in the guidelines mentioned above.

This audit was identified with a view to ascertaining performance against the standards set by National Institute for Clinical Excellence (NICE) guidelines on physical health monitoring of thirty children and adolescents prescribed antipsychotics in neurodevelop-mental clinics in Northumberland and identifying areas for improvement in practice[15]. The audit focused only on those clients who had already been initiated and stabilised on a dose of antipsychotic medication for at least a period of one year prior to the time frame chosen for audit. The time frame covered was from 1st November 2015 to 30th October 2016.

MATERIALS AND METHODS

The audit involved a review of recorded documentation pertaining to physical health monitoring in patient electronic records pertaining to those children and adolescents attending neurodevelopmental clinics in Northumberland prescribed antipsychotics. Clients were also contacted by telephone if relevant documentation could not be identified or retrieved to confirm the details. Thirty-two case notes were perused of which 2 were excluded as they had refused to have venepuncture which was documented in the electronic records. Hence, the total number of clients included in the audit was 30. The sample was collated by means of consecutive sampling of convenience. Data collection took place from 1 November 2016 to 30 March 2017 and data analysis was completed in 30 April 2017. A quality review of the results of this audit was undertaken by the second author during July 20, 2017 to August 03, 2017 to provide assurance on the accuracy of the findings in this report. The audit was registered with the audit department of Northumberland, Tyne and Wear NHS foundation trust.

The NICE guidelines recommend annual physical health monitoring of following parameters for patients already stabilised on antipsychotic medications: Biannual monitoring for weight, height, pulse, blood pressure, fasting blood glucose, HbA1c and blood lipid levels, review of side effects and annual monitoring for liver function tests, renal function tests and serum electrolytes as well as full blood count. The expected compliance rate was 100% (gold standard) with respect to all the above parameters.

Statistical analysis

The data was analysed using SPSS 15.0 (Statistical package for social science). The data was analysed using appropriate parametric and non-parametric tests based on the distribution of data including χ^2 test for categorical variables and *t*-test for continuous variables. $P < 0.05$ was considered significant.

RESULTS

The study sample included 28 males and 2 female clients (male: female ratio of 14:1). The two antipsychotics prescribed were risperidone (77%) (n = 23) and aripiprazole (23%, n = 7). The daily dose range for risperidone was 0.25-2 mg and for aripiprazole was 0.5-4 mg. The mean dose of risperidone used was 0.88 mg (SD: 0.11) and mean dose of aripiprazole used was 1.87 mg (SD: 0.23). The mean age of initiation of antipsychotic in this sample was 13.45 years (SD: 1.23). The average duration of antipsychotic use in months was 15.67 mo (SD: 1.98) (Table 1).

Bi-annual recording of height, weight, blood pressure, pulse rate and review of side effects was completed in 100% of subjects. However, annual monitoring for blood tests including liver function, renal function full blood count as well as biannual monitoring of serum prolactin, serum lipid profile was completed only in 56% of subjects. It was also noted that in five of the subjects in whom the physical health monitoring was carried out according to guidelines, the initial lab result summary did not contain serum prolactin which

Table 1 Baseline characteristics of the audit sample (n = 30)

Variable	Mean	SD
Age (yr)	13.45	1.23
Duration of antipsychotic use (mo)	15.67	1.98
Average number of clinical reviews	3.43	0.46
Variable	*n*	%
Age groups (yr)		
12-17	17	56.67
< 12	13	43.33
Gender		
Male	28	93.33
Female	2	6.67
Antipsychotic		
Risperidone	23	76.67
Aripiprazole	7	23.33
Psychiatric diagnosis		
ADHD	12	40.00
ASD	4	13.33
ADHD + ASD	6	20.00
ADHD + other diagnosis	6	20.00
ASD + other diagnosis	2	6.67

ADHD: Attention deficit hyperactivity disorder; ASD: Autism spectrum disorder.

was subsequently carried out after a second request (possibly missed out initially due to oversight).

Comparing the baseline characteristics between the groups for whom antipsychotic physical monitoring guidelines were followed and not followed, there were no differences based on antipsychotic prescribed, duration of antipsychotic use or number of reviews carried out in the neurodevelopmental clinics. However, the proportion of patients who were monitored for physical health according to guidelines was higher in the age group of 12-17 years as compared to < 12 years, though not statistically significant (χ^2 = 1.236; P = 0.24). There were also no significant differences in the proportion monitored for physical health based on the diagnosis (ADHD; ASD; ADHD+ASD; ADHD + other mental health disorders; ASD + other mental health disorders) (χ^2 = 1.345; P = 0.27). The "other" diagnoses included oppositional defiant disorder (n = 3), tic disorder (n = 3) and conduct disorder (n = 2). We did not carry out a gender-wise comparison, since there were only two female clients in the audit sample (Table 2).

The overall audit results demonstrated partial compliance with NICE guidelines on physical health monitoring in children and adolescents prescribed antipsychotics. However, it was interesting to note that, the monitoring guidelines were followed in a larger proportion of patients in 12-17 year age range as compared to < 12 years (though not statistically significant). To summarise, there was no statistical difference between the groups that completed and did not complete physical health monitoring according to NICE guidelines based on any baseline socio-demographic or clinical variables.

Table 2 Factors associated with likelihood of testing

Age groups (yr)	Total number	Number monitored
12-17	17	12
< 12	13	5
Antipsychotic		
Risperidone	23	13
Aripiprazole	7	4
Psychiatric diagnosis		
ADHD	12	7
ASD	4	2
ADHD + ASD	6	3
ADHD + other diagnosis	6	4
ASD + other diagnosis	2	1
Average duration of antipsychotic use	Mean	SD
Group A[1]	15.98	1.21
Group B[2]	15.42	1.32
Average number of clinical reviews	Mean	SD
Group A[1]	3.52	0.32
Group B[2]	3.31	0.36

[1]Group A: Group that completed physical health monitoring requirements according to National Institute for Clinical Excellence (NICE) guidelines; [2]Group B: Group that did not complete physical health monitoring requirements according to NICE guidelines. ADHD: Attention deficit hyperactivity disorder; ASD: Autism spectrum disorder.

DISCUSSION

The findings from our audit are broadly similar to previous published literature. A similar audit carried out recently in an inpatient setting in United Kingdom on children and adolescents prescribed antipsychotics demonstrated adherence rates of 20%-60% on different parameters[16]. In comparison, an audit of similar parameters in a community based setting focusing on adult patient's demonstrated partial adherence to guidelines in around half the patients[17]. Both the above audits were carried out with standards set by NICE as the reference.

Outside the United Kingdom, there are studies or audits published from North America and Europe on the same theme. A large scale longitudinal retrospective cohort study using data from 2000-2006 from the PharMetrics data base (an insurance claims database) in United States demonstrated 12 wk lipid and blood sugar monitoring rates of 6.8% and 9% respectively in patients under 65 years (which also includes children and adolescents) receiving second generation antipsychotics[18]. It also interestingly demonstrated rise in these rates to 14.1% and 17.9% post introduction of ADA (American diabetic association) guidelines in 2004. Of even more importance, is the fact that 0-11 years and 11-17 years fared the worst when different age groups were compared for 12 wk monitoring of blood glucose and blood lipids[18].

The limitations of our audit include a small sample size and lack of representation from female patients with neurodevelopmental disorders, receiving an

antipsychotic. Also, the results are specific for our service and cannot be generalised to other parts of the country considering the heterogeneity in the way neurodevelopmental services as well as physical health services are organised in different parts of the country.

Several guidelines based on available evidence base have been developed (mentioned earlier) for both baseline and ongoing monitoring of physical health parameters for children and adolescents prescribed antipsychotics. However, most of these guidelines are extrapolated at least in part from the equivalent guidelines for adults. They fail to capture the complexities and intricacies of antipsychotic prescribing, particularly in younger children, especially the usually short term symptomatic use.

The common barriers cited for non-adherence to guidelines on physical health monitoring in children and adolescents prescribed antipsychotics include ethical and practical difficulties in taking blood from children (*e.g.*, In children with autism and challenging or oppositional behaviours)[3]. This could also be the possible basis for the audit finding that a higher proportion of adolescents on antipsychotics were monitored for physical health parameters than younger children on antipsychotics (though not statistically significant). This could also possibly reflect the tendency of mental health professionals to treat adolescents more like young adults while in case of children, the attitude of clinicians is generally quite different. There is also uncertainty regarding the impact of abnormal results on clinical management (*e.g.*, asymptomatic hyperprolactinaemia)[3]. Sometimes, logistic challenges including inadequate number of skilled phlebotomists and lack of a reliable pathway for carrying out these investigations and retrieving the results could be a barrier to following these guidelines (for example, in many cases psychiatrists depend on general practitioners or hospitals for organising blood tests while in some services in house phlebotomy and lab services are offered). However, most clinicians do support the development of physical health monitoring guidelines for antipsychotic use in children and adolescents, albeit advocating guidelines more appropriately constructed for this target population and taking into account the complexities involved.

Some published literature on quality improvement projects in this regard demonstrated simple methods like a visual prompt questionnaire tool along with review paperwork, new formatting of clinical letters to general practitioners, psychoeducation of both clinical practitioners and patients, easy read leaflets and posters which did produce a significant improvement in adherence to clinical guidelines[16,17]. On a larger scale, in Europe, the Therapeutic Drug Monitoring (TDM) run by the German-Austrian Swiss "Competence Network on TDM in Child and Adolescent Psychiatry" and the Paediatric Atypical Antipsychotic Monitoring Safety Study (PAMS) in the United Kingdom have been developed as pharmacovigilance projects[19,20].

Development of tailored and specific guidelines for physical health monitoring in children and adolescents prescribed antipsychotics based on age of initiation, dose and type of antipsychotic is likely to improve adherence rates. Some room for flexibility, taking into consideration appropriate clinical judgement on a case by case basis may also be beneficial in this regard. Similarly, understanding attitudes and psychological barriers in both patients and clinicians to regular monitoring, particularly blood parameters can provide useful insight in addressing the generally low compliance rates to these guidelines worldwide. We also need further studies to identify those children and adolescents with a possibly higher risk of side effects (*e.g.*, a positive family history of physical morbidity) to allow us to tailor a more intensive monitoring regimen for this subset of population receiving antipsychotics. Tailored guidelines for children and adolescents and a customised approach is needed to match clinical effectiveness and safety profile.

ARTICLE HIGHLIGHTS

Research background

Despite limited literature on long term effectiveness and side effects of antipsychotics in children and adolescents, antipsychotics are frequently used in this population in Europe and North America. In fact, recent trends of increased antipsychotic prescribing for this population has been well-documented. These medication are associated with physical health side effects though the extent of these side effects when used in lower doses or prolonged duration in children and adolescents have not been adequately studied. However, a number of popular guidelines exist pertaining to physical health monitoring in children and adolescents on antipsychotics.

Research motivation

The current study is an audit of physical health monitoring in children and adolescents prescribed antipsychotics in neurodevelopmental clinics in Northumberland. A comparative review of similar audits carried out from different regions can address pertinent issues like association between standards set by different guidelines and the concordance rates with the same.

Research objectives

To ascertain performance against the standards set by National Institute for Clinical Excellence (NICE) guidelines on physical health monitoring of thirty children and adolescents prescribed antipsychotics in neurodevelopmental clinics in Northumberland and identifying areas for improvement in practice.

Research methods

The audit involved a review of recorded documentation pertaining to physical health monitoring in patient electronic records pertaining to those children and adolescents attending neurodevelopmental clinics in Northumberland prescribed antipsychotics. Clients were also contacted by telephone if relevant documentation could not be identified or retrieved to confirm the details. 32 case notes were perused of which 2 were excluded as they had refused to have venepuncture which was documented in the electronic records.

Research results

The overall audit results demonstrated partial compliance with NICE guidelines on physical health monitoring in children and adolescents prescribed antipsychotics. Bi-annual recording of height, weight, blood pressure, pulse rate and review of side effects was completed in 100% of subjects. However, annual monitoring for blood tests including liver function, renal function full blood count as well as biannual monitoring of serum prolactin, serum lipid profile was completed only in 56% of subjects. Comparative e baseline characteristics

between the two groups (compliant and non-compliant with guidelines) found no differences based on any socio-demographic or clinical variables. However, the proportion of patients in the compliant group was higher in the age group of 12-17 years as compared to < 12 years (70.58% *vs* 38.46%), though not statistically significant (χ^2 = 1.236; *P* = 0.24).

Research conclusions

Development of tailored and specific guidelines for physical health monitoring in children and adolescents prescribed antipsychotics taking into consideration clinical effectiveness and safety profile is likely to improve adherence rates.

Research perspectives

The methodology into development of tailored guidelines for antipsychotic monitoring in children and adolescents need to be adequately focused upon. A comparative review of the audits on antipsychotic physical health monitoring guidelines carried out till date in different regions of the world based on different guidelines might shed some light on this important topic.

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ORIGINAL ARTICLE

Clinical Practice Study

Factors associated with tobacco, alcohol, and other drug use among youth living in West Central Mexico

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Abstract

AIM

To determine the prevalence of drug and substance abuse among high school students in Jalisco and its association with the severity of health, behavior and psychosocial problems in order to provide evidence for possible prevention and treatment needs.

METHODS
A multi-stage random sample of Jalisco high school students was given a paper-and-pencil survey based upon an adapted version of the drug use screening inventory (DUSI) (n = 24699; n = 2832). The DUSI showed adequate psychometric characteristics in this population. The statistical analyses accommodated the complex survey design with attention to unequal probability of selection and clustering of participants within schools and regions.

RESULTS
An estimated 44% of the students had smoked tobacco, one in five students was a current smoker, and one in four students used to smoke but had not smoked for one year or more. By contrast, 6.8% of the students reported having used marijuana, cocaine, or both. Behavioral problems, deviant peer affiliation, and troubled families were independently associated with drug use. One in two students who used tobacco or alcohol had used these drugs in the past year (46% and 54%, respectively), and one in four students who used marijuana or cocaine in their lifetime had used those drugs in the past year (28% in both cases).

CONCLUSION
The rates of cocaine use as well as the proportion of current users were higher than expected among high school students and indicate changing patterns of drug use in Mexico. These results corroborate that the general trend of drug use by youth in Mexico is increasing. Results from this study help us better understand the needs of at-risk youth and the need for new treatment and prevention strategies.

Key words: Tobacco; Alcohol; Marijuana; Illegal drugs; Mexico; Students; Epidemiology

Core tip: Drug and substance use is a public health problem around the world. Prevention efforts are carried out with varying results. One of the main targets in prevention is the risk factors associated with drug use. There are several instruments to study the risk factors which provide critical information to establish guidelines to control and prevent drug use. We used a well known validated and accepted instrument (drug use screening inventory) to investigate the prevalence and psychosocial factors associated with tobacco, alcohol and drug use in high school students in Mexico. We found higher prevalence of substance use than expected: 44% of the students had smoked tobacco and one in five students was a current smoker while over 40% had history of binge drinking. On the other hand, 6.8% of the students reported having used marijuana, cocaine, or both. Behavioral problems, deviant peer affiliation, and troubled families were independently associated with drug use. These results will help in the application of control and prevention programs among high school students. This is the first survey representative of a West Central state in Mexico: Jalisco which is an important Mexican state because it has a significant drug production and trafficking problem, and on the other hand, it provides a great number of migrants to the United States creating social, cultural and health problems associated with risk behaviors.

Campollo O, Sheikhattari P, Alvarez C, Toro-Guerrero J, Sanchez Avila H, Wagner FA. Factors associated with tobacco, alcohol, and other drug use among youth living in West Central Mexico. *World J Psychiatr* 2018; 8(1): 33-42 Available from: URL: http://www.wjgnet.com/2220-3206/full/v8/i1/33.htm DOI: http://dx.doi.org/10.5498/wjp.v8.i1.33

INTRODUCTION

Drug use is a public health problem with increasing trends in Mexico[1-3] where only tobacco and alcohol products are legally available while other drugs such as marijuana (except the recently legalized medical marijuana)[4], cocaine, heroin, methamphetamines, and synthetic drugs of abuse are not. In fact, although the 2016-2017 National Drug, Alcohol and Tobacco Consumption Survey may not provide an accurate comparison with previous surveys on account of the modified methodology[3], according to the National Addiction Surveys (Encuesta Nacional de Adicciones, ENA)[1,2], the prevalence of cocaine and marijuana use almost doubled in the past decade. More specifically, in 2012, 43% of the individuals between the ages of 12-25 reported being exposed to drug use, among them half experimented with drugs, and 13% used drugs frequently[1,2]. In spite of recent efforts to provide up-to-date epidemiologic information, since 1991 there has not been a published regional or state drug abuse survey performed in Jalisco, a state in the West Central Region of Mexico with a population of over 8 million. The most recent available information from the Mexican National Survey from 2016 estimated that 15.3% of the 12- to 65-year-old population in Jalisco had never used drugs[3]. Among youths of high school age, the ENA estimated that 2.7% of males and 1.1 % of females have used illegal drugs[2]. However, these figures may not apply directly to Jalisco given the significant heterogeneity within this particular region. To the extent that drug use differs across rural/urban areas in Mexico[5-7], pooled drug use estimates for the region may mask important within-region differences.

Interest in drug use trends in the State of Jalisco is warranted in light of its large population and a very strategic geo-politic location as a narcotic production enclave and a route for drug trafficking directed to the United States[8]. Jalisco is also a large contributor of documented and undocumented workers to the United States, many of which make frequent

roundtrips[9]. In addition, drug use may correlate with other risk behaviors that increase the risk of HIV/AIDS, viral hepatitis, and other sexually transmitted infections[10,11]. Therefore, it is important to recognize that health profiles and risk behaviors in one region, and even a sub-region, may have consequences in many other regions in spite of geographic, language, cultural, and legal barriers.

Surveys are one of the main sources of information to understand the nature and extent of drug abuse in different populations, and they support evidence-informed development of policies and practice guidelines[12]. Thus, in this study, we sought to improve on the few existing studies about treatment needs for drug abuse among youths in Mexico. Hence, the aim of this study was to investigate the prevalence of substance use and associated factors amongst high school students from the Mexican West-Central State of Jalisco, to identify treatment and prevention needs, and to explore the association between drug involvement and selected psychosocial covariates. We conducted the first survey representative of Jalisco's sub-regions performed in the 21st century.

MATERIALS AND METHODS

Data were collected through a cross-sectional survey using a multi-stage, random sample of high school students, from 10 geo-political sub-regions in the State of Jalisco, Mexico. A total of 25 public high schools participated in the survey. The mean number of students per school was 524 with a maximum of 2242 and a minimum of 132 (the sample included regional high schools and smaller high school "modules"). The universe included 24699 students and a final sample of 2832 students participated. The project was approved by the University of Guadalajara's Research Committee of the Health Sciences Center. We obtained authorization from the principal of each participating high school, and no school refused to participate in the study. The inclusion criteria were regular attendance in the participating school and consenting to participate in the study. Irregular students and students who did not complete the survey were excluded. At the time of the survey, students were informed that their participation was voluntary and they could choose not to participate in the survey without any penalties. Almost all of the students consented to participate in the study (only 4 refused). Data confidentiality and anonymity were explained twice; once in their classroom at the time of randomization, and once in the auditorium where all participants were gathered.

Procedures

We used a self-administered, school-based paper-and-pencil anonymous questionnaire. In each school, the survey was conducted in one day, and it was administered by the principal investigator and members of the research team. The survey was administered at the school's auditoriums. To assure and preserve confidentiality, no teachers or school staff members were allowed to be present in the auditorium at the time of the application, nor were they allowed to see the completed questionnaires. The questionnaires were scanned with an optical reader which recorded filled or blank dots.

Measures used

Students completed the abbreviated Spanish version of the drug use screening inventory (DUSI) for youth developed by Tarter[13] and further adapted for the Mexican population by Diaz *et al*[14]. The abbreviated DUSI-RM includes 95 yes/no questions assessing the 10 domains of drug and alcohol use, psychiatric disorders, health status, behavior patterns, school performance, family system, peer relationships, social competence, work adjustment, and leisure/recreation. Of particular interest for the present analyses is the substance abuse domain which assesses the type and substance use on the day of the survey, as well as the past week, month, year, and before then. In addition, the survey questionnaire includes questions on demographics such as age, gender, high school grade, occupation, family income, school shift, and school location (urban *vs* rural).

As with the original DUSI and other adaptations for Latin American countries[15], the DUSI-RM in this sample had good to excellent reliability, with a 0.79 Chronbach's alpha coefficient for the overall instrument and domain-specific scores[16] ranging from 0.57 to 0.80. Due to non-normality of the data, each participant's domain-specific scores were recoded into three levels to contrast the bottom two deciles (No Problem) from the six subsequent deciles (Low Problem), and the highest two deciles (High Problem).

Statistical analysis

After exploratory data analyses to check for variable distribution and data preparation for multivariate analyses, logistic regression models were used to estimate the association of each DUSI-RM domain with tobacco use, alcohol use, as well as marijuana and cocaine use, while controlling for age, sex, and socio-economic status (SES). The analyses were done with STATA version 10.0 (STATA Corp, College Station, TX, United States), and they accommodated the complex survey design with attention to unequal selection probabilities and clustering of participants within schools[17].

RESULTS

Table 1 summarizes results regarding drug involvement in the surveyed sample. More than half of the students (55.8%) had never used tobacco, one in five (20.2%) had smoked it in the past year, and about

Table 1 Drug and substance use by high school students in Jalisco, Mexico (*n* = 2816)

Prevalence	Tobacco use		Binge drinking		Marijuana		Cocaine		Any illegal	
	n	%	*n*	%	*n*	%	No.	%	*n*	%
Never	1564	55.77	1590	57.03	2596	92.48	2611	92.50	2517	89.47
Past year	556	20.21	984	35.01	129	4.41	127	4.84	191	6.83
Former	696	24.02	242	7.96	91	3.11	78	2.66	108	3.70

Table 2 Cross-tabulation of past-year tobacco, alcohol, and illicit drug use by socio-demographic characteristics and drug use screening inventory problem areas (*n* = 2816)

Variables	Total (*n* %)	Past year smoking (*n* %)			Past year alcohol use (*n* %)			Past year illicit drug use (*n* %)		
		No	Yes	*P* value	No	Yes	*P* value	No	Yes	*P* value
Total	2816 (100)	2260 (79.8)	556 (20.2)	n/a	1832 (65.0)	984 (35.0)	n/a	2721 (96.6)	191 (6.8)	n/a
Age (yr)										
>16	2358 (83.7)	1875 (79.2)	483 (20.8)	0.112	1482 (62.8)	876 (37.2)	< 0.001	2183 (92.5)	175 (7.5)	0.005
≤ 16	458 (16.3)	385 (82.8)	73 (17.2)		350 (76.1)	108 (23.9)		442 (96.3)	16 (3.7)	
Gender										
Female	1460 (52.0)	1223 (83.7)	237 (16.3)	< 0.001	1050 (71.8)	410 (28.2)	< 0.001	1413 (96.8)	47 (3.2)	< 0.001
Male	1356 (48.0)	1037 (75.5)	319 (24.5)		782 (57.6)	574 (42.4)		1212 (89.3)	144 (10.7)	
Employment										
Not working	1937 (69.5)	1590 (81.5)	347 (18.5)	0.013	1279 (65.9)	658 (34.1)	0.097	1828 (94.2)	109 (5.8)	0.01
Employed	879 (30.5)	670 (75.9)	209 (24.1)		553 (62.9)	326 (37.1)		797 (90.7)	86 (9.3)	
Behavioral pattern										
No problem	622 (22.5)	558 (89.6)	64 (10.4)	< 0.001	497 (79.5)	125 (19.5)	< 0.001	607 (98.0)	15 (2.0)	< 0.001
Low	1651 (58.2)	1341 (81.0)	310 (19.0)		1094 (66.3)	557 (33.7)		1556 (94.1)	95 (5.9)	
High	543 (19.3)	361 (64.7)	182 (35.3)		241 (44.2)	302 (55.8)		462 (84.8)	81 (15.2)	
Psychiatric disorder										
No problem	564 (19.9)	471 (83.4)	93 (16.6)	0.002	403 (71.6)	161 (28.4)	< 0.001	534 (94.7)	30 (5.3)	0.104
Low	1692 (60.1)	1377 (80.9)	315 (19.1)		1122 (65.9)	570 (34.1)		1585 (93.6)	107 (6.4)	
High	560 (20.0)	412 (72.9)	148 (27.1)		307 (55.8)	253 (44.2)		506 (90.4)	54 (9.6)	
Social competence										
No problem	565 (19.8)	463 (81.2)	102 (18.8)	0.44	364 (65.1)	201 (35.0)	0.016	525 (92.9)	40 (7.1)	0.741
Low	1683 (60.2)	1339 (79.2)	344 (20.8)		1074 (63.5)	609 (36.5)		1567 (93.1)	116 (6.9)	
High	568 (20.0)	458 (80.0)	110 (20.0)		394 (69.3)	174 (30.7)		533 (93.7)	35 (6.3)	
Family system										
No problem	574 (20.3)	510 (88.4)	64 (11.6)	< 0.001	474 (83.6)	100 (16.4)	< 0.001	560 (97.8)	14 (2.2)	< 0.001
Low	1676 (60.0)	1352 (80.2)	324 (19.8)		1083 (63.9)	593 (36.1)		1570 (93.6)	106 (6.5)	
High	566 (19.7)	398 (69.8)	168 (30.2)		275 (49.0)	291 (51.0)		495 (87.2)	71 (12.8)	
School adjustment										
No problem	824 (29.3)	747 (90.2)	77 (9.8)	0.001	659 (80.1)	165 (19.9)	< 0.001	805 (98.1)	19 (1.9)	< 0.001
Low	1425 (50.7)	1161 (81.1)	264 (18.9)		946 (66.2)	479 (33.8)		1364 (95.5)	61 (4.5)	
High	567 (20.0)	352 (61.2)	215 (38.8)		227 (39.7)	340 (60.3)		456 (80.1)	111 (19.9)	
Peer relationship										
No problem	596 (21.4)	543(91.2)	53 (8.8)	< 0.001	481 (81.3)	115 (18.7)	< 0.001	592 (99.3)	4 (0.7)	< 0.001
Low	1656 (58.5)	1340 (80.3)	316 (19.7)		1089 (65.5)	567 (34.5)		1581 (95.5)	75 (4.5)	
High	564 (20.1)	377 (66.3)	187 (33.7)		262 (46.2)	302 (53.8)		452 (79.8)	112 (20.2)	
Leisure/recreation										
No problem	573 (19.9)	511 (88.6)	62 (11.4)	< 0.001	452 (80.3)	121 (19.7)	< 0.001	560 (98.3)	13 (1.7)	< 0.001
Low	1677 (60.2)	1362 (80.6)	315 (19.4)		1112 (65.8)	565 (34.2)		1571 (93.4)	106 (6.7)	
High	566 (19.9)	387 (68.4)	179 (31.6)		268 (47.2)	298 (52.8)		494 (87.5)	72 (12.5)	

one in four (24%) had used tobacco at some time more than a year before. Also, more than half (57.0%) stated they had never gotten drunk, one third (35.0%) had experienced it in the past year, and an additional 8% had gotten drunk at some time more than a year before. In total, 7.5% of the students reported to have used marijuana on at least one occasion, and 4.4% had used it in the past year. A similar proportion of students had a history of cocaine use, and 4.8% had used in the past year. Although there can be much overlapping between marijuana and cocaine use, it is important to note that close to one in 15 students (6.8%) had ever used an illegal drug, the majority of them within the past year.

Table 2 provides data on sample characteristics and rates of past year use of tobacco, alcohol, and illicit drugs based on age, sex, working status, and DUSI domains. The age range of the participants was 14 to 22 years, and most (83.7%) were 16 years of age or older; 52% were female, and 48% were male. About a third of the students (30.5%) had a part-time or full-time job. The overall percentage distribution of students by DUSI-problem area score conformed to the expected 20% for the top scores (high problem),

Table 3 Association of past year tobacco, alcohol, illicit drug use and drug use screening inventory-RM domains among high school students in the State of Jalisco, Mexico (*n* = 2816)

Variables	Past year smoking				Past year alcohol use				Past year illicit drug use			
	aOR	95%CI		*P* value	aOR	95%CI		*P* value	aOR	95%CI		*P* value
Age (yr)												
>16	1.00		Reference		1.00		Reference		1.00		Reference	
≤ 16	0.94	0.70	1.24	0.628	0.56	0.46	0.69	< 0.001	0.56	0.34	0.90	0.020
Gender												
Female	1.00		Reference		1.00		Reference		1.00		Reference	
Male	1.26	0.93	1.72	0.127	1.61	1.36	1.91	< 0.001	2.28	1.44	3.61	0.001
Employment												
Not working	1.00		Reference		1.00		Reference		1.00		Reference	
Employed	1.14	0.83	1.56	0.412	0.81	0.66	1.01	0.058	1.03	0.73	1.46	0.870
Behavioral pattern												
No problem	1.00		Reference		1.00		Reference		1.00		Reference	
Low	1.63	1.21	2.19	0.002	1.43	1.09	1.88	0.012	2.04	1.03	4.02	0.040
High	2.62	1.91	3.59	< 0.001	2.34	1.72	3.18	< 0.001	3.11	1.51	6.40	0.004
Psychiatric disorder												
No problem	1.00		Reference		1.00		Reference		1.00		Reference	
Low	0.79	0.63	0.99	0.045	0.84	0.71	1.01	0.063	0.60	0.24	1.46	0.244
High	0.89	0.66	1.22	0.458	0.88	0.67	1.15	0.329	0.58	0.23	1.45	0.230
Social competence												
No problem	1.00		Reference		1.00		Reference		1.00		Reference	
Low	1.86	1.45	2.40	< 0.001	1.83	1.47	2.27	< 0.001	1.65	1.09	2.49	0.019
High	3.00	2.26	3.98	< 0.001	2.40	1.87	3.06	< 0.001	2.93	1.53	5.65	0.003
Family system												
No problem	1.00		Reference		1.00		Reference		1.00		Reference	
Low	1.23	0.91	1.65	0.168	2.01	1.60	2.53	< 0.001	1.70	0.91	3.16	0.092
High	1.53	1.04	2.24	0.031	2.75	2.16	3.50	< 0.001	2.29	1.29	4.06	0.007
School adjustment												
No problem	1.00		Reference		1.00		Reference		1.00		Reference	
Low	1.80	1.18	2.74	0.008	1.57	1.18	2.10	0.004	1.54	0.63	3.78	0.326
High	3.51	2.25	5.45	< 0.001	3.25	2.30	4.58	< 0.001	4.77	1.65	13.78	0.006
Peer relationship												
No problem	1.00		Reference		1.00		Reference		1.00		Reference	
Low	1.90	1.41	2.56	< 0.001	1.54	1.19	1.99	0.002	3.82	1.09	13.43	0.038
High	2.47	1.70	3.61	< 0.001	2.01	1.49	2.71	< 0.001	11.53	2.80	47.44	0.002
Leisure/recreation												
No problem	1.00		Reference		1.00		Reference		1.00		Reference	
Low	1.37	0.89	2.12	0.140	1.53	1.22	1.92	0.001	2.35	1.17	4.70	0.018
High	1.72	1.15	2.59	0.011	2.12	1.48	3.05	< 0.001	2.43	1.21	4.87	0.015

All estimates were obtained accommodating the complex sample design. aOR: Adjusted odds ratio.

50%-60% for those with intermediate scores (low problem) and 20% for those with the lowest scores (no problem level).

Results of the bivariate analyses for smoking tobacco in the past year are presented in columns 3 to 5 of Table 2. No statistically significant difference was observed based on age, but the rate was higher among males compared to females (24.5% *vs* 16.3% respectively; $P < 0.001$), and among youth who studied and worked, compared to those who did not (24.1% *vs* 18.5%, respectively; $P < 0.02$). The rate of smoking in the past year was also higher in the student population with the top 20% scores in DUSI problem areas compared to those with lower scores ($P < 0.001$).

As presented in columns 6 to 8 of Table 2, an estimated 35% of the students reported alcohol consumption within the past-year, and the rate was higher among older students (those 16 and older, 37.2%), males (42.4%), and those with higher DUSI scores, except the "*Social Competence*" domain.

Results in terms of illegal drug use (mainly marijuana or cocaine) are summarized in the last three columns of Table 2. The overall prevalence of past-year illegal drug use (mainly marijuana or cocaine), was 6.8%. Similar to tobacco and alcohol use, the prevalence of illicit drug use was higher in older students compared to younger students (7.5% *vs* 3.7%, respectively, $P = 0.005$). The rates were also higher among males compared to their female counterparts (10.7% *vs* 3.2%, respectively, $P < 0.001$), those who worked and studied compared to those who did not (9.3% *vs* 5.8 %, respectively, $P < 0.001$), and those with higher DUSI scores ($P < 0.001$) in most problem areas.

Multivariate analyses were conducted to examine the association between different DUSI domains with past year tobacco, alcohol, and drug use while controlling for participants' socio-demographic characteristics. Table 3 summarizes the results,

including adjusted odds ratios (aOR) and 95%CI.

Past year tobacco use showed no statistically significant association with age, gender, or employment status. However, the odds were higher among students who had the top 20% scores in the DUSI problem areas, specifically on "*Behavioral Pattern*" (aOR = 2.62); "*Social Competence"* (aOR = 3.00); "*Family System*" (aOR = 1.53); "*School Adjustment*" (aOR = 3.51); "*Peer Relationships*" (aOR = 2.47) and "*Leisure/Recreation*" (aOR = 1.72) (Table 3). An association with tobacco smoking in the past year was also observed for the group with intermediate scores (*i.e.*, the 20-80 percentiles grouped together) in certain DUSI problem areas, such as "*Behavioral Patterns*" (aOR = 1.63); "*Social Competence*" (aOR = 1.86); "*School Adjustment*" (aOR = 1.80); and "*Peer Relationships*" (aOR = 1.90). On the other hand, an inverse association was observed between smoking in the past year and the students with top 20% scores on the "*Psychiatric Disorder*" domain (aOR = 0.89).

In terms of binge drinking in the past year, students who were 16 years and younger had about half the odds compared to older students (aOR = 0.56; 95%CI: 0.46-0.69; $P < 0.001$), and odds were higher in males than females (aOR = 1.61; 95%CI: 1.36-1.91; $P < 0.001$) (Table 3). Those employed had lower odds of alcohol consumption during the past year, albeit with borderline statistical significance (aOR = 0.81; 95%CI: 0.66-1.01; $P = 0.058$). The odds were also higher for students with the highest scores in the DUSI problem areas. Students who had the top 20% of scores on most DUSI domains had consistently higher odds of alcohol consumption in the past year compared to those in the lowest 20%; the domains included "*Behavioral Pattern*" (aOR = 2.34); "*Social Competence*" (aOR = 2.40); "*Family System*" (aOR = 2.75), "*School Adjustment*" (aOR = 3.25), "*Peer Relationships*" (aOR = 2.01), and "*Leisure/Recreation*" (aOR = 2.12). With somewhat attenuated associations, participants who scored within higher than 20% and lower than 80% in most domains, had higher odds of past year´s alcohol use compared to those who scored within the bottom 20%. For example, for students with intermediate scores in "*Behavioral Pattern*", the odds of past year drinking were about 1.5 times higher (aOR = 1.43; 95%CI: 1.09-1.88; $P = 0.012$), and so forth.

The last three columns of Table 3 convey the estimated association between past-year illegal drug use and DUSI psychosocial covariates, adjusted for all variables shown in the table. Younger students had lower odds of drug use than older students (aOR = 0.56; 95%CI: 0.34-0.90; $P = 0.02$). Males were estimated to have twice the odds of past-year drug use than females (aOR = 2.28; 95%CI: 1.44-3.61; $P = 0.001$). Most DUSI problem areas showed that students with higher scores had higher odds of illegal drug use than those with lower scores; these domains included "*Behavioral Patterns*" (aOR = 3.11; 95%CI: 1.51-6.40; $P = 0.004$); "*Social Competence*" (aOR = 2.93; 95%CI: 1.53-5.65; $P = 0.003$); "*Family System*" (aOR = 2.29; 95%CI: 1.29-4.06; $P = 0.007$); "*School Adjustment*" (aOR = 4.77; 95%CI: 1.65-13.78; $P = 0.006$); "*Peer Relationships*" (aOR = 11.53; 95%CI: 2.80-47.44; $P = 0.002$); and "*Leisure/Recreation*" (aOR = 2.43; 95%CI: 1.21-4.87; $P = 0.015$).

DISCUSSION

The DUSI has been used to measure the severity of problems in 10 different domains to allow identification of drug use problem areas and their relationship with psycho-social adjustment[13,18]. The main findings of the present study demonstrate higher rates of tobacco (20.2%), alcohol (35%), and illegal drug use (6.8%) among high school adolescents in Jalisco, Mexico, compared to national rates reported by the ENA in 2002 (10.1%, 25.7%, and 4.6%, respectively), 2008 (alcohol 26.6%, illegal drugs 5.2%), and in 2012 (16%, 14.5%, and 1.6, respectively)[1,2,19]. Compared to studies conducted in Mexico city with a similar research design to the present study, our findings are similar to those reported for tobacco (22.8%), alcohol (35.2%), and marijuana (3.95%) in high school students[20]. The lifetime rate of cocaine use was higher than expected in this population (7.5%) and higher than the 1.6%-4.0% rates in comparable Mexico City surveys[20,21]. This higher rate of cocaine use may indicate that the epidemiologic situation is changing and new patterns of drug use in Mexico are rising, which may be creating new treatment needs and complexities. The high combined rates of marijuana and cocaine use demonstrate a critical problem with illegal drug use in Jalisco's high schools, which add to the already high rate of binge drinking in this population.

There has been an increasing trend in drug use in Mexico[3,22]. Reasons for this increase may be multi-factorial including the transition from a mainly trafficking country to a user country[21,23,24], as well as the increased use of addictive "legal" substances, such as alcohol and tobacco, by youth. Therefore, it is important to understand the psychological and socio-demographic profile of youth at risk of developing substance use disorder in order to propose and develop effective local treatment and prevention interventions.

In this study, older age was significantly associated with past year use of alcohol, which is consistent with other studies[25-28]. This may mean that older students in Jalisco also face a higher risk of alcohol-related consequences (*e.g.*, aggression, unprotected sexual activities, *etc.*) compared to younger students[21,28]. Smoking among young people in Mexico increased from 10.1% in 2002 to 14.9% in 2008, and to 16% in 2012[1,2,19]. This evidence calls for targeted school-based preventive interventions, along with better enforcement of regulatory measures, which has been recognized as a weak point in public health

policy[30]. The results showed no age differences in the past year use of tobacco. This is problematic because it may be due to one or a combination of the following possibilities: (1) Youths are experimenting tobacco at younger ages; (2) those who initiate may be transitioning faster to regular tobacco use; (3) starting younger students may be finding it harder to quit. Each of these possibilities would require further investigation. In addition, it is important to note that these students are still within the age range with highest risk for experimenting or becoming a regular tobacco user, which highlights the importance of prevention and cessation interventions[31].

Gender was found to be an important factor associated with higher odds of alcohol and illegal drug use, but not the use of tobacco products (Table 3), which is not consistent with findings from other studies[26,27,32,33]. Replication of these findings and future research is needed to understand if there have been changes in cultural norms that have protected women from being exposed to opportunities to use tobacco (and other drugs)[34,35].

The psychosocial factors explored in this study were found to be associated with the outcome measures in most of the domains. The predictive values and validity of the DUSI have been well documented in prior reports[13,18,36,37]. Consistent with other research, higher scores in the subscale measuring problems of *Behavior Pattern* (aggressiveness and impulsivity) were found to be associated with substance use and could serve as a tool for screening, early detection, and intervention design[26,27,38-41]. Higher scores in the subscale of *Psychiatric Disorders* were also associated with drug involvement. The utility of the DUSI for implicating current psychiatric diagnosis in adolescents has been demonstrated[42]. In prior research, individuals with behavior and affection problems were estimated to be at a greater risk of using illegal drugs[32,38,39]. In the present study, the bivariate analyses showed an association between "*Psychiatric disorders*" and both past-year smoking and alcohol use, but even with this large sample size, the study lacked sufficient statistical power to detect associations with past-year substance abuse. We could not find a significant association between this domain and past year use of any substances in the multivariate analyses either, but this could be due to the strong correlation between psychiatric disorders and the other DUSI domains simultaneously controlled for in the analysis, in addition to the relatively low statistical power. Of note is that there may be a misclassification of problem substance use disorders for up to 28% of the cases, which may as well bias the estimates towards the null hypothesis[13]. Another explanation could be related to neurobehavioral disinhibition as explained by indicators of executive cognitive functioning, emotion regulation, and behavior control[43], which we did not explore in this study. It has also been reported that the correlates from the psychiatric domain have not been able to differentiate between experimenters and users[44], which could be another possibility in our study.

Nevertheless, the findings highlight the importance of detecting mental health problems earlier and referring cases for specialized care[26]. In this study, consistent with previous research, problems with "*Family System*" were associated with higher odds of using tobacco, alcohol, and illegal drugs. Family factors have been demonstrated to influence drug and substance use particularly at younger ages[27]. Family issues are major risk factors to the overall health among children and adolescents, and they include parental adjustment problems, inadequate parental communication and affection, negative family interaction patterns, and poor relationship or weak parent-child bonding[26,38-41]. On the other hand, family factors such as family attention, parental monitoring, and living in a two-parent household can also act as resilient factors[25,32,45]. The subscale on "*Social Competence*" measures problems in areas such as social skills, assertiveness, and social interaction. In this study, participants with the highest scores in "*Social competence*" problems had higher odds of substance use. However, the opposite has also been observed by other researchers: those with stronger social competence skills had lower risks of alcohol use[40]. These factors are important internal resources and can inform preventive interventions that specifically support those students in greater need.

The relationship between the use of substances such as tobacco products, alcohol, and illegal drugs and health problems is well documented[26,46]. Tobacco is the leading cause of death globally, killing almost 480000 individuals every year in the United States alone[47]. There is evidence of higher likelihood of disease and more severe addiction among those with early initiation of substance use[25,28,38]. Programs that include school-based interventions have been shown to reduce tobacco use amongst youths and subsequently decrease the burden of diseases[48]. Using alcohol and illegal drugs have severe social implications as well, including violence, absenteeism, poor academic performance, crime, and family disruptions[16,38,39,49]. The social consequences increase with the level of abuse and addiction[50,51]. Therefore, early identification and treatment of students with substance abuse will have greater impact on the individual lives, families, schools, and society. Control and prevention of drug use could be achieved using standardized screening instruments to identify those students with treatment needs and those with higher risk of getting involved with substances, followed by school-based interventions[52]. However, interventions should be coordinated among different providers such as the National Prevention Program based on Clinics for the Attention and Prevention of Addictions and other organizations like the education department with its *Safe School* program[53], in close collaboration with families and the surrounding community. Finally,

environmental interventions have proven to be very effective in reducing the risk of substance use. Some examples include enforcing age restrictions for sale and consumption to limit the access to and reduce the use of alcohol and tobacco products among high school students and correcting the exaggerated perception of normative values for using substances by peers[54] to mention a few. Intervening through social networks, especially in partnership with student leaders, may be a promising approach in promoting healthy behaviors by influencing the social norms and reducing peer pressure in high schools[55].

Mexico is a large and populous country, and there are stark regional differences (*i.e.*, North, Central, and South). Those differences are particularly evident in terms of the epidemiology and prevalence of drug use. Jalisco is one of the largest and most resourceful states in Mexico, but generalizing the results from the present study to other States should be done with caution. Another limitation of this study is that we only included youths at school, and there is an important segment of the youth population with no school access or attendance. Also, we are aware of the limitations of a cross-sectional study in terms of looking at "risk factors" as opposed to a longitudinal study. Nevertheless, data for the present analyses come from the first survey on drug use in the State of Jalisco in the 21st century, which used a probability sampling and is representative of the high school population of the State of Jalisco. The data were collected using a standardized questionnaire that was adapted and tested for the Mexican population. One limitation of this questionnaire (DUSI-RM) is that it asks about the time of use, but it does not measure frequency or the amount of substance use, or in the case of tobacco, the number of cigarettes. It does, however explore the relation of psycho-social factors with drug or substance use.

This study confirms trends of increasing prevalence of alcohol, tobacco, and illegal drug use among Mexican youths, with new patterns of drug use in Jalisco that may be creating new treatment needs. Drug use problems in Jalisco may be becoming more complex, requiring a set of prevention alternatives and control programs (as opposed to a one-fits-all approach). Appropriate interventions for both legal and illegal substances should be planned and executed accordingly. New prevention efforts are urgently needed to target youth at the early stages of drug use to stop or delay their further involvement. This is a new need as the proportion of new users is increasing.

ARTICLE HIGHLIGHTS

Research background

We sought to improve on the few existing studies about drug and substance abuse among high school students in Jalisco, Mexico; particularly its association with health, behavior and psychosocial problems in order to provide evidence for possible prevention and treatment needs. Jalisco is an important state in Mexico for its strategic geo-politic location as a narcotic production enclave and a route for drug trafficking directed to the United States, and also because it is a large contributor of documented and undocumented workers to that country. The socio-economic change from a from a production entity to a consumer one could be taking place.

Research motivation

There has not been a published regional or state drug abuse survey performed in Jalisco, a state in the West Central Region of Mexico, for more than a decade. The most recent available information comes from the Mexican National Survey. However, the figures may not apply directly to Jalisco given the significant heterogeneity within this particular region on the one hand and on the other, because of the limitations of the methodology utilized for the national surveys: household and, most frequently, indirect interviews.

Research objectives

The aim objectives were to investigate the prevalence of substance use and associated factors amongst high school students from the Mexican West-Central State of Jalisco, to explore the association between drug involvement and selected psychosocial factors, and to identify treatment and prevention needs.

Research methods

We designed a cross-sectional survey using a multi-stage, random sample of 2832 high school students, from 25 public high schools distributed in 10 geo-political sub-regions in the State of Jalisco, Mexico. The participants were given a paper-and-pencil survey based upon an adapted version of the drug use screening inventory (DUSI-RM). The DUSI showed adequate psychometric characteristics in this population. The statistical tests included multivariate analyses with logistic regression models to estimate the association of each DUSI-RM domain with the use of tobacco, alcohol, as well as marijuana and cocaine use, while controlling for age, sex, and socio-economic status. The analyses were done with STATA version 10.0 (STATA Corp, College Station, TX, United States).

Research results

An estimated 44% of the students had smoked tobacco and 35% of the students reported alcohol consumption within the past-year. The rate of alcohol use was higher among older students, males, and those with higher DUSI scores. By contrast, 6.8% of the students reported having used marijuana, cocaine, or both. Of all 10 DUSI domains behavioral problems, deviant peer affiliation, and troubled families were independently associated with drug use.

Research conclusions

The main findings of the present study demonstrate higher rates of tobacco, alcohol , and illegal drug use among high school students in Jalisco, Mexico, compared to national rates although similar to those reported for tobacco, alcohol, and marijuana in México city, the largest city in the country. Appropriate interventions for the use of both legal and illegal substances in young people should be planned and executed accordingly. New prevention efforts are urgently needed to target youth at the early stages of drug use to stop or delay their further involvement. These results suggest that there is an epidemiological transition in the prevalence and patterns of drug use in the state of Jalisco which could be influenced by geographical and economical factors like the local production of legal (alcohol) and illegal drugs (marijuana and methamphetamines). This is the first study representative of the West Central area in Mexico. These data corroborate national trends of increased prevalence of illegal drug use and, in some cases (cocaine), even higher rates. The results however, are similar to those from studies conducted in Mexico city, the largest city in the country. Some areas of the country, like Jalisco, may be changing from a predominantly productive area to a mixed productive-consumer area. We conducted a study in an area with a relatively high production of illegal drugs (marijuana and synthetic drugs) and obtained results of higher use rates than the national surveys and comparable to those obtained in the largest urban area of the country (Mexico city). Similar studies should be conducted in other high and low production areas to investigate the influence of production factors on drug use prevalence. With this study we could confirm the hypothesis that the prevalence of drug use in the State of Jalisco was higher than that reported

in national surveys. One of the reasons for those differences could me in the methods employed confidential direct anonymous questionnaires in this case compared to home indirect interviews in the national surveys. The methodology used for designing and conducting drug and substance use national surveys should be improved.

Research perspectives

We suggest that epidemiological studies by independent researchers with up-to-date methodology, similar to the one presented herein should be conducted in other Mexican states independently from official national surveys.

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ORIGINAL ARTICLE

Observational Study

Bullying among people with visual impairment: Prevalence, associated factors and relationship to self-efficacy and life satisfaction

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Informed consent statement: All participants gave their informed consent to take part in the study.

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Abstract

AIM

To examine associated factors of bullying and to determine associations between bullying and psychosocial outcomes among individuals with visual impairments (VI).

METHODS

We conducted an age-stratified cross-sectional survey of adults with VI who were recruited from the Norwegian Association of the Blind and Partially Sighted. Data were collected through structural telephone interviews in the period between February and May, 2017. Linear regression models were used to examine factors related to bullying and associations of bullying with self-efficacy and life satisfaction.

RESULTS

A total of 736 individuals were interviewed. The lifetime and 6-mo prevalence of bullying was 41.7% and 8.2%, respectively. The majority of bullied participants reported VI-specific bullying (65.1%). Victimization of bullying was associated with young age, early onset-age of VI, and having other impairments. Participants who reported bullying had lower levels of self-efficacy [Adjusted relative risk (ARR): 0.40, 95% confidence interval (CI): 0.19-0.85] and life satisfaction (ARR: 0.68, 95%CI: 0.51-0.91).

CONCLUSION

Bullying is highly prevalent among individuals with VI. Our findings suggest that interventions to reduce bullying may be beneficial for improving the well-being and life quality of people with VI.

Key words: Blindness; Bullying; Life satisfaction; Risk factors; Self-efficacy; Victim; Visual impairment

Core tip: People with impairments are at risk of social exclusion. A high rate of bullying of people with visual impairment (VI) demonstrates how deviations from the social norm can lead to sanctions from the environment. The more different, the higher the risk of bullying, illustrated by the fact that people with functional impairments in addition to VI were even more prone to bullying. For those who are victimized, the consequences may be serious in terms of lower self-esteem and lower quality of life. A continuous focus on bullying is necessary to protect people with VI from bullying.

Brunes A, Nielsen MB, Heir T. Bullying among people with visual impairment: Prevalence, associated factors and relationship to self-efficacy and life satisfaction. *World J Psychiatr* 2018; 8(1): 43-50 Available from: URL: http://www.wjgnet.com/2220-3206/full/v8/i1/43.htm DOI: http://dx.doi.org/10.5498/wjp.v8.i1.43

INTRODUCTION

Bullying represents an extreme form of systematic and enduring social alienation which is assumed to exceed the boundaries of other forms of interpersonal aggression such as incivility, social undermining, and verbal abuse[1]. Formally, bullying is defined as a situation in which one or several individuals persistently and over a period of time, perceives to be on the receiving end of negative actions from another person and where the target of the bullying finds it difficult to defend him/herself against these actions[2]. Although there is no definitive list of bullying behaviors, bullying may involve actions like harmful physical contact, verbal harassment, rumour spreading, and intentionally excluding a person from a group[3]. In many cases, it is the accumulated exposure that constitutes the threat, not the specific behaviours.

Research on bullying has mainly been conducted in school and working life. Based on data from a large cross-national study, the percentage of 11 to 15 year old children who reported bullying at least once in the past 2 mo was 29%, ranging from 8% to 60% across the European countries[4]. Research on bullying among adults has mainly been restricted to working life. A meta-analysis on the occurrence of workplace bullying showed that 11% to 18% of employees on a global basis perceived themselves as victims of bullying[5]. Depending on measurement method, a 6-mo prevalence between 2% and 14% has been established among a representative sample of Norwegian employees[6]. As most studies on prevalence have examined bullying within a six to 12 mo timeframe, there is a shortage of studies on lifetime prevalence of bullying.

Bullying may have considerable impact on the health and well-being for those being affected, including a higher risk of anxiety[7-9], depression[8,9], suicidal ideation[9,10], headache[9,11], and sleep problems[9,12,13]. In a meta-analysis it was found that exposure to bullying predicted subsequent increase in mental health complaints (OR = 1.68; 95%CI: 1.35-2.09) and somatic complaints (OR = 1.77; 95%CI: 1.41-2.22) after adjusting for baseline health status[14]. Insufficient evidence exists of bullying in its association with life satisfaction and psychosocial functions like self-esteem[7,9,15].

Persons with impairments, such as visual impairment (VI), are more likely to be seen as different and of lower social rank by peers, and therefore become trapped into an ongoing victimization of bullying. In a meta-analysis of 7 studies involving people with VI, Pinquart[16] showed that children with VI had an 80% greater risk of experiencing peer victimization compared with sighted children. However, VI is a heterogeneous condition in terms of cause, onset-age, and progression rate of the vision loss[17], and is usually classified into moderate VI, severe VI, blindness, and unspecific VI[18]. Since the previous studies have assessed only a few VI-related (*e.g.*, wearing eye patches) and non-VI related factors[19-21], more research is needed to determine whether some forms of VI are more strongly associated with bullying than others.

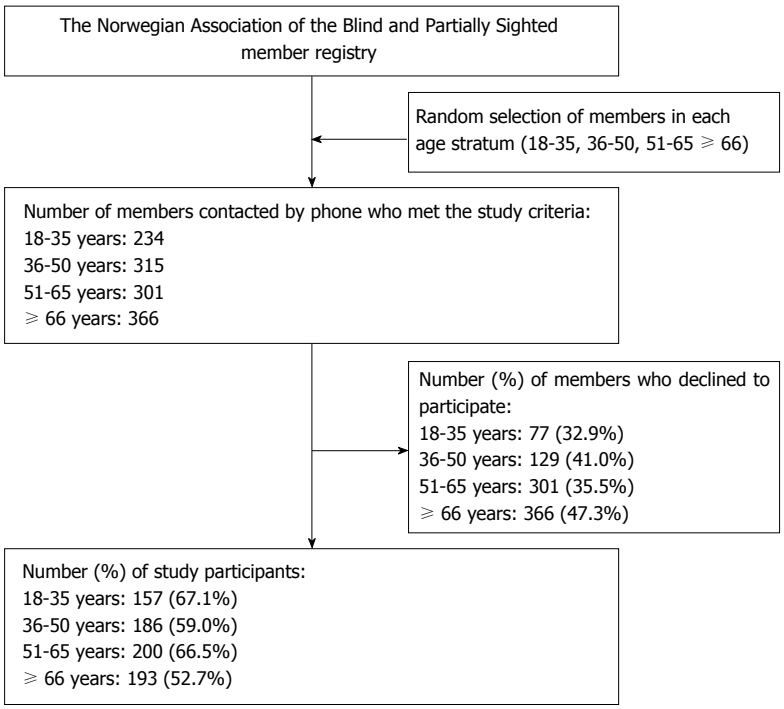

Figure 1 Selection of study participants.

To our knowledge, the possible consequences of bullying among people with Ⅵ have been assessed in two studies[21,22], and both studies included convenience samples of children or adolescents. Consequently, the impact of bullying on the health and functioning in adult life remains to be studied. In order to add to the current knowledge, this cross-sectional study examined prevalence, associated factors, and psychosocial outcomes of bullying using a large age-stratified, probability sample of adults with Ⅵ. The study had the following three aims: (1) To study the prevalence of bullying; (2) to describe demographic and visual factors associated with lifetime bullying; and (3) to examine the association of lifetime bullying with self-efficacy and life satisfaction.

MATERIALS AND METHODS

Ethical considerations

The study was carried out anonymously and at request the Regional Committee for Medical and Health Research Ethics required no further formal ethical approval (Reference number: 2016/1615A). All participants gave their informed consent for taking part in the study. Study participation was voluntarily, and the participants were informed that they could withdraw from the study at any time.

Design and participants

This cross-sectional observational study included a sample of adults who were members of the Norwegian Association of the Blind and Partially Sighted. The organization has about 10000 members[23], which comprise 0.2% of the Norwegian population. Adults were eligible if they were aged ⩾ 18 years and reporting a degree of Ⅵ. Data were collected *via* telephone interviews in the period between February and May, 2017. The interviews were carried out by experienced interviewers hired at a private survey company. The structured interview guide included questions about the participants' sociodemographic characteristics, type and nature of Ⅵ, bullying, and various aspects of quality of life. To ensure inclusion of participants at all age groups, a random sampling technique was performed within each of the following age strata: 18-35, 36-50, 51-65, and ⩾ 66. A total of 1216 adults with Ⅵ were contacted, and 736 (61%) participated by completing the interview. The response rate for each age group is displayed in Figure 1.

Assessment and evaluation

Bullying: Victimization from bullying was assessed by a single-item question retrieved from the General Nordic Questionnaire for Psychological and Social Factors at Work[24]. This self-labelling approach has been considered a valid measurement of bullying[25]. Before being presented to the question, the following definition of bullying were given to the participant: "To label something bullying or harassment, the offensive behaviour has to occur repeatedly over a period of time, and the person confronted has to experience difficulties defending himself/herself." Lifetime bullying was assessed through asking the participants whether they have been subjected to any bullying or harassment. The response alternatives were "yes" and "no". Those who responded "yes" to the question about

bullying were then asked to report whether they had been victims to bullying in the past 6 mo and whether the bullying was targeted towards their VI.

Self-efficacy: The participants' general perception of self-efficacy was measured by the General Self Efficacy Scale (GSE scale). The Norwegian version of the GSE scale has been shown to have a high test-retest reliability (r = 0.82) and acceptable correlations with life satisfaction (r = 0.26) and positive affect (r = 0.40)[26]. The scale consists of 10 statements about the participant's belief in one's ability to adequately respond to novel or challenging situations and to cope with a variety of stressors, and is scored on a 4-point Likert scale from 1 (not at all true) to 4 (exactly true). A sum score was calculated based on all 10 items, with higher scores representing greater self-efficacy. The sum score was treated as an untransformed continuous variable in our main analyses. The GSE scale had a Chronbach's alpha of 0.89.

Life satisfaction: Cantril's Ladder of Life Satisfaction (CLLS) was used to measure current life satisfaction[27]. The participants were asked to imagine themselves a ladder with 10 steps, of which the bottom of the ladder represented the worst possible life for them (a score of 0) and the top of the ladder represented the best possible life for them (a score of 10). Life satisfaction was treated as an untransformed continuous variable in the main analyses.

Covariates: The following covariates were identified as relevant in the current study: Gender, age (18-35, 36-50, 51-65, ≥ 66), current education level (< 10 years, 10-13 years, ≥ 14 years), marital status (single, married/partner, former married/partner), parental ethnicity (Norwegian, non-Norwegian), working or studying (no, yes, retired), urbanicity (< 50000 inhabitants, ≥ 50000 inhabitants), having other impairments (no, yes), severity of VI (moderate VI or other types of VI, severe VI, blindness), onset-age of VI (since birth, 1-24 years, ≥ 25 years), and VI stability (progressive, stable).

Statistical analysis

We tabulated lifetime and 6-mo prevalence of bullying with corresponding 95% binomial confidence intervals (CIs). Associated demographic and visual factors of past bullying experiences were assessed by using generalized linear models (GLMs) with a binomial distribution and log-link function. We selected a few important covariates prior to the analyses (age, gender, and severity of VI), as well as covariates having the best fit to the data in terms of Akaike's Information Criterion[28].

GLMs with a Gaussian distribution and identity-link function were used to estimate mean scores of self-efficacy and life satisfaction among individuals who had experienced bullying compared with the referent category of individuals not being bullied. The choice of distribution was determined by searching for the model that fitted the data best in terms of log-likelihood. The selection of possible confounding factors was based on previous publications and a priori reasoning[12,16,19,21,29-31]. In order to produce better confidence limits[28], we bootstrapped the CI estimates with 10000 replacements and a variance adjustment of 1.

A supplementary analysis was conducted of the association between bullying and self-efficacy and life satisfaction by using binomial GLM in order to check whether the choice of statistical model influenced our findings. In this analysis, all outcomes were dichotomized by its median value.

All regression analyses were either univariable or multivariable. The results were presented in terms of relative risks (RRs) and corresponding 95%CIs. The significance level was set at P = 0.05. The statistical analyses were carried out using Stata Version 14 (Stata Corp., Texas, United States).

RESULTS

Table 1 shows the characteristics of the study population. The lifetime prevalence of bullying was 41.7% (95%CI: 38.1-45.3) and the 6-mo prevalence of bullying was 8.2% (95%CI: 6.3-10.4). The majority of participants being bullied reported that the bullying experience was partly or completely related to their visual impairment (65.1%).

Associated factors of previous bullying experiences are presented in Table 2. In the univariable analyses, a significantly higher risk of bullying was found among participants with a lower age, having other impairments, having severe VI or blindness, and the onset of VI occurring early in life. All covariates, except for VI severity and residence, remained statistically significant in the multivariable models. The two strongest associated factors were lower age and early onset-age of VI. Bullying was not related to gender, parental ethnicity, or VI stability.

As shown in Table 3, compared with those not being bullied, individuals with past experiences of bullying had significantly lower scores on self-efficacy and life satisfaction. The strength of the associations remained fairly similar after adjusting for gender, age, current education level, working or studying, other impairments, marital status, severity of VI. The findings from the supplementary analysis showed that the association of bullying with self-esteem and life satisfaction became weaker, but remained statistically significant, in the binomial GLMs compared with the Gaussian GLMs (results not shown).

DISCUSSION

Key findings

Data from this cross-sectional study showed that four

Table 1 Study characteristics (n = 736)

Characteristics	n (%)
Age (yr)	
18-35	157 (21.3)
36-50	186 (25.3)
51-65	200 (27.2)
⩾ 66	193 (26.2)
Gender	
Male	333 (45.2)
Female	403 (54.8)
Marital status	
Single	260 (35.3)
Married/partner	347 (47.2)
Former married/partner	129 (17.5)
Working or studying	
No	248 (33.7)
Yes	295 (40.1)
Retired	193 (26.2)
Urbanicity	
< 50000 inhabitants	400 (54.4)
⩾ 50000 inhabitants	336 (45.7)
Parental ethnicity	
Norwegian	645 (87.6)
Non-Norwegian	91 (12.4)
Education	
< 10 yr	115 (15.6)
10-13 yr	286 (38.9)
⩾ 14 yr	335 (45.5)
Age at VI onset	
Since birth	329 (44.7)
Childhood or youth (1-24 yr)	143 (19.4)
Adulthood (⩾ 25 yr)	264 (35.9)
VI severity	
Moderate VI/other	186 (25.3)
Severe VI	296 (40.2)
Blindness	254 (34.5)
Stability of VI	
Progressive	231 (28.9)
Stable	523 (71.1)
Other impairments	
No	478 (65.0)
Yes	258 (35.0)

in ten Norwegian individuals with VI have experienced bullying, one in ten have experienced bullying during the past 6 mo, and more than sixty percent of those who have been bullied said that bullying was related to their VI. Bullying was associated with young age, early onset-age of VI, and having other impairments. Those who had experienced bullying had lower levels of self-efficacy and life satisfaction compared with those who had not experienced bullying.

Comparison with the literature

To our knowledge, this is the first study with a nation-wide probability sampling addressing the prevalence and associated factors of bullying among individuals with VI, as well as the relation of bullying with well-being. Our findings demonstrate that bullying is frequent and potentially detrimental problem among people with VI, showing somewhat higher 6-mo prevalence rates than what have been found in comparable studies of general Scandinavian populations (2.8%-8.2%)[6,32-34]. Thus, our results are in agreement with previous research suggesting that VI is a risk factor for bullying[16].

The findings that early onset-age of VI, young age, and having additional impairments were associated with the risk of being bullied support the notion that childhood and young adulthood are vulnerable periods in life for persons with some sort of deviance from the social norm[35,36] and that having additional impairments may reinforce those differences.

Some of the non-significant covariates need to be discussed. A noteworthy finding of this study was that the occurrence of bullying was similar for women and men with VI. This is in line with previous research[19,20], and indicates that the risk of bullying following VI is not determined by gender.

The lack of association between severity of vision loss and the occurrence of bullying are not in line with the findings from previous research[19,21]. For example, in an age-matched sample of 196 German students, Pinquart and Pfeiffer[21] found that students with low vision reported on average more relational and overt bullying compared with students who were blind and students without vision loss. As we examined the lifetime prevalence of bullying, a possible explanation for our null findings may be that specific VI characteristics are important risk factors for bullying at different points in life.

Our findings of bullying being associated with poorer life satisfaction are in agreement with that of previous research including people with different impairments[21,37]. Life satisfaction is a general evaluation of one's own life[27] and bullying may have negative consequences on a wide-range of life domains[9]. Furthermore, to our knowledge, this is the first study that have examined the relationship between bullying and general self-efficacy in populations with VI, showing lower levels of self-efficacy for those being bullied compared with those who have not been bullied.

Assuming bullying as a potential causal factor, as well as ignoring the possibilities for residual confounding and reversed effects, there may be several explanatory hypotheses for these relationships. First, models on stress and coping suggest that prolonged exposure to a given stressor, such as bullying, leads to a sustained cognitive activation[38]. Problems handling this unbearable state of mind may reduce one's belief in coping with challenging situations, and the persistent activation could be subsequently manifested as reductions in well-being and unwanted behavioural reactions like social withdrawal[7]. Second, the theory of learned helplessness may also explain the associations between bullying and the above indicators of well-being. Learned helplessness is a state of mind that may evolve when exposed to repeated and enduring painful or otherwise aversive stimuli which the targeted person is unable to escape or avoid[39]. Consequently, a target of bullying who perceives him-/herself to be unable to defend him-/herself against the systematic

Table 2 Univariable and multivariable regression analyses of factors associated with lifetime bullying among individuals with VI (*n* = 736)

Covariates	% of bullying	Univariable RR (95%CI)	Multivariable RR (95%CI)
Age (yr)			
18-35	58.0	2.62 (1.95-3.51)	2.09 (1.53-2.85)
36-50	51.1	2.26 (1.68-3.05)	2.04 (1.51-2.77)
51-65	38.5	1.77 (1.30-2.41)	1.66 (1.12-2.26)
≥ 66	22.8	1.00	1.00
Gender			
Male	38.7	1.00	1.00
Female	44.2	1.14 (0.96-1.36)	1.15 (0.98-1.34)
Parental ethnicity			
Norwegian	41.2	1.00	1.00
Others	45.1	1.09 (0.86-1.40)	1.00 (0.81-1.25)
Urbanicity			
< 50000 inhabitants	46.3	1.00	1.00
≥ 50000 inhabitants	36.3	0.79 (0.66-0.94)	1.01 (0.84-1.21)
Other impairments			
No	38.1	1.00	1.00
Yes	48.5	1.27 (1.07-1.51)	1.35 (1.15-1.57)
Severity of VI			
Blind	41.9	1.19 (0.93-1.50)	1.05 (0.84-1.30)
Severe VI	47.0	1.33 (1.08-1.63)	1.18 (0.97-1.42)
Moderate VI/other	35.4	1.00	1.00
Age at VI onset			
Since birth	52.0	1.91 (1.53-2.38)	1.55 (1.22-1.96)
Childhood or youth (1-24 yr)	44.8	1.64 (1.26-2.15)	1.27 (0.98-1.68)
Adulthood (≥ 25 yr)	27.3	1.00	1.00
VI stability			
Stable	43.0	1.00	1.00
Non-stable	38.5	0.90 (0.74-1.19)	0.92 (0.76-1.11)

RR: Relative risk; VI: Visual impairment.

Table 3 Unadjusted and adjusted regression analyses addressing bullying exposure and its association with self-efficacy and life satisfaction among individuals with VI (*n* = 736)

Lifetime bullying	Mean (SD)	Unadjusted[1] RR (95%CI)	Adjusted[1,2] RR (95%CI)
Self-efficacy			
No (*n* = 429)	32.0 (4.8)	Reference	Reference
Yes (*n* = 307)	30.8 (5.4)	0.28	0.41 (0.19-0.87)
Life satisfaction			
No (*n* = 429)	7.0 (1.9)	Reference	Reference
Yes (*n* = 307)	6.5 (2.2)	0.60	0.69 (0.52-0.91)

[1]CI estimates were bootstrapped with 10000 replications and a variance multiplied by 1; [2]Adjusted for gender, age (18-35, 36-50, 51-65, ≥ 66), current education level (< 10 years, 10-13 years, ≥ 14 years), working or studying (no, yes, retired), other impairments (no, yes), marital status (single, married/partner, former married/partner), and severity of VI (moderate VI/other, severe VI, blindness). RR: Risk ratio; SD: Standard deviation; VI: Visual impairment.

mistreatment should be more likely to resign and go into a state of helplessness. A third theory on the consequences of bullying is that of internalization, in which people accepts a belief or behavior and agrees with others both privately and publicly[40]. For example, when perpetrators repeatedly tell the bully victim that he/she is useless or unworthy, the victim may in turn accept and personally agree with the public opinion about his/her uselessness or unworthiness.

Strengths and limitations

The main strength of this study is the size and nature of the sample, which was selected through a probability mechanism and stratified on age. Furthermore, the use of validated assessment tools and the data collection procedure increase the credibility of our findings. While these characteristics may represent strengths of the study, it should be noted that studies using probabilistic sampling, including a definition of bullying, and recruiting participants from Scandinavian countries have established the lowest prevalence rates with regard to bullying[5]. Hence, it is likely that our prevalence is relatively low compared to studies using other methods and samples.

Several limitations should be considered. In resemblance with all observational studies that analyses cross-sectional data, we had limited possibilities to address relationships of cause and effect, and, although we controlled for some potentially confounding factors, we cannot rule out the possibility of residual confounding. Second, the use of self-reports may have affected the accuracy of the estimates, and could lead to information biases like disclosure bias and recall bias. The possible impact of recall bias may have been greatest among the oldest participants, reflecting the low rates of bullying in this age group. Further, our data on bullying relied on a few validated questions about the overall exposure to bullying or harassment. We also lacked information about the perpetrator, as well as information related to how, when, where, and how often the participants had experienced bullying. With regard to the latter, including a behavioural experience checklist such as the Negative Acts Questionnaire[41] would have provided specific information about the nature and content of the bullying. Third, we had limited information about the non-responders and do not know how non-responding might have influenced our results. Advance information contained general descriptions of topics such as coping with traumatic events, mental health and wellbeing, and did not specifically pinpoint bullying. Thus, we think it is less likely that prevalence estimates of bullying were biased by participations' motivation to share their history of being bullied. Also, we believe that bias in sample selection more likely may have affected the prevalence estimates of socioeconomic factors or VI characteristics and to lesser extent their associations to bullying[42,43]. Fourth, the generalizability in studies of membership organizations may be questionable. We have no knowledge about how bullying and psychological consequences in people with VI who are not organized in the Norwegian Association of the Blind and Partially Sighted.

Implications

Bullying is a social problem with detrimental implications for the individual being affected. People with VI are at higher risk of bullying compared to the general population, and there should be increased awareness about this issue in school, social, and working life. There may be a need for interventions to prevent bullying, and for those who have been bullied, measures to increase self-efficacy.

In summary, our findings showed that bullying is highly prevalent among individuals with low vision and blindness, and especially among those with a young age, early onset-age of VI, and having other impairments. Furthermore, we found strong associations between lifetime bullying and lower levels of self-efficacy and life satisfaction. Increased awareness of bullying in school, social, and working life is recommended to protect people, and especially people from social minorities, from bullying. Future research should include longitudinal studies, focusing particularly on the risk and impact of bullying among those who have lost their vision at birth or during childhood.

ARTICLE HIGHLIGHTS

Research background

Persons with impairments, such as visual impairment (VI), may be more likely to be seen as different and of lower social rank by peers, and therefore become trapped into an ongoing victimization of bullying. To our knowledge, previous studies of risk of bullying in people with VI are restricted to include convenience samples of children and adolescents.

Research motivation

In order to add to the current knowledge, we conducted a cross-sectional study in the adult population of people with VI, having the following three main aims: (1) To study the lifetime prevalence of bullying, (2) to describe demographic and VI-related factors associated with lifetime bullying, and (3) to examine the association of lifetime bullying with self-efficacy and life satisfaction.

Research methods

The study was a cross-sectional interview-based survey conducted between February and May, 2017, including an age-stratified probability sample of adults with VI. All participants were recruited through the members list of the Norwegian Association of the Blind and Partially Sighted. A total of 736 (61%) adults with VI participated by completing the interview.

Research results

The lifetime and 6-mo prevalence of bullying was 41.7% and 8.2%, respectively. The rates are greater than what have been found in comparable studies of general Scandinavian populations. The majority of bullied participants (65.1%) reported that bullying was related to their vision loss. Victimization of bullying was associated with young age, early onset-age of VI, and having additional impairments. The findings illustrate that being different in terms of having visual impairment or other impairments in addition to the vision loss put individuals at increased risk of being victimized to bullying. Bullying was negatively associated with self-efficacy [adjusted relative risk (ARR): 0.40, 95% confidence interval (CI): 0.19-0.85] and life satisfaction (ARR: 0.68, 95%CI: 0.51-0.91). If bullying was the underlying causal factor, our results suggest that bullying may have profound adverse effects on personality and wellbeing in adult life.

Research conclusions

To our knowledge, this is the first research study demonstrating high rates of bullying in people with VI, both in a lifetime perspective and in adult life. Individuals with young age, early onset age of VI, or other additional impairments were at greatest risk of bullying. Most of those who had been exposed perceived that bullying was related to their vision loss. Efforts should be made to increase awareness about this issue in school, social, and working life. Our findings that bulling was negatively related to outcomes of self-efficacy and life satisfaction emphasize the need of professional assistance of those who have been bullied. Universal design and access to professionals who are trained to the needs and challenges of people with VI are recommended.

Research perspectives

Our research findings should be supported by population-based cohort studies of individuals with and without VI. Moreover, future research should include longitudinal studies of the risk and impact of bullying in people with VI, especially among those who have lost their vision at birth or during childhood.

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Editorial Board Member of *World Journal of Psychiatry*, Uwe Herwig, MA, MD, Associate Professor, Psychiatric University Hospital, University of Zürich, Zürich CH-8021, Swaziland

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REVIEW

Glutamate transporters, EAAT1 and EAAT2, are potentially important in the pathophysiology and treatment of schizophrenia and affective disorders

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Abstract

Glutamate is the predominant excitatory neurotransmitter in the human brain and it has been shown that prolonged activation of the glutamatergic system leads to nerve damage and cell death. Following release from the pre-synaptic neuron and synaptic transmission, glutamate is either taken up into the pre-synaptic neuron or neighbouring glia by transmembrane glutamate transporters. Excitatory amino acid transporter (EAAT) 1 and EAAT2 are Na^+-dependant glutamate transporters expressed predominantly in glia cells of the central nervous system. As the most abundant glutamate transporters, their primary role is to modulate levels of glutamatergic excitability and prevent spill over of glutamate beyond the synapse. This role is facilitated through the binding and transportation of glutamate into astrocytes and microglia. The function of EAAT1 and EAAT2 is heavily regulated at the levels of gene expression, post-transcriptional splicing, glycosylation states and cell-surface trafficking of the protein. Both glutamatergic dysfunction and glial dysfunction have been proposed to be involved in psychiatric disorder. This review will present an overview of the roles that EAAT1 and EAAT2 play in modulating glutamatergic activity in the human brain, and mount an argument that these two transporters could be involved in the aetiologies of schizophrenia and affective disorders as well as represent potential drug targets for novel therapies for those disorders.

Key words: Glia; Excitatory amino acid transporter;

Psychiatry; Affective disorders; Glutamate transporter; Glutamate; Schizophrenia

Core tip: Following release from the presynaptic neuron, the majority of glutamate within the human cortex is taken up into glia cells where it is converted into glutamine for recycling back into glutamate. Glutamate transporters excitatory amino acid transporter (EAAT) 1 and EAAT2 are predominantly localized in the glial plasma membrane, and are responsible for the majority of glutamate uptake within the human brain. Here we provide a comprehensive review of the unique regulation of EAAT1 and EAAT2 mRNA and protein in health and psychiatric disorder, and in response to medication use.

Parkin GM, Udawela M, Gibbons A, Dean B. Glutamate transporters, EAAT1 and EAAT2, are potentially important in the pathophysiology and treatment of schizophrenia and affective disorders. *World J Psychiatr* 2018; 8(2): 51-63 Available from: URL: http://www.wjgnet.com/2220-3206/full/v8/i2/51.htm DOI: http://dx.doi.org/10.5498/wjp.v8.i2.51

GLUTAMATE AND EXCITOTOXICITY

Glutamate has long been recognized as the principal excitatory neurotransmitter of the mammalian brain[1]. It has been shown that glutamate concentration in the CNS extracellular space (approximately 0.6-2 μmol/L)[2-4] is comparatively lower than levels in cell cytoplasm (approximately 1-10 mmol/L)[5-7]. It is necessary for the level of extracellular glutamate to be kept low to allow for a high signal-to-noise ratio following the release of glutamate into the synapse and to prevent glutamate-mediated neuronal degeneration[8-10] as high levels of extracellular glutamate causes excitotoxicity and nerve damage[10]. The extracellular/intracellular glutamate gradient is at least partly maintained through the activity of Na^+-dependent excitatory amino acid transporters (EAATs) which are in the membrane of pre-synaptic neurons and glia. Whilst glutamate uptake into astrocytes is also mediated by Na^+-independent, chloride-dependent antiporters, this family of transporters appears to be responsible for less than 5% overall glutamate uptake[11]. Thus, this review will focus solely on the Na^+-dependent EAAT family.

THE EAAT FAMILY: OVERVIEW

The EAAT family of transporters consists of five Na^+-dependent high-affinity glutamate transporters termed EAAT1 [also known as solute carrier family 1 member 3 (SLC1A3)][12,13], EAAT2/SLC1A2[13,14], EAAT3/SLC1A1[13,15], EAAT4/SLC1A6[16] and EAAT5/SLC1A7[17]. In this review, the accepted nomenclature of "EAAT" will be used in discussing data from both humans and other mammalians. These subtypes are quite differentiated - EAAT1, EAAT2 and EAAT3 only share 51%-55% amino acid sequence homology[18].

THE EAAT FAMILY: FUNCTION

The functionality of the glutamate transporters reflects their coupling to the electrochemical potential gradients of Na^+, K^+ and H^+/OH^-. Specifically, glutamate is co-transported across the plasma membrane 1:2-3 with Na^+ and 1:1 H^+ (or counter-transport of OH^-) and counter-transported 1:1 with K^+[4,19,20]. This ionic association provides a net positive charge to glutamate transport[20] however a relatively slow turnover rate of approximately 70 ms makes it unlikely that this electrogenic attribute contributes significantly to the electrochemical gradient of the cell[21,22]. Furthermore, this slow turnover rate suggests that the transporters act first to buffer glutamate away from the synapse, and transport glutamate into glia at a slower rate. The quantity of charge transferred per molecule of glutamate is highly voltage dependant due to the existence of a thermodynamically uncoupled, transporter substrate-specific movement of chloride ions through the transporter[16,23]. The ion- and voltage- dependant uptake of glutamate makes this process highly susceptible to changes in the immediate cellular environment and plasma membrane potential.

THE EAAT FAMILY: LOCALISATION

Some of the functional properties of the EAATs can be attributed to their differential localisation. EAAT3 and EAAT5 are exclusively neuron-specific[17,24], with EAAT5 expression restricted to neurons and Müller cells of the retina[17]. By contrast, EAAT1 and EAAT2 are predominantly localised on astrocytes and are highly expressed in the cerebellum and hippocampus, respectively[25-27]. EAAT1, EAAT2 and EAAT3 have been reported to make up approximately 20%, 80% and 1% of all cell-surface glutamate transporters in the adult rat hippocampus, respectively[24]. EAAT4 is found in Purkinje neurons of the cerebellum[28].

THE EAAT FAMILY: ROLE IN GLIAL METABOLISM OF GLUTAMATE

Glial metabolism of glutamate is now recognised as a major factor in the control of glutamatergic neurotransmission[9], as, following the release of glutamate from the pre-synaptic neuron, the majority of the neurotransmitter diffuses out of the synaptic cleft where it is taken up into glial cells[29-31]. This effectively means that the astrocytic EAATs play a significant role in controlling the extent of glutamatergic activation by preventing neurotransmitter spill-over into neighbouring

synapses[20,22,32].

Once taken up by astrocytes, glutamate is either converted to glutamine by the glia-specific glutamine synthetase (GS)[33], or converted to α-ketoglutarate (α-KG) (also known as 2-oxoglutarate) through oxidation by glutamate dehydrogenase (GLDH) or transamination by aspartate aminotransferase[34,35]. α-KG may then be converted to succinate with a by-production of ATP (Figure 1) as part of the tricarboxylic acid cycle[34,35]. The formation of glutamine - the predominant metabolic pathway for glutamate - is followed by the transport of glutamine to neurons where it undergoes synthesis back into glutamate *via* the enzyme glutaminase[36] (Figure 1).

It is now acknowledged that glutamate excitotoxicity can potentially lead to problems in CNS functioning[8]. Significantly, it is now being speculated that glutamatergic excitotoxicity may in part be due to a reduction in glutamate uptake by astrocytic glutamate transporters and subsequent conversion of glutamate to glutamine by GS. Such an hypothesis is supported by research showing that inhibition or antisense oligonucleotide-knockdown of astrocytic glutamate transporters EAAT1 and EAAT2 results in excitotoxic oligodendrocyte death and nerve damage[37]. Moreover, whilst glutamate is usually taken into astrocytes under physiological conditions, it has been suggested that Ca^{2+}-dependent activation of select signalling molecules, intracellular increase in Na^{+} and glutamate, ATP depletion or cell swelling can lead to glutamate release through EAAT transporter reversal/reverse uptake[11,38]. Such an outcome represents another mechanism that can lead to glutamate excitotoxicity.

THE EAAT FAMILY: A FOCUS ON EAAT1 AND EAAT2

The focus of this review is the potential involvement of glutamate transporters in the aetiology of psychiatric disorders. At present, most evidence implicating glutamate transporters in the aetiologies of psychiatric disorders is from the study of EAAT1 and EAAT2. Hence the remainder of this review will focus on those two forms of glutamate transporters.

EAAT1

The *EAAT1* gene has been localised to human chromosome 5p11-12[39] and 5p13[40,41]. *EAAT1* is highly expressed in the glial cells of the cerebellar Purkinje cell layer[12,13,42] and generally is expressed at higher levels in astrocytes and oligodendrocytes compared to microglia[43].

The *EAAT1* gene encodes a 59 kDa protein that undergoes glycosylation to produce native 64 kDa and 70 kDa glycoproteins[44-46]. Post-translational modification of EAAT1 is developmentally regulated, with glycosylated EAAT1 increasing and non-glycosylated EAAT1 decreasing after birth[47]. Glycosylation does not affect EAAT1 transport activity, however research by Conradt *et al*[46] suggests that the addition of carbohydrates does impact EAAT1 homodimerisation. This is significant because it has been suggested that activation of astrocytes increases homodimerisation of EAAT1 and trafficking of the transporter to the plasma membrane[48]. In addition to homodimers, EAAT1 protein has shown potential to form homotrimers[49]. Moreover, it has been reported that cell-surface protein expression of EAAT1 is upregulated by exogenous glutamate[50-52], a process suggested to be mediated through transporter activity[51] and/or ionotropic glutamate receptor signalling[50,52]. EAAT1 protein levels have also been reported as being downregulated by the group Ⅰ metabotropic glutamate receptor (mGluR) agonist, DHPG, which selectively activates mGluR1 and 5, and upregulated by the group Ⅱ mGluR agonist, DCG-IV, which activates mGluR 2 and 3[53]. Further work is therefore required to fully elucidate which glutamate receptors are critical in controlling levels of EAAT1 at the cell surface.

At the level of protein localisation, high levels of EAAT1 protein can be observed on rat astrocytic membranes opposed to synaptically dense regions of the CNS and at higher levels on astrocytes facing capillaries, pia mater or stem dendrites[27]. Although predominantly a glial transporter, EAAT1 protein has also been detected in deep cerebellar rat neurons and transient protein expression of EAAT1 has been observed in cultured rat embryonic hippocampal neurons[26,54]. Rat neuronal EAAT1 protein expression appears to be restricted to perinuclear localizations, in particular the Golgi apparatus and associated vesicles[26]. Soluble factors secreted from astrocytes appear to induce the repression of neuronal protein expression of EAAT1[55], which supports the aforementioned lack of EAAT1 protein at the neuronal cell surface. It is possible that, at least in the adult brain, neuronal EAAT1 is redundant, and may be upregulated where there is an inadequate presence of EAAT1-expressing astroglia.

The *EAAT1* gene is expressed in its full length coding sequence of 10 exons[39] and as three splice variants which encode shorter protein isoforms known as EAAT1a, EAAT1b and EAAT1c.

EAAT1a lacks exon 3 - which ordinarily encodes the first and second transmembrane domain and the first extracellular loop[45] - and has been detected in rat brain and retina[45,56]. Significantly, it has been proposed that the splicing of exon 3 may reverse the orientation of EAAT1a within the membrane, and therefore the direction of glutamate transport[45]. EAAT1a has been shown to be predominantly expressed within internal vesicles, rather than on the cell membrane, in an osteocyte cell line[57]. Interestingly, an unglycosylated variant of EAAT1a protein has also been detected in rat brain[45]; as glycosylation has previously been associated with trafficking of EAAT1 to the cell surface, this may explain the localization of EAAT1a to internal vesicles.

mRNA for EAAT1b, which lacks exon 9[58], has been

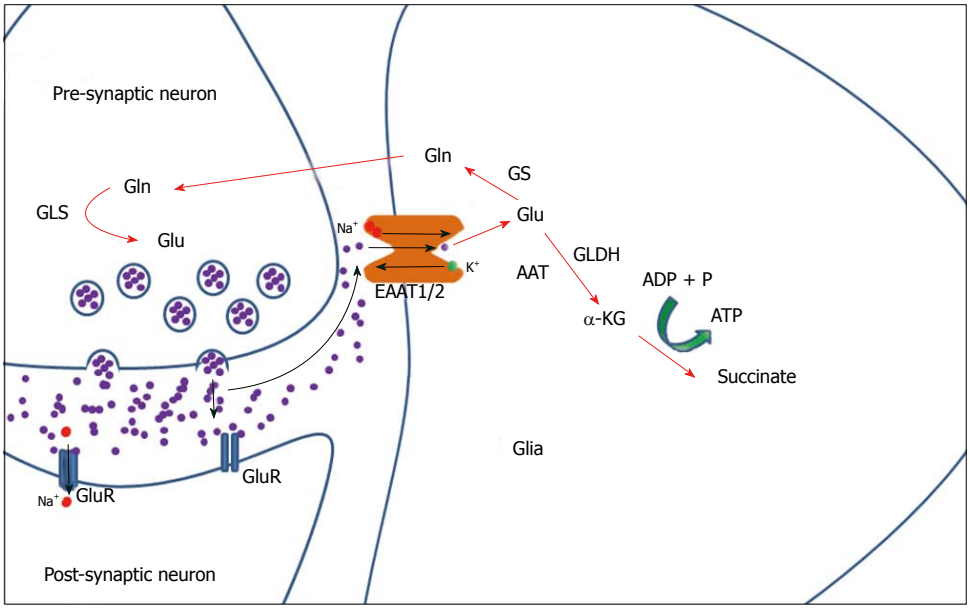

Figure 1 The metabolic fate of glutamate in glia cells. Glutamate is released from the pre-synaptic neuron to induce activation of the post-synaptic neuron *via* GluR. Spill-over of excess glutamate from the synaptic cleft is prevented through uptake by glial glutamate transporters EAAT1 and EAAT2, following which glutamate is converted to glutamine by GS for recycling back into glutamate, or α-KG for entrance into the tricarboxylic acid cycle. AAT: Aspartate Aminotransferase; α-KG: Alpha ketoglutarate; EAAT1/2: Excitatory amino acid transporter 1 and 2; GLDH: Glutamate dehydrogenase; Gln: Glutamine; GLS: Glutamate synthase; GS: Glutamine synthase; Glu: Glutamate; GluR: Glutamate receptors; Na+: Sodium; K+: Potassium.

detected in both human grey matter and axonal tracts at levels that are 10%-20% that of the full length EAAT1[58]. EAAT1b localization has been associated with the endoplasmic reticulum[58], intracellular inclusions and the plasma membrane[59], where it appears to have no functional glutamate uptake activity[58]. Rather, it has been suggested that EAAT1b negatively regulates levels of full-length EAAT1 at the cell surface by preventing the insertion of the latter into the plasma membrane[58], possibly by interacting directly with full length EAAT1. EAAT1b appears to be particularly localised to cortical neurons[59] where it is suggested to play a role in preventing ectopic neuronal expression of EAAT1. Immunoperoxidase-labelling of EAAT1b was associated with the plasma membrane for morphologically healthy neurons and in punctate intracellular inclusions of neurons that appeared degenerate[59]. Furthermore, EAAT1b expression was increased in neuronal populations - and to a lesser extent astrocytes - that were subject to hypoxia, in histologically degenerate brain regions which also displayed a downregulation of glial EAAT1[60].

EAAT1c mRNA, which lacks exon 5 and 6 of the full coding sequence, has been detected in astrocytes and oligodendrocytes of the human cortex, retina and optic nerve, as well as pig forebrain, midbrain, hindbrain and cerebellum[61]. The approximately 47 kDa glia-specific EAAT1c protein has been shown to have an intracellular perinuclear localization, with rapid redistribution to the cell surface following astrocytic stimulation[61]. Furthermore, EAAT1c does not undergo glycosylation[61]. Unfortunately the only study to examine EAAT1c was not able to determine its function, with the two most likely (default) candidates remaining as a regulator of full length EAAT1 cell surface expression, or as a *bona fide* transporter trafficked to the cell surface under appropriate conditions.

EAAT2

The EAAT2 gene is localized within human cytogenetic bands 11p12-13[62], and is responsible for the majority of glutamate uptake within the EAAT family (see[63] for review). EAAT2 expression appears to be restricted to the brain and placenta in humans[13] and has also been detected in cultured hippocampal neurons from rat embryo[64]. The mRNA expression of EAAT2 was found to be greater in cultured rat oligodendrocytes than astrocytes or microglia[43].

While EAAT2 protein expression has an overall homogenous brain distribution, it predominates across the forebrain with a particular focus in the hippocampus[26,65,66]. EAAT2 appears to be a predominantly glial glutamate transporter, with up to 80% of EAAT2 protein detected in glia plasma membrane, 6% localized to plasma membrane of pre-synaptic neurons and 8% to the axonal plasma membrane in the stratum radiatum of the rat hippocampal subregion CA1[67]. In line with the detection of EAAT2 mRNA[64], EAAT2 protein expression has similarly been recorded in cultured rat embryonic hippocampal neurons[54,64]. Like EAAT1, EAAT2 protein undergoes glycosylation, which produces a 5-15 kDa shift in molecular weight[48,68] and mediates its cell surface expression[68]. EAAT2 also exists in the plasma membrane as a multimer, with the potential to form dimers and trimers[49,69].

EAAT2 would seem to have a complex role in devel-

opment as it is transiently detected in neurons throughout ovine forebrain and cerebellum at 71 d gestation, and lost by 136 d gestation[70]. In addition, EAAT2 and glial fibrillary acidic protein (GFAP) have been reported to not be expressed by the same cells at 71 d ovine gestation but showed region-specific colocalization by 136 d gestation[70]. A similar transition from prenatal axonal pathways to astrocytic EAAT2 protein expression was also seen in rat[47]. Interestingly, it appears as if neuronal soluble factors may be required for proper expression of EAAT2 in neighbouring astrocytes[53,71] with EAAT2 protein levels quantitatively higher in the synaptically dense regions of glial cells[27].

The human *EAAT2* gene consists of 11 exons[72]. Two functional splice variants of EAAT2, termed EAAT2b and EAAT2c, contain unique C-terminal domains and have been detected in rat brain (EAAT2b) and retina (EAAT2c)[73,74]. Additional splice variants which share the C-terminals of EAAT2 and EAAT2b, but have a unique N-terminal domain, have also been detected in mouse and rat liver and referred to as mGLT-1A/rGLT-1A and mGLT-1B, respectively[75] (see[74] for a comparison of amino acid terminal sequences). While the unique N-terminals has been proposed to regulate tissue-specific expression, the function of the differing C-terminal of mGLT-1A and mGLT-1B is less clear - the authors propose that it may be related to the retention time of the transporter in the plasma membrane[75]. As mGLT-1A/rGLT-1A and mGLT-1B are localized to the liver[75], they will not be discussed further in this review. Rather, further evidence for the role of the C-terminus can be presented using data on rat EAAT2b, which will be discussed in the following paragraph.

Full length EAAT2 (commonly referred to as EAAT2a) expression is about 25-fold and 10-fold higher than EAAT2b in human and rat brain, respectively[76]. EAAT2b protein is similarly found in glia, localized close to or within the plasma membrane[77-79], however transcript and protein have also been detected in neurons[78]. While EAAT2 is constitutively trafficked to the cell surface membrane, localization of EAAT2b is mediated through its C-terminal, which is predicted to interact with the postsynaptic density-95/Discs large/zona occludens-1 (PDZ) domain-containing protein disks large homolog-1 (DLG1)[80]. The interaction between EAAT2b and DLG1 is itself regulated through AMPA-associated intracellular calcium levels, with exogenous glutamate resulting in dissociation of EAAT2b and DLG1 and subsequent internalization of EAAT2b[80]. EAAT2b also coimmunoprecipitates with the excitatory postsynaptic density scaffolding protein, PSD-95, as well as the ionotropic N-methyl-D-aspartate receptor (NMDAR), both found within the postsynaptic neuron[81]. Significantly, EAAT2 has also been detected in these protein complexes, through the indirect formation of a hetero-oligomer with EAAT2b[81]. This suggests that EAAT2b may assist in conditional neuronal cell-surface expression of EAAT2. EAAT2b represented 6% of total rat hippocampal EAAT2 variants at 8 wk of age, compared to EAAT2 at 90%, whereas the equally functional EAAT2c sits at just 1%[77].

EAAT2c is made up of exons 1-10 from the EAAT2 transcript plus a unique eleventh exon and C-terminus spliced from intron 10 - thereby losing the original eleventh exon from EAAT2 - similarly contains a PDZ-binding domain and is pre-synaptically expressed in the rat and human retina[74].

Aberrant EAAT2 splice variants which skip exons have also been discovered: In particular, EAAT2 exon7skipping and EAAT2 exon9skipping lack glutamate transport functionality and must form multimers with functional EAAT2 or EAAT2b (see[82] for review). These splice variants add another layer of complexity to what has been considered a predominantly astrocytic glutamate transporter.

EAAT1 vs EAAT2: A summary

Despite belonging to the same family of transporters, sharing 52% amino acid identity[18] and being localized within the same astrocytic plasma membrane[49], EAAT1 and EAAT2 display many differences in their functionality. EAAT1 protein levels have been shown to function approximately 6 times slower than EAAT2, and be expressed at a level approximately 6 times higher in the adult rat cerebellar molecular layer[21,65]. On the other hand, EAAT2 protein levels are upwards of 4 times higher than EAAT1 in the adult murine hippocampus[65]. Furthermore, unlike EAAT1, cell-surface protein expression of EAAT2 appears unaffected by exogenous glutamate levels but rather, is regulated by neuronal soluble factors[50-52]. Finally, within the EAAT family, only EAAT2 can be competitively inhibited by kainic acid (KA) and dihydrokainic acid (DHK)[13]. Conversely, KA has been shown to increase EAAT1 protein levels[50]. It is possible that this increase in EAAT1 protein in response to KA is a homeostatic mechanism, counterbalancing for the inhibition of EAAT2.

The fact that EAAT1 and EAAT2, and their functionally distinct splice variants, may be differentially regulated by internal and external factors presents us with two distinct transporters that are part of a system that is highly responsive to cellular physiology. In the following paragraphs, we will present the current knowledge surrounding EAAT1 and EAAT2 in psychiatric illness, as well as their responsiveness to medication and potential as drug targets (refer to Table 1 for a summary).

EAATS IN PSYCHIATRIC ILLNESS

Glial dysfunction has been implicated in a range of psychiatric illnesses, including major depressive disorders (MDD)[83,84], schizophrenia[85], bipolar disorders (BD)[86] and post-traumatic stress disorder (PTSD)[87]. Glia dysfunction has also been associated with suicide completion[88,89]. The association between the glutamatergic

Table 1 The role of EAAT 1 and 2 in psychiatric disorder and medication use

EAAT1	Genetic studies	
	BD	SNP rs2731880 T/T genotype associated with worse working memory and selective attention during a depressive episode[102]
		SNP rs2731880 T/T genotype increased negative fMRI BOLD coupling between the amygdala and AnCg[103]
	Scz	SNP rs2731880 T/T genotype associated with worse executive function, verbal fluency and verbal memory[104]
		No association between EAAT1 SNPs rs1428973, rs2033267, rs426040, rs4869684, rs1544795, rs3776585, rs962686, rs2303716, rs3776586, rs1049524, rs1529461 and Scz[112]
	mRNA studies	
	MDD	↓Lower levels in the DLPFC[83], AnCg[83], locus coeruleus[105] and hippocampus[106]
		↑Higher cortical levels in suicide completers with a MDD diagnosis compared to those without a diagnosis[118]
	Scz	↑Higher mRNA in the cerebellar vermis[113], AnCg[114], thalamus[115] and prefrontal cortex[116]
		→No change in the DLPFC or primary visual cortex[76,114]
		↓Lower levels in the prefrontal cortex of subjects who completed suicide compared to those who did not[117]
	Medication use	↑Haloperidol has been associated with an increase in EAAT1 mRNA in the thalamic medial dorsal nucleus[121]
		↑Chronic sodium valproate resulted in an upregulation of EAAT1 mRNA in chick cerebellar BGC culture[110]
	Protein studies	
	Scz	↓Decreased in the prefrontal cortex[114]
		↓N-glycosylation of EAAT1 monomer was decreased in the AnCg[114, 119]
	PTSD	↓Hippocampal EAAT1 protein was lower in a single prolonged stress (SPS) rat model of PTSD[108]
	Medication use	→Clozapine did not affect EAAT1 protein levels in rat[113,122]
		↑Chronic sodium valproate resulted in an upregulation of EAAT1 protein in rat hippocampus and chick cerebellar BGC culture[109,110]
EAAT2	Genetic studies	
	Scz	SNP rs4354668 G/G associated with poorer working memory performance[104,138] and a reduction in frontal grey matter[139]
	mRNA studies	
	MDD	↓Lower levels in DLPFC and AnCg[83]
		↑Higher levels in subjects who had completed suicide without a diagnosis of MDD compared to those with a diagnosis[118,127]
		↓Lower levels in the hippocampus, cerebral cortex and striatum of a rat model of depression[128, 129]
	Scz	↓Lower levels in the parahippocampal gyrus[140] and prefrontal cortex[141]
		↑Higher levels in the thalamus[115] and prefrontal cortex[142]
		→No change in EAAT2 or EAAT2b mRNA in the DLPFC or primary visual cortex[76]
	Medication use	↓Clozapine decreased levels in hippocampal CA1, parietal temporal, frontal and cingulate cortical[144], and striatal[145] brain regions of male Sprague-Dawley rats
		↓Haloperidol decreased frontal and cingulate cortical[144], as well as striatal[145], EAAT2 expression in rat
		↓Levels were higher in untreated subjects with Scz than in those prescribed typical or atypical antipsychotics[142]
		↓Increased levels caused by chronic stress were normalised by tianeptine treatment in rat[130]
		↓Increased hippocampal levels caused by stress were normalised by lithium administration in rat[137]
		↑Fluoxetine increased rat hippocampal and cortical levels[136]
		↑Tranylcypromine increased levels in rat amygdala[136]
	Protein studies	
	Scz	↓ N-glycosylation of EAAT2 multimer was lower in the DLPFC[119]
		↑ EAAT2b increased in extrasynaptic membrane/cytosol fractions from the DLPFC[143]
	PTSD	↓Hippocampal EAAT2 protein was lower in the single prolonged stress (SPS) rat model of PTSD[108]
	Medication use	↓Clozapine decreased protein levels in astrocyte culture[147]
		↓Clozapine reduced protein levels in the cerebral cortex of adult rats[146]
		↓Increased levels caused by chronic stress were normalised by tianeptine treatment in rat[130]
		→Increases in EAAT2b protein caused by chronic stress were unaffected by tianeptine treatment in rat[130]
		↑Chronic sodium valproate increased hippocampal EAAT2 protein in rat[109]

All research refers to human studies unless explicitly stated otherwise. References numbered as they are in the Reference section. ↑: Increase; ↓: Decrease; →: No change; AnCg: Anterior cingulate cortex; BGC: Bergmann glia cell; DLPFC: Dorsolateral prefrontal cortex; BD: Bipolar disorders; BOLD: Blood-oxygen dependent contrast imaging; fMRI: Functional magnetic resonance imaging; MDD: Major depressive disorders; PTSD: Post-traumatic stress disorder; Scz: Schizophrenia.

neurotransmitter system and psychiatric illness is not new[90,91]; originally based on the observation that phenylcyclidine (PCP), and later ketamine - both NMDA receptor antagonists - could induce schizophrenia-like positive and negative symptoms, as well as cognitive impairment[92-94]. While glutamatergic dysfunction is also hypothesized to be involved in other neurodevelopmental disorders such as autism[95] and attention deficit hyperactivity disorder[96,97], neurodegenerative disorders such as dementia[98,99], substance abuse/addiction[100] and chronic pain[101] (the latter two referenced reviews are written with a focus on EAATs), these topics are outside the scope of the current review.

EAAT1 in psychiatric illness

The rs2731880 (C/T) single nucleotide polymorphism (SNP) of *EAAT1* has been associated with deficits in working memory and selective attention in patients with

Type 1 bipolar disorder during a depressive episode, with T/T homozygotes displaying significantly worse performance[102]. Furthermore, bipolar disorder patients with the rs2731880 T/T genotype have displayed an overall negative correlation between amygdala and subgenual anterior cingulate cortex (AnCg) functional magnetic resonance imaging (fMRI) blood-oxygen-level dependent (BOLD) contrast imaging during a task which involved the processing of emotional or neutral faces, whereas in carriers of the C allele the coupling was absent[103]. SNP rs2731880 is a putative functional polymorphism within the promoter region of *EAAT1*, with the T/T genotype proposed to be associated with lower expression[104]. In support of the hypothesis that lower EAAT1 expression is associated with affective disorders, lower levels of EAAT1 mRNA have been reported in the human dorsolateral prefrontal cortex (DLPFC)[83], AnCg[83], locus coeruleus[105] and hippocampus[106] from subjects with MDD. Interestingly, Group II mGluR receptors - the agonists of which have been shown to upregulate EAAT1 protein levels[53] - are also decreased in MDD[107].

Furthermore, Feng *et al*[108] detected an increase in CSF glutamate levels and decrease in hippocampal EAAT1 protein levels in the single prolonged stress (SPS) rat model for PTSD. Interestingly, administration of fibroblast growth factor 2 (FGF2) alleviated the SPS-induced PTSD-like behaviour, promoted glutamate uptake and increased EAAT1 protein expression, thereby suggesting that astrocyte activation (and EAAT1 upregulation) may be advantageous in the treatment of PTSD[108].

Short-term sodium valproate treatment augmented EAAT1 translocation to the cell membrane, whereas prolonged or chronic sodium valproate treatment resulted in an upregulation of EAAT1 mRNA and protein levels, as well as glutamate transport and production of glutamine[109,110]. The ability of sodium valproate treatment to increase EAAT1 mRNA and protein levels, which are downregulated in affective disorders, contributes EAAT1 dynamics to an understanding of the medication's effectiveness[111]. This is not surprising, given that sodium valproate is used to treat both epilepsy - a disorder of excitotoxicity - and bipolar disorders.

Carriers of the rs2731880 SNP T/T genotype with a diagnosis of schizophrenia performed worse in tests of executive function, verbal fluency and verbal memory than the C carrier group[104]. This association has overlap with cognitive performance of subjects with bipolar disorder I[102]. Furthermore, Deng *et al*[112] analysed 11 *EAAT1* SNPS - exclusive of rs2731880 - in a Japanese population and found no association between *EAAT1* genotype and schizophrenia. These genotypic association studies suggest that while there may exist a relationship between *EAAT1* genotype and cognition, particularly within the context of psychiatric disorder, it is not a susceptibility locus specific to either schizophrenia or bipolar disorders.

Levels of EAAT1 mRNA have been reported as higher in the cerebellar vermis[113], AnCg[114], thalamus[115] and prefrontal cortex[116] of subjects with schizophrenia. In comparison, other studies have found no changes in EAAT1 expression in the DLPFC[76,114] or primary visual cortex[76] of subjects with schizophrenia. However, lower levels of EAAT1 mRNA were found in the prefrontal cortices of subjects with schizophrenia who completed suicide relative to those who did not[117], a confounding factor that many studies have not taken into consideration. Conversely, it has also been reported that EAAT1 mRNA levels were higher in the cortex of suicide completers without a prior diagnosis of MDD but not those with the diagnosis[118]. These data suggest complex expression x diagnoses x suicide factors that need to be considered when contemplating the role of EAAT1 in psychiatric disorders. Finally, monomeric EAAT1 protein expression was decreased in the DLPFC of elderly subjects with schizophrenia[114], while N-glycosylation of EAAT1 protein monomer was decreased in the AnCg[119]. Animal models have shown that *EAAT1* knock-out mice displayed locomotor hyperactivity in response to a novel environment which was exacerbated by NMDAR antagonists – two phenotypes considered to be relevant models for the positive symptoms of schizophrenia[120].

Interestingly, the locomotor hyperactivity in *EAAT1* knock-out mice could be normalised by treatment with haloperidol or the mGluR 2/3 agonist LY379268[120]. As EAAT1 protein levels have previously been shown to increase with administration of the mGluR 2/3 agonist DCG-IV[53], the data in *EAAT1* knockout mice suggests that activation of mGluR 2/3 may impact on a function downstream of glial glutamate uptake. Haloperidol has similarly been associated with an increase in EAAT1 RNA in the thalamic medial dorsal nucleus in subjects with schizophrenia[121]. On the other hand, administration of clozapine did not appear to affect EAAT1 protein levels in treated Sprague-Dawley rats[113,122], possibly due to the fact that clozapine, but not haloperidol, increases NMDAR-mediated neurotransmission through synaptobrevin-associated glial release of glutamate and D-serine[123]. If clozapine administration induces glutamate release from glia, it seems unlikely that glia would simultaneously increase a means to re-uptake glutamate. In conclusion, it appears that while the actions of haloperidol indirectly affect EAAT1 expression, clozapine seems to act through an alternative mechanism that is unrelated to EAAT1.

In summary, current data suggest an overall decrease in EAAT1 mRNA in affective disorders, while an increase in EAAT1 mRNA and decrease in EAAT1 protein is associated with schizophrenia; results which are further complicated by suicide completion and medication use. These factors must be taken into consideration when studying EAAT1, and the glutamatergic system as a whole, in terms of treatment for psychiatric illness.

EAAT2 in psychiatric illness

EAAT2 translation may be regulated by a large range

of molecules, including the stress-related glucocorticoids[124-126], creating a putative link between EAAT2 protein levels and stress-induced biological responses. To date, one study has recorded a lower levels of EAAT2 mRNA in the DLPFC and AnCg of subjects with MDD[83]. Interestingly, as with EAAT1, levels of EAAT2 mRNA were higher in the cortex of subjects who had completed suicide without a history of MDD, but not in those with a prior diagnosis[118,127]. EAAT2 mRNA was also lower in the hippocampus and cerebral cortex of learned helplessness rats – an established animal model of depression[128] and in the hippocampus, striatum, and frontal cortex of prenatally, restraint- stressed juvenile rats displaying increased behavioural despair[129].

Hippocampal EAAT2 protein levels were also observed to be lower in a SPS rat model of PTSD, which, like EAAT1 protein levels, could be alleviated by treatment with FGF2[108]. Interestingly, a rat model of chronic stress produced upregulated EAAT2 mRNA and protein levels in the hippocampus[130], suggesting that EAAT2 regulation may respond differently to the type, duration and severity of stress stimuli. Finally, amygdala specific DHK-inhibition of EAAT2 activity in rat resulted in reduced social interaction – a behavioural phenotype that could be blocked by the NMDA receptor antagonist, AP5[131].

Cerebrospinal fluid glutamate levels have been reported as higher in patients with obsessive compulsive disorder (OCD)[132,133]. To date however, an association between OCD and the glutamate transporters has only been proposed for the neuronal EAAT3, which is significantly less involved in glutamate uptake when compared to EAAT1 and EAAT2[134]. That said, astrocyte-specific inducible knockout of EAAT2 in adolescent - but not prenatal or adult - mice has been shown to result in glutamatergic hyperexcitability-related pathological repetitive self-grooming and tic-like head shakes[135]. Interestingly, these mice did not present with increased anxiety or social impairments[135].

It seems that the lower EAAT2 expression associated with depression and learned helplessness can be rescued by mood stabilizers. Chronic sodium valproate treatment increased EAAT2 protein levels in the rat hippocampus, but not other brain regions[109]. The antidepressant fluoxetine (class: SSRI) also produced rat hippocampal and cortical increases in EAAT2 expression, while tranylcypromine (class: monoamine oxidase inhibitor) resulted in an amygdala-specific increase[136]. In contrast to a depressive state, increases in EAAT2 mRNA and protein caused by chronic stress could be normalised by the antidepressant tianeptine in rat[130]. Interestingly, EAAT2b protein, but not mRNA, was also increased by chronic stress, however remained unaffected by tianeptine treatment[130]. A similar stress-induced increase in hippocampal EAAT2 mRNA expression was countered by food-based administration of lithium in rat[137]. This increase in EAAT2 expression in response to chronic stress lies in stark contrast to the previously mentioned decreases in EAAT2 expression associated with depression and learned helplessness, and suggests that EAAT2 is highly responsive to, or correlated with, different mood states.

EAAT2 SNP rs4354668 (T/G), located in the gene promoter region and associated with lower transport activity, has been correlated to cognitive dysfunction in schizophrenia, with the lower activity G allele linked to poorer working memory performance[104,138] and a reduction in frontal grey matter[139]. EAAT2 mRNA levels have been reported as lower in the parahippocampal gyrus -but not other hippocampal regions[140] and prefrontal cortex[141], and higher in the thalamus of subjects with schizophrenia[115]. In contrast, Matute *et al*[142] found an increase in EAAT2 expression in the prefrontal cortex. Finally, Lauriat *et al*[76] found no change in EAAT2 or EAAT2b mRNA in the DLPFC or primary visual cortex of subjects with schizophrenia, however the authors acknowledge the potential masking effect of antipsychotics on their results. N-glycosylation of the EAAT2 multimer was reduced in the DLPFC from subjects with schizophrenia[119], which may be associated with ER retention and reduced trafficking of EAAT2 to the plasma membrane[68]. The splice variant EAAT2b was increased in extra-synaptic membrane/cytosol post-mortem fractions from the DLPFC of subjects with schizophrenia[143]. As EAAT2b cell-surface expression is internalised in response to increases in intracellular calcium[80], it is possible that the elevated cytosolic localization of EAAT2b is a countermeasure to excitotoxicity.

Clozapine treatment has been reported to decrease EAAT2 expression in hippocampal CA1, parietal temporal, frontal and cingulate cortical[144], and striatal[145] brain regions of male Sprague-Dawley rats. EAAT2 protein levels and glutamate uptake were similarly reduced in the cerebral cortex of clozapine-treated adult rats with an accompanying increase in extracellular glutamate[146]. Clozapine also induced a decrease in EAAT2 protein in astrocyte culture, which was accompanied by a reduction in glutamate uptake[147]. This response to clozapine, which contrasts with the lack of effect that clozapine had on EAAT1 expression (discussed earlier in this review), suggests once again that the two EAAT subtypes are intrinsically different. Haloperidol similarly decreased frontal and cingulate cortical[144], as well as striatal[145], EAAT2 expression in rat. Matute and colleagues have provided support to the argument that antipsychotic drug treatment can affect EAAT2 expression by showing the higher levels of EAAT2 mRNA in the prefrontal cortex of untreated subjects with schizophrenia were not detectable in those with the disorder who had received typical or atypical antipsychotics[142].

CONCLUSION

Given the differential expression of EAAT1 and EAAT2 throughout brain development[47] and their importance in normal brain development[148], it is not surprisingly

that abnormal levels of these glutamate transporters have been found in the pathophysiology of psychiatric illness. It is imperative, however, that the subtype splice variants and glycosylation states be taken into consideration when researching the EAATs, as their unique attributes make them just as susceptible to disorder. The ability to analysis EAAT dynamics in a pre-mortem setting will assist in understanding the cause for their dysregulation and through that, the glutamatergic role in psychiatric disorder. Such information will allow for the prescription of medication with an understanding of how it may, or may not, affect the glutamatergic system. This review concludes with the contention that the EAAT family is dynamically regulated by a range of internal and external factors and offer a viable means to region-specific, subtype-specific therapeutic targets with the potential to respond to the immediate environment. However, a better understanding of the dynamic regulation of EAATs within the convoluted context of psychiatric disorder will be advantageous in advancing drug discovery.

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REVIEW

Melatonin in drug addiction and addiction management: Exploring an evolving multidimensional relationship

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Abstract

Melatonin is a pleiotropic signalling molecule that regulates several physiological functions, and synchronises biological rhythms. Recent evidences are beginning to reveal that a dysregulation of endogenous melatonin rhythm or action may play a larger role in the aetiology and behavioural expression of drug addiction, than was previously considered. Also, the findings from a number of animal studies suggest that exogenous melatonin supplementation and therapeutic manipulation of melatonin/melatonin receptor interactions may be beneficial in the management of behavioural manifestations of drug addiction. However, repeated exogenous melatonin administration may cause a disruption of its endogenous rhythm and be associated with potential drawbacks that might limit its usefulness. In this review, we examine the roles of melatonin and its receptors in addictive behaviours; discussing how our understanding of melatonin's modulatory effects on the brain rewards system and crucial neurotransmitters such as dopamine has evolved over the years. Possible indications(s) for melatonergic agents in addiction management, and how manipulations of the endogenous melatonin system may be of benefit are also discussed. Finally, the potential impediments to application of melatonin in the management of addictive behaviours are considered.

Key words: Dopamine; Drug dependence; Biological rhythms; Neuroplasticity; Brain reward

Core tip: Melatonin is a pleiotropic signalling molecule that regulates several physiological functions, and synchronises biological rhythms. Recent evidences are beginning to reveal that a dysregulation of endogenous melatonin rhythm or action may play a larger role in the aetiology and behavioural expression of drug addiction, than was previously considered. This review, using inf-

ormation garnered from extant literature, examines the roles played by melatonin and its receptors in addictive behaviours, addiction related changes in brain chemistry and brain plasticity; and its possible benefits in the management of drug associated withdrawal syndrome, relapse and behavioural sensitisation.

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INTRODUCTION

Drug addiction or substance use disorder has been defined as a chronic disease of the brain which is characterised by uncontrollable and compulsive drug-seeking and use; and which is associated with the development of a negative emotional state in the absence of drug access[1,2]. There have been suggestions that drug addiction is both a social and a medical problem dating as far back as recorded human history[3] and which continues to be a cause for global health concern[4]. Reports suggest that an estimated total of 246 million people, or approximately 1 in 20 people aged between 15 and 64 years were exposed to illicit drug in 2013; with surveys showing that approximately 1 in 10 of these have a drug-addiction problem[5]. Substance use disorder is arguably a serious public health issue, with a significant economic and health burden on affected individuals and their families[5]. There is also a significant societal burden measured in lost productivity, lawlessness, crime and increased health-care costs. Substance-use disorders have also been associated with worsening of co-morbid psychiatric and/or medical illness, risky behaviours and increasing mortality. While the global and economic burden of addiction continues to increase worldwide, current psychopharmacological therapies are falling short of the desired goals of therapy[6,7].

Over the past few centuries, several theories (social, biological or psychological) have been proposed to aid in understanding the aetiology of drug addiction[8]. Also, while the distinct aetiological bases for drug addiction are yet unclear, advances in neuroscience have continued to aid our understanding of the possible mechanisms that underlie the alterations in emotional balance and decision-making ability that occur with drug addiction[9]. Genetic, environmental, neurodevelopmental and sociocultural factors have been listed as important contributors to the development of drug addiction[10]. These factors have also been shown to increase the susceptibility of an individual to initiation or sustenance of drug use; and potentiate the development of structural brain changes that perpetuate drug use and are characteristic of drug addiction[9,11,12].

Presently, there is a growing body of evidence associating disruptions in circadian rhythms and circadian genes with the development and progression of drug addiction[13,14]. Studies in human subjects have demonstrated circadian rhythm disruptions in individuals with addiction, with suggestions that environmental and/or genetic alteration of the normal sleep wake cycle increases vulnerability to drug use[13,15]. Studies in rodents have also demonstrated that diurnal variations in the behavioural responses to different addiction paradigms exist[16-18]. In rodents, an increase in cocaine self-administration, and the intake of drugs of abuse have been observed at night[16,17,19,20]. There have also been suggestions that the continued craving for drugs of abuse is potentiated through the entrainment of the circadian clock[16,21,22].

Melatonin is a neurohormone that is important in the entrainment of circadian rhythms, as well as in the modulation of behaviour and physiological functioning in all mammals[23]. Some studies have observed a reduction in melatonin levels, and a delay in attaining its nocturnal peak concentration in alcohol-dependent humans and rodents[23]. Studies have also demonstrated melatonin's ability to modulate the reinforcing effects of a number of drugs of abuse with suggestions that it may play a crucial role in drug addiction[24]. In this review, we examine the roles of melatonin and its receptors in drug addiction, by discussing how our understanding of melatonin's modulatory effects on the brain reward system and crucial neurotransmitters such as dopamine has evolved over the years. Possible indications(s) for melatonergic agents in addiction management, and how manipulations of the endogenous melatonin system may be of benefit are also discussed. Finally, the potential impediments to application of melatonergic agents in the management of addictive behaviours are considered.

Neurobiological and neurochemical basis of drug addiction

Substance dependence can be described as a disorder which involves the motivational systems of the brain[25]. Repeated exposure to drugs of abuse has been linked to the development of long-lasting alterations in brain structure and neuronal circuitry. In the last decade or more, studies have demonstrated that repeated use of addictive drugs can alter the neural circuitries that are involved in reward/ motivation, learning/memory, affect, stress response and decision-making[26]. These regions which include the ventral tegmental area (VTA), nucleus accumbens (NAc) and amygdala form a part of the mesolimbic dopaminergic system and are important in reward-related processes[27]. Adaptations in cortical regions, including the prefrontal cortex, orbitofrontal cortex and the anterior cingulate gyrus, which form the mesocortical pathway, have also been implicated in addiction[28]. Increase in dopamine release in the mesolimbic or mesocortical brain regions have been sug-

gested to occur in parallel, appearing to mediate different phases or aspects of drug addiction. The mesolimbic regions (amygdala and hippocampus) have been linked to mediating conditioned learning in addiction; while the prefrontal cortex, orbitofrontal cortex and the anterior cingulate gyrus mediate executive control and emotional response to drugs[26].

Chronic drug use has also been associated with alterations in the "anti-reward" pathway which include the hypothalamic-pituitary-adrenal axis[29,30]. Adaptations in stress response, involving levels of corticosterone cortisol releasing factor and the adrenocorticotrophic hormone have also been reported to occur with drug addiction[31,32].

Brain neurotransmitter/neuromodulator changes also occupy a central role in the establishment, management and extinction (or otherwise) of addictive behaviours. In the brain, the neurochemical targets for a number of drugs of addiction have been identified[33]. Also, while the pharmacological profiles of the drugs of addiction are diverse, drug-receptor interactions can largely explain the wide range of physiological and behavioural changes that occur with drug use[26]. Also, there have been reports that suggest that despite the diversity of behavioural responses, drugs of addiction may share a common reward neural circuitry. Studies have shown that most of the addictive drugs appear to activate the reward system, directly or indirectly stimulating dopamine release[34,35].

Research has shown that dopaminergic (DA) neurons that project from the VTA to the NAc play a crucial role in the processing of stimuli associated with substance-related reward[36]. As a part of their pharmacological effects, substances with abuse potentials stimulate the brain reward system by increasing DA release from the NAc[37]. Also, there are reports that drugs of abuse induce their initial reinforcing effect by stimulating supraphysiologic levels of DA in the NAc. These DA surges (acting *via* D1 receptors) activate the striatal pathway (direct), while inhibiting the striato-cortical pathway (indirect) through D2 receptors[10]. Repeated drug use has also been associated with triggering neuroplastic changes that involve the glutamatergic inputs to the striatum and midbrain DA neurons, these alterations enhance the ways the brain reacts to drug cues, weakening self-regulation, reducing sensitivity to non-drug rewards and increasing sensitivity to stress[10].

There is also ample scientific evidence to suggest that there are DA-independent reinforcement pathways in the acute rewarding or pleasurable effects of addictive drugs. A number of studies in animals have shown that alcohol, opioids, nicotine and amphetamines may produce reinforcing effects *via* DA-independent mechanisms[38-40].

The involvement of some other neurochemicals and neuromodulators such as opioids, gamma-aminobutyric acid, glutamate, noradrenaline, cannabinoids and serotonin in drug addiction have also been suggested[41]. Reports from brain imaging studies have demonstrated an increase in opioid receptors density in persons experiencing withdrawal from alcohol[42], opioids[43] and cocaine[44]. Studies have also shown that the corticostriatal glutamate pathway may be important in the initiation and/or expression of a number of addictive behaviours; examples include conditioned place preference, drug seeking behaviour and locomotor sensitisation[45]. The overall conclusion is that although a number of neurotransmitters and neuromodulators are involved in the short-term reinforcing effects of addictive drugs; the dopaminergic reward pathway is central to the reinforcing properties of drugs and the initiation of the cycle of addiction. However, other mediators are believed to exert their influence *via* dopamine modulation[26,41].

The roles played by neuropeptides in addiction-related behaviours have also been examined; and for the most part, neuropeptides including signalling molecules like substance P, endogenous opioids, and neuropeptide Y have been studied extensively as possible therapeutic targets for addiction management[26].

Drug addiction and circadian rhythm/gene abnormalities

There is ample scientific evidence to suggest the importance of chronological events like the biological rhythms in determining response to drugs of abuse. Earlier studies have argued that chronobiological variables including time of day, sleep-wake patterns and light-dark cycles may modulate the development and maintenance of drug addiction[46]. More recent evidences derived from animal models suggest and support the existence of strong links between appetitive processes and various circadian genes[47]. Also, while details of the exact mechanisms are still being studied; it is becoming more obvious that a strong relationship exists between disturbance of circadian rhythms (as a result of factors like alteration of normal light-dark cycle) and the development of addiction[48].

It also appears that circadian phase-shifting activities such as repeated travels across time zones may influence the pattern of consumption of certain substances with addictive potentials; and this has also been demonstrated in experimental animals[49]. Using male Sprague-Dawley rats, Doyle *et al*[49] studied the effects of experimentally-induced chronic jet lag on methamphetamine consumption; and concluded that pre-exposure to methamphetamine (*via* 2 wk of forced consumption through drinking water) was associated with a significantly higher consumption of methamphetamine in phase-shifted rats (four consecutive 6-h advancing phase shifts of the light-dark cycle) during the second week following abstinence, when compared to those with undisturbed rhythms[49].

Earlier studies in humans had observed that drug-seeking behaviours are probably linked to mutations in certain key genes that are related to circadian rhythm maintenance; suggesting a link between abnormalities of circadian rhythm maintenance and addiction[47]. However, the associations between these genetic alterations and addiction have also been demonstrated in animals by using specific experimental paradigms. In male

Wistar rats, a month of constant light exposure exerts a significant effect on voluntary consumption of morphine, exhibition of withdrawal symptoms, plasma concentration of melatonin [evaluated by enzyme-linked immunosorbent assay (ELISA)] and the mRNA expression of period homolog genes (Per1, Per2) and dopamine (D1) receptors in the striatum and prefrontal cortex[48]. One month exposure to constant light caused a significant decrease in melatonin concentration, an upregulation of mRNA levels of Per2 and D1 receptor in the striatum and prefrontal cortex, up-regulation of Per1 gene in the striatum of rats under constant light (in comparison to those under standard light cycle), increased morphine consumption and preference ratio, and also a significant increase in severity of naloxone-induced withdrawal syndrome[48]. In humans, more studies are beginning to demonstrate that core genes that are involved in circadian rhythm maintenance are also important regulators of reward-related behaviours which occur in response to common substances of abuse[50]. On the other hand, substance use has been known to cause disruptions in circadian rhythms and affect functions such as the sleep/wake cycle; hence, the relationship that exists between substance abuse/addiction and circadian rhythm abnormalities is bidirectional, such that one could lead to the other, and vice versa. Also, abnormalities of sleep and circadian rhythms appear intimately linked to substance abuse, and they could appear as either predictors or consequences of substance abuse[47]. Documented effects of substance use on sleep is not only dependent on the class of agents, but also on the phase of usage, with acute sleep effects, chronic sleep effects, and sleep effects due to withdrawal or abstinence being described. Acute ingestion of drugs such as cocaine and amphetamine which have stimulant effects have been associated with a light, restless and disrupted sleep[51]; while ingestion of drugs with depressant effects such as benzodiazepines, alcohol and opiates can have an initial sleep-promoting effect (increased daytime sleepiness and reduced sleep latency) but sleep disruptions (increased night awakenings) later in the night, as a result of acute withdrawal effects[51,52].

There are reports that chronic use of substances may alter sleep quality and quantity in ways that are similar across different substances[53]. Extended sleep onset latency (SOL), a reduction in total sleep time (TST), increased frequency of night-time awakenings, reduced slow-wave sleep (SWS) and rapid eye movement (REM) sleep have all been described[47]. However, withdrawal from alcohol or stimulants may be associated with distinct time-related changes in pattern of TST and REM sleep[51,54]. Acute withdrawal from substance use may also be associated with sleep disturbances such as extended SOL, reduced TST, and reduced SWS[51]. Also, sleep disturbances such as REM sleep disturbances may continue weeks into abstinence; and polysomnographic evidences in cocaine-dependent participants still show increased SOL, and decreased TST, SWS, and REM sleep[55]. In heavy marijuana users, polysomnography had shown that over two weeks of abstinence, increases in wake time after sleep onset (WASO) and decreases in TST, sleep efficiency and REM sleep had been observed[56]. A persistence of sleep disturbances is believed to be a risk factor for relapse[55,56]. Overall, the relationship between circadian rhythm abnormalities/sleep disorders and addiction/substance abuse appears to be a complex one; with one pair increasing the predisposition to the other pair, and vice-versa.

MELATONIN

Melatonin is an endogenously-produced indolamine that is predominantly secreted by the pineal gland, and widely recognised as a regulator of several physiological functions. Melatonin production is controlled by the photoperiod through the suprachiasmatic nucleus (SCN), with production peaking at night and being at its lowest in daytime. In mammals, melatonin is a master synchroniser of biological rhythms, a regulator of physiological processes such as cardiac function; and an important modulator of behaviours, body posture and balance[57-59]. Fluctuations in melatonin levels (in a 24 h period) tune the body's cellular activities to the actual time-of-day; and while high levels of melatonin potentiate behaviours and physiological functions associated with darkness, low levels attenuate such behaviours and functions[23].

In biological systems, melatonin's effects are exerted *via* interactions with melatonin receptors (MT_1 and MT_2), orphan nuclear receptors, and intracellular proteins like calmodulin[60-62]. As an ampiphillic molecule, melatonin is capable of autocrine, paracrine and endocrine signalling; and it permeates several body compartments to exert effects on a variety of functions such as diurnal/seasonal rhythms, reproduction, neurobehaviour, antioxidant defense and general immunity.

Over the years, exogenous melatonin and melatonin analogues have been known to have an established role in the management of a range of sleep disorders. However, melatonin's therapeutic application is not limited to the central nervous system; and research has continued to shed light on the potential use of melatonergic drugs for the management of an increasing number of disorders/diseases including respiratory ailments such as asthma, pneumonias, chronic obstructive airway diseases, pleural cavity diseases, vascular pulmonary disease, and even lung cancer[63] Melatonin administration had also been shown to be protective against intestinal ischaemic-reperfusion injury in young male Sprague-Dawley rats[64] and Wistar albino rats[65].

From the foregoing, it is obvious that due to its unique chemical characteristics and diverse effects, melatonin may be useful in the management of several human diseases/disorders including those of the central nervous system such as drug addiction. Therefore, a better understanding of melatonin's role in addiction might open a new door in addiction management.

Melatonin and drug addiction

The roles played by circadian rhythm/gene abnormalities in the development or entrainment of addiction–related behaviours, or in potentiating changes in neurohormone, neuromodulator or neurotransmitter levels which result in the development of addiction are well-documented[24]. Melatonin's role in the entrainment of circadian rhythms is also well-documented. Observations that alcohol consumption altered the circadian profile of melatonin production in alcohol-dependent humans and alcohol drinking rodents[66,67] have also increased interests in the importance of melatonin in addiction[23].

Studies by Uz *et al*[68], and Kurtuncu *et al*[69] demonstrated loss of diurnal variation in cocaine-induced locomotor sensitisation and cocaine-induced place-preference respectively, in melatonin-deficient pinealectomised mice, suggesting that the cocaine-induced diurnal variations were mediated by melatonin[68,69]. There have also been reports suggesting that (drug-induced) hypothermic responses to injections of morphine, nicotine or ethanol varied with the light-dark cycle[70]. There have been suggestions that disturbances in sleep observed after months of abstinence in humans with alcohol-dependence could be linked to delayed peak of melatonin's nocturnal rise and lower melatonin levels[68,71]. Studies in rodents have also demonstrated similar alterations[67], further buttressing the role of the melatonergic system in drug addiction.

The effects of exogenous melatonin in modulating behavioural responses to specific drugs of abuse have also been studied. Vengeliene *et al*[23] demonstrated that administration of melatonin modulates alcohol-seeking or wanting and/or relapse-like drinking behaviours[23]. Results of *in vitro* electrophysiological studies have also shown that in cerebellar neurons, nicotine-stimulated currents decreased with application of increasing concentrations of melatonin[72]. Markus *et al*[73] also reported nocturnal elevations of melatonin-mediated nicotine-induced glutamate release by cerebellar neurons[73]. Finally, studies have demonstrated that melatonin is able to modulate the reinforcing or relapsing effects of certain drugs of abuse[23,24].

Melatonin receptors and drug addiction

Melatonin exerts its effects on behaviours and physiological functions largely *via* the melatonin (MT) receptors 1 and 2[74,75]. Also, while research has continued to demonstrate the possible roles that melatonin may play in drug addiction, including modulation of the development of dopaminergic behaviours, like drug-seeking behaviours or psychostimulant-induced diurnal locomotor sensitisation; the contributions of melatonin receptors, especially as it relates to specific drugs, are still being evaluated[23]. Research has demonstrated the presence of the MT1 receptor subtype in a number of brain regions, including areas like the prefrontal cortex, hippocampus, nucleus accumbens and amygdala which have been associated with regulating the effects of addictive drugs or behaviours[76,77]. Uz *et al*[76] studied the expression pattern of MT1 receptors in the dopaminergic system of the human and rodent brain, and observed the presence of MT1 receptor in these regions of the post-mortem human brain; while in the mouse brain, they observed a diurnal variation (high protein levels and low mRNA at night) in the expression of the mouse MT1 receptor in the dopaminergic system[76]. A few studies have also observed an increase in melatonin receptor-related cyclic AMP in the mesolimbic dopaminergic system[62]. In another study, prolonged treatment with antidepressants and cocaine was associated with alteration in the content of melatonin receptor mRNA, with the effects of these drugs on MT1/MT2 mRNAs being brain region-specific[78]; however, prolonged cocaine use did not alter MT2 receptor expression[78,79]. There have been reports suggesting that genetic deletion of MT1 and MT2 receptors abolished the development and expression of methamphetamine-induced locomotor sensitisation[79], and methamphetamine-induced reward[80] in melatonin-expressing C3H/HeN mice. Uz *et al*[68] however reported that MT1, and not MT2 receptor was required for cocaine-induced locomotor sensitisation in rodents. In another study by Hutchinson *et al*[81], this time comparing the differences in locomotor sensitisation observed following a single dose of methamphetamine in low melatonin-expressing C57BL/6 wild-type and MT1 knockout mice, to melatonin-proficient C3H/HeN mice; it was reported that methamphetamine pre-treatment induced locomotor sensitisation during the light period in C3H and C57 wild-type mice. A diminution in magnitude of sensitisation in C57 mice in the dark period, and a complete abrogation in the MT1 receptor knockout (MT1KO) mice was observed; buttressing the role of MT1 receptors in the possible management of drug addiction[81]. On the other hand, MT2 receptors have been linked to the modulation of hippocampal-dependent long-term potentiation; with a few studies demonstrating loss of long-term potentiation in transgenic mice deficient of MT2 receptors[82]. There were also reports of loss of experience–dependent short term latency to enter the closed arm on the second day of elevated plus maze exposure; a feature which suggests that MT2 receptors may play an important role in modulating memory processes and hippocampal synaptic plasticity[82]. These properties may prove useful in the management of addiction-related neuroplasticity.

MELATONIN AND THE PHARMACOLOGIC MANAGEMENT OF DRUG ADDICTION

Information garnered from years of research into the aetiopathogenesis of addiction point to the conclusion that drug-dependence is a multifactorial behavioural and biological disorder, which is amenable to medical treatment. The current treatment protocol for drug

use disorders involves the use of psychosocial and pharmacological interventions[5]. The main goals of management include: (1) reduction of drug use and drug craving; (2) improvement of general wellbeing and functioning of the individual; and (3) decreasing the risk of the development of complications and/or recurrence[5]. However, currently-available treatment options remain inadequate, with varying addiction relapse rates, depending on the drugs involved[83,84]. Thankfully, advances in science and research are opening new vistas for possible therapeutic interventions, and as such, current research interests are directed at developing or discovering new treatments options like the use of melatonin (a regulator of the circadian rhythm and potent antioxidant) that could be beneficial in reducing craving/withdrawal period and preventing relapse.

The ability of melatonin to mitigate different aspects of addiction neurobiology has been examined extensively. Studies have reported the efficacy of melatonin supplementation in the control of drug-seeking behaviour, opiate withdrawal/ relapse[24], behavioural sensitisation[84,85], regulation of the sleep and or circadian rhythm disorders[86], neuroplasticity, and prevention of: Mitochondrial-induced autophagy, apoptosis, oxidative stress and neurotoxic injury[84] in brain areas linked to reward and emotionality.

Melatonin, withdrawal syndrome and relapse

Prolonged use or abuse of drugs (such as opioids) by humans have been linked to the development of physical dependence and/or addiction, which is usually associated with alterations in brain biochemistry and hormone levels; and disruption of the sleep/wake cycle[87-89]. Also, sudden clearance or reduction in the plasma concentration of opioids of abuse results in withdrawal symptoms, including circadian rhythm disturbances like insomnia, jitteriness and restlessness[90,91]. Studies in animals have reported that chronic morphine administration resulted in a reduction in total activity within a 24 h period, and a dampening of the circadian amplitude in locomotor activity rhythm[92,93]. Abrupt withdrawal of morphine administration in rats has also been associated with sustained disruption of the circadian rhythms in locomotor activity, and alterations in plasma melatonin, β-endorphin, corticosterone, adenocorticothrophic hormone, and orexin concentrations[93-95]. Studies have also reported evidence of anxiety-related behaviour following cocaine withdrawal[96].

The possible effects of melatonin on withdrawal symptoms have also been examined; and while there is a dearth of clinical trials, studies in rodents have demonstrated its effectiveness. Zhdanova and Giorgetti[96] assessed the effects of melatonin supplementation on cocaine-induced anxiety-like behaviour and nucleus accumbens cyclic adenine monophosphate (AMP) levels in rats. In their study, melatonin (200 ng/mL) was administered in drinking water (at night) to groups of rats that had been exposed to repeated cocaine administration (15 mg/kg *i.p.*), or during its withdrawal. Results showed that melatonin caused a reduction in anxiety-like behaviour in a defensive withdrawal paradigm, 48 h after the last injection of cocaine[96]. Melatonin pretreatment also attenuated the augmentation of cAMP levels in the nucleus accumbens following acute administration of cocaine. These results suggest that a low-dose night-time melatonin treatment was effective in militating against symptoms of cocaine-withdrawal in rats[96]. Bondi *et al*[97] conducted a single-centre, randomised, double-blind, placebo-controlled, parallel-group trial to assess the effect of melatonin (5 mg) compared to placebo as adjuvant treatment (alongside behavioural and pharmacotherapy) on weekly self-reported severity of depression, anxiety, stress, and insomnia complaints in recovering substance use disorder subjects males (aged 18 years or older) who were at a residential program. Results showed no significant differences were observed for baseline characteristics; although the frequency of reported adverse events was higher in the melatonin group[97]. The authors were of the opinion although the diversity of medication regimens and behavioural interventions provided increase the complexity of assessing melatonin's efficacy with regards to the measured outcome, there is insufficient evidence to demonstrate melatonin's benefits as an adjuvant in addiction recovery[97].

The use of melatonin for its antioxidant effects during recovery from drug abuse has also been studied. The naloxone-induced heroine withdrawal syndrome has been associated with derangement in antioxidant enzymes and bio-elements which are essential for the maintenance of life[98]. Cemek *et al*[98] examined the effect of melatonin supplementation on the levels of antioxidant enzymes and bio elements in naloxone induced heroine withdrawal syndrome and reported a reversal in heroine withdrawal related alteration in glutathione, catalase levels, and the levels of bio elements (iron, manganese, magnesium, aluminium, calcium and copper). The researchers concluded that exogenous melatonin could be effective in militating bio element and antioxidant enzyme derangements in heroine withdrawal syndrome[98].

A very powerful challenge to drug addiction treatment is the high incidence of drug- use relapse during abstinence[99]. However, years of extensive clinical and preclinical research on drug-use relapse[100,101] have done little to reduce relapse rates[83,102]. Reports from a number of studies have reported that drug-use relapse is usually triggered by acute exposure to the self-administered drug[103], stress[102], the presence of drug-related cues and contexts[104], and protracted periods of withdrawal or exposure to cure that have been previously associated with withdrawal[105]. Extensive research work has led to the identification of possible cellular, neurotransmitter, and/or receptor mediated mechanisms that increase the risk of relapse to drug-use with the intent of identifying novel pharmacological treatment options[106-108]. Takahashi *et al*[24] assessed

the effects of melatonin supplementation (administered at either 25 or 50 mg/kg body weight) on cocaine self-administration and relapse-like behaviours in male Sprague-Dawley rats (which had been exposed to long-term cocaine self-administration training). Behavioural parameters measured included the motivation for cocaine self-administration in the break point test, relapse-like behaviour in the cue-induced reinstatement test, sucrose preference and distance travelled in the open field. Results showed a reduction in the cocaine-seeking behaviour and the desire to self-administer cocaine. The researchers concluded that melatonin supplementation could be beneficial in reducing relapse[24].

Melatonin, addiction-related behavioural sensitisation, neuroplasticity and neurotoxicity

Chronic intermittent use of cocaine and a number of other psychostimulants have been associated with the development of a progressive, long-lasting enhancement of psychomotor effects which have been referred to as cocaine or psychostimulant sensitisation. Studies have demonstrated that behavioural sensitisation to psychostimulants is associated with an increase in nitric oxide synthase[109]. While examining the effect of melatonin on cocaine-induced behavioural sensitisation in rats, Sircar[85] reported that: (1) acute or repeated melatonin injections on its own did not affect locomotor behaviour in rats; (2) acute melatonin pre-exposure augmented the acute locomotor effects of cocaine; and (3) repeated melatonin pre-exposure prevented the development of cocaine induced behavioural sensitisation, while a single injection of melatonin did not halt behavioural sensitisation in rats already sensitised to cocaine. Sircar[85] concluded that while melatonin supplementation increased cocaine's acute behavioural effects and prevented the development of cocaine's behavioural sensitisation, it had no effect in militating fully-developed cocaine behavioural sensitisation[85]. Itzhak *et al*[110] studied the effects of melatonin supplementation on the development of methamphetamine (METH)-induced behavioural sensitisation and reported that pre-treatment with melatonin at 10 mg/kg body weight prevented the development of METH-induced depletion of dopamine and/or its metabolites and depletion of dopamine transporter binding sites. It also attenuated METH-induced behaviours and diminished METH-induced hyperthermia, although it did not reverse fully-developed METH–induced behavioural sensitisation[110]. Feng *et al*[84] also examined the effects of melatonin on morphine-induced behavioural sensitisation and reported that pre-treatment with melatonin prevented the development of morphine-induced behavioural sensitisation and analgesic tolerance; effects which were dose-dependent[84].

The development of long-lasting addiction-related behavioural dysfunction and structural deficits in the brain have been linked to alterations in the methylation processes for purine metabolism/serotonin pathways[111], oxidative stress-induced autophagy[84], mitochondrial mediated apoptosis[112,113], alteration in mitochondrial DNA copy number in distinct brain regions[81], and neurotoxicity[84,114]. Li *et al*[95] also reported that protracted opiate withdrawal in rats was associated with the disruption of the circadian rhythm of hormones (adrenocorticotropin, orexin and corticosterone), leading to the induction of neurobiological changes which may worsen the risk of relapse[95].

Feng *et al*[84] examined the ability of melatonin to militate against the deleterious effects of opiate addiction and reported that melatonin was able to reverse morphine induced mitochondrial dysfunction and oxidative stress, in cultured cells. They also demonstrated that melatonin reversed morphine-induced autophagy and changes in mitochondrial DNA copy number in cultured cells and neurons[84]. *In vivo* studies using a mouse model of morphine addiction demonstrated that melatonin also counteracted morphine–induced autophagic effects and decrease in mitochondrial DNA copy number in the hippocampus[84].

Melatonin in the management of drug-addiction related sleep and circadian rhythm disorders

Sleep and circadian rhythm disorders have been well-defined in a number of substances use disorders, including those of marijuana[115], alcohol[52,116,117], nicotine[118], benzodiazepines[86,119] and cocaine[51]. Also, results from a number of rodent studies have reported interactions between alcohol and homeostatic mechanisms[120] and/or circadian systems[121-123]. Treatment options for insomnias in drug addiction are limited, largely because traditional hypnotics that target benzodiazepine receptors are associated with abuse potential, withdrawal effects, and the potential for overdose. Melatonin supplement has been found particularly valuable in the management of circadian rhythm disorders[124], in the treatment of insomnias in subjects with chronic schizophrenia[125], in the elderly[126,127], and among children with sleep onset insomnia[128]. However, its benefits in addiction-related sleep and/or circadian rhythm disorders are still being evaluated. A double-blind cross-over control study that examined melatonin's ability in militating sleep difficulties associated with benzodiazepine (BDZ) withdrawal reported that while melatonin did not increase the likelihood of BDZ discontinuation, it improved sleep quality, especially in subjects who continued to use BDZ[86].

Its use in alcohol addicts have been supported by studies that have reported low plasma melatonin levels in this group of substance users[66,129]. Other studies have examined the efficacy of melatonin analogs in militating addiction-related sleep disorders. Brower *et al*[116] examined the ability of the melatonin receptor agonist ramelteon to attenuate insomnia in recovering alcoholics, and reported an improvement in sleep quality and quantity. Another study using ag-

omelatine (a melatonergic agonist at MT1 and MT2 receptors, and a 5-HT2C antagonist approved for use as an antidepressant) reported improved sleep in alcohol-dependent subjects with insomnia; with participants reporting improved subjective sleep quality after 6 wk of administration[130].

CONCLUSION

To date, melatonin and its analogs have continued to show promise in the management of drug addiction. However, the use of melatonin may be limited by its short half-life and an additive sedative effect when used alongside BDZs and other drugs such as morphine; also, its safety in the younger age groups are still being debated. Despite these, evidences from both animal and human studies continue to show the potentials of melatonin and its analogs in the management of drug addiction. Therefore, research must continue to focus on the applications of melatonergic agents in drug addiction management, especially, beyond their established use for associated sleep disorders.

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EDITORIAL

Successful treatment of nightmares may reduce psychotic symptoms in schizophrenia

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Abstract

Nightmares occur more frequently in patients with schizophrenia than they do in the general population. Nightmares are profoundly distressing and may exacerbate daytime psychotic symptoms and undermine day-to-day function. Clinicians do not often ask about nightmares in the context of psychotic illness and patients may underreport them or, if nightmares are reported, they may be disregarded; it may be assumed that they will disappear with antipsychotic medication and that they do not, therefore, require separate intervention. This is a missed opportunity because Image Rehearsal Therapy, among other psychological and pharmacological interventions, has proven effective for nightmares in non-schizophrenia populations and should be considered at an early stage of psychotic illness as an important adjunct to standard treatment. There is active ongoing research in this field, which will undoubtedly benefit patients with schizophrenia in the future.

Key words: Sleep; Nightmares; Psychosis; Nightmare-inducing drugs; Image rehearsal therapy

Core tip: A substantial percentage of persons suffering from psychotic illness such as schizophrenia experience frightening nightmares that aggravate their disease symptoms. New treatments for nightmares in the general population are starting to be applied to schizophrenia patients, as are new treatments for other associated sleep problems. This is very promising research that clinicians need to heed, as the lessening of nightmare distress will also help to alleviate daytime psychotic symptoms.

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INTRODUCTION

Hearing or imagining malevolent threats is the hallmark

of delusions and hallucinations in people with psychotic illness; it is also the stuff of nightmares. The DSM-5 identifies nightmares as being extremely distressing, long-lasting, and well-remembered dreams that involve threats to survival, security, or physical integrity. There are many ways in which the delusions and hallucinations of psychotic illness overlap with the substance of nightmares: in the centrality of the protagonist to the plot of the story line, in the illusion of reality despite improbable circumstances, in the thematic content (persecution, danger, humiliation) and in the resulting emotions[1,2]. Nightmares can be conceptualized as forming part of the ego disorders that lead to "bizarre" or unreal delusions, considered by Bleuler as fundamental dimensions of schizophrenia[3,4]. Bleuler also believed that the thought disorders found in schizophrenia mirrored the condensation, displacement and symbolic distortions that characterize dreams and nightmares[5].

Almost everyone experiences nightmares occasionally, and they are especially commonplace in childhood. About 50%-60% of children aged 5 to 10 years have frequent nightmares[6] and approximately 2.5% of these children continue to have nightmares after the age of 10[7]. Prevalence studies in adults report that from 2% to 6% of the general population have frequent (one or more per week) nightmares[8,9], but that the prevalence is higher in psychiatric patients[8,10,11].

NIGHTMARES AND SCHIZOPHRENIA

In the context of schizophrenia, approximately 10% of persons with this diagnosis have been reported to experience frequent nightmares[12]. Some reports place the prevalence from somewhat to substantially higher in schizophrenia[13]. Although frequency is important, it is the distress of the nightmares that predicts both psychopathology and day time function[14] because nightmares interfere with restorative sleep and because the distress experienced at night carries over to the day.

Compared to bad dreams, nightmares are more bizarre or outlandish; they usually involve violence, and the narrative almost always ends in failure and misfortune for the dreamer. The usual reaction to nightmares is terror[15]. For reasons of personality traits or past experience, some individuals are more at risk than others, both for nightmare frequency and for the resulting distress[16]. What is clinically worrisome is that, even when a person with a diagnosis of psychotic illness reports the disturbing occurrence of nightmares (which they do not do unless specifically asked), it is rarely addressed in therapy. This is in marked contrast to the deliberate clinical targeting of nightmares when reported by persons with a diagnosis of posttraumatic stress syndrome. Nightmares need to be addressed in the context of schizophrenia for three main reasons. Firstly, they can be early warning signs of impending psychotic illness requiring early intervention[17,18]. Secondly, they often signal increased delusional severity as well as cognitive decline and, therefore, may require treatment reconsideration[12]. Thirdly, there is a strong association between nightmares and suicide, which demands serious attention[19-23].

TREATMENT PERSPECTIVE

The first step toward treatment is always to inquire about bad dreams and nightmares during the initial assessment, and subsequently during follow up visits. Whenever these are endorsed, the next step is a drug screen because it is possible that drugs utilized to treat the patient are promoting the induction of nightmares[24,25]. The drugs that tend to do so fall into several main categories: Hypnotics, beta blockers, statins, dopamine agonists, anti-epileptics, antibiotics, and antidepressants. Anti-epileptics and antidepressants are frequently used to treat persons with psychosis and should be re-evaluated in the presence of nightmares. The most common agents used to treat psychosis are, of course, antipsychotic drugs, which, while able to dampen arousing dream content[26], have not, in general, been found effective for reducing the distress of nightmares, nor for lowering their frequency.

There are specific treatments that have been found effective for nightmares in the non-psychotic population and these are: (1) Relaxation (instructions about relaxing and practice exercises in breathing); (2) Recording (encouraging the writing out of the details of nightmares); (3) Imaginal exposure (deliberately reliving the nightmare in one's imagination); (4) Imagery rehearsal (deliberately changing the script of recurring nightmares, providing happy endings and frequently rehearsing the rewritten script); and (5) Lucid dreaming (learning to become aware during a nightmare that one is dreaming and then changing the script of the nightmare while still dreaming[27-31]. Lucid dreaming is interesting because neural correlates of lucid dreaming and of insight deficits in psychosis show striking overlap; fronto-parietal regions are involved in both phenomena[32].

Several specific pharmacological treatments for nightmares have also been evaluated. Prazosin, an anti-alpha adrenergic agent, has shown most evidence of efficacy[33-35]. Thus far, the therapies for nightmares with the most evidence to support their use are prazosin and Image Rehearsal Therapy (IRT)[35-37]. For those interested in understanding the procedure of IRT, I refer the reader to a very helpful online guide[38].

Specifically in reference to patients with psychosis, IRT has been successfully used for nightmares in inpatient psychiatric settings, but patients with psychosis were excluded from these studies on the assumption that they would not be able to follow instructions[39-41]. These studies do show, however, that IRT can be used safely and effectively in psychiatric hospital environments where patients tend to be severely ill. Sheaves *et al*[42] treated 5 patients with psychosis with IRT, too small a number to demonstrate effectiveness, but sufficient to show acceptability and feasibility.

The caveats of this approach are that effective treat-

ment of nightmares has not yet been convincingly demonstrated in individuals with psychosis, nor is there evidence that the alleviation of nightmares will reduce psychotic symptoms. On the other hand, psychotic patients are known to respond well to cognitive behavior therapies for other sleep conditions, such as insomnia[43,44], so the chances are that they will be able to respond equally well to nightmare therapies. Nightmares in this population may also respond to post traumatic stress disorder (PTSD) therapies since rapid eye movement (REM) sleep interruption correlates with nightmare complaints caused by stress[45].

Patients with psychosis themselves claim that treatment of sleep problems has a positive impact on many aspects of their lives[46]. The better their sleep is, the milder their psychotic symptoms. And vice versa: The less they suffer from psychotic symptoms during the day, the better they are able to sleep[39].

Clinicians also recognize the link, but the treatment of sleep disturbances in this population continues to be limited[47,48]. On the whole, mental healthcare providers are not well informed about the consequences of nightmares nor do they know about available treatment options[49,50]. Patients may underreport nightmares and rarely seek treatment for them, considering them irrelevant to their main concerns[51]. Mental healthcare practitioners may consider sleep problems as mere accessories to a larger psychiatric condition, and, thus, not requiring specific attention[52]. This is a missed opportunity because IRT has been shown to be an effective treatment for nightmares in other populations[40,53] and should be considered at an early stage of psychotic illness, as an adjunct to standard mental health treatment.

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EDITORIAL

Psycho-emotional content of illness narrative master plots for people with chronic illness: Implications for assessment

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Abstract

Illness narratives are stories of illness told by patients with chronic illness. One way of studying illness narratives is by considering illness narrative master plots. An examination of illness narrative master plots has revealed the importance of psycho-emotional information contained within the story that is told. There is a need for research to capture this information in order to better understand how common stories and experiences of illness can be understood and used to aid the mental well-being of individuals with chronic illness. The current editorial provides a suggestion of how this is possible. This editorial identifies that stories can be "mapped" graphically by combining emotional responses to the illness experience with psychological responses of the illness experience relating to hope and psychological adaptation. Clinicians and researchers should consider the evidence presented within this editorial as: (1) A possible solution for documenting the mental well-being of individuals with chronic illness; and (2) As a tool that can be used to consider changes in mental well-being following an intervention. Further research using this tool will likely provide insights into how illness narrative master plots are associated together and change across the course of a chronic illness. This is particularly important for illness narrative master plots that are difficult to tell or that are illustrative of a decline in mental well-being.

Key words: Illness narratives; Assessment; Emotions; Psychological adaptation; Hope

Core tip: This editorial provides implications for how illness narratives can be assessed. It identifies how and why the assessment is useful and crosses the academic disciplines of medical sociology and psychology.

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ILLNESS NARRATIVES AND THEIR IMPORTANCE

Illness narratives reflect stories told by patients about their experience of illness. The term narrative is generally regarded as including at least "one character who experiences one event" but most narratives will have multiple events associated together in a suggested causal sequence within a particular setting[1]. Health care professionals (HCP) can use illness narratives as an effective vehicle to help behaviour change in patients [2]. Being able to share narratives with HCPs enables a patient's agency, self-esteem and self-respect[3]. However, it is acknowledged that psychosocial, political and environmental factors influence a patients' shared expression[4-6].

There are clear reported benefits of using illness narratives for the purpose of rehabilitation compared to traditional rehabilitation approaches including, a reduced counter argument against advice given to patients from HCPs and greater illustration of pathways or strategies for managing illness[7]. The use of illness narratives can also reduce interactions which lack emotional support and create barriers to behaviour change[3]. This is important as emotional support is consistently associated with more positive psychological adaptation to chronic illness, whereas negative experiences of support may hinder cognitive processes associated with psychological adaptation and mental well-being[8]. The term mental well-being is defined as defined as satisfaction, optimism and purpose with life, a sense of mastery, control, belonging, and perceiving social support[9].

ILLNESS NARRATIVES MASTER PLOTS IN CHRONIC ILLNESS

Illness narratives contain a plot that often contains a beginning, middle and end[2]. Illness narrative master plots are common stories of illness that use a distinct or common plot as a response to illness, for an overview of 13 common illness narrative master plots see Soundy *et al*[10]. The master plots illustrate the impact of an illness on a patient focusing on key psychological attributes including emotions, adaptation and hope. Each master plots references time indicating psychological adaptation to what life was like in the past, what it is currently like and what it could be like in the future[10,11]. Different and seemingly contrasting illness narrative master plots can be told simultaneously by a patient, this is an important process as it reflects key stages in illness adaptation[11].

Illness narrative master plots generated out of loss and change from illness symptoms are some of the most important and critical stories told by people with chronic illness. They are important because certain illness narrative master plots can be difficult to hear or can be denied by others[12]. HCPs need to have an awareness of the psychological meaning behind a patient's narrative master plots. However, evidence has suggested that further understanding is needed[3] and that clinical practice may prevent or inhibit this, *e.g.*, as empathy can be lost through training[13].

NEED TO UNDERSTAND EMOTIONS, HOPE AND PSYCHOLOGICAL ADAPTATION WITHIN ILLNESS NARRATIVES

Specific emotions felt by a patient following chronic or palliative illness or symptom change will clearly influence subsequent their decision making and responses to illness[14]. Specific emotions can be related to specific cognitive processes, for instance, fear may be associated with a low level of perceived control over one's situation whereas anger can be associated with a high level of perceived control. It has been identified during times of change, including diagnosis or symptom change that patients with chronic illness express far more unpleasant than pleasant emotions. For instance, a recent review[15] that grouped emotional expressions as part of the experience of living with a chronic illness only identified one consistently pleasant emotion; relief (identified in 16/47 studies). Far more apparent were unpleasant activated emotions such as panic, fear or being scared (19/47), anger (15/47) or frustration (18/47 and deactivated unpleasant emotions such as sadness (12/47), depression (12/47), pessimism (7/47), or feeling upset (14/47). The impact of emotions on a patient's responses must have further consideration. If patients feel overwhelmed with fear or worry and powerless within the experience of illness the cognitions expressed by them may be more likely to lead to a succumbing illness response, dominated by an inability to access coping resources[16].

Research[11] has suggested that emotions, hope and adaptation can be assessed and used to represent the distinct narrative master plots by using the circumplex model of affect[17,18] to capture emotions alongside the hope and adaptation scale[19]. The latter scale requires the patient to identify what for them is perceived as most difficult aspect of their life to adapt to following an illness onset or change. This is then considered in relation to their own ability to adapt to what has happened and hope for change. These two brief scales have been combined together to represent a model of emotion, adjustment and hope[15]. As narrative master plots can be represented by particular psycho-emotional components[11], it is possible to suggest that these combined tools and model can be used to map illness

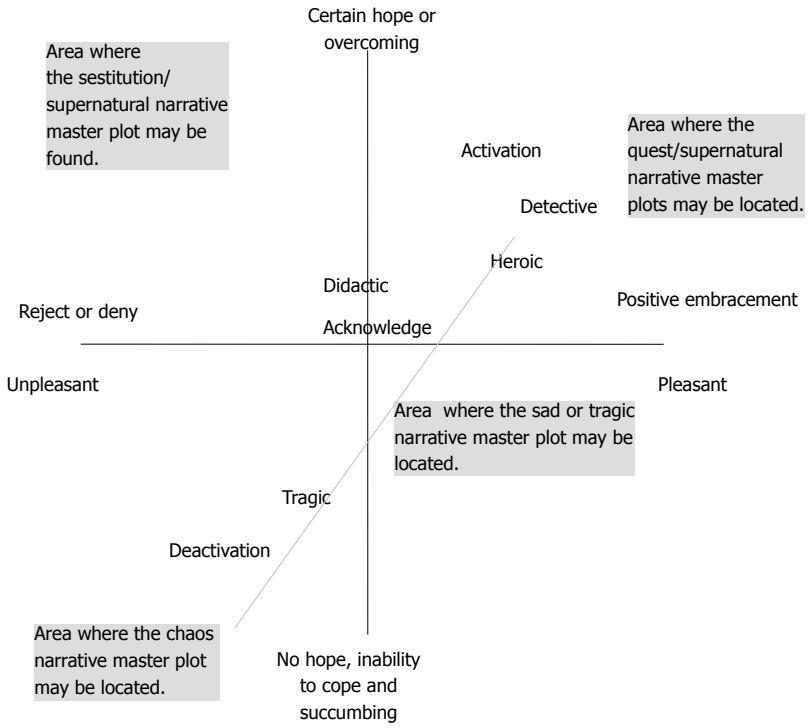

Figure 1 The possible placement and mapping of illness narrative master plots within the Model of Emotional Adjustment and Hope (Circumplex Model of effect on the horizontal axis, combined with the Hope and Adaptation Scale on the vertical axis).

narrative master plots (Figure 1).

NEED TO MAP ILLNESS NARRATIVE MASTER PLOTS

By mapping narrative master plots HCPs and researchers may be able to capture a patient's underlying psychological and emotional responses to illness. This enables a consideration of how; plots vary across time, what plots may be dominant for particular conditions or time following illness symptom change and how, and if, particular master plots are associated with one another. There is also a need to use the understanding of emotive and cognitive components of different master plots to target psychological interventions, *e.g.*, the emotional reaction expressed by a patient may be that of fear of what is happening which may cause them to want to escape or deny their circumstances[20]. In addition, understanding the cognitive processes of adaptation and hope may provide a point of discussion from where psychological intervention can begin.

HCPs should be able to map patient's response on a session by session basis, *e.g.*, HCPs by their responses have an opportunity to aid a patient's mood. For instance, a poor choice of words and an inability to listen may generate negative moods from interactions and be regarded as a perceived threat by an HCP. The mapping of illness narratives may provide greater clues to how particular narratives dominant or become dominant in a patient.

There is a need to consider how illness narratives are linked to one another and if targeting a particular aspect of the inventories is more effective. Further, there is a need to consider how changeable narratives are and if certain master plots are more resistant to change. Using tools identified above, narratives can be established and the meaning behind the narrative can provide a greater understanding and insight to the mental well-being of the patient.

CONCLUSION

Mapping an individual's master plots and understanding the psycho-emotional content of them may provide an essential tool for understanding the mental well-being of patients. Further research is needed in order to clarify and consider these points further.

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MINIREVIEWS

Single men seeking adoption

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Abstract

It was once impossible anywhere in the world for single adults to adopt children, and this is still the case in many jurisdictions. Elsewhere, however, single adults are now being actively recruited primarily because they are more willing than are married couples to adopt older or disabled children or to adopt across racial or other barriers. This is true for single men as well as for single women, but single men seeking to adopt continue to be widely viewed with skepticism and are reportedly often judged to be inappropriate parents. This paper reviews the sparse fostering and adoption literature on single heterosexual males and addresses the evident ambivalence with which parenting by single men is held among both child and adult mental health professionals. The paper also discusses the parenting styles of mothers and fathers, the ways that the central nervous system in both sexes has been found to respond to parenthood, the similarity of outcomes between single male and single female parenting, and the availability in North America of support and training for foster and adoptive single parents. The paper concludes that, in general, single men have as much to offer an adopted child as do single women and that seeming discrimination against them by childcare agencies requires investigation.

Key words: Single parents; Male adoption; Foster parents; Fathers

Core tip: Since contemporary definitions of masculinity have changed, men are no longer afraid to express emotions and to be nurturing fathers. More single men are now seeking to adopt children but, although male role models are very much needed for children in care, childcare agencies continue to be wary of single would-be fathers.

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INTRODUCTION

As much of the world's conceptions of family structure changes, a growing literature has arisen that addresses

single motherhood, as well as two-mother households and two-father households[1]. There remains, however, only a very modest childcare literature on single, especially single and heterosexual, fatherhood[2].

The relative lack of discussion of single male parenthood in the psychiatric and childcare literature is probably due to the assumption that heterosexual men have no innate desire for children unless they are in a committed relationship with a female partner. Motherhood is traditionally construed as central to a woman's sense of self[3], but relatively peripheral to a man's. Men are said to priorize career over family[4]. Exceptions to this generalization are generally acknowledged, however, especially in the case of gay men. Eighteen years ago, in 2000, one in five male same-sex couples were reported to be raising children[5]. Gay fathers, when interviewed[5] clearly articulated their motives for parenthood: They enjoyed the company of children, they valued family ties, they wanted to nurture and rear children of their own, particularly once they had reached a relatively mature stage of life and had achieved financial stability. Although, now that old-fashioned concepts of masculinity have become outdated[6], these same motives are likely to apply equally to heterosexual men, although the literature indicates that it remains somewhat unusual for unpartnered heterosexual men to actively seek fatherhood. This is the case despite the fact that, when comparing single mothers and single fathers, DeJean *et al*[7] found that single fathers were generally perceived in their communities in more positive terms than were single mothers. In contrast to single fathers, single mothers were described by participants in this study as "less intelligent, less desirable, less secure, less fortunate, less satisfied with life, less moral, less reputable, less of a good parent and less economically advantaged[7]." This perception of single fathers being "better" than single mothers is surprising. Surprising or not, it appears to do nothing to change suspicious attitudes among the general public and child care personnel about single fathers who seek to adopt children[8]. Should the single man seeking adoption have a history of a stigmatized condition, mental illness for instance, his chances of fostering or adopting children through either public or private channels become essentially nil[9,10].

Arbitrary restrictions to fostering and adoption based on demographics and discredited health conditions have become less intransigent over time, and most experts now agree that what is critical to successful adopting is filling the needs of the specific child, not concerning oneself with a would-be parent's marital status or psychiatric diagnosis. In the United States, single adults may now adopt in any state as long as they meet state-specific criteria for adoption[11]. In addition, over the last decade, many American States have added language to their child welfare statutes that protects persons with disabilities (this includes psychiatric disabilities) from discrimination when they attempt to exercise their fundamental right to create and maintain families[12]. Based on available statistics, however, most single adoptive parents continue to be female[13]; an apparent suspicion of would-be fathers remains prevalent[14]. It constitutes a form of anti-male sexism that is shared by many childcare professionals and is shown in a number of childcare proceedings, for instance by the failure to include fathers in case planning discussions around children, by the exclusion of birth fathers as placement options for children, and by home visits conducted when fathers are absent[14].

LITERATURE

The method for conducting this minireview was to scour the social work, psychology, childcare, and psychiatric literature for articles about fostering or adoption by single, heterosexual males. Very few articles were found.

MOTIVES FOR SINGLE FATHERHOOD

Motives for single full time fatherhood have been reported in Coles' ethnographic study of Black single birth fathers[15]. In that study (which was not about fostering or adoption), a sense of duty and responsibility led the men to become full time parents. They expressed a need to the interviewer to make up for their own fathers' absence, and a desire to model high quality fatherhood for their children[15]. At a June 2016 meeting sponsored by the Society for Research in Child Development, the consensus of an interdisciplinary group of scholars was that these same motives applied to single men, both gay and straight, who sought to foster or adopt children[16].

MALE FOSTER PARENTS

The literature on male foster carers[17] is almost always limited to males who are part of a married couple. Exceptions are Gilligan[18] and Newstone[19] who talked to a range of men who foster children, among whom were a few single males. Both these authors address the ambivalence towards males that, they claim, is often shown by childcare professionals. Both report that men are marginalized by social workers and childcare agencies because they are thought to represent a potential risk in the sense that foster fathers are often subject to improper sexual allegation. More rarely, men have, in fact, abused children in their care. Most child abuse in foster care is, as is true for aggressive acts everywhere, perpetrated by men[20]. On the other hand, a significant proportion of children who require fostering and adoption have, in their earlier lives, lacked a consistent male figure so that strong, dependable paternal role models are very much in demand. Over time, this demand has led to a gradual reconsideration of single males as potential foster parents. In 2003 in the United Kingdom, 20% of foster parents were unmarried singles. Two percent of these were single males[21]. The percentage today of single

male foster parents is unknown, but is likely to differ in different parts of the world.

SINGLE MALE ADOPTION

As early as 1977, Feigelman and Silverman[22] were reporting that adoption by single individuals, though historically considered "unthinkable" before the mid to late 1960s, had become possible in some jurisdictions as a result of the influx of growing numbers of children who needed a home. Singles were being actively recruited, they reported, for a specific reason - their relative willingness to adopt older, at-risk, and hard-to-place youth. It is known that the children who are adopted by single men through foster care in North America are usually older than average, more of them are disabled, and more of them are dark skinned[23,24]. In the Feigelman and Silverman[22] survey sample, 60% of single men adopted a child over 6 years of age whereas this was true for only 23% of single women and a mere 9% of couples. Forty-seven percent of single males in this sample adopted a child of a race different from their own, compared to 30% of single women and only 10% of couples. In 1997, Byrne[25] reported that 21% of children adopted by single males were physically or mentally disabled.

Despite the willingness of single men to adopt hard-to-place children, the majority of single adoptive parents continue to be women because childcare agencies are reportedly still making it relatively difficult for single men to adopt[23]. Although records of total adoption statistics (domestic, international, private) can never be totally accurate, it was estimated in 2015 that, of adoptions through foster care, only 3% (approximately) were by single men, most often gay men[23]. This may simply reflect the ratio of women to men who seek adoption, but it does suggest that childcare agencies are not actively recruiting men.

PATERNAL STYLES OF PARENTING

To better understand gender differences in parenting styles, Heslop[26] conducted an interview study of 23 foster fathers. The participants in this study were co-parents rather than single men, but their stories speak to the way contemporary men conceptualize their paternal role. The men in Heslop's study[26] filled traditional masculine parenting roles (as supporters and disciplinarians), but also felt comfortable in less traditional roles (sharing emotions and providing comfort to their children). Historically, male ways of parenting have been described as limited to roles such as encouraging friendships, teaching life lessons, and engaging children in active play[27,28]. Fathers have been described as interacting with their children mainly through the sharing of activities such as sports, yard work and home repair[29]. Many studies, however, indicate that, over time, fathers who stay at home with their children increase the amount of time they spend in care as distinct from play; they create relationships with children based not only on shared activities but also on emotional expressiveness, tenderness and love[30,31]. Hook and Chalsani[32] are of the opinion that, faced with identical tasks, parenting behaviors of single mothers and single fathers become progressively more and more similar, gender differences being overridden by the necessities of single parenthood. In her recent review of single father families, Coles[23] supports this view.

PLASTICITY OF THE PARENTAL BRAIN

In mammalian brain, the birth of offspring triggers a set of parental behaviors aimed to ensure the infant's survival. While it is well known that hormone levels play a defining role in this process in females, less is known about what happens in the male brain that prepares and sustains men when they become parents. Recently, significant brain changes have been identified in new fathers, changes that facilitate increased vigilance and socio-emotional engagement, changes that are similar, though not identical, to those found in new mothers[33,34]. In fathers, these brain changes are not driven by hormones but are activated by the experiences of childcare. It is postulated that these experiences provide emotional feedback that progressively shapes and patterns the paternal brain[33-35].

OUTCOMES OF CHILDREN REARED BY FATHERS

There has been no specific research on outcome parameters in children adopted by single men who are not their birth fathers. All single parent participants in outcome studies conducted thus far have been biological parents who are separated, divorced or widowed. Reviewing this literature, Biblarz and Stacy[36] report that, despite early findings that adolescents living with single mothers were more securely attached, had fewer behavioral problems, higher academic test scores and achieved higher educational and occupational status than those living with comparable single fathers, the literature as a whole concludes that children's achievements are essentially the same whether their single parent is a man or a woman. The Biblarz and Stacy review[36] hypothesizes that single-sex parenting fosters androgynous parenting practices, so that, as a result of necessity, the parenting styles of men and women become indistinguishable over time. These investigators found that, once family size was controlled, the number and severity of child behavior problems were similar whatever the single parent's gender. It has been known for some time that children in single-father or single-mother families do less well academically, on average, than children in two-parent families[37]. While this is true, and while parenting behaviors may also differ on average between single mothers and single fathers, Dufur *et al*[38] are of the opinion that such differences do not exert any perceptible

long-term effects.

OUTCOMES FOR MALE AND FEMALE PARENTS

Parenting is universally acknowledged as stressful and capable of contributing to mental ill health in mothers and fathers. A United States study[39] reported that continuously single fathers had significantly more mental health problems than continuously married fathers. This finding is supported by United Kingdom research on rates of common mental disorders in single parents of both sexes[40]. This research[40] found the risk to be almost twice higher in single compared to married mothers and almost three times as high in single compared to married fathers. Among the four groups (male single, male married, female single, female married), the lowest rate of mental disorder was found among married fathers. A relatively recent New Zealand study[41] with data on 905 single parents and 4860 partnered parents, found that 15.7% of single mothers and 9.1% of single fathers endorsed high to very high levels of psychological distress as compared to 6.1% of partnered mothers and 4.1% of partnered fathers. The relatively poorer mental health of single mothers compared to single fathers was attributed to socioeconomic factors since single women, on average, earn lower wages than single men.

CONCLUSION

This brief review about the current state of knowledge on single fatherhood strongly suggests that men on their own are able to adequately care for adopted children. This has been made easier since pre-adoption training and post-adoption support for single parenting is readily accessible in many parts of the world[42-45]. Support and training are important for all adoptive parents, but probably more so for single men for whom this continues to be, for the time being at least, a novel role. As pointed out by Atkinson and Riley[46], child and adult mental health professionals also require training so that discrimination against qualified would-be parents, whether single, male, gay, physically disabled or with a past history of psychiatric illness, ceases to dominate fostering and adoption decisions.

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ORIGINAL ARTICLE

Observational Study

Drinking plain water is associated with decreased risk of depression and anxiety in adults: Results from a large cross-sectional study

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Abstract

AIM

To investigate the relation between plain water drinking and risk of depression and anxiety among a large sample of Iranian adults.

METHODS

A total of 3327 Iranian general adults were included in this cross-sectional study. Validated Iranian version of the Hospital Anxiety and Depression Scale was used to assess anxiety and depression. Water consumption was assessed by asking about the number of glasses of water that consumed daily. Water consumption was categorized into < 2, 2-5, and ⩾ 5 glasses of water/d.

RESULTS

In the crude model, the lowest level of water drinking (< 2 glasses/d) compared with reference group (⩾ 5 glasses/d) doubled the risk of depression and anxiety (P < 0.0001). After adjusting potential confounders, this inverse link remained significant for depression (OR: 1.79; 95%CI: 1.32, 2.42; P < 0.0001), but not for anxiety (OR: 1.49; 95%CI: 0.98, 2.25; P = 0.109). In stratified analyses by sex, after controlling for potential confounders, water drinking < 2 glasses/d was associated with 73% and 54% increment in the risk of depression in men and women, respectively (P < 0.05), whilst no significant association was observed for anxiety either in men or in women.

CONCLUSION

We found inverse associations between plain water consumption and depression. Also, these findings showed a tended risky association, but not statistically significant, between lower levels of water consumption and anxiety. These findings warrant evaluation in prospective and clinical trials studies to establish the plausible role of water in mental health status.

Key words: Water; Anxiety; Depression; Psychological disorders; Iranian

Core tip: Evidence supports the relation between water consumption and health outcomes. Validated Iranian version of the Hospital Anxiety and Depression Scale was used to assess anxiety and depression. Water consumption was assessed by asking about the number of glasses of water that consumed daily. After adjusting potential confounders, an inverse link was observed between water and depression, but not for anxiety, though in the crude model both disorders were inversely related to water drinking. These findings warrant evaluation in prospective studies to establish the plausible role of water in mental health status.

Haghighatdoost F, Feizi A, Esmaillzadeh A, Rashidi-Pourfard N, Keshteli AH, Roohafza H, Adibi P. Drinking plain water is associated with decreased risk of depression and anxiety in adults: Results from a large cross-sectional study. *World J Psychiatr* 2018; 8(3): 88-96 Available from: URL: http://www.wjgnet.com/2220-3206/full/v8/i3/88.htm DOI: http://dx.doi.org/10.5498/wjp.v8.i3.88

INTRODUCTION

The prevalence of common psychological disorders has been increasing over recent decades[1,2]. Approximately, 29.2% of people are suffering from one of the common mental disorders worldwide[3]. Brain disorders, including both mental and neurologic disorders account for one-third of the economic cost of all diseases[4].

Drinking plenty of water is publicly believed to be useful for health and has been recommended in various dietary guidelines. Findings from a systematic review revealed that increased water consumption had a weight-reduction effect[5], and it has widely been known as an approach in weight-loss programs[6]. In addition, several studies have reported a bidirectional link between excess body weight[7,8] or diabetes[9] and mental disorders. It has been indicated that pathogenic substrates are the same in both metabolic and brain disorders; and therefore, the term of "metabolic-mood syndrome" has been suggested[10]. Lifestyle changes may to some extent explain the concurrency of obesity and mental disorders. Replacing water with sugar sweetened beverages might be the reason for inverse link between water consumption and obesity[11,12]. There is also evidence indicating the higher risk for mental disorders especially depression with higher consumption of sugar sweetened beverages[13], as well as higher glycaemic index diets[14,15].

Overall, accumulating evidence suggests that the beneficial relation between water ingestion and mental disorders is possible. However, the knowledge regarding beneficial effects of water consumption in mental health is rare. Water facilitates signaling pathway and nutrients delivery to the brain, removes toxins and inflammatory markers and provides energy sources for brain, and thereby improves brain function. Although several studies have shown that water insecurity is associated with psychological distress and anxiety[16,17], to the best of our knowledge, there is no study assessing the association between the water quantity and common

mental disorders including depression and anxiety. In the current study, therefore, we aimed to evaluate whether decreased plain water intake is associated with higher risk of mental disorders and whether it is gender-specific.

MATERIALS AND METHODS

Subjects

This cross-sectional study was carried out within the framework of the cross- sectional study on the Epidemiology of psychological, Alimentary health and Nutrition (SEPAHAN) project. The main aim of this project was to investigate the relationship between functional gastrointestinal disorders and lifestyle, nutritional factors and psychological profiles. The details of the project have been provided in Alibi *et al*[18] (2012). Briefly, the participants of the study were selected using multistage cluster and convenience sampling method amongst non-academic Isfahanian adults working at Isfahan University of Medical Sciences (IUMS) in 20 cities across Isfahan province. Each city was consider as a first stage's cluster and health centers affiliated to IUMS in each city were considered as second stage clusters and among them, considering the full coverage of geographic regions, some centers were selected randomly and those participants who were willing to participate in SEPAHAN study were recruited. In order to increase the participation rate and the data collection accuracy, the project was conducted in two phases. In the first phase, 10087 questionnaires were distributed to the participants, collecting information about anthropometric measures, demographic profile, lifestyle, nutritional factors and physical activity. 8691 completed questionnaires were returned in the first phase (response rate: 86.16%). In the second phase, psychological data were collected (response rate: 64.6%). Finally, after matching returned questionnaires in phase 2 with their equivalents in phase 1, we reached 4763 questionnaires. Of these, 2904 persons had complete information about both water consumption and psychological profile which were included in the statistical analysis. The study protocol was reviewed and approved by the ethical committee of Isfahan University of Medical Sciences.

Water consumption was assessed by asking about the average number of glasses of plain water that usually consumed in a day by each participant. The possible items to answer were < 2 glasses/d, 2-5 glasses/d and ⩾ 5 glasses/d.

Mental disorders assessment

A validated Iranian version of the Hospital Anxiety and Depression scale (HADS) was used to assess anxiety and depression[19]. HADS is a simple psychological questionnaire includes two separate parts to screen the severity of anxiety and depression. Each part includes 7 questions with a four-point rating scale (0-3); higher scores indicate greater degree of anxiety or depression. For both disorders, the score range is from 0 to 21. To identify the presence of either disorder, score 8 was considered as the cut point. Therefore, score 8 or greater were considered to have depression or anxiety and scores ⩽ 7 were considered normal[20].

Covariates assessment

Dietary intakes of participants were assessed using a valid and reliable 106-item dish-based food frequency questionnaire[21]. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). The current level of participants' physical activity was assessed using General Practice Physical Activity Questionnaire[22] and participants were categorized as physically moderately active, active, moderately inactive and inactive. Because of close relation between gastrointestinal disorders and psychological health, we considered functional gastrointestinal disorders (FGID) as an important covariate in our analysis. Suffering from gastrointestinal disorders was assessed using a valid and modified Iranian version of ROME Ⅲ questionnaire[23]. FGID was defined as suffering from at least one of the following main gastrointestinal disorders: gastroesophageal reflux, dyspepsia, irritable bowel syndrome and constipation.

Statistical analysis

General characteristics in categories of plain water intake were reported as means and standard error (SE) or percentage for continuous variables and categorical variables, respectively. To examine the differences across plain water categories, analysis of variance (ANOVA) for continuous variables and χ^2 test for categorical variables were used. All dietary intakes were adjusted for age (yr) and weight (kg) by analysis of covariance (ANCOVA). Multiple logistic regression was used to estimate odds ratios (OR) (95%CI) for the presence of depression and anxiety across categories of plain water intake in crude and multivariable-adjusted models. In adjusted models, we controlled confounding impacts of age, sex, marital status (married, single, divorced, widowed), educational level (less than 12 years, 12-16 years and more than 16 years), BMI (continuous), smoking (non- and ex-smokers vs. current smokers), physical activity (moderately active and active vs. moderately inactive and inactive), FGIDs (Yes/No), intake of anti-psychotic medicines (Yes/No), and dietary intakes which play role in mental health [magnesium, riboflavin, pyridoxine, folate, cobalamin, Docosahexaenoic acid (DHA), Eicosa pentaenoic acid (EPA), energy, fibre and caffeine]. All confounders, including energy intake, were included in the statistical analysis as covariates. We performed stratified analyses, applying the above-mentioned models, by sex to evaluate potential modifying effect of sex related to mental health status. The adjusted models were also controlled for the same potential confounders, mentioned above. In all logistic regression analyses, *P* for linear trends was determined by Mantel-Haenszel

Table 1 General characteristic of participants across categories of plain water consumption

Variables	Plain water drinking			*P* value[1]
	< 2 glasses/d	2-5 glasses/d	⩾ 5 glasses/d	
Participants (*n*)	854	1764	709	
Age (yr)[2]	37.2 ± 0.3	36.1 ± 0.2	34.8 ± 0.3	< 0.0001
BMI (kg/m^2)[2]	24.7 ± 0.1	24.7 ± 0.10	25.5 ± 0.2	< 0.0001
Anxiety score[2]	4.0 ± 0.1	3.5 ± 0.10	3.0 ± 0.1	< 0.0001
Depression score[2] *n* (%)	6.8 ± 0.1	6.1 ± 0.09	5.3 ± 0.1	< 0.0001
Anxious	136 (16.2)	244 (14.1)	61 (8.7)	< 0.0001
Depressed	303 (36.0)	478 (27.7)	151 (21.6)	< 0.0001
Male	242 (28.3)	757 (42.9)	387 (54.6)	< 0.0001
Marital status				0.035
Married	680 (81.4)	1431 (82.9)	549 (78.8)	
Single	135 (16.2)	271 (15.7)	139 (19.9)	
Other	20 (2.4)	25 (1.4)	9 (1.3)	
Anti-psychotic medicines use	56 (6.6)	91 (5.2)	39 (5.5)	0.342
Current smokers	147 (17.2)	243 (13.8)	70 (9.9)	< 0.0001
Moderately active and active	303 (39.6)	729 (45.7)	350 (56.1)	< 0.0001
Educational level				0.005
⩽ 12 yr	333 (39.8)	633 (36.9)	301 (43.1)	
12-16 yr	438 (52.4)	956 (55.6)	347 (49.7)	
⩾ 16 yr	65 (7.8)	129 (7.5)	50 (7.2)	
FGID[3] (%)	488 (57.1)	892 (50.6)	321 (45.3)	< 0.0001
Nutrients[4]				
Energy (kcal/d)	2306.1 ± 30.1	2385.8 ± 20.7	2487.9 ± 34.7	0.001
Protein (% of total calorie)	84.3 ± 1.2	88.5 ± 0.8	93.2 ± 1.4	< 0.0001
Fat (% of total calorie)	95.5 ± 1.3	98.7 ± 0.9	103.1 ± 1.5	0.001
Carbohydrate (g/d)	285.3 ± 4.2	294.5 ± 2.9	306.3 ± 4.9	0.006
Fibre (g/d)	22.0 ± 0.2	22.5 ± 0.1	23.0 ± 0.2	0.003
Caffeine (mg/d)	106.7 ± 3.1	96.7 ± 2.2	96.0 ± 3.7	0.022
Magnesium (mg/d)	314.1 ± 4.3	327.2 ± 3.0	349.6 ± 5.0	< 0.0001
Thiamin (mg/d)	1.8 ± 0.03	1.8 ± 0.02	1.9 ± 0.03	0.062
Riboflavin (mg/d)	1.8 ± 0.03	1.9 ± 0.02	2.0 ± 0.03	< 0.0001
Pyridoxine (mg/d)	1.9 ± 0.03	2.0 ± 0.02	2.1 ± 0.03	< 0.0001
Folate (mg/d)	562.4 ± 5.8	573.8 ± 4.0	600.2 ± 6.7	0.801
Cobalamine (mg/d)	2.8 ± 0.05	3.0 ± 0.03	3.1 ± 0.05	< 0.0001
DHA (g/d)[3]	0.2 ± 0.01	0.2 ± 01	0.2 ± 0.01	< 0.0001
EPA (g/d)[3]	0.06 ± 0.003	0.1 ± 0.002	0.1 ± 0.003	< 0.0001
Food groups				
Fruits (g/d)	285.8 ± 8.7	322.4 ± 6.0	351.1 ± 10.1	< 0.0001
Vegetables (g/d)	215.4 ± 4.8	241.4 ± 3.3	264.7 ± 5.5	< 0.0001
Nuts, legumes and soy (g/d)	55.5 ± 1.5	56.8 ± 1.0	60.9 ± 1.7	0.047
White meat (g/d)	59.4 ± 1.8	64.03 ± 1.2	67.5 ± 2.02	0.009
Red meat (g/d)	75.4 ± 1.8	78.4 ± 1.2	84.5 ± 2.06	0.004
Refined grains (g/d)	401.6 ± 7.1	390.7 ± 5.4	389.4 ± 9.11	0.473
Whole grains (g/d)	39.5 ± 2.9	40.8 ± 1.1	52.1 ± 3.40	0.007

[1]Derived from one way ANOVA and chi-square test for continuous and categorical variables, respectively and analysis of covariance (ANCOVA) for nutrients and food groups; [2]Values are means ± SEs; [3]FGID defined as suffering from at least one of the following gastrointestinal disorders: Gastroesophageal Reflux, dyspepsia, irritable bowel syndrome and constipation; [4]The nutrients were adjusted for age and body weight. DHA: Docosahexaenoic acid; EPA: Eicosa pentaenoic acid.

extension chi-square test. All statistical analyses were done using Statistical Package for Social Sciences (SPSS, Inc., Chicago IL, United States; version 20). $P < 0.05$ was considered significant in all statistical analyses.

RESULTS

In terms of water intake, participants were categorized into three major classes (< 2 glasses, 2-5 glasses, ⩾ 5 glasses/d). Those consumed more water had higher BMI ($P < 0.0001$) and were more probably to be younger, male, physically active (all $P < 0.0001$) and single ($P < 0.05$), but less educated compared with those who consumed less water ($P = 0.005$). Greater plain water drinking was associated with lower prevalence of smoking, anxiety, depression ($P < 0.0001$). Consistently, those consumed greater plain water had lower anxiety and depression score compared with those in the lowest category of plain water intake (< 2 glasses/d) ($P < 0.0001$). Water consumption was strongly associated with increased risk of FGID ($P < 0.0001$) (Table 1). Greater plain water consumption was associated with higher intakes of energy, protein, fat, carbohydrate, fibre, magnesium, riboflavin, pyridoxine, cobalamin, docosahexaenoic acid (DHA), eicosa pentaenoic acid (EPA), fruits, vegetables and red meat (*P* for all <

Table 2 General characteristics of participants based on categories of anxiety and depression *n* (%)

	Depression		*P* value[1]	Anxiety		*P* value[1]
	Yes (28%)	No (72%)		Yes (13.1%)	No (86.9%)	
Age (yr)[2]	36.3 ± 0.3	36.1 ± 0.2	0.562	35.4 ± 0.2	36.3 ± 0.3	0.020
BMI (kg/m^2)[2]	24.8 ± 0.1	24.9 ± 0.1	0.712	25.0 ± 0.2	24.9 ± 0.1	0.636
Male	285 (30.2)	1082 (46.0)	< 0.0001	117 (26.1)	1251 (43.9)	< 0.0001
Anti-psychotic medicines	106 (11.2)	76 (3.2)	< 0.0001	70 (15.6)	113 (4.0)	< 0.0001
Current smokers	164 (17.4)	290 (12.3)	< 0.0001	84 (18.8)	370 (13.0)	0.001
Moderately active and active	338 (39.7)	1028 (48.8)	< 0.0001	155 (38.5)	1212 (47.4)	0.001
Educational level			< 0.0001			< 0.0001
< 12 yr	153 (16.7)	236 (10.2)		84 (19.3)	306 (11.0)	
12-16 yr	715 (78.1)	1876 (81.4)		337 (77.5)	2255 (80.9)	
⩾ 16 yr	48 (5.2)	194 (8.4)		14 (3.2)	228 (8.2)	
Marital status			0.001			0.001
Married	733 (79.4)	1901 (82.4)		361 (83.2)	2274 (81.3)	
Single	163 (17.7)	380 (16.5)		58 (13.4)	486 (17.4)	
Other	27 (2.9)	26 (1.1)		15 (3.5)	38 (1.4)	
FGID[3]	665 (70.5)	1022 (43.4)	< 0.0001	357 (79.7)	1329 (46.6)	< 0.0001
Water drinking			< 0.0001			< 0.0001
< 2 glasses/d	303 (32.5)	539 (23.1)		136 (30.8)	706 (25.0)	
2-5 glasses/d	478 (51.3)	1246 (53.4)		244 (55.3)	1481 (52.4)	
⩾ 5 glasses/d	151 (16.2)	548 (23.5)		61 (13.8)	639 (22.6)	

[1]Derived from independent t-test and chi-square test for continuous and categorical variables, respectively; [2]Values are means ± SEs or percent; [3]FGID defined as suffering from at least one of the following gastrointestinal disorders: Gastroesophageal Reflux, dyspepsia, irritable bowel syndrome and constipation.

0.01). Tiamin, folate, white meat, refined grains, whole grains, nuts, legumes and soy consumptions were not significantly different across the categories of plain water intake.

Table 2 presents the general characteristics of study population stratified by the status of anxiety or depression. Individuals, who were anxious, but not depressed, were younger than healthy subjects. The prevalence of both depression and anxiety was higher among women, anti-psychotic medicines users, smokers and individuals who suffered from FGID. Conversely, healthy subjects were more probably to be physically active or moderately active, have higher education levels and drink more glasses of water. Whilst depression was less prevalent among married individuals, anxiety was more prevalent.

Crude and multivariable-adjusted ORs (95%CIs) of depression and anxiety across the categories of plain water intake are illustrated in Table 3. Compared with the reference group (⩾ 5 glasses/d), lower levels of water consumption (< 2 glasses/d) was associated with a greater chance of having depression (OR: 2.04; 95%CI: 1.62, 2.56; $P < 0.0001$) and anxiety (OR: 2.02; 95%CI: 1.46, 2.78; $P < 0.0001$) in crude model. Adjustment for multiple potential confounders slightly weakened these associations, but remained strongly significant for depression ($P < 0.0001$). However, after adjustment for dietary intakes, the lower levels of plain water consumption was a risk factor for anxiety however the significant link disappeared (for < 2 glasses/d: OR: 1.49; 95%CI: 0.98, 2.25, and for 2-5 glasses/d: OR: 1.58, 95%CI: 1.08, 2.30; $P = 0.109$; *vs* ⩾ 5 glasses/d).

In all crude and adjusted models, lower levels of water consumption (< 2 glasses/d) compared with the reference group (⩾ 5 glasses/d) was associated with a greater chance of having depression either in men or in women not only in crude but also in fully adjusted models (2-5 glasses/d: OR: 1.54; 95%CI: 1.00, 2.36 and < 2 glasses/d: OR: 1.73; 95%CI: 1.02, 2.93; $P = 0.04$) for men and in women (2-5 glasses/d: OR: 1.18 ; 95%CI: 0.86, 1.63 and < 2 glasses/d: OR: 1.54; 95%CI: 1.09, 2.15; $P = 0.007$). In the crude model drinking lower levels of water was associated with increased risk of anxiety in men (2-5 glasses/d: OR: 2.01; 95%CI: 1.20, 3.34 and < 2 glasses/d: OR: 1.83; 95%CI: 0.97, 3.43; $P = 0.041$) and in women (2-5 glasses/d: OR: 1.42 ; 95%CI: 0.98, 2.05 and < 2 glasses/d: OR: 1.59; 95%CI: 1.08, 2.34; $P = 0.026$); nevertheless, after adjustment for various confounders the significance associations disappeared in both genders.

DISCUSSION

In this analysis of a large cross-sectional study of general adults, lower daily plain water intake was associated with increased risk of depression and anxiety in the crude model. Although controlling for potential confounders attenuated these associations, the inverse link for depression remained strongly significant, whilst anxiety risk tended to be higher for lower water intake in the final model.

To our knowledge, this was the first investigation to examine the association of plain water consumption and common mental disorders, although the linkage of water/fluid consumption with obesity[6,12,24], coronary diseases[25], hyperglycaemia or diabetes[26,27], cancer[28] and mortality[29,30] has been examined in earlier studies. Some of these studies[6,12,24,25], but not all[26-30], confirm

Table 3 Multivariable-adjusted ORs (and 95%CIs) for depression and anxiety across categories of plain water consumption in the whole population and stratified by sex

	Plain water drinking			*P* trend[1]
	< 2 glasses/d	2-5 glasses/d	⩾ 5 glasses/d	
Depression				
Crude model	2.04 (1.62, 2.56)	1.39 (1.13, 1.71)	1 (reference)	< 0.0001
Model 1[2]	1.75 (1.35, 2.26)	1.30 (1.02, 1.64)	1 (reference)	< 0.0001
Model 2[2]	1.84 (1.37, 2.45)	1.39 (1.07, 1.80)	1 (reference)	< 0.0001
Model 3[2]	1.84 (1.40, 2.49)	1.41 (1.07, 1.84)	1 (reference)	< 0.0001
Model 4[2]	1.79 (1.32, 2.42)	1.37 (1.04, 1.80)	1 (reference)	< 0.0001
Anxiety				
Crude model	2.02 (1.46, 2.78)	1.73 (1.29, 2.32)	1 (reference)	< 0.0001
Model 1[2]	1.53 (1.07, 2.17)	1.44 (1.04, 1.99)	1 (reference)	0.026
Model 2[2]	1.58 (1.06, 2.36)	1.60 (1.11, 2.30)	1 (reference)	0.029
Model 3[2]	1.56 (1.03, 2.35)	1.63 (1.12, 2.40)	1 (reference)	0.066
Model 4[2]	1.49 (0.98, 2.25)	1.58 (1.08, 2.30)	1 (reference)	0.109
Men (n = 1386)				
Depression				
Crude model	1.77 (1.19, 2.63)	1.37 (0.99, 1.90)	1 (reference)	0.004
Model 1[2]	2.00 (1.26, 3.20)	1.45 (0.98, 2.13)	1 (reference)	0.003
Model 2[2]	1.95 (1.18, 3.21)	1.59 (1.06, 2.38)	1 (reference)	0.008
Model 3[2]	1.73 (1.02, 2.92)	1.54 (1.01, 2.36)	1 (reference)	0.037
Model 4[2]	1.73 (1.02, 2.93)	1.54 (1.00, 2.36)	1 (reference)	0.040
Anxiety				
Crude model	1.83 (0.97, 3.43)	2.01 (1.20, 3.34)	1 (reference)	0.041
Model 1[2]	2.36 (1.17, 4.74)	1.55 (0.87, 2.78)	1 (reference)	0.016
Model 2[2]	2.15 (1.02, 4.54)	1.59 (0.86, 2.95)	1 (reference)	0.042
Model 3[2]	1.76 (0.81, 3.84)	1.55 (0.82, 2.94)	1 (reference)	0.147
Model 4[2]	1.74 (0.80, 3.80)	1.52 (0.80, 2.88)	1 (reference)	0.161
Women (n = 1941)				
Depression				
Crude model	1.75 (1.30, 2.35)	1.26 (0.95, 1.67)	1 (reference)	<0.0001
Model 1[2]	1.61 (1.17, 2.21)	1.21 (0.90, 1.63)	1 (reference)	0.001
Model 2[2]	1.61 (1.16, 2.23)	1.21 (0.89, 1.65)	1 (reference)	0.002
Model 3[2]	1.61 (1.15, 2.26)	1.22 (0.89, 1.67)	1 (reference)	0.003
Model 4[2]	1.54 (1.09, 2.15)	1.18 (0.86, 1.63)	1 (reference)	0.007
Anxiety				
Crude model	1.59 (1.08, 2.34)	1.42 (0.98, 2.05)	1 (reference)	0.026
Model 1[2]	1.35 (0.89, 2.05)	1.41 (0.95, 2.07)	1 (reference)	0.264
Model 2[2]	1.39 (0.91, 2.13)	1.44 (0.97, 2.15)	1 (reference)	0.233
Model 3[2]	1.37 (0.88, 2.13)	1.44 (0.95, 2.18)	1 (reference)	0.288
Model 4[2]	1.30 (0.83, 2.02)	1.40 (0.92, 2.12)	1 (reference)	0.420

[1]Derived from a Mantel-Haenszel extension chi-square test; [2]Model 1: Adjusted for age, sex (in the whole population), marital status, educational level, model 2: Further adjustment for BMI, smoking, physical activity, model 3: Additional control for functional gastrointestinal disorders (FGID) and anti-psychotic medicines, model 4: Further control for magnesium, riboflavin, pyridoxine, folate, cobalamin, DHA and EPA, energy, fibre and caffeine. DHA: Docosahexaenoic acid; EPA: Eicosa pentaenoic acid.

the beneficial effects of water drinking in reducing diseases' risk. Therefore, due to bidirectional link between metabolic status and mental health[10], it might be concluded that water consumption can affect mental disorders risk *via* affecting metabolic status.

The bidirectional link between obesity and mental disorders is based on some shared peripheral and central pathological pathways, as well as genetic and environmental risk factors[10]. However, in line with some studies[26,31-33], we found that higher water consumption was associated with greater BMI. Therefore, some other plausible mechanisms may explain this inverse link. Our results indicate that higher water intake is associated with various healthy behaviours such as being more physically active and consuming greater amounts of nutrients particularly those involved in the nervous system (*e.g.*, riboflavin, magnesium, pyridoxine and cobalamin), which is consistent with previous studies[31,34]. Beneficial effects of these nutrients in neurotransmitters synthesis and transportation, as well as activity of many enzymes in the nervous system have been shown earlier[35,36]. Nevertheless, even after controlling for dietary intakes, depression was significantly related to water consumption, and anxiety tended to be higher in those who drank less water. A possible reason for the inverse link between water consumption and the risk of depression might be the decreased activity of the sympathetic nervous system by drinking water which reduces plasma levels of norepinephrine[37]. Elevated level of norepinephrine is a characteristic of psychosomatic depression[38] which may induce noradrenergic-vasopressinergic activation,

and consequently the activation of the hypothalamic-pituitary-adrenal (HPA) axis. Increased vasopressinergic activation of the HPA axis has been suggested as a plausible mechanism in all depressive disorders[38], which can be involved in mental symptoms production. In spite of similar link between water drinking and depression risk in men and women, the linkage for anxiety was stronger in men than women, though adjustment for antipsychotic medicines and FGIDs eliminated it. This difference between men and women might be related to sex-differences in the use of coping strategies[39]. However, the reasons for this difference are not clear and require further investigation.

In the current analysis, water consumption was evaluated using a direct question regarding the average amount of daily consumption of water, and data regarding other beverages intake and moisture contents of food were not considered. In addition, we provided predefined categories of plain water intake for participants. These factors may lead to misclassification of participants and decrease the reliability of our findings. However, it should be taken into account that noncalorically sweetened beverages are not public among Iranians and they are not used generally. Moreover, tea and coffee are mostly consumed with sugar. Therefore, since all other beverages, which consumed by this population, had calorie and we controlled the confounding effect of energy in our analysis, it could be concluded that our findings have enough precise. The consistence between our study's results and available evidence regarding the health beneficial of water intake might be further reason to confirm the accuracy of our findings.

The limitations of the current study are using self-administered questionnaires for evaluating the study variables. However, the validity of all used instruments has been approved among Iranians. Although using self-reported tools of habitual fluid/water intake is a common limitation in this area of research, the validity of self-reported measures has been approved in earlier studies[40,41]. In addition, no ideal method has been determined to assess beverage consumption and applying 24-h recall or frequency questionnaire beside a computer program on food composition is the existing recommend method in this regard[42]. The cross-sectional design is another limitation that does not allow causal inferences. Indeed, it is possible that individuals with mental disorders tend to drink less water. Nevertheless, such changes would have weakened the associations identified. Therefore, the true estimates are probably even stronger than those we found. Moreover, since we studied the participants who are staffs of IUMS, although they were not academic and medical experts, this sample may not be representative of the entire general population and therefore the results of our study may not be generalizable to other individuals in our society. The strengths of this study are the large sample size and controlling various confounders' effects.

In conclusion, we found inverse associations between plain water consumption and common psychological disorders. After controlling for various potential confounders, this association was stronger for depression, whilst for anxiety tended to be higher. These findings warrant evaluation in prospective studies to establish the plausible role of water in the mental health status.

ARTICLE HIGHLIGHTS

Research background

Drinking a plenty of plain water has been known as a healthy behavior.

Research motivation

The association between drinking water and mental disorders has not been investigated.

Research objectives

We aimed to assess whether drinking water is associated with mental disorders, and also examine the sex-specific associations.

Research methods

Three thousand three hundred and twenty-seven adults in a cross-sectional study were categorized into three groups according the amount of water drinking (< 2, 2-5, and ⩾ 5 glasses of water/d). The risk of depression and anxiety was evaluated across different categories.

Research results

After controlling for various potential confounders, we found inverse associations between plain water consumption and depression, whilst for anxiety tended to be significant. These findings warrant evaluation in prospective studies to establish the plausible role of water in the mental health status.

Research conclusions

There were inverse associations between plain water consumption and common psychological disorders.

Research perspectives

Prospective studies to establish the plausible role of water consumption levels in the mental health status are needed.

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SYSTEMATIC REVIEWS

Antidepressant foods: An evidence-based nutrient profiling system for depression

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Abstract

AIM

To investigate which foods are the most nutrient dense sources of nutrients demonstrated by the scientific literature to play a role in the prevention and promotion of recovery from depressive disorders.

METHODS

A systematic literature review was conducted to derive a list of Antidepressant Nutrients from the 34 nutrients known to be essential for humans using level of evidence criteria. Nutritional data was extracted for a subset of foods with a high content of at least 1 Antidepressant Nutrient using a USDA database. These foods were analyzed for Antidepressant Nutrient density resulting in an Antidepressant Food Score (AFS). Plant and animal foods were analyzed separately.

RESULTS

Twelve Antidepressant Nutrients relate to the prevention and treatment of depressive disorders: Folate, iron, long-chain omega-3 fatty acids (EPA and DHA), magnesium, potassium, selenium, thiamine, vitamin A, vitamin B6, vitamin B12, vitamin C, and zinc. The highest scoring foods were bivalves such as oysters and mussels, various seafoods, and organ meats for animal foods. The highest scoring plant foods were leafy greens, lettuces, peppers, and cruciferous vegetables.

CONCLUSION

The AFS is based on a nutrient profiling system devised to identify foods with the highest nutrient density of nutrients with clinical evidence to support their

role in depressive disorders. This list of foods and food categories with the highest density of the 12 Antidepressant Nutrients, the Antidepressant Foods, should be considered by researchers in the design of future intervention studies and clinicians as dietary options to support prevention and recovery from depression disorders.

Key words: Depressive disorder; Mental disorders; Diet; Diet therapy; Food

Core tip: The Antidepressant Food Score was designed to identify the most nutrient-dense individual foods to prevent and promote recovery from depressive disorders and symptoms. Results can be used to inform the design of future research studies or clinical dietary recommendations. This tool is based on a systematic literature review, evidence-informed list of Antidepressant Nutrients, and nutrient density calculation. The highest scoring animal foods were bivalves such as oysters and mussels, various seafoods, and organ meats. The highest scoring plant-based foods were leafy greens, lettuces, peppers, and cruciferous vegetables. These foods can be integrated into any dietary pattern.

LaChance LR, Ramsey D. Antidepressant foods: An evidence-based nutrient profiling system for depression. *World J Psychiatr* 2018; 8(3): 97-104 Available from: URL: http://www.wjgnet.com/2220-3206/full/v8/i3/97.htm DOI: http://dx.doi.org/10.5498/wjp.v8.i3.97

INTRODUCTION

Mental illnesses are highly prevalent, disabling, costly, and inadequately treated. Among individuals aged 15-44, depressive disorders are the leading cause of disability worldwide[1]. Improving public awareness and increasing treatment options for psychiatric illnesses is imperative to public health. A growing evidence base, including the first randomized controlled trial[2], suggests that dietary pattern and food choice may play a role in the treatment and prevention of brain-based disorders, particularly depression. The first nutritional guidelines to prevent depression were published this year. They recommend following a traditional dietary pattern such as the Mediterranean diet, consuming adequate amounts of omega-3 fatty acids, and avoiding processed foods, for example those high in refined carbohydrate or sugar[3]. Furthermore, an international consortium of mental health and nutrition researchers recently recommended "nutritional psychiatry" become a routine part of mental health clinical practice[4].

A number of nutrients are implicated in the patho-physiology of depression, for instance: the long-chained omega-3 fatty acids, B-vitamins, zinc, magnesium, and vitamin D[5,6]. Deficiencies of these nutrients can cause depressive symptoms, and in supplement form are used in clinical treatment[7-9]. Recent literature on nutrition and psychiatry has shifted from studying individual nutrients to evaluating overall dietary patterns. Prospective epidemiological studies have repeatedly found that "traditional" or "whole foods" dietary patterns are significantly correlated with a decreased prevalence and incidence of depressive disorders or symptoms. A Western dietary pattern has been found to be associated with an increased relative risk of the same[4,10-12]. The SUN cohort study followed 10094 university students for 4 years and found those with the highest adherence to the Mediterranean dietary pattern (MDP) showed a greater than 30% reduced risk of developing depression over the study period compared with participants with the lowest adherence to the Mediterranean dietary pattern[13]. Studies of traditional diets in Japan, Norway, and China found similar results[14-16]. A systematic review and meta-analysis of whole-diet interventions for depression and anxiety symptoms attempted by Opie *et al*[17] found the heterogeneity of the studies precluded analysis. However, among the 47% of studies that found a positive impact of a dietary intervention, common recommendations were to increase consumption of fruit, vegetables, fiber, and fish[17]. Dietary counselling used as an active control in a trial of problem-focused therapy for the prevention of depression in 122 elderly adults with sub-syndromal depressive symptoms, found a significant and sustained 40% reduction in Beck Depression Inventory scores at two years in participants who received 5.5 h of food counselling over 6-12 wk[18]. The SMILES (Supporting the Modification of Lifestyle in Lowered Emotional States) trial, the first randomized controlled trial of a dietary intervention to treat major depressive disorder, found that prescribing a modified Mediterranean diet as an adjunctive treatment resulted in 31% achieving remission compared with placebo and a number needed to treat of 4.1[19].

Brain health and mental illness are impacted by nutrition *via* several mechanisms. A full discussion is beyond the scope of the current paper, though we would like to highlight a few relevant mechanisms here. Nutrients such as the long-chained omega-3 fatty acids, zinc, magnesium, and a number of phytonutrients promote the expression of Brain Derived Neurotropic Factor (BDNF) and thus influence neuroplasticity[20]. Additionally, food is a modifiable determinant of systemic inflammation, which has been described as a major cause and consequence of depression according to the neuroinflammatory hypothesis of this disorder[21]. Finally, the emerging role of gut flora (*i.e.,* the microbiome) as a possible key player in the regulation of mood, cognition, and anxiety suggests that we are only beginning to discover the potential of food as medicine[22]. Dietary fiber is a prebiotic and its consumption can alter the composition of the microbiota[22].

Table 1 Levels of evidence

Levels of evidence: Observational studies	Levels of evidence: Experimental studies
1. At least 2 prospective cohort studies with adequate sample size and/or meta-analysis with narrow confidence intervals	1. At least 2 RCTs with adequate sample sizes, preferably placebo-controlled, and/or meta-analysis with narrow confidence intervals
2. At least 1 prospective cohort study with adequate sample size and/or meta-analysis with wide confidence intervals	2. At least 1 RCT with adequate sample size and/or meta-analysis with wide confidence intervals
3. Cross-sectional or case control studies	3. Non-randomized, controlled prospective studies (open-label) or high-quality retrospective studies (*i.e.*, case series)
4. Expert opinion/consensus	4. Expert opinion/consensus
5. Evidence is equivocal/unavailable	5. Evidence is equivocal/unavailable

RCT: Randomized controlled trial.

There are inherent challenges in prescribing a dietary pattern that is foreign to an individual. A Japanese or MDP may not be practical or palatable for many patients. Instead, ranking foods and highlighting food categories with a high density of nutrients demonstrated to be beneficial for depression could lead to specific food recommendations that can be incorporated into a whole-foods dietary pattern of the patient's choosing[3]. For the purpose of the current paper, nutrient density is defined as the ratio of a foods' nutrient value to its caloric content.

A review of 23 existing nutrient profiling schemas found them to be oriented towards improving a number of health outcomes. While many nutrient profiling scales currently exist, created by government agencies, researchers, and the food industry, none focus on mental disorders or brain health[23]. Additionally, no scale is based on nutrients that are supported by scientific literature to be involved in the prevention of and recovery from psychiatric disorders. The objective of this study is to determine which foods are the most nutrient dense sources of nutrients demonstrated by human studies published in the current scientific literature to play a role in the prevention and promotion of recovery from depressive disorders.

MATERIALS AND METHODS

A list of 34 essential nutrients for humans was compiled based on the Institute of Medicine's Dietary Reference Intakes[24]. A reference librarian at Columbia University was consulted to develop a systematic search strategy to further refine an evidence-based list of Antidepressant Nutrients. Computerized searches of OVID Medline, Embase, and Embase Classic dating back to 1946 were conducted during February 2017 using the search terms "Depressive Disorder, Major (MeSH)" and "Depression (MeSH)" in combination with the following nutrients: Arsenic, biotin, boron, calcium, carotenoids, choline, chromium, copper, dietary fiber, fluoride, folic acid, iodine, long chain omega-3 fatty acids (docosahexanoic acid and eicosapentanoic acid), magnesium, manganese, molybdenum, niacin, nickel, phosphorus, potassium, pyridoxine, riboflavin, selenium, sodium, silicon, sulfates, vanadium, vitamin A, vitamin B12, vitamin C, vitamin E, vitamin K, and zinc. Search terms were adapted to different databases. Titles and abstracts were read by both of the study authors to determine if retrieved papers were relevant to the topic under study according to the following inclusion criteria: Observational or experimental studies of an essential nutrient for the treatment or prevention of depressive disorders or symptoms (unipolar) in humans. Exclusion criteria included non-English language articles, review articles, and opinion pieces. Next, nutrient by nutrient, relevant articles underwent full-text review and data extraction by both study authors. Study findings were coded as positive, negative, or equivocal in regard to the prevention or recovery from depressive disorders. Discrepancies were resolved by both authors *via* consensus.

Statistical analysis

A system to rank the level of evidence in support of each potential antidepressant nutrient was developed based on level of evidence criteria used in various clinical practice guidelines in psychiatry[25]. The level of evidence was established for both observational and experimental human studies for each nutrient under consideration using the following guidelines shown in Table 1. Nutrients were included in the list of Antidepressant Nutrients if they had a combined score of less than or equal to 5. For example, magnesium received a total score of 4. There was one positive RCT and one positive prospective cohort study, both with adequate sample sizes, resulting in a level of evidence score of 2 for both experimental and observational studies.

Lists of the top 20 plant and animal whole food sources of each Antidepressant Nutrient were compiled in July 2017 based on the USDA nutrient database[26]. After duplicates were removed, this preliminary list consisted of 213 foods. An additional 23 commonly recommended healthy foods such as whole wheat, blueberries, and yogurt were added to this list to assess their AFS.

The nutrient content for each Antidepressant Nutrient was gathered using the database for each of the 236 foods. Nutrient content was expressed as a percent daily value. When percent daily values were not available, such as for long chain omega-3 fatty acids, we extracted the absolute nutrient amount per 100 g raw serving. This was then later converted to a percent daily value. For

Table 2 Antidepressant foods

Antidepressant animal foods	AFS range	Antidepressant plant foods	AFS range
Oyster	56%	Watercress	127%
Liver and organ meats (spleen, kidneys, or heart)	18%-38%	Spinach	97%
Poultry giblets	31%	Mustard, turnip, or beet greens	76%-93%
Clam	30%	Lettuces (red, green, romaine)	74%-99%
Mussels	28%	Swiss chard	90%
Octopus	27%	Fresh herbs (cilantro, basil, or parsley)	73%-75%
Crab	24%	Chicory greens	74%
Goat	23%	Pummelo	69%
Tuna	15%-21%	Peppers (bell, serrano, or jalapeno)	39%-56%
Smelt	20%	Kale or collards	48%-62%
Fish roe	19%	Pumpkin	46%
Bluefish	19%	Dandelion greens	43%
Wolffish	19%	Cauliflower	41%-42%
Pollock	18%	Kohlrabi	41%
Lobster	17%	Red cabbage	41%
Rainbow trout	16%-17%	Broccoli	41%
Snail or whelk	16%	Brussels sprouts	35%
Spot fish	16%	Acerola	34%
Salmon	10%-16%	Butternut squash	34%
Herring	16%	Papaya	31%
Emu	16%	Lemon	31%
Snapper	16%	Strawberry	31%

AFS: Antidepressant food score.

long chain omega-3 fatty acids, we based this calculation on a recommended daily intake of 1000 mg of long chain omega-3 fatty acids (EPA + DHA) based on a review of available guidelines[27].

Data was gathered for a 100 g serving of each food in the raw form. This was done because various cooking methods can alter the nutrient content, nutrient bioavailability, and water content of foods. In addition, nutrients vary largely with respect to bioavailability and form between plant and animal foods. For instance, heme-iron is only found in animal foods, and with the exception of certain sea vegetables, long chain omega-3 fatty acids are not found in plant foods. Separating plant and animal foods also served to minimize heterogeneity in bioavailability and content of nutrients across foods.

The mean Antidepressant Nutrient density was calculated for each food included in our list. This generated a nutrient density score, which was expressed as a percentage. The percent daily value for each nutrient was capped at 100% so that one nutrient would not overly influence the AFS. Our methods were adapted from a recent nutrient profiling study of "powerhouse" fruits and vegetables[28]. The following formula was used to calculate the Antidepressant Food Score: [(Σ % daily value per Antidepressant Nutrient / 12) / calories per 100 g serving] × 100.

RESULTS

Literature review

Our initial searches resulted in 1628 results and screening by title and abstract resulted in 213 relevant results eligible for full-text review. The following 12 nutrients met level of evidence criteria and were considered Antidepressant Nutrients: Folate, iron, long chain omega-3 fatty acids (EPA, DHA), magnesium, potassium, selenium, thiamine, vitamin A, vitamin B6, vitamin B12, vitamin C, and zinc.

Antidepressant food score

The top Antidepressant Foods based on the AFS are displayed in Table 2. Foods were grouped into categories and ranked in Table 3. Grouping foods into categories serves to ease implementation of results by providing the researcher or clinician with more flexibility[29]. The complete list of foods analyzed, Antidepressant Nutrient content per 100 g serving, AFS, and level of evidence per nutrient are displayed in the Supplementary Materials. The authors excluded the following 6 foods from analysis, as data was not available for greater than two nutrients: whale liver, caribou liver, blackfish, boar, antelope, and longan.

DISCUSSION

To our knowledge, The Antidepressant Food Score (AFS) is the first nutrient profiling system created to inform dietary recommendations concerning mental health. This evidence-based approach is unique in that it is based on Antidepressant Nutrient density. That is, nutrients considered have been shown in human studies to be beneficial with regards to treatment or prevention of depressive disorders. Our findings include a list of individual foods as well as food rankings within categories that can be incorporated in the design of subsequent research studies or recommended to patients as part of a healthy dietary pattern of their choosing.

Table 3 Food categories and mean antidepressant food score

Food category	Mean AFS
Vegetables	48%
Organ meats	25%
Fruits	20%
Seafood	16%
Legumes	8%
Meats	8%
Grains	5%
Nuts & seeds	5%
Dairy	3%

AFS: Antidepressant food score.

Interestingly, many foods with a high AFS are not commonly eaten as part of the Western dietary pattern. Specifically, the majority of the United States adult population does not meet daily recommendations for vegetables. The Healthy People 2010 initiative aimed to increase vegetable consumption of adults and found that only 27.2 percent ate three of more servings of vegetables per day[30]. Average annual seafood intake for Americans is 14.6 pounds, and the USDA estimates that 80-90 percent of the population fails to meet the recommendation of two servings of seafood per week[31]. On the contrary, top scoring foods on the AFS; seafood, leafy greens, cruciferous vegetables, and nuts are commonly consumed as part of a variety of traditional diets. The Mediterranean dietary pattern is but one example of a consistent pattern: traditional diets contain more nutrient dense foods and fewer highly processed foods. The evidence linking dietary patterns and depressive disorders supports the consumption of a whole-foods based traditional diet as opposed to a Western dietary pattern to prevent and promote recovery from depression. This emerging literature provides some external validity to the results of the AFS while our study serves to identify what some of the "active ingredients" of these traditional diets may be.

Selecting foods based on nutrient density is one way to meet daily nutrient requirements without consuming excessive calories, which may have benefits beyond mental health[32]. This is particularly important considering that a number of Antidepressant Nutrients have high rates of dietary insufficiency, meaning many individuals do not meet the Recommended Dietary Allowance (RDA). For example, 55% of the American population does not meet the RDA for vitamin A, 75% for folate, and 68% for magnesium[33].

It is worth discussing how our results differ from certain currently accepted dietary guidelines and nutrient profiling systems[28,32,34]. For instance, the AFS is focused on depression and does not consider dietary constituents to avoid such as saturated fat, cholesterol, and sodium. A recent review suggests that nutrient profiling scales designed to improve consumer food choices should be based on nutrients known to be beneficial for health as opposed to nutrients to avoid[29]. Moreover, the harmfulness and potential benefit of nutrients such as saturated fat, cholesterol, and sodium for both physical and mental health is being called into question based on more recent research, and cholesterol is no longer considered a nutrient of concern according to the most recent Dietary Guidelines for Americans[35-37]. Lastly, the AFS only ranks whole, unprocessed foods free of added sodium and fats. Recommending that patients continue to avoid fat, cholesterol, and sodium can potentially steer them away from consuming entire potentially nutritious food categories, such as seafood.

Certain nutrients, such as long-chain omega-3 fats, vitamin B12, and heme-iron are only found in animal foods such as seafood, meat, eggs, and dairy and these foods are generally absent from existing nutrient profiling scales. This may occur because a certain scale incorporates dietary cholesterol, saturated fat, or sodium as nutrients to avoid while others simply omit animal foods entirely. As health recommendations have trended towards more "plant-based" diets, one must consider the higher rates of B vitamin deficiencies in both vegetarian and vegan populations. A recent large study found higher levels of depressive symptoms in vegetarian men[38]. Our findings highlight the importance of including animal foods as an important part of a healthy dietary pattern to prevent and promote recovery from depressive disorders. That being said, there is a divergence between the animal foods that score highly on our scale such as organ meats and seafoods, and the processed meats typically consumed as part of the Western dietary pattern. The results of our study add to the current discussion in the nutrition literature about the importance of "plant based" diets by presenting a complimentary recommendation: Consuming animal products such as seafoods, organ meats, and small amounts of other traditionally-raised minimally processed meats is an important part of a healthy diet for depression. This is relevant as the majority of eaters consume animal products.

Gut health is increasingly understood as critical for brain health[22]. Along with being nutrient-dense sources of vitamins and minerals, two components of plants are relevant to mental health, but not well represented in the literature: fiber and phytonutrients. Generally, fiber is lacking in Western diets, and this influences the population and diversity of bacterial species that comprise the microbiome, the collection of bacteria that reside in the gut[39]. Phytonutrients are plant-based compounds, such as lycopene and quercetin, that are traditionally thought of as "antioxidants" but play clear cell signaling roles that influence genetic expression and modulate inflammation[40]. Ranking foods by phytonutrients content was not feasible, nor is there sufficient evidence linking individual phytonutrients to brain health. Fiber did not reach our level of evidence cutoff for inclusion and clearly more studies are needed.

The AFS ranks foods and nutrients with an established dietary reference intake included in the USDA database for standard reference at the time of analysis. Our

determination of Antidepressant Nutrients was based on the currently available scientific literature based on our search strategy at the time of our literature searches. As such, certain nutrients such as phytonutrients and other antioxidants were automatically excluded from our algorithm either based on a lack of established dietary reference intake, lack of inclusion in the USDA database, or lack of human studies supporting their effectiveness in treating or preventing depressive disorders. Finally, clinical trials of nutrients often use doses of supplements far beyond those possible *via* food consumption. If a high dose of vitamin B12 can promote depression recovery, it does not necessarily follow that foods with high nutrient density of vitamin B12 do as well.

Findings from the current study can be incorporated into the design of subsequent research studies. For instance, in developing a dietary intervention for depression, researchers should consider including and emphasizing foods that score highly on the AFS. Furthermore, upon publication of the current paper, the authors plan to make our database publicly available online for use by clinicians, researchers, and patients alike. Next steps also include expanding our database to include all foods listed in the USDA database.

In conclusion, a nutrient profiling system focused on mental health yielded rankings of plant and animal foods according to nutrient density of the 12 nutrients supported by current evidence: Folate, iron, long chain omega-3 fatty acids (EPA, DHA), magnesium, potassium, selenium, thiamine, vitamin A, vitamin B6, vitamin B12, vitamin C, and zinc. Evidence-informed dietary recommendations are critical to the employment of nutritional psychiatry in clinical practice. Considering cost, stigma, and access, nutritional interventions provide a unique treatment opportunity for mental health patients. Additionally, mental health professionals are well versed in supporting behavioral changes, of which dietary change is simply an example. As the evidence-base for nutrition as a modifiable factor influencing both the risk and prognosis of mental illness continues to expand, the AFS is a tool to help researchers refine nutritional recommendations to inform the design of future studies and to help clinicians guide patients towards healthier food choices today.

ARTICLE HIGHLIGHTS

Research background

The Western dietary pattern is insufficient in a number of essential nutrients. Evidence suggests dietary pattern is key to the prevention and treatment of depressive disorders, yet treatment rarely includes food recommendations. Nutrient profiling systems rank foods according to nutrient density and guide clinical recommendations, research study design, and patient choices. No current food rating scale focuses on nutrients required for mental health.

Research objectives

The objective of this study is to determine which foods are the most nutrient dense sources of nutrients demonstrated by the scientific literature to play a role in the prevention and promotion of recovery from depressive disorders.

Research methods

A systematic literature review was conducted to derive a list of Antidepressant Nutrients from the 34 nutrients known to be essential for humans using level of evidence criteria. Nutritional data was extracted for a subset of foods with a high content of at least 1 Antidepressant Nutrient using a USDA database. These foods were analyzed for Antidepressant Nutrient density resulting in an Antidepressant Food Score (AFS). Plant and animal foods were analyzed separately.

Research results

Twelve Antidepressant Nutrients relate to the prevention and treatment of depressive disorders: Folate, iron, long-chain omega-3 fatty acids (EPA and DHA), magnesium, potassium, selenium, thiamine, vitamin A, vitamin B6, vitamin B12, vitamin C, and zinc. The highest scoring foods were bivalves such as oysters and mussels, various seafoods and organ meats for animal foods. The highest scoring plant foods were leafy greens, lettuces, peppers, and cruciferous vegetables.

Research conclusion

The AFS is based on a nutrient profiling system devised to identify foods with the highest nutrient density of nutrients with clinical evidence to support their role in depressive disorders. This list of foods and food categories with the highest density of the 12 Antidepressant Nutrients, the Antidepressant Foods, should be considered by researchers in the design of future intervention studies and clinicians as dietary options to support prevention and recovery from depression.

Research perspectives

The AFS was designed to identify the most nutrient-dense individual foods to prevent and promote recovery from depressive disorders and symptoms. Results can be used to inform the design of future research studies or clinical dietary recommendations. This tool is based on a systematic literature review, evidence-informed list of Antidepressant Nutrients, and nutrient density calculation. The highest scoring animal foods were bivalves such as oysters and mussels, various seafoods, and organ meats. The highest scoring plant-based foods were leafy greens, lettuces, peppers, and cruciferous vegetables. These foods can be integrated into any dietary pattern.

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LETTERS TO THE EDITOR

Psychic euosmia and obsessive compulsive personality disorder

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Abstract

Patients with obsessive compulsive personality disorder (OCPD) often refer to a prompt mood improvement upon encountering good scents in general, or fresh laundry borax on their clothes, pillows or home settings. The Authors propose the new term psychic euosmia in the mean of an overstated psychological predisposition for a real pleasant smell that elicits an immediate sense of pleasure, order and calm. The prompt reactions to a pleasant odor might be explained by the involvement of rhinencephalon and its proximity to mood-related limbic circuits, which bypass the cognitive awareness. Cleanliness may not preclude a subject to enjoy a good smell, even if we are representing smells that resemble freshness, in other words order. A potentially even more important argument is given by the continuum of personality disorders and their variability. Not all personality characteristics led to disturbed behaviors. In evolutionary perspectives having the ability to differentiate between unpleasant and pleasant odors should have made the difference in surviving. On the other hand, psychic euosmia could be considered a normal reaction, but in our clinical experience it is over-represented among OCPD subjects with marked orderliness and disgust. Therefore, detecting psychic euosmia might vicariously confirm the relevance of disgust as a cognitive driver of OCPD. Hereby we support research to characterize psychic euosmia as a feature of orderliness and cleanliness for OCPD.

Key words: Psychic euosmia; Obsessive compulsive personality disorder; Orderliness; Pleasure; Positive emotion; Pesonality

Core tip: Patients with obsessive compulsive personality disorder (OCPD) often refer to a prompt mood improvement upon encountering good scents in general,

or fresh laundry borax on their clothes, pillows or home settings. The Authors propose the new term psychic euosmia in the mean of an overstated psychological predisposition for a real pleasant smell that elicits an immediate sense of pleasure, order and calm. Detecting psychic euosmia might vicariously confirm the relevance of disgust as a cognitive driver of OCPD. Hereby we support research to characterize psychic euosmia as a feature of orderliness and cleanliness for OCPD.

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TO THE EDITOR

Pierre Janet, in his conceptualization of obsessions and compulsions, described an inability to achieve perfection[1]. This phenomenon characterizes both obsessive compulsive personality disorders (OCPD) and OCD. Available literature indicates that two main factors of OCPD, order/control and hoarding/indecision, were identified among OCPD patients[2]. Hyper-control and orderliness, cleanliness other than perfectionism are often awkward and dysfunctional in these subjects. Yet, OCPD manifestations are generally considered ego-syntonic and are perceived by affected individuals as appropriate and correct. In many OCPD subjects perfectionism does not represent a maladaptive variant as a rule. In any case, there are several effects of orderliness behaviors that result in an underrated emotion of pleasure, even thought subjects are aware of its pathological nature. This is the case of a peculiar manifestation of orderliness. Clinicians involved in the treatment of OCPD are aware of how their patients often refer to a prompt mood improvement upon encountering good scents in general, or fresh laundry borax on their clothes, pillows or home settings. In medical terminology parosmia is defined as an olfactory dysfunction to properly identify an odor' s "natural" smell, while euosmia is a form of parosmia in which a neutral odor is transcribed into a pleasant odor. Here we refer to psychic euosmia in the mean of an overstated psychological predisposition for a real pleasant (not neutral) smell that elicits an immediate sense of pleasure, order and calm. It could be seen as the opposite reaction of irritability of sensory experiences called misophonia[3]. For OCPD patients, congenial odors resemble a sensation of freshness, not simply an essence or perfume.

Some may argue that this is exactly the counterpart of chaos, of disgust, that was associated to contamination and moral purity. Disgust-sensitivity is a well-know framework in cognitive models of OCD, but it fits to OCPD too, perhaps better. From a biological perspective unpleasant odors activate insula and caudate[4]. More, enlarged gray matter volume of the left medial orbital gyrus was found by using the Sniffin' Sticks test[5]. The prompt reactions to a pleasant odor might be explained by the involvement of rhinencephalon and its proximity to mood-related limbic circuits, which bypass the cognitive awareness.

To our knowledge there are no studies regarding neurobiological abnormalities or clinical aspects that investigate the correlates of psychic euosmia in OCD and OCPD subjects. As an explanation in mental health, researchers and clinicians are automatically looking at pathological aspects of phenomena. In his nonconforming paper Bentall stressed that psychopathologists tautologically are not concerned about elation and joy[6] Hence we posit that a pathological issue, as an overrepresented psychic euosmia, should not have a positive emotional consequence in reason of being pathological *per se*. Thus, cleanliness may not preclude a subject to enjoy a good smell, even if we are representing smells that resemble freshness, in other words order. A potentially even more important argument is given by the continuum of personality disorders and their variability. Not all personality characteristics led to disturbed behaviors. In this way, having OCPD traits could be not dysfunctional at all, and many individuals with OCPD traits deal with head positions in their activities. In evolutionary perspectives having the ability to differentiate between unpleasant and pleasant odors should have made the difference in surviving[7]. On the other hand, psychic euosmia could be considered a normal reaction, but in our clinical experience it is over-represented among OCPD subjects with marked orderliness and disgust. Therefore, detecting psychic euosmia might vicariously confirm the relevance of disgust as a cognitive driver of OCPD. Hereby we support research to characterize psychic euosmia as a feature of orderliness and cleanliness for OCPD.

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ORIGINAL ARTICLE

Observational Study

Role of rumination in the relationship between metacognition and shyness

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Abstract

AIM

To explore the association between metacognitive beliefs, rumination and shyness in a non-clinical sample of adults.

METHODS

One hundred and three healthy subjects from the general population were enrolled in the study. Shyness was evaluated using the Revised Cheek and Buss Shyness Scale, rumination was assessed using the Ruminative Response Scale, metacognition was evaluated using the Meta-Cognitions Questionnaire 30, and anxiety levels were measured using the State Trait Anxiety Inventory form Y. Correlation analyses, mediation models and 95% bias-

corrected and accelerated (BCaCI) bootstrapped analyses were performed. Mediation analyses were adjusted for sex and anxiety.

RESULTS

Shyness, rumination and metacognition were significantly correlated ($P < 0.05$). The relationship between metacognition and shyness was fully mediated by rumination (Indirect effect: 0.20; 95% BCaCI: 0.08-0.33).

CONCLUSION

These findings suggest an association between metacognition and shyness. Rumination mediated the relationship between metacognition and shyness, suggesting that rumination could be a cognitive strategy for shy people. Future research should explore the relationship between these constructs in more depth.

Key words: Social anxiety; Shyness; Rumination; Post-event; Metacognitive beliefs

Core tip: No previous studies have explored the relationship between metacognitive belief, rumination and shyness in a sample of adults. This research, based on the self-regulatory executive function model, explores the association between metacognitive beliefs, rumination and shyness. Results show a correlation between shyness, rumination and metacognition. Moreover, the relationship between metacognition and shyness was fully mediated by rumination. These findings have important implications for strengthening the social skills of shy individuals.

Palmieri S, Mansueto G, Scaini S, Fiore F, Sassaroli S, Ruggiero GM, Borlimi R, Carducci BJ. Role of rumination in the relationship between metacognition and shyness. *World J Psychiatr* 2018; 8(4): 108-113 Available from: URL: http://www.wjgnet.com/2220-3206/full/v8/i4/108.htm DOI: http://dx.doi.org/10.5498/wjp.v8.i4.108

INTRODUCTION

The self-regulatory executive function model (S-REF)[1] has been proposed by Well and Matthews to describe dysfunctional cognition in psychological distress. The S-REF model posits that psychological dysfunction may be maintained by a combination of attentional focusing on threat, rumination, worry, and dysfunctional behaviours, which constitute the Cognitive Attentional Syndrome (CAS)[2]. CAS is activated and maintained by metacognitive beliefs, which are defined as the information that an individual has about his/her own cognition and coping strategies, which ultimately impact CAS[2]. Metacognitive beliefs take two forms: Positive and negative. Positive metacognitive beliefs motivate the use of CAS. Negative metacognitive beliefs concern the significance, uncontrollability and danger of thoughts[3]. In the S-REF model, CAS is considered problematic because it causes negative thoughts and emotions to persist, leading to failed modifications of dysfunctional metacognitive beliefs and stably resolved self-discrepancies[4].

The importance of metacognitive beliefs can be explained with reference to generalized anxiety disorder[5]. In the presence of a trigger (*e.g.,* intrusive thoughts and/or external factors), positive metacognitive beliefs about the usefulness of worrying as a coping strategy toward a threat are activated and persist until the person achieves a desired internal feeling state. Positive beliefs are not sufficient to lead to generalized anxiety disorder, and the development of negative beliefs about worrying contributes to an intensification of anxiety symptoms[5].

Rumination is one component of CAS and it has been defined, in the context of social anxiety, as repetitive thoughts about subjective experiences during a recent social interaction, including self-appraisal and the external evaluations of partners and other details of the event[6].

Several studies have found a significant correlation between metacognitive beliefs and rumination in both clinical and non-clinical samples[7-9]. Metacognitive beliefs and rumination have been found to be positively-correlated with a wide range of psychological disorders[4,10-12], including social anxiety[13,14]. Patients with social anxiety focus their attention onto an "observer" image of themselves in social circumstances by engaging in ruminative activities after social encounters[5]. The post-event involves ruminations about what happened in the social situation, is focused on negative emotions and image of oneself, and leads to reinforced beliefs about one's poor social performance and negative self-perceptions[5].

In comparison with a non-clinical control group, patients with social anxiety reported higher levels of negative metacognitive beliefs regarding the uncontrollability and dangerousness of thoughts[15]. For those in clinical samples with beliefs about the need to control thoughts[16], positive and negative metacognitive beliefs were positively-associated with social anxiety symptoms[13]. Similarly, in non-clinical samples, a positive correlation was reported between positive metacognitive beliefs about post-event rumination, negative metacognitive beliefs and social anxiety[13].

Although it has been hypothesised that shyness could be qualitatively different from social anxiety[17], some evidence places shyness and social anxiety on a continuum or spectrum in which social anxiety is conceptualised as "extreme shyness"[6,17-19]. Such a conceptualisation also suggests that the two may share similar features at the somatic, behavioural and cognitive levels[17,20,21], even though shyness is not pathological[17]. More specifically, it might be assumed that shy and socially anxious subjects also share similar features in terms of metacognitive beliefs and ruminative processes. An evaluation of whether rumination and metacognitive beliefs are associated with shyness could enrich the literature on the possible aetiological factors of shyness. Although it might be

considered as a source of limited evidence to support this specific assumption, Vassilopoulos *et al*[22] suggested that during preadolescence, shyness might be correlated with post-event processing. However, no studies to date have explored the proposed a relationship between metacognitive belief, rumination and shyness in a sample of adults.

Based on the S-REF model[2], this study aims to explore the association between metacognitive beliefs, rumination and shyness in a non-clinical sample of adults. We hypothesised that higher levels of metacognitive belief and rumination would be associated with higher levels of shyness.

MATERIALS AND METHODS

Participants

One hundred and three healthy subjects were recruited from the general population on the basis of the following inclusion criteria: At least 18 years old and fluent in Italian. In terms of exclusion criteria, individuals with personality disorders were excluded on the basis of a diagnostic interview conducted by psychologists who assessed demographic data, past or current emotional disorders, or psychological and/or psychopharmacological treatments. All participants provided informed consent.

Instruments

Shyness was evaluated using the Revised Cheek and Buss Shyness Scale[23], a 14 item self-report scale. Each item is rated on a five-point Likert scale. Higher scores indicate greater levels of shyness. The Revised Cheek and Buss Shyness Scale possesses good psychometric properties[24,25]. The official Italian translation of this scale by Marcone and Nigro[24] was used.

Rumination was measured by the Ruminative Response Scale[26], a 22 item self-report scale assessing the propensity to ruminate in response to depression. Respondents are required to indicate the degree to which they engage in a ruminative thinking style when they feel depressed. Each item is rated on a four-point scale ranging from one (almost never) to four (always). Higher scores indicate higher levels of rumination. This scale possesses good psychometric properties[27]. The English version of this scale was back-translated into Italian by a native Italian speaker who was not familiar with the questionnaire.

Metacognition was assessed using the Meta-Cognitions Questionnaire 30[28], a 30 item self-report instrument assessing individual differences in metacognitive beliefs, judgments and monitoring tendencies. Higher scores indicate greater levels of maladaptive metacognitive beliefs. The Meta-Cognitions Questionnaire 30 possesses good psychometric properties[28,29].

Anxiety levels were measured using the State Trait Anxiety Inventory form Y[30] for assessing trait anxiety. This form is a 40 item self-report scale in which participants rate the extent to which they experience various manifestations of anxiety. This form possesses good psychometric properties[30].

Statistical analysis

In order to evaluate the association between shyness, rumination and metacognition, Pearson's correlation analyses were performed. Mediation models[31] were tested in order to evaluate the mediating role of rumination in the association between metacognition and shyness. In accordance with Baron and Kenny[31], a correlative analysis was used before evaluating the mediation effects to ensure that metacognition (independent variable Ⅳ), shyness (dependent variable DV) and rumination (mediator) correlated with each other. The mediation model was tested according to Baron and Kenny's criteria[31], which assume that a fully- or partially-mediating relationship occurs when the relationship between the Ⅳ and DV is non-significant or still significant, respectively, after controlling for the effect of the mediator. In this study, the mediation model was performed using the SPSS macros for bootstrapping[32] as provided by Preacher and Hayes[33]. The indirect effect was tested using a bootstrapping procedure[32,33]. Mediation analyses were controlled for sex and anxiety. Statistical analyses were performed using SPSS 21.

RESULTS

Kolmogorov-Smirnov tests indicated that the distribution of variables was normal. Sixty percent of the samples were female with an average age of 35.8 (SD ± 5.98) and a mean school education of 13.70 years (SD ± 3.66). Significant correlations were found between shyness, rumination and metacognition (Table 1). Rumination mediated the association between metacognition and shyness (Table 2 and Figure 1).

DISCUSSION

In this study, we examined the link between metacognition and shyness, as well as the mediation role of rumination. To our knowledge, no study has addressed this important issue, despite its obvious relevance and potential in reducing the negative effects of extreme shyness on human well-being. Rumination is known to be a crucial correlate of metacognition[2] and has recently been shown to be related to shyness and social anxiety[5,22]. Building on previous research, the core finding of the present study was the mediating role of rumination in explaining the relationship between metacognition and shyness. In this regard, rumination could be a helpful cognitive strategy for shy individuals.

The second important finding of this research was the significant association between metacognition and shyness. Such results are in accordance with previous studies on social anxiety[5], a similar construct to shyness. The results of this study seem to indicate that rumination as a mediator explains only a small

Table 1 Correlation analyses

	STAI-Y anxiety	RCBS-shyness	MCQ-metacognition	RRS-rumination
	r (p)	r (p)	r (p)	r (p)
STAI-Y anxiety	1			
RCBS-shyness	0.022 (0.82)	1		
MCQ-metacognition	0.19 (0.05)	0.223 (0.02)	1	
RRS-rumination	0.071 (0.47)	0.413 (< 0.001)	0.734 (< 0.001)	1

STAI-Y: State trait anxiety inventory form Y; RCBS: Revised cheek and buss shyness scale; RRS: Ruminative response scale; MCQ: Metacognitions questionnaire 30.

Table 2 Mediating effects of rumination in the relationship between metacognitive beliefs and shyness (controlled for sex and anxiety)

	B	SE	*P*	95% BCaCI	
Step 1					
Sex	2.32	2.43	0.34	-0.49	
Anxiety	0.09	0.12	0.46	-0.49	
Metacognition (IV)	0.11	0.05	0.02	0.01-0.21	
Shyness (DV)					
Step 2					
Sex	4.11	1.78	0.02	0.57-7.65	
Anxiety	0.12	0.09	0.19	-0.36	
Metacognition (IV)	0. 41	0.03	< 0.001	0.33-0.48	
Rumination (M)					
Step 3					
Sex	0.28	2.33	0.9	-9.28	
Anxiety	0.03	0.11	0.77	-0.46	
Metacognition (IV)	-0.08	0.06	0.23	-0.28	Total Effect: 0.11; BC: 0.01-0.22; *P*: 0.02
Rumination (M)	0.49	0.12	< 0.001	0.23-0.75	Direct Effect: 0-0.08; BC:-0.22-0.05; *P*: 0.23
Shyness (DV)					Indirect Effect: 0.20; CB: 0.08-0.33

IV: Independent variable; DV: Dependent variable; M: Mediator; 95% BCaCI: 95% bias-corrected and accelerated.

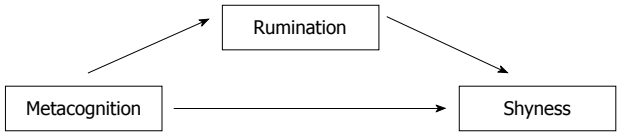

Figure 1 Mediating role of rumination in the association between metacognition and shyness (controlled for sex and anxiety).

percentage of variance in predicting shyness. Thus, future studies should investigate other possible factors that might also serve to mediate the relationship between metacognition and shyness, such as worry. In support of such reasoning, several studies have shown high levels of ruminative thinking about future difficulties and strategies by shy people in order to avoid anxiety-provoking situations (for a review, see Cowden[34]). In this negative circle, it seems that positive metacognitive processes induce the belief that worry could be useful to solve problems and help to prevent negative future events[35]. Thus, metacognition causes an increase in worry, and rumination becomes a problem. Worry could contribute to the development of negative perceptions of events that shy individuals avoid. Moreover, while shy individuals are worrying about the opinions of others and the impressions they make on others, such cognitive interference may result in them missing important information and cues from the environment, which could reduce their ability to execute the social skills needed to perform successfully during social situations.

It is also possible that metacognition directly influences shyness. Such data highlight the pressing need for a longitudinal investigation of these constructs to confirm the proposed relationship. The failure of shy individuals to respond appropriately in social situations is associated with the non-adaptive control of cognitive beliefs and type of metacognitive beliefs (*e.g.*, the tendency for shy individuals to make internal attributions in response to interpersonal failures)[36], rather than to the usual schema's content (*e.g.*, the more general self-serving attribution bias to make external attributions for personal failures)[37].

The present research constitutes a novel contribution to the literature, given that the association between metacognition, rumination and shyness has not previously been addressed. We have only just begun to unravel the mechanisms through which metacognition and shyness are linked, and more research is needed to explore the relationship between these constructs.

Limitations and implications of the research

Some limitations of the present work must be acknowledged. The first limitation is its cross-sectional design.

A longitudinal study would be a more appropriate design for investigating the causal relationship between metacognition, rumination, shyness and their association over time. Secondly, although ours could be considered a sizeable sample, a larger one would have allowed us to go beyond our current level of analysis to explore, for example, gender or age differences. A third, more technical limitation of this study has to do with shared-method variance, as a result of using (only) self-administered instruments for variables of interest. However, as these variables are internal and subjective processes, self-report measures seemed appropriate. Furthermore, our study focused on metacognitive beliefs and did not investigate cognitive errors[38], and therefore should be considered exploratory.

We believe that the different patterns of associations that emerged have important practical implications for shy individuals. Starting from the position that shyness is neither a disease nor a psychiatric disorder[39], these results could be relevant in helping individuals to understand the nature and dynamics of shyness by addressing its cognitive components[40,41]. Carducci[42] and Sirikantraporn *et al*[43] have previously noted the value of examining the cognitive-related self-selected strategies used by shy individuals to deal with their shyness as a means of helping them to more effectively understand and respond to their shyness. Furthermore, with respect to the implications based on the results of the present study, the metacognitive model[44] should be a potentially valuable framework for improving the social skills of shy subjects. Based on the metacognitive model[44], the evaluation of metacognitive beliefs and ruminative thinking could be considered in shy subjects, given that this model is mainly focused on the modification or reduction of these aspects[44].

ARTICLE HIGHLIGHTS

Research background

Metacognitive beliefs and rumination are correlated with social anxiety, which is located on a continuum of shyness. To our knowledge, no studies have explored the association between metacognitive beliefs, rumination and shyness in a non-clinical sample of adults.

Research motivation

To add to current knowledge about the association between metacognitive beliefs, rumination and shyness.

Research objectives

The main aim was to explore the association between metacognitive beliefs, rumination and shyness in a non-clinical sample of adults.

Research methods

This was an observational study, comprising a sample of 103 healthy subjects recruited from the general population.

Research results

Shyness, rumination and metacognition were significantly correlated ($P < 0.05$). The relationship between metacognition and shyness was fully mediated by rumination (Indirect effect: 0.20; 95% bias-corrected and accelerated: 0.08-0.33). These results build upon previous research.

Research conclusions

To our knowledge, no other study has investigated the link between metacognition and shyness, as well as the mediating role of rumination. The core findings of the study are: (1) The significant association between metacognition and shyness; and (2) the mediating role of rumination in explaining the relationship between metacognition and shyness. These results could have important implications for shy people. Although shyness is not a disease, the findings could be relevant in helping individuals understand the nature of their shyness by addressing its cognitive components.

Research perspectives

Our research appears to indicate that future studies should longitudinally investigate the causal relationship between metacognition, rumination and shyness. Moreover, future studies should explore other possible factors, in addition to rumination, that might explain the relationship between metacognition and shyness.

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EDITORIAL

Treatment alliance and adherence in bipolar disorder

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Abstract

The clinician patient relationship lies at the core of psychiatric practice and delivery of mental health care services. The concept of treatment alliance in psychiatry has its origins in psychotherapy, but has also been influenced by several other constructs such as patient-centred care (PCC) and shared decision-making (SDM). Similarly, there has been a shift in conceptualization of treatment-adherence in psychiatric disorders including bipolar disorder (BD) from illness-centred and clinician-centred approaches to patient-centred ones. Moreover, the traditional compliance based models are being replaced by those based on concordance between clinicians and patients. Newer theories of adherence in BD place considerable emphasis on patient related factors and the clinician patient alliance is considered to be one of the principal determinants of treatment-adherence in BD. Likewise, current notions of treatment alliance in BD also stress the importance of equal and collaborative relationships, sensitivity to patients' viewpoints, sharing of knowledge, and mutual responsibility and agreement regarding decisions related to treatment. Accumulated evidence from quantitative research, descriptive accounts, qualitative studies and trials of psychosocial interventions indicates that efficacious treatment alliances have a positive influence on adherence in BD. Then again, research on the alliance-adherence link in BD lags behind the existing literature on the subject in other medical and psychiatric conditions in terms of the size and quality of the evidence, the consistency of its findings and clarity about underlying processes mediating this link. Nevertheless, the elements of an effective alliance which could have a positive impact on adherence in BD are reasonably clear and include PCC, collaborative relationships, SDM, open communication, trust, support, and stability and continuity of the relationship. Therefore, clinicians involved in the care of BD would do well to follow these principles and improve their interpersonal and communication skills in order to build productive alliances with their patients. This could go a long way in confronting the ubiquitous problem of non-adherence in BD. The role of future research in firmly establishing the alliance-adherence connection and uncovering the processes underlying this association will also be vital in devising effective ways to manage non-adherence in BD.

Key words: Treatment; Alliance; Adherence; Bipolar disorder; Components; Mediators

Core tip: A collaborative treatment alliance is central to tackling the ubiquitous problem of non-adherence in bipolar disorder (BD). Studies examining the link between alliance and adherence in BD have shown that an effective alliance positively impacts adherence. However, the existing literature is relatively limited, often of variable quality, and has not been able to clearly delineate the mediators of the alliance-adherence connection. Nevertheless, the key elements of productive alliances in BD which could positively influence treatment-adherence are reasonably clear. They can be readily implemented in clinical practice to enhance adherence in BD, till future research further clarifies the alliance-adherence association.

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INTRODUCTION

The changing face of mental health care

With the introduction of the concepts of patient-centred care (PCC) and shared decision-making (SDM) since the 1990s the face of health-care delivery has undergone a remarkable transformation. The preceding years had seen many clinical, economic and social changes such as the growing numbers of elderly patients and those with chronic conditions, the increasing complexity and cost of treatments, together with repeated calls for greater patient autonomy and choice by consumer advocacy groups. The PCC and SDM approaches were driven by the need to reorient and redesign an increasingly fragmented system of health-care in order to face these challenges[1-4].

PCC and SDM

The concept of PCC began attracting increasing attention from the 1990s as a result of two landmark publications by the Picker Institute and the United States Institute of Medicine[5,6]. PCC began to be acknowledged as a central component of health-care when the Institute of Medicine included it as one on the six components of high quality care[6]. The principle attributes of PCC include responsiveness (sensitivity to patients' values and preferences), respect (according dignity to patients), autonomy (acknowledging patients' rights of informed choice), empowerment (enabling patient and family participation in care), collaboration (equal and supportive partnerships), holism (bio-psychosocial approach), individualization (personalized care), communication (information sharing), access, coordination and continuity of care[1-3,7,8]. SDM is derived from the PCC paradigm and is based on the same guiding principles of patient autonomy, informed choice and collaborative alliances between with clinicians[9-14]. Additionally, it is an evidence based and patient-centred process of decision-making consisting of information sharing, elicitation of patients' preferences, mutual deliberation and agreement on the treatment decisions between patients and clinicians[9,15,16]. The traditional, paternalistic model of clinician-centred care, which was in vogue prior to these approaches, had been criticized for vesting power in the clinician to make all treatment decisions, often overlooking patients' preferences. In contrast, both the PCC[3,7,8,17] and SDM approaches[9,12,15,18] propagated power sharing and mutual responsibility for the treatment undertaken. Thus, they shifted the locus of care from the clinician to the patient and reduced the disparity between them. These attributes made these new approaches more ethical, more acceptable to patients, and enhanced their potential to improve health-care outcomes[3,4,18-20]. Not surprisingly, the notion of collaborative treatment alliances has constituted one of the chief components of PCC[1,3,7,21,22] as well as SDM[12,23-26]. Moreover, these constructs have led to a broader understanding of the concepts of treatment-adherence and engagement with services[2,8,26-28]. The principles of autonomy, holism and humanistic care espoused by the PCC[29-31] and SDM[18,19,26,32,33] models had always been a part of mental health care. In fact, a second report of the Institute of Medicine was devoted exclusively to the application of principles of PCC to mental and substance use disorders[29,34]. Nevertheless, implementation of both PCC and SDM in mainstream psychiatric practice has been poor and there is limited research regarding their impact on mental health outcomes[18,26,32,33,35].

TREATMENT ALLIANCE IN PSYCHIATRIC PRACTICE

The concept of treatment alliance in psychiatry has its origins in psychoanalysis and psychotherapy[36-39]. However, rather than the transference based psychoanalytic concepts of therapeutic relationships, psychiatry has found it easier to adopt the pan-theoretical construct of working alliance proposed by Bordin[40], which focuses on a "here and now" approach to alliance. The central characteristic of working alliance which determines its beneficial effects is therapist and client collaboration. Within this collaborative framework working alliance is composed of three elements: An affective bond between the client and the therapist, mutually shared goals, and agreement on treatment tasks. However, even this concept is not easily extrapolated to routine psychiatric

practice because of several differences between psychotherapeutic and psychiatric settings[37,39,41-43]. These include a wider range of patients, professionals and settings; greater variability in treatment goals and interventions; and, differences in frequency and duration of contact in clinical practice. Patients with severe illnesses compromised awareness and increased risks of harm to self or others pose the greatest problems for establishing a working alliance. The necessity for use of coercive treatment measures in this group directly conflicts with the clinician's role as a therapist. Consequently, a number of other theoretical constructs have been utilized to establish the concept of alliance in psychiatry. Apart from the PCC and SDM models, these have included theories of health-behaviour, newer concepts of medication-taking such as concordance, and the use of recovery-orientated approaches to define the success of psychiatric treatment[41,44-46]. However, regardless of the conceptual framework it amply clear that collaborative partnerships, personal bonds and mutual agreement on tasks and goals between patients and clinicians lie at the heart of the treatment alliance in psychiatry. Moreover, these are the very same characteristics that determine the positive impact of effective alliances on several treatment outcomes including adherence to treatment. A systematic review by Thompson and McCabe[45] identified 10 studies, which had examined the association between treatment alliance and adherence. The majority of the studies had been conducted among patients with either depression or psychosis, while only three had included patients with bipolar disorder (BD). Eight of these 10 studies found a significant association between adherence and some component of the treatment alliance. A collaborative relationship, agreement on treatment tasks and stability of the alliance were the more salient determinants of adherence with treatment.

TREATMENT ALLIANCE AND ADHERENCE IN BD

The changing concepts of treatment-adherence

Newer approaches to medication-taking in chronic illnesses had also started to emerge around the 1990s. Much like PCC, a patient-centred view of treatment-adherence began to replace the earlier illness-centred orientations as it gradually became apparent that patients' views on medication-taking played a central role in determining adherence[47]. This change was driven by years of research on predictors of non-adherence, which revealed that demographic, clinical and treatment related determinants were not able to fully account for the extent of non-adherence. Simultaneously, the emergence of a number of health-behaviour models prompted a move away from biomedical to bio-psychosocial approaches to adherence[48]. This put the emphasis back on patients' perceptions, the clinician patient relationship, and on other influences in the patient's sociocultural environment. Eventually, traditional compliance-based approaches to medication-taking which were rooted in unequal and paternalistic clinician patient relationships, gave away to adherence and concordance based approaches[49]. The concepts of concordance, PCC and SDM are all based on the common principles of collaboration, responsiveness, open communication and mutual agreement on treatment between patients and clinicians[8,24,25,28]. It was therefore not surprising that psychiatry readily embraced these concepts in an effort to deal with the common and unrelenting problem of treatment non-adherence[50-53]. More pertinently, concordant and collaborative approaches to treatment have currently gained widespread recognition in the existing research on adherence in BD[44,54-57].

The association between treatment alliance and adherence in BD

Despite this recognition the evidence linking treatment alliance with adherence is still quite limited in BD, especially compared to other psychiatric and medical disorders. The table below summarizes this research.

The majority of studies included in the Table 1 have found a positive association between alliance and medication-adherence, while only five have failed to find such an association[58,59,67-69]. However, there was considerable variation in study designs. Measures of medication-adherence linked with alliance have varied from patient reports or clinician ratings, to persistence with treatment, dropout rates, missed medication days, and adherence with appointments or service engagement. Only about half of the studies have used validated scales of alliance; the rest have relied on self-designed questionnaires, treatment-attitude scales, or ratings of therapist interventions. Similar to studies of treatment alliance in other psychiatric disorders, the Working Alliance Inventory, based on Bordin's construct, was the most common scale used[45]. However, such overreliance on one instrument may have limited the scope of findings[37]. Though prospective studies are better indicators of the alliance-adherence link, three studies with longitudinal designs were unable to demonstrate an association between alliance and adherence on follow-up despite finding a positive association at baseline[69,72,76]. Finally, quite a few of the studies had small sample sizes and almost all included hospital attendees rather than community based patients, which meant that the results were not readily applicable to all patients with BD. Thus, the somewhat inevitable conclusion from these studies is that though there is definite evidence linking treatment alliance with adherence in BD, an unequivocal association between the two is still lacking.

Fortunately though, several other types of studies have endorsed the notion that effective treatment alliances have an important bearing on treatment-adherence in BD. Frank *et al*[78] provided their subjective impressions about "alliance building" among patients with mood disorders undergoing trials of acute and

Table 1 Treatment alliance and adherence in bipolar disorder

Ref.	Details of the studies	Findings
Connelly *et al*[58], 1982	48 outpatients on lithium; cross-sectional study; adherence by serum levels; alliance by self-designed questionnaire based on the HBM	Satisfaction with the clinician and perception of continuity of alliance was not associated with medication adherence. Perception of continuity linked to appointment adherence
Connelly *et al*[59], 1984	75 outpatients on lithium; cross-sectional study; adherence by serum levels and SCQ; alliance by self-designed questionnaire	Satisfaction with the clinician and perception of continuity of alliance was not associated with medication adherence. Perception of continuity linked to appointment adherence
Cochran and Gitlin[60], 1988	48 outpatients on lithium; cross-sectional study; adherence by self-report questionnaire; alliance as a part of an "Attitude Questionnaire"	Treatment alliance and positive attitudes to treatment explained about half of the variance in adherence. Alliance mediated the relationship between attitudes and adherence
Ludwig *et al*[61], 1990	118 outpatients and inpatients; 37 with BD; cross sectional study; adherence by physician judgment; alliance by two attitude scales: COSS and KK Skala	Adherence was associated with "reliance on the physician" using the COSS scale, but not with the KK Skala scale
Lee *et al*[62], 1992	50 Chinese outpatients on lithium; cross-sectional study; adherence by serum levels, case-notes review and patient reports; knowledge by self-designed questionnaire	A high rate of adherence was found despite inadequate knowledge about lithium. Authors concluded that an effective treatment alliance was of greater importance in ensuring adherence than imparting information
Taylor *et al*[63], 2001	30 trial patients on maintenance lithium treatment and psychotherapy; cross-sectional study; adherence by RBC lithium levels; alliance by TATIS scale to assess therapists' techniques	TATIS scores were significantly associated with RBC lithium levels. Medication adherence improved with increased focus on collaborative relationship building, positive treatment-attitudes, acceptance of BD and necessity for long-term treatment
Kleindienst and Greil[64], 2004	171 trial patients on lithium or cabamazepine; 2.5 yr follow-up; adherence indexed by time to dropout; alliance by the ICS scale	Trust in medications, trust in clinicians and absence of negative treatment expectations were associated with longer time to dropoutin those on lithium, but not carbamazepine.
Patel *et al*[65], 2005	32 African-American and Caucasian adolescent outpatients; cross-sectional study; adherence by patient reports and from records; alliance by subjective perceptions of medications and mental health contact helpfulness	Medication adherence in African-American adolescents was significantly correlated with ratings of drug usefulness and helpfulness of mental health contacts. Helpfulness of mental health contacts was not associated with adherence among Caucasian adolescents
Guandiano and Miller[66], 2006	61 trial patients on medications and family intervention; 28 mo follow-up; adherence indexed by number of months in treatment; alliance by WAI - P and C versions	Alliance was associated with number of months in treatment, dropout rate, percentage of time depressed and expectations from treatment
Sajatovic *et al*[67], 2006	184 trial inpatients; cross-sectional study; adherence by patient interviews; alliance by WAI - P and C	Alliance scores did not differ between adherent and non-adherent groups
Lecomte *et al*[68], 2008	118 patients from early intervention services; 13 with BD; cross-sectional study; adherence by the MAS scale; alliance by WAI-P	Alliance scores were not associated with medication adherence but predicted poor service engagement
Sajatovic *et al*[69], 2008	302 trial patients; 3 yr follow-up; adherence by patient interviews; alliance by WAI - P and C	Alliance scores did not differ between adherent and non-adherent groups
Zeber *et al*[70,71], 2008 and 2011	435 inpatients and outpatients; cross-sectional study; adherence by patient-report of missed medication days and MMAS; alliance by HCCQ	Overall alliance scores were associated with self-report of missed medication days and individual items of the HCCQ were linked to MMAS and missed medication days
Perron *et al*[72], 2009	429 inpatients and outpatients; 1 year follow-up; adherence by MMAS; alliance by HCCQ	Treatment alliance demonstrated a small but significant association with medication at baseline, but not at follow-up
Cely *et al*[73], 2011	124 outpatients; cross-sectional study; adherence by MMAS; alliance by self-designed questionnaire	A negative perception of the treatment alliance among patients was significantly more common in the non-adherent group compared to the adherent group
Sylvia *et al*[74], 2013	3037 outpatients from the STEP-BD study; 1 yr follow-up; adherence by a clinical monitoring form; alliance by HAQ	Patients' perceptions of the strength of the treatment alliance were associated with adherence Perceptions of collaboration, empathy and accessibility were the elements of the alliance linked to adherence
Kassis *et al*[75], 2014	628 inpatients and outpatients; 76 with BD; cross-sectional study; adherence by patient-report and from records; alliance by PDRQ	Patients in the adherent group were more satisfied with their psychiatrists, including availability and accessibility of psychiatrists and agreement with them on symptoms
Kutzelnigg *et al*[76], 2014	891 outpatients on olanzapine and mood-stabilizers; 2 yr follow-up for 657 patients; adherence by clinician judgments; alliance by self-designed scale	Patients in the highly adherent group had a better treatment alliance than those in the non-adherent group at baseline but not during the follow-up period
Novick *et al*[77], 2015	903 outpatients on olanzapine; 291 with BD; 1 yr follow-up; adherence by MARS; alliance by WAI-C	Alliance scores were associated with medication-adherence both at baseline and after 1 yr of follow-up

COSS: Compliance self-rating scale; HAQ: Helping alliance questionnaire; HBM: Health belief model; HCCQ: Health care climate questionnaire; ICS: Illness concept scale; KK Skala: Krankheits konzept skala; MARS: Medication adherence rating scale; MAS: Medication adherence scale; MMAS: Morisky medication adherence scale; PDRQ: Patient doctor relationship questionnaire; SCQ: Standardized compliance questionnaire; STEP-BD: Systematic treatment enhancement program for bipolar disorder; TATIS: Treatment adherence training interventions scale; WAI - P and C: Working alliance inventory - patient and clinician versions.

maintenance treatment. They noted that information-exchange, active patient participation and collaborative decision-making all promoted alliance and led to very high rates of medication-adherence and low dropout rates. Havens and Ghaemi[79] stated that a sound treatment alliance could have inherent mood stabilizing effects and could supplement the benefits obtained by medication treatment of BD. Scott and Tacchi[80] have shown that psychosocial interventions promoting concordant relationships have the ability to enhance medication-adherence in BD. Finally, findings from qualitative studies have found that a successful clinician patient relationship is one of the most important determinants of adherence in BD[81-84]. However, many participants of these studies seem to have found such healthy relationships hard to come by, and mostly reported unhelpful and frustrating interactions with mental health professionals[85-87].

COMPONENTS OF AN EFFECTIVE TREATMENT ALLIANCE IN BD

Since treatment alliance is a multi-dimensional concept, an understanding of specific aspects of the alliance that influence medication-taking may inform efforts to prevent non-adherence[45]. Studies of BD have revealed the following as the principal components of an effective alliance, which have a bearing on adherence.

PCC

First and foremost a successful alliance in BD is built on the principles of PCC[44,88,89]. Studies of BD have shown that patients favour a patient-centred approach and may be less likely to engage in treatment when faced with paternalistic and authoritarian approaches based on the traditional medical model[90-92]. Awareness and sensitivity to views of patients is also crucial to a patient-centred approach[74]. A large number of studies of BD have shown considerable differences between views of patients and clinicians regarding medication-taking[81,93-96]. It is obvious that this clinician patient divide can only be overcome if clinicians are aware of patients' views and preferences and respond to them appropriately[44].

Collaboration

A collaborative clinician patient relationship appears to be one of the principal facets of treatment alliance that fosters adherence in BD[44,57,97]. Sylvia *et al*[74] found that more than any other aspect of alliance, patients' perceptions of collaboration in their relationships with clinicians was associated with adherence in BD. In another qualitative study, patients with BD felt that interactive relationships with their clinicians, based on equal participation and sharing of responsibilities were more likely to result in adherence[82]. Similar results have been obtained by several other studies of BD[75,78,84,96,98]. The most compelling evidence however, comes from the growing evidence of the efficacy of psychosocial interventions in augmenting treatment-adherence in BD[99,100]. It has been proposed that the efficacy of psychosocial treatments largely stems from their collaborative and patient-focused elements[44,57,101].

SDM

Similar to PCC, SDM is not only one of key components of an efficacious treatment alliance in BD, but also the one most likely to influence adherence[56,88,102,103]. However, literature on SDM in BD is sparse. A recent systematic review found only 13 studies on the subject[89]. Nevertheless, these studies have shed light on several important aspects of SDM in BD. This review found that most treatment related decisions in BD involved those pertaining to adherence. The greater part of patients with BD preferred a SDM approach and wanted information about treatment choices, but many relied on their clinicians to take the final treatment related decisions. Certain demographic factors such as age, gender, educational level and ethnicity had some bearing on preferred involvement in SDM, though the findings were not always consistent. Similarly, it was not clear whether patients with BD sought greater involvement in decision-making than patients with other psychiatric disorders. Symptom severity, rather than diagnosis appeared to have a greater impact on patient involvement in SDM. However, regardless of the preferred level of involvement, almost all patients reported that SDM was not as commonly practiced in actual clinical settings as they had wanted. Though the implementation of SDM was low in routine care, collaborative decision-making was more likely if decisions were of complex nature and when patients initiated the process. Patients also wanted clinicians to pay attention to both interpersonal and affective elements of SDM. A sound alliance based on SDM was associated with a number of positive outcomes, mostly greater patient satisfaction, while the association with treatment-adherence was found in only two studies[74,104]. These findings were remarkably similar to what has been found among patients with medical illnesses[8,18,105,106], as well as those with other psychiatric disorders[23,25,33,107,108]. Moreover, a similar profile of patient preferences, patient and clinician involvement in SDM, and low implementation of SDM in clinical practice has been found in a number of other quantitative[109-112] and qualitative studies of BD[82-84,92,98], as well as surveys of patients with BD[96,113]. Another aspect that deserves mention is the use of decision-aids to further the process of SDM in BD. Decision-aids are tools based on updated evidence, which help patients compare different treatment options and provide them structured assistance through all steps of SDM[34,114]. Though decision-aids have been used for other psychiatric disorders[23,25,34,107], they have not yet been developed for BD[115]. A particular concern about the use

of SDM among patients with psychiatric disorders has been the problem of decisional incapacity. When acutely ill, patients might not have the capacity of making proper decisions; this may represent a significant barrier to application of SDM to psychiatric disorders. Advance directives have been proposed as a solution to this dilemma. They are documents completed by patients while still in possession of decisional capacity, regarding treatment decisions that could be made on their behalf in the event they lose the ability to make proper decisions when they are acutely ill. Some efforts have been made to implement advance directives among patients with schizophrenia[25,108], but research on such directives in BD is still at a very preliminary stage[116].

Communication

Constructive communication practices, referred to as collaborative or participatory styles of communication are based on the PCC and SDM approaches[8,45,117,118]. A participatory style of communication not only helps in building a strong alliance, but also has a positive effect on treatment-adherence by promoting positive attitudes to treatment among patients[44,45]. A meta-analysis among patients with various medical conditions found that communication practices of physicians were significantly associated with adherence and poor communication led to a 19% increase in non-adherence[119]. The review by Thompson and McCabe[45] found treatment-adherence to be associated with some or the other aspect of communication practices in eight of the 12 studies of patients with psychiatric disorders. Collaborative communication has a significant impact on adherence among patients with BD as well[44,97,120]. A two-way communication between the patients and clinicians allowing open discussions and free expression of patients' concerns appear to be the main constituents of a beneficial communication pattern in BD[78,89,98,121]. Exchange of information, particularly about medications is also accorded high priority by patients[83,96,98,113,122]. Other clinician attributes considered important by patients with BD include clinicians' ability to listen to, understand and value their views on medication-taking, along with flexibility regarding treatment options and devoting sufficient time to treatment related discussions[75,82,89,96,121].

Trust and support

Trust in the clinician is considered an important aspect of a successful alliance in BD[101,103]. Kleindienst and Greil[64] found that trust in the clinician was associated with lower dropout rates among patients on maintenance lithium treatment. Trusting and collaborative clinician-patient relationships can enhance adherence by fostering improved treatment-attitudes and aiding effective decision-making[75,82,84,86,123]. Both emotional and practical support are also essential components of a healthy alliance in BD. Strauss and Johnson[124] found that productive treatment alliances were associated with greater levels of social support among patients with BD. Similarly, the importance of a supportive relationship with the clinician in alliance building has formed a major theme in several qualitative studies of BD[83,98,125].

Stability and continuity

Continuity of care, ideally by a single treatment-team, frequent follow-ups and longer sessions with patients have all been emphasized as crucial elements of a alliance in BD[56,57,120]. Zeber *et al*[70] found that treatment-adherence was better when clinicians remained in constant contact with their patients and regularly monitored their patients' progress. Patient perceptions regarding continuity of care were found to be associated with attendance rates in other studies of BD[58,59]. Patients with BD also consider stability, consistency and continuity of treatment alliances as critical influences on their medication-taking behaviour[83,85,92,98].

Self-management

The recovery-orientated approach to care is currently being promoted as an key element of care in psychiatric disorders including BD. One aspect of recovery-orientated care is its emphasis on self-management or self-directed care[126]. Self-management strategies are adopted by many patients with BD and are also essential components of psychosocial treatments for BD[44,127]. Promoting self-management has thus been advocated as a necessary component of effective alliances in BD[88,89].

MEDIATORS OF THE ALLIANCE-ADHERENCE LINK IN BD

The positive association between treatment alliance and adherence in BD could be attributed to a number of intervening variables or mechanisms. An effective alliance results in less negative attitudes, a greater acceptance of illness, and the ability to tolerate medication side effects eventually leading to improved adherence[44,60,61,123,124]. Other potential mediators, which have demonstrated a positive association with treatment alliance in BD include reduction of symptom severity[66,72,77,124,128], enhancement of insight[77], and improvement in patient functioning or quality of life[72,77,129]. Certain psychosocial processes could also mediate the association between alliance and adherence. An efficacious treatment alliance has been linked with increased patient satisfaction[74,83,123,128,129], positive treatment expectancies[64,66], reduced stigma[124], improved self-efficacy[128], higher levels of perceived support[124,125], and some aspects of locus of control among patients with BD[130]. However, the association between all these variables and alliance in BD has often been inconsistent and largely correlational than causal. Therefore, there is still considerable uncertainty about the mechanisms underlying the beneficial effects of a successful alliance on adherence in BD.

IMPLICATIONS FOR RESEARCH AND PRACTICE

Despite the sizeable body of literature on treatment alliance and related concepts such as PCC and SDM, there is still considerable scepticism in the field of mental health regarding these approaches because of the lack of conceptual uniformity and clarity, uncertainty regarding their impact on salient patient outcomes such as treatment-adherence and barriers to their optimum implementation in routine psychiatric settings[15,44,89,108]. Doubts have also been raised about the cross-cultural validity of these concepts[89,131-133]. This is especially true for BD, where research lags behind other medical and psychiatric disorders in all these aspects. Nevertheless, several implications of the existing evidence are reasonably clear for clinicians as well as researchers. It has to be acknowledged that the locus of health-care has irrevocably shifted from the clinician to the patient. Therefore, professionals would do well to be aware of the essentials of alliance building and follow these principles in order to build productive alliances with their patients. Not only is this the right approach, but it is probably the most effective one while confronting the ubiquitous problem of non-adherence in BD. Priorities for further research are reaching a consensus on what constitutes an effective alliance in BD, establishing the connection between alliance and adherence more firmly, and working out the processes underlying this link. The success of such research endeavours will hold the key to developing successful alliances and effective treatments, both of which may reduce the burden of non-adherence in BD.

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REVIEW

Women who suffer from schizophrenia: Critical issues

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Abstract

Many brain diseases, including schizophrenia, affect men and women unequally - either more or less frequently, or at different times in the life cycle, or to varied degrees of severity. With updates from recent findings, this paper reviews the work of my research group over the last 40 years and underscores issues that remain critical to the optimal care of women with schizophrenia, issues that overlap with, but are not identical to, the cares and concerns of men with the same diagnosis. Clinicians need to be alert not only to the overarching needs of diagnostic groups, but also to the often unique needs of women and men.

Key words: Schizophrenia; Women; Gender differences; Unmet needs

Core tip: Schizophrenia and related disorders are expressed differently in men and women. Causative factors may differ, as can the expression, timing and severity of symptoms. Prevention, course of illness, and treatment response are all intimately linked to gender.

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INTRODUCTION

This review focuses on my experience dealing with clinical issues critical to women with schizophrenia. My work in this field began many years ago, and results are being continually updated as new information emerges. The paper is divided into the following main sections: Potential prevention strategies for women, the need for early and accurate diagnosis, the troubling complexities of the mental health system, effective treatment of schizophrenia and avoidance of adverse effects, the provision of access to vocational and avocational opportunities, attention to stigma, self-harm and suicide, the need for maintenance of physical, reproductive, and

emotional health. Many of these issues are not specific to schizophrenia, nor are they all specific to women. But, directly or indirectly, they all bear on the health and well being of women with schizophrenia.

In each of the sections listed above, I reference my own work plus recent key papers from the PubMed database. Most of these topic areas continue to be the focus of intense research, and many questions await resolution. The paper ends by broadly outlining future directions for the field.

POTENTIAL PREVENTION STRATEGIES

Schizophrenia is defined by its symptoms, which are thought to arise from the interaction of inherited or *de novo* genetic polymorphisms with exposure to environmental stressors at critical periods of a person's life. The details of specific gene mutations, the severity and identity of stressors, and critical chronology remain largely unknown. The strongest contributor to identifiable disease risk is a history of schizophrenia in close family members[1]. Knowledge of family history can now be combined with genetic risk scores from whole genome scans, which together, provide valuable information about a person's vulnerability to schizophrenia[2]. Nevertheless, when it comes to prevention, even in the era of Clustered Regularly Interspaced Short Palindromic Repeats (commonly known as CRISPR)[3], it is not possible to edit out the hundreds of genes that potentially contribute to schizophrenia in any one individual. Even if in the future all suspicious genes could be eliminated, profound ethical concerns make this form of prevention doubtful[4,5].

Some investigators believe that prevention strategies for men and women need to differ. The genetic predisposition to schizophrenia may, for instance, be sexually dimorphic[6-8], although evidence for this is sparse. On the other hand, because male and female DNA is so often exposed to somewhat dissimilar environmental inputs, it may well transpire that the turning off and on of genes in particular sets of cells - the domain of epigenetics - is relatively sex-specific. Therefore, developments in epigenetics may one day enable the prevention of sex-specific expression of schizophrenia-inducing genes[9,10]. However, for the time being, genetic counseling for women and men[11] and individual contraception counseling[12] are the best ways to try to prevent the transmission of schizophrenia at the gene level.

Women with schizophrenia planning to be mothers and wanting to prevent schizophrenia in their offspring can be counseled (although this is, of course, impractical) to choose relatively young - but not too young - mates with no family history of psychosis[13] and to strategically plan the conception in order to avoid giving birth during late winter or early spring[14]. There is no direct evidence that this will work to prevent schizophrenia in the next generation, but there is an association (which does not imply causation) between season of birth and schizophrenia in offspring. The potential connection has been attributed either to fetal and/or neonatal exposure to infectious/immune factors or to the lack of sunlight and low levels of vitamin D. Associated preventive measures include adequate nutrition during pregnancy, and Vitamin D and folic acid supplements[15]. Other suggestions for mothers with schizophrenia to boost the health of their infants are: limits on maternal weight gain during pregnancy, appropriate immunization, low doses of antipsychotic (AP) drugs during pregnancy and lactation, abstention from tobacco, alcohol and other substances[16-18], and rapid treatment of infection and inflammation[19-21]. Nutritional deficiency, stress, and toxic substances in pregnant women have long been recognized to increase the risk for schizophrenia in offspring[22-24]. Infection, inflammation and immune reactivity have more recently been considered serious contributors to schizophrenia susceptibility[21,25].

Obstetric complications pose a potential risk to the infant brain. They are more common in the birth history of those who go on to develop schizophrenia than in their psychiatrically well peers, but it is not known whether obstetric complications arise from prior fetal problems or whether they result from substandard obstetric care[26,27]. Regardless, women with schizophrenia require exemplary care during pregnancy, labor, and delivery. The quality of maternal care of young children is also critical, as early physical and psychological trauma have been associated (again, this is an association that may not be contributory) with the later development of schizophrenia[26,28,29]. Such trauma is theoretically preventable through parent support and parent training groups, family health education, and child welfare monitoring, but interventions such as these require intensive collaborative work at the level of whole communities.

Further theoretical possibilities for prevention (based entirely on studies of association) are keeping children in their country of birth, since migration is a risk factor for schizophrenia[30,31], residing in rural rather than urban parts of the country[32,33], keeping children and adolescents away from alcohol and drugs[34] and teaching them emotion-regulating strategies (reappraising, accepting, and refocusing[35]) to prevent adversities such as discrimination and social defeat from culminating in paranoid delusions[36].

Given that fewer women than men are reported to develop schizophrenia (2/1 male/female ratio in the under-20 age bracket, although the discrepancy tends to even out with increasing age)[37], that the "female" hormone estrogen is known to be neuroprotective[38,39], and that women are especially vulnerable to psychosis during the postpartum period when estrogen levels precipitously drop[40], my research group predicted in the 1990s that, among women with schizophrenia, girls with early menarche (early pubertal rise in estrogen levels) would show a later onset of schizophrenia than girls who enter puberty at older ages[41]. This is precisely what we found in our clinic population, and this finding has been replicated by some groups, but not by all[42-44].

If accurate, this observation could lead to weight gain strategies[45] that bring menarche forward. This would, of course, not prevent schizophrenia, but might delay its onset in vulnerable women.

Knowing that low estrogen periods are times of special risk for psychotic episodes is especially useful for secondary prevention (prevention of recurrent episodes of psychosis) in women diagnosed with schizophrenia. Relapse can be prevented by increasing the dose of AP medication at low estrogen times in the menstrual month[46,47], during the postpartum period[48], after menopause[49,50], whenever therapeutic estrogen is stopped[51,52], or during therapy with anti-estrogen drugs[53,54]. These theoretical examples suggest that effective prevention of schizophrenia may, in the future, be possible in a sex-specific manner[55,56], though this is not the case presently.

EARLY ACCURATE DIAGNOSIS

It is well-established that delay in seeking treatment once psychotic symptoms have emerged is associated with impaired treatment response and a relatively poor prognosis[57]. Our group found that, on retrospective interview, the first sign of behavioral disturbance eventually leading to a diagnosis of schizophrenia occurred at approximately the same age in women and men, but that the pre-psychotic prodrome was almost twice as long for women[58]. The duration of untreated psychosis did not differ between the two sexes, but the interval between first behavioral sign and first treatment did - the lag was six years for men and nine years for women[58]. The corollary to this finding is that factors other than early diagnosis must determine prognosis because women's outcome relative to men's, despite a longer untreated interval, is generally superior, at least over the reproductive years[59,60]. Potential factors that favor women, besides estrogen levels, are premorbid functioning generally superior to that of premorbid men, more friendships, closer family relations, greater academic success, and a relative absence of substance abuse[61-63].

As important as the speed of diagnosis is its accuracy. Diagnosis leads, at least in theory, to disease-specific treatment, although this is not always true in psychiatry where illness categories often overlap and the same treatments are used for different diagnostic entities. Nevertheless, it is my clinical experience that women's diagnoses frequently changes from depression to posttraumatic stress syndrome to eating disorder to schizophrenia to bipolar disorder (not necessarily in that order). This may be because it is more difficult to apply textbook schizophrenia criteria to women than to men. Women do not always exhibit the characteristic symptoms; they show few "negative" symptoms, few cognitive symptoms, and they rarely show flattened affect[64-66]. Prior to being diagnosed with a schizophrenia-related disorder, women with psychosis are often considered to be suffering from a mood disorder whereas, in men, a first tentative diagnosis is frequently alcohol or drug-induced psychosis[67]. Differential diagnoses sometimes missed in women include thyroid disease, autoimmune disorder, corticosteroid treatment, and anorexia-related starvation. All these conditions are much more prevalent in women than in men[68,69] and need to be ruled out before a diagnosis of schizophrenia is made.

COMPLEXITY OF THE MENTAL HEALTH SYSTEM

The mental health system in most countries is very complex and leaves individuals who experience mental distress not knowing whether to turn to physicians or social workers or psychologists or spiritual counselors. Family doctors may or may not recognize symptoms of early psychosis and, even when they do, may not know where to refer their patients. Waiting lists for the various mental health professionals are often long. Visits may or may not be covered by available insurance. Navigation services that help patients identify financial, linguistic, cultural, logistical and educational barriers to mental health care and provide guidance to access are badly needed by both women and men[70]. The routes to care differ in the two sexes, obstetricians and midwives sometimes serving as intermediaries for women, and guidance counselors and police more often paving care routes for men.

EFFECTIVE TREATMENT

Treatment is known to be most effective when it is individualized to meet the specific needs of the person being treated. Gender, age, family situation, place of residence, state of health, and personal preferences all play a part in determining optimal intervention. One example is the decision-making process around drug dosing. In women of reproductive age, effective drug doses can usually be lower than doses recommended for men[71-75]. Women's ability to respond at lower doses has been attributed to the effects of female hormones on the absorption and metabolism of AP drugs and also to women's relatively increased blood flow to the brain, carrying with it more drug to cell receptor targets[76]. The presence of estrogen at the dopamine receptor site helps to slow the transmission of dopamine[77], an excess of which is thought responsible for psychotic symptoms.

In addition, because AP drugs are lipophilic and women's reserves of adipose tissue are on average larger than men's, women store these drugs in their bodies for comparatively longer periods. This means that psychotic relapse after drug discontinuation is not as rapid in women[78-80]. It also means that, in theory, the intervals between women's intramuscular depot AP injections can be longer than those in men, but the sex-specific spacing of AP depot drugs has not yet been researched.

Another reason why AP drug doses can generally be

Table 1 Side effects of antipsychotics that negatively affect appearance[124]

Weight gain
Bad teeth
Hirsutism
Acne
Hair loss
Salivation
Slurred speech
Blepharospasm
Parkinsonian gait
Dyskinesias
Urinary incontinence

lower in women than in men is because many women take more concomitant drugs than men do, notably antidepressants, mood stabilizers, analgesics, and contraceptives or hormone replacements, all of which can interact with and influence the blood level of AP medication[78,81].

An important aspect of pharmacotherapy for women is that levels of female hormones change over the course of a monthly cycle and also over reproductive phases such as pregnancy, lactation, and menopause. This affects the dosage requirement of AP medication, *i.e.*, there will be a need for higher doses during low estrogen phases[47-50,82,83]. Adjunctive estrogen or selective estrogen receptor modulators can make treatment more effective and can reduce AP doses and, thus, help to prevent side effects. This applies to both sexes, but is especially applicable to women[84-90].

Besides pharmacotherapy, other aspects of schizophrenia treatment need to be differentiated according to the patient's gender, *e.g.*, substance abuse treatment, cancer screening (breast, prostate, cervix)[91-96], interventions for sexual dysfunction[97-99], contraceptive prescribing[12], treatment of comorbidities (osteoporosis and cardiovascular care for instance[100,101]), safeguards against domestic abuse and victimization[102-108], screening for proclivity to violence[109], provision of parenting support and child custody issues[110-112].

DRUG SIDE EFFECTS

Effective treatment means the removal of symptoms and improvement of function; ideally, it also means freedom from adverse side effects. Side effects cause distress, stop patients from regularly taking the medicines they need, and often cause serious harm to health, perhaps even contributing to the high mortality rate among individuals with schizophrenia[113]. Unfortunately, AP medications have many side effects[114] and on average, women suffer more negative effects than men[115,116]. Women may be more vulnerable than men to adverse drug reactions because the doses recommended when a drug goes on the market are calculated on the basis of a 70 kg man.

There are well-known gender differences in drug reactions. In a recent study of over a thousand patients with psychosis, twice as many women as men described their side effect burden as severe. In this study[117], the effects that women complained of (more than men) included: Concentration difficulties, sedation, blurred vision, nausea, constipation, dizziness on rising, heart palpitations, pruritus, photosensitivity, increased pigmentation, weight change, galactorrhoea and headache.

Women have unique risk factors for some adverse effects of APs, such as Torsade de Pointes[118], which is a form of ventricular tachycardia that occurs in patients whose QT interval is relatively long. The QT interval is a measure of the time between the start of the Q wave and the end of the T wave on the electrocardiogram; it is the time it takes for the heart to come back to normal after depolarization, which, on average, is longer in postpubertal women than it is in men. For this reason, two-thirds of Torsade de Pointes occur in women[118]. That being said, more men with schizophrenia than women die of heart disease. Much remains unknown about gender differences in cardiovascular function and cardiac response to therapeutic drugs.

The hypercoagulability state induced by APs raises the risk for venous thromboembolism, pulmonary embolism, and cerebrovascular accident. The use of oral contraceptives, as well as hormone replacement therapies, pregnancy, the immediate postpartum state, and obstetrical complications are all risk factors for these complications[119]. There are many such factors, however, including ethnicity[120]. Despite the many contributing factors, pregnant women on APs have been shown to be at significantly higher risk for venous thromboembolism than pregnant women in the general population[121,122].

With respect to the potential for AP to heighten the risk of breast cancer *via* weight gain and prolactinemia, the jury is still out[94] on this important concern. What is known, however, is that the cancer death rate of women with schizophrenia is high relative to women in the general population[95], although this cannot be attributed to AP drugs. Many side effects of APs, *e.g.*, weight gain, skin blemishes, and hair loss[123], negatively affect appearance (Table 1)[124]. Women are more sensitive to such effects than men are.

APs also have negative reproductive effects. They can disrupt menstrual cycles[125], interfere with a woman's ability to conceive[126], increase the risk for gestational diabetes[127], increase the risk of premature labor[127] and, by entering breast milk, can make breastfeeding a risk for infants of mothers with schizophrenia[128]. The secondary effect of hyperprolactinemia can lead to hirsutism, amenorrhea, galactorrhea, pseudocyesis[129], and osteoporosis[125].

In addition, older women may be more susceptible than older men to tardive dyskinesia (TD)[114]. It is known that TD prevalence is influenced not only by age and sex, but also by many confounding factors, such as individual genetics[130], the specific AP used, its dose, treatment duration, alcohol, tobacco, and marijuana usage, ethnicity, the precise definition of TD, the rating

scale used to assess TD, the predominant symptoms (positive or negative) and the presence or absence of prior brain damage. Because estrogen modulates dopamine-mediated behaviors and protects against oxidative stress-induced cell damage caused by long-term exposure to AP medication, one hypothesis is that when all the confounding factors are controlled, TD prevalence is equal in women and men prior to menopause and becomes subsequently higher in women[131].

Because of sex differences in immunity, women are also more susceptible to the agranulocytosis inducible by clozapine[132]. In general, older individuals, men as well as women, are at relatively increased risk of adverse effects of all drugs[133].

VOCATIONAL AND AVOCATIONAL OPPORTUNITIES

Women with schizophrenia want meaning in their lives, as do men. Meaning comes in several forms: hope in the future, the belief that one is needed, interest in what one is doing, earning money, engaging in artistic endeavors, pursuing a goal. In our study of clinic members with longstanding schizophrenia, more women than men were working outside the home[134], probably because "women's" jobs were more plentiful at the time in our region. Job availability always depends on time, place, and economic conditions. When homeless, or living in room and board homes or with parents, the housewife role is not readily available to women with schizophrenia. Many prefer self-employment opportunities[135] and appreciate assistance in the form of supported employment, individual placement, and job buddies. They welcome opportunities to learn, to volunteer and to be of help to others. Like men, women need creative channels to enable self-expression as they seek ways to be meaningfully occupied[136].

FREEDOM FROM STIGMA

Stigma (being devalued and discriminated against, with consequent loss of self-respect) is a significant problem in schizophrenia[137]. The diagnostic label of schizophrenia is itself frightening to many people, conjuring up fears of dangerousness, unprovoked and uncontrollable violence, irrationality, and incurability. The population at large does not always appreciate the fact that those who suffer from schizophrenia, and this is especially true for women, are more often victims than perpetrators of violence[138]. Different studies have used different definitions of both violence and of victimization, making these terms difficult to quantify across studies. Within a one-year period, it has been estimated that between 11% and 52% of persons with serious mental illness (SMI) exhibit violence at a 2-8 higher rate than that found in the general population[139]. The same study found rates of victimization in persons with SMI to be between 20% and 42%, 23 times that of the general population. Perpetration of violence and victimization are risk factors for each other and often overlap in the same person. Interestingly, Desmarais *et al*[139] reported higher rates of perpetration of violence among women with SMI than among men. They speculate that this is due to the fact that violence in this population most often occurs in the context of close relatives, and women with SMI are more likely than men to be living with family; consequently, they have more opportunity to vent their rage at domestic targets such as husbands and parents.

Women with schizophrenia are too often victims of sexual exploitation, domestic abuse, and random violence[106-108]. Risk factors are age, place of residence, and degree of psychopathology, in addition to personality and behavioral factors[140]. The factors that contribute to the perpetration of violence have been described by the same research team as substance abuse, young age, homelessness, unemployment, low educational attainment, low socioeconomic status, membership in an ethnic minority, past hospitalization for psychosis, past conviction for violent crime, personality factors, and residence in disorganized neighborhoods[140]. These are risk factors for both women and men, but they occur more frequently in men.

In general, schizophrenia is a heavily stigmatized illness, men perhaps suffering more than women because of the perception that they are prone to act out violently and indiscriminately. Women, however, suffer from a specific form of stigma - the frequent conviction of health workers that individuals with schizophrenia should not bear children, and, in the event of pregnancy, should seek abortion. Women with this illness are widely considered incapable of being good mothers, making prenatal care more problematic, as women fear disclosing that they are pregnant, afraid that their infants will be apprehended at birth[141,142]. Healthcare professionals may not be aware of their own discriminatory attitudes, often communicated inadvertently by words and gestures[143]. Finding effective ways of combating biased attitudes both in oneself and in others is a critical issue for all care providers treating patients with stigmatized illnesses.

RELIEF FROM THOUGHTS OF SELF-HARM AND SUICIDE

In the context of schizophrenia, triggers for male suicidal activity (ideation, attempts, and completed suicide) have been described as being: (1) psychotic symptoms and (2) the prospect of chronic disability, while triggers for suicidal activity in women have been mainly attributed to depression. Male suicides in this population decline with age, whereas this is not the case for women. In a longitudinal study, a 10.5% rate of suicide in the first two years after hospital discharge in men dropped to 0% twenty years later, while women's rate of suicide (6%) was spread more evenly over the twenty years[144].

Table 2 Existential concerns[179,180]

Meaning
Fear
Justice
Mortality
Identity
Relatedness
Freedom of choice

Suicide in women with schizophrenia is not as rare (relative to men) as it is in the general population[145]. The clinical implications are that both depression and substance abuse need to be vigorously treated in patients with schizophrenia because both contribute to impulsive acts of self-harm. In treatment settings, suicidal ideas are often "contagious"[146], with one completed suicide sometimes sparking a series of further self-harm attempts[147]. The index of suspicion needs to be high and suicidal ideation needs to be taken seriously[148].

PHYSICAL HEALTH

The life expectancy of individuals with schizophrenia is significantly shorter than that of the general population, with 90% of deaths attributable to physical illness. The assumption is that early mortality in schizophrenia is secondary, if not to suicide, then to lifestyle factors such as heavy smoking, alcohol abuse, and lack of physical activity[149-151]. More recently, a new understanding of the brain-gut connection[152] has implicated nutritional factors. In addition, there is the probability of shared susceptibility genes between schizophrenia and physical diseases that can decrease health-related quality of life and hasten death, auto-immune disease (*e.g.*, Crohn's disease, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes, and ulcerative colitis) being one such category of illness[153].

Social precipitants of early death are critical in this population: Poverty[154], homelessness[155], social isolation[156], poor hygiene[157], malnourishment[158], exposure to toxic substances[159] and adverse treatment effects[114]. High mortality from diabetes, cardiovascular disease and malignancies can, in part, be due to a relative lack of screening, delays in diagnosis, and suboptimal treatment[94,95,160-162]. Javatilleke *et al*[163] conclude their list of causes of lost life expectancy in severe mental illness by pointing out that the range of causes is very broad, with many putative causes varying according to gender.

REPRODUCTIVE HEALTH

Reproductive health includes sexual health (libido, sexual function, the ability to establish and maintain sexual relationships)[99,164,165], menstrual health[47,125,166], the preservation of fertility[167,168], contraception[12], prenatal care[122], pregnancy[18,169], postpartum care[170] and lactation support[171], parenting support and training groups, home visiting, peer support, respite care[111,112,172,173], and menopausal care[49,50,83,174].

Clinicians may not realize that during pregnancy, physiological changes such as delay in gastric emptying and increase in gastric pH prolong the time it takes for AP drugs to reach peak levels. Increased cardiac output steps up blood flow to the liver and may boost the speed of drug elimination. There is an overall increase in body water, which only affects hydrophilic drugs such as lithium, and there is also an increase in the lipid compartment, which provides extra storage space for lipophilic drugs (including APs). The blood flow to the kidneys is increased, as is the glomerular filtration rate, which means a greater degree of renal clearance. The plasma albumin concentration is reduced so that more free drug is available to the brain. Enzyme activity is affected by the increase in pregnancy hormones; some enzymes are affected more than others. For most APs, the net serum concentration in the third trimester is significantly decreased from what it was at the beginning of pregnancy. The exceptions are olanzapine and clozapine, both of which are inactivated by Cytochrome P450 enzyme 1A2, whose activity decreases during the 2nd and 3rd trimester of pregnancy because of rising estrogen levels. This enzyme is also highly inducible by smoking and, since women tend to reduce their cigarette smoking during pregnancy, the activity of this enzyme is further reduced. Therefore, the serum levels of olanzapine and clozapine rise during pregnancy[175-177].

FURTHER AREAS OF CONCERN

There are other areas of concern to women with schizophrenia. Some of these are the availability of crisis support[178], the achievement of nightmare-free restorative sleep[179-182], the safety of treatment settings[104,183], the safety and affordability of housing[184], access to skills training in new technologies[185] and assistance with existential concerns[186,187]. Whereas existential issues such as free will, personal identity, fears for the future, contemplation of mortality, justice concerns, finding meaning in life, and relating to others are all similar in men and women, as women age, they express more security fears, while aging men are more likely to report not being valued and fearing that they are a burden to others. Physical appearance may be more central to identity for women than for men[188] (Table 2).

FUTURE DIRECTIONS

Many of the issues that are critical to the care provision of women diagnosed with schizophrenia stem from a failure to recognize male/female differences in this illness. Sex differences are based in dimorphic brain structure and function, particularly evident in the dopaminergic system that is so crucial to the development of schizophrenia[189]. They are driven by sex hormones, but also depend, to an extent not yet fully understood, on non-gonadal functions of the X and

Y chromosomes because genes on sex chromosomes influence brain development disproportionally to their relatively small number. The number of sex chromosomes, X chromosome inactivation patterns, X-linked imprinting effects, and the indirect effects of sex chromosomes on the expression of autosomal genes all contribute to sex differences in neuropsychiatric disease[190].

Future research into sex differences in brain disorders such as schizophrenia will benefit from a fuller understanding of the causes of sex differences and their effects not only on brain and behavior but also on metabolic, cardiovascular, inflammatory and immune parameters. The field also needs to better understand the timing of the emergence of sex differences. Longitudinal studies that track developmental processes over time are needed. The effect of puberty with its influx of sex-specific hormones on brain maturation needs to be better understood. Biological sex differences need to be disentangled from environmental influences, an important issue for all psychiatric diseases. Sex differences in the brain, whether innate or secondary to exposure and learning, confer differential risk or resilience that fosters or inhibits the expression of specific symptoms, psychiatric diagnoses, and their outcomes.

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