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EDITORIAL

Neuropsychiatric genetics in developing countries: Current challenges

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Abstract

Neuropsychiatric disorders (NPDs) constitute a heavy burden on public health systems around the world and studies have demonstrated that the negative impact of NPDs is larger in Low and Middle Income Countries (LMICs). In recent decades, several studies have come to the understanding that genetic factors play a major role in the risk for a large number of NPDs. However, few neuropsychiatric genetics studies have been published from LMICs. In this Editorial, we discuss important issues impinging on advances in neuropsychiatric genetics research in LMICs. It is essential that scientists educate policymakers and officials of funding agencies on the importance of providing adequate funding for research in these areas. Development of local well-supported research programs focused on NPD genetics should be an important asset to develop; it would facilitate the establishment of sustainable research efforts that could lead to appropriate diagnosis and specific, affordable and feasible interventions in LMICs. It is important to point out that research into the biological basis of human NPDs is not only an academic effort reserved for a few elite institutions in economically developed countries, but it is vitally important for the mental health of people around the world.

Key words: Neurogenetics; Psychiatric genetics; Mental health; Neurosciences; Public health

Core tip: Neuropsychiatric Disorders (NPDs) constitute a heavy burden on public health systems around the world. Studies have demonstrated that the negative impact of NPDs is larger in Low and Middle Income Countries (LMICs). However, few neuropsychiatric genetics studies have been published from LMICs. In this Editorial, we discuss important issues impinging on advances in neuropsychiatric genetics research in LMICs. It is essential that scientists educate policymakers and officials of funding agencies on the importance of providing adequate funding for research in these areas. Development of local research programs focused on

NPD genetics should be an important asset to develop in LMICs.

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IMPORTANCE OF NEUROPSYCHIATRIC GENETICS IN DEVELOPING COUNTRIES

Neuropsychiatric Disorders (NPDs) constitute a heavy burden on public health systems around the world, as they represent around 30% of the disability-adjusted life-years associated to non-communicable diseases[1]. Considering the severity and chronicity of some of these disorders, such as major depression or substance abuse, the annual costs of NPDs can be estimated at several trillion dollars around the world[2,3]. Furthermore, studies have demonstrated that the negative impact of NPDs is substantially greater in Low and Middle Income Countries (LMICs), also called developing countries, given their particular demographic, cultural and economic conditions[1,4]. Until recently, the negative effect of some NPDs on LMICs was underestimated due to a historical emphasis on the study of infectious diseases.

In recent decades, the understanding that genetic factors play a major role in the risk for a large number of NPDs has increased[5]. Heritability ranges from 40% to 80% for several major NPDs and hundreds of studies have been published exploring genetic factors for NPDs, mainly in populations of European descent[5,6]. However, few neuropsychiatric genetics studies have been published from LMICs[7]. In this Editorial, we discuss important issues impinging on advances in neuropsychiatric genetics research in LMICs.

Why is basic genetic research necessary in LMICs? Why not extrapolate findings from existing studies from the rest of the world? Populations differ in their susceptibility to diseases while disease prevalence differs across populations. Replicability of genetic findings is notoriously difficult and replicability across populations is needed to identify "genuine" genetic associations[7]. Few examples of genetic studies of NPDs and related endophenotypes in LIMCs are found, in a global perspective; some led by local scientists and others led by researchers from developed countries[8-16].

Research in mental health is a challenging task in LMICs[17] due to lack of resources and trained personnel. The relative lack of local research infrastructure in many LMICs arises due to cultural and economic factors (poor funding sources, internal conflicts, general poverty or massive external debt) and political aspects (lack of vision about the importance of public funding of research and innovation, for example). There is also a scarcity of local human resources, which is more evident in neuropsychiatric genetics: in addition to the need for personnel with adequate formal clinical training and experience, there is an urgent need for scientific personnel with adequate research training and experience.

Research into biological basis of mental disorders is a relatively recent scientific effort, in comparison to other biomedical areas[18]. Lack of awareness about its importance is exacerbated in LMICs because of specific cultural and educational factors, especially stigma[19]. So, it is important that laboratory-based researchers educate health professionals, and the general public, on the relevance of basic biomedical research into NPDs and the underlying basic concepts[20]. Clinicians should understand that basic research is a crucial way to understand mechanisms of NPDs that could lead to discoveries for better treatments and diagnosis strategies in the future. Well-planned and organized collaborations between geneticists, psychiatrists, neurologists and psychologists are vital[21], to select those pathologies to be studied, based on criteria such as prevalence, severity and heredability. This is more important in LIMCs because the knowledge gained through genetic research may help health professionals provide better care, given the difficulty of patient access to advanced healthcare facilities. It is also essential that scientists educate policymakers, officials of funding agencies and advocacy groups, on the importance of providing adequate funding for research on these areas[20]. When results from research are available, policymakers should create the mechanisms to improve the identification of patients at genetic risk for suffering NPDs and establish the means for consultation and management once the symptoms appear.

It must be kept in mind that genetic epidemiology of NPDs is not equal in all regions of the world, so scientists should insist on having their own data. Development of local well-supported research programs focused on NPD genetics should be an important asset to develop; it would facilitate the establishment of sustainable research efforts that could lead to appropriate diagnosis and specific, affordable and feasible interventions in LMICs. Given that there is an international bias toward research into genetics of specific disorders[7], researchers from LIMCs should be able to study those NPDs of high importance in their regions[22]. In addition to the participation of scientists from LMICs in research networks led by institutions in developed countries, a consolidation of the collaborations between groups from different LMICs would lead to additional advantages[23], such as establishment of international research consortia that could lead to studies with larger samples sizes. Advances in genomics of NPDs will benefit the entire humanity rather than one or other population group.

Finally, we suggest that scientists in developed countries, especially those acting as peer reviewers of grant applications and journals, should try to understand the constant challenges that scientists in LIMCs face to carry

out their research. It is important to point out that research into the biological basis of human NPDs[1,18,24] is not only an academic effort reserved for a few elite institutions in economically developed countries, but it is vitally important for the mental health of people around the world.

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REVIEW

Pharmacological management of behavioral symptoms associated with dementia

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Abstract

Dementia is a clinical syndrome with features of neurocognitive decline. Subtypes of dementia include Alzheimer's, frontotemporal, Parkinson's, Lewy body disease, and vascular type. Dementia is associated with a variety of neuropsychiatric symptoms that may include agitation, psychosis, depression, and apathy. These symptoms can lead to dangerousness to self or others and are the main source for caregiver burnout. Treatment of these symptoms consists of nonpharmacological and pharmacological interventions. However, there are no Food and Drug Administration-approved medications for the treatment of behavioral and psychological symptoms of dementia. Pharmacological interventions are used off-label. This article reviews the current evidence supporting or negating the use of psychotropic medications along with safety concerns, monitoring, regulations, and recommendations.

Key words: Alzheimer's disease; Dementia; Pharmacological management; Psychotropics; Antipsychotics

Core tip: Dementia may present with neuropsychiatric symptoms that may require pharmacological interventions. Medications used for the behavioral symptoms associated with dementia are not Food and Drug Administration-approved and hence are being used off-label in the United States. The decision to start medications is based on a judicious consideration of risks and benefits. The choice of the agent should be guided by a thorough understanding of its pharmacologic properties and safety profiles, concomitant medications, and concurrent medical conditions. This article reviews the current evidence for psychotropic medications and presents recommendations with an algorithm for the treatment of neuropsychiatric symptoms associated with dementia.

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INTRODUCTION

Dementia is a clinical syndrome which includes a heterogeneous group of disorders that lead to cognitive decline in the absence of delirium[1]. Although the cognitive decline is a core feature of dementia, this may be associated with a variety of neuropsychiatric symptoms[1]. These symptoms are as follows: (1) affective and motivational symptoms; (2) perceptual disturbances; (3) delusions; (4) disturbances of basic drives; and (5) disinhibition and inappropriate behaviors[1]. A five-year study on the

prevalence of these symptoms by Steinberg shows that 97% experienced at least one symptom, with depression, apathy, or anxiety being the most frequent among these symptoms[2]. Although dementia is a heterogeneous group with subsyndromes including Alzheimer's, frontotemporal, Parkinson's, Lewy body disease, and vascular type, and involving distinct pathologies and symptoms, this article will focus on Alzheimer's disease (AD) and its pharmacological management. The pharmacological management does not differ significantly except that in Lewy body disease and Parkinson's disease, the use of antipsychotic medications can lead to worsening of the Parkinsonian symptoms. These medications are generally not advised in these conditions.

AD is a major cause of neurocognitive decline with gradual progression of cognitive and behavioral symptoms. Neuropsychiatric symptoms fluctuate throughout the course and may be distressing to the patient and caregiver[2]. This disease was first described in 1906 by Dr. Alzheimer[3], as a cluster of symptoms that included cognitive impairment and psychosis. Apathy was consistently rated highest in symptom severity[2]. Additionally, psychosis of AD, featuring symptoms of delusions and hallucinations, agitation, and aggression may be a distinct clinical entity with poor outcome[4]. Jeste *et al*[5] published the diagnostic criteria for psychosis of AD, which are: (1) delusions and/or hallucinations (auditory or visual) of 1 mo duration or longer and are severe enough to cause disruption in patients' and/or others' functioning; (2) criteria for dementia of Alzheimer type are met; (3) these symptoms have not been present continuously prior to the onset of symptoms of dementia; (4) criteria for schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features have never been met; and (5) symptoms do not occur exclusively during the course of delirium and are not better accounted for by another general medical condition or direct physiological effects of a substance.

This is a clinically-oriented review meant for the practicing clinician. We selected studies based on their relevance to the topic.

MANAGEMENT

Management of the behavioral and psychological symptoms of AD includes both nonpharmacological and pharmacological interventions (Figure 1). Without treatment, these symptoms can lead to a potential for harm to self or others. Depression and apathy can lead to poor self-care, and excitement and agitation may lead to altercations or injuries. Paranoia may lead to seclusive behavior and refusal of care.

Initial assessment includes a thorough history and physical examination to identify antecedents and any underlying medical conditions such as infections, neurological insults, or medication changes which can cause delirium. The target symptoms should be identified. The justification for treatment will depend upon whether the benefits outweigh the risks.

Although this article does not cover the nonpharmacological interventions, it is important to note that these interventions should be employed as first-line in the management of behavioral and psychological symptoms of AD. When these measures fail, pharmacological treatment may be considered.

PHARMACOLOGICAL INTERVENTIONS

Pharmacological interventions are necessary when nonpharmacological interventions are unsuccessful, symptoms are severe, or when patients present with symptoms that meet the criteria for psychosis of AD.

Antidepressants

A meta-analysis of antidepressants for treatment of agitation and psychosis in dementia showed reduction in symptoms compared with placebo, with two studies favoring sertraline and citalopram[6]. A comparative study of citalopram and risperidone did not show any statistical difference in the treatment of agitation or psychosis of dementia[7]. A more recent study of citalopram for agitation in dementia again showed significant improvement compared to placebo. However, this study also revealed that patients in the citalopram group had no significant improvement in activities of daily living or use of rescue medication lorazepam, and was associated with worsening of cognition and prolongation of QT interval[8]. Although these medications have been shown to be tolerated reasonably well, concerns include risk of bleeding and vasospasm due to the blockade of serotonin uptake in platelets and pulmonary endothelial metabolism of serotonin[9].

Trazodone has been useful in the management of agitation in dementia with partial success[6]. Two open label studies on buspirone for agitation and aggression in dementia suggested some benefit[10,11]. The first showed significant decrease in agitation scores at an average dose of 35 mg/d. The second involved 16 dementia patients with severe agitation and aggression and showed significant improvement for 6 patients. A pilot placebo-controlled study on trazodone and buspirone suggested benefits for trazodone but not buspirone in behaviorally disturbed AD patients[12]. In a 12-wk open label prospective study for efficacy of mirtazapine in 16 agitated patients with AD, Cakir *et al*[13] found significant reduction in the Cohen-Mansfield Agitation Inventory-Short form and Clinical Global Impression-Severity scales ($P < 0.001$) between pre- and post-treatment. There were no significant side effects or cognitive worsening. The authors suggested that mirtazapine may be an effective alternate for treatment of patients with AD and agitation. However, there are no controlled studies or other studies to support or negate mirtazapine use for this purpose[13-15].

Sedative-hypnotics

Benzodiazepines can be used for acute agitation. A

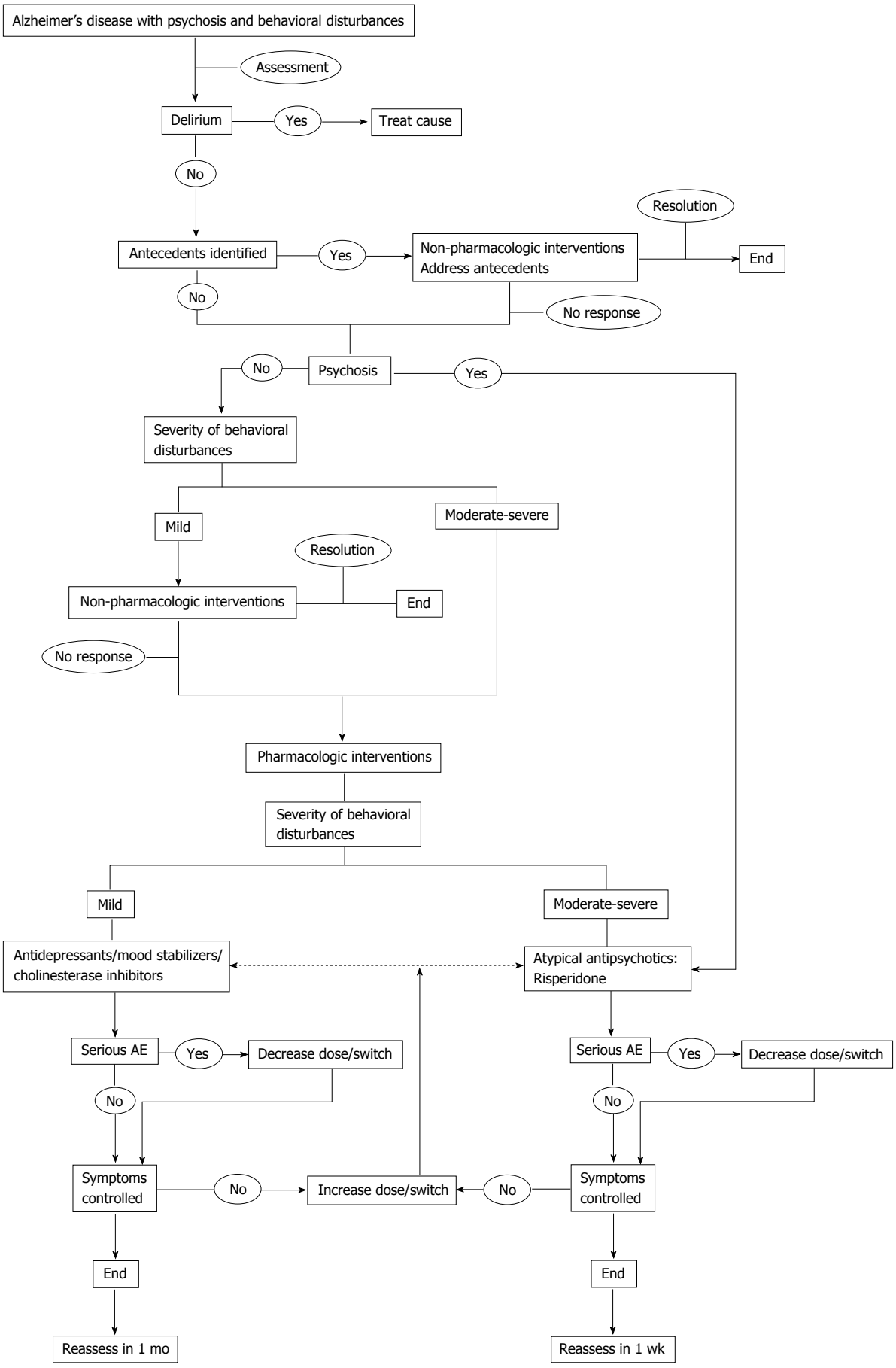

Figure 1 Algorithm for the treatment of behavioral and psychological symptoms of Alzheimer's disease[49]. Reproduced with minor changes, with permission from Psychiatric Times ©2014. AE: Adverse effect.

systematic review showed no significant differences between oxazepam, lorazepam, and alprazolam and other psychotropics including thioridazine, haloperidol, and olanzapine[16]. However, benzodiazepines are associated with sedation and increased risk for falls. Madhusoodanan *et al*[17] have addressed the safety concerns of benzodiazepine use in the elderly in a previous publication.

Cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists

Studies on cholinesterase inhibitors including donepezil, rivastigmine, and galantamine have shown modest improvements for behavioral symptoms. However, the patient population in these studies generally had low baseline Neuropsychiatric inventory (NPI) scores[18]. Memantine did not achieve significant improvement in agitation in a recent study among patients with moderate to severe AD. However, it improved the cognition compared to placebo[19].

Mood stabilizers

There are mixed results regarding the use of divalproex in the treatment of behavioral symptoms of dementia. An initial study showed efficacy in treating aggressive behaviors and agitation[20]. However, this was not replicated in a subsequent double-blind, placebo-controlled study[21]. A recent review confirms that it is ineffective in the treatment of agitation, and is associated with adverse effects, such as sedation, falls, infection, and gastrointestinal side effects[22].

A systematic review that included carbamazepine, valproate, gabapentin, lamotrigine, topiramate, and oxcarbazepine, showed that only carbamazepine had efficacy in behavioral and psychological symptoms in controlled trials. Carbamazepine, however, is associated with significant adverse effects including sedation, hyponatremia, and leukopenia. It is also a strong inducer of the enzyme CYP450 3A4[23].

Gabapentin showed improvement in several case reports and open studies and was well-tolerated. However, there are no controlled studies regarding the efficacy of gabapentin[23].

There is insufficient data regarding lamotrigine and oxcarbazepine use in dementia. Lamotrigine can cause Stevens-Johnson syndrome, and the risk of this side effect may be potentiated by combination with valproate. Topiramate may have adverse effects on cognition and is not recommended[23].

Antipsychotics

Conventional antipsychotics were widely used for managing the behavioral and psychological symptoms of dementia until the advent of second-generation antipsychotics.

Efficacy of conventional antipsychotics had been established by controlled studies[24]. Unfortunately, these are also associated with serious cardiovascular and anticholinergic adverse effects, extrapyramidal symptoms, and tardive dyskinesia. The occurrence of extrapyramidal symptoms may lead to decreased mobility, increased risk for infections, falls, the need for personal care, nursing home admission, and increased mortality risk[25,26]. Atypical antipsychotics are the most widely used class of psychotropic medications in the treatment of behavioral and psychological symptoms of dementia. The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer Disease study (CATIE-AD) showed benefits of risperidone and olanzapine on the NPI total score. However, there was high rate of discontinuation due to adverse effects[27]. Quetiapine was shown to have limited efficacy on symptoms which may have been related to the low doses prescribed. Overall, treatment in the CATIE-AD study did not result in improvement in functioning, care needs, or quality of life. Atypical antipsychotics were also associated with worsening of cognitive function compared to placebo[28]. A meta-analysis of atypical antipsychotics for aggression and psychosis in AD showed improvement in aggression with risperidone and olanzapine. Risperidone also improved psychosis. However, both risperidone and olanzapine had higher rates of serious cardiovascular events, and extrapyramidal symptoms[29].

Risperidone is the best studied of all the atypical antipsychotics used for behavioral and psychological symptoms of dementia and its efficacy has been established. It has minimal sedation, less weight gain, and fewer metabolic and anticholinergic effects compared with olanzapine and clozapine[30]. Adverse effects include dose-related extrapyramidal symptoms, hyperprolactinemia, osteoporosis, orthostatic hypotension and its attendant fall risk, and metabolic adverse effects. A long-acting injectable formulation is available. A study on relapse risk showed that discontinuation of risperidone among AD patients with psychosis or agitation was associated with increased risk of relapse[31].

Olanzapine was shown to decrease psychosis and behavioral symptoms but is associated with significant adverse effects which include sedation, weight gain, metabolic syndrome, orthostatic hypotension, extrapyramidal symptoms, and anticholinergic effects[29]. Olanzapine is also available in both short-acting and long-acting intramuscular formulations. The long-acting injectable preparation may be associated with post-injection delirium sedation syndrome; hence it is advised that the patient be monitored for 3 h post-administration[32].

A placebo-controlled study did not establish the efficacy of quetiapine at mean daily dose of 100 mg/d for psychotic symptoms, though it showed improvement in secondary measures of agitation[33]. A more recent placebo-controlled study suggests efficacy at 200 mg/d in the treatment of agitation; and the 100 mg/d group did not differentiate from placebo[34]. Another study comparing quetiapine to risperidone showed that low doses (mean doses quetiapine 77 ± 40 mg/d, risperidone 0.9 ± 0.3 mg/d) are equally effective[35]. Quetiapine has negligible extrapyramidal symptom risk, minimal anticholinergic effects, and fewer metabolic adverse effects[36]. The main concerns include sedation and orthostatic hypotension. Quetiapine is also available in

extended-release formulation. A study comparing the tolerability of immediate and extended release formulations for dementia patients with psychosis or agitation showed similar results for doses up to 300 mg/d[37].

Aripiprazole showed modest improvements in psychosis and agitation in placebo-controlled clinical trials[38]. It is generally well-tolerated with the most reported adverse event being mild somnolence. This was not associated with falls or accidental injury. No clinically significant electrocardiogram abnormalities or weight changes were seen[39]. It is available in both short-acting and long-acting intramuscular formulations. A placebo-controlled study of the short-acting formulation of 10 mg to 15 mg in divided doses in dementia patients suggests that it is efficacious for acute agitation[40]. There are no studies regarding the long-acting preparation in this connection.

There are no controlled trials of clozapine for patients with behavioral and psychological symptoms of AD. It has a lesser risk of extrapyramidal symptoms and tardive dyskinesia[36]. Adverse effects include serious agranulocytosis, decreased seizure threshold, myocarditis, metabolic effects, weight gain, and orthostatic hypotension.

The efficacy of the newer atypical antipsychotics including ziprasidone, paliperidone, asenapine, and lurasidone has not been established in controlled trials for patients with behavioral and psychological symptoms of AD. These medications have been used for mood and psychotic disorders in the elderly, and may be associated with more favorable metabolic profile. Adverse effects include extra pyramidal symptoms, akathisia, sedation, and prolongation of the QT interval. Further studies are needed to establish the efficacy of these drugs in the treatment of behavioral and psychological symptoms of AD.

DISCUSSION

AD with behavioral and psychological symptoms can be difficult to manage, often leading to caregiver burnout. A study on institutional placement of dementia patients shows that the predictive factors include caregiver's depression and patient's behavioral change[41]. The severity of symptoms in institutionalized patients is higher than those in the community, based on our clinical experience. Pharmacological interventions are frequently used in the institutional settings.

Management of behavioral and psychological symptoms of AD involves a complex interplay of factors that include severity of acute symptomatology, medical co-morbidities, concurrent medications, and even caregiver interactions. Further compounding this dilemma is the non-approval status of any medication by the Food and Drug Administration (FDA) for the treatment of these symptoms. Therefore, medications are used off-label, and each one carries its own risk and benefits. In the United Kingdom, Australia, and Canada, risperidone has been approved for psychosis and dementia by their administrative agencies for drug use[42-44].

In April 2005, an analysis of 17 placebo-controlled studies in dementia patients led to the FDA black box warning of increased mortality risk and cerebrovascular accidents in elderly patients treated with atypical antipsychotics for behavioral disturbances associated with dementia[45]. The analysis showed a mortality rate of 1.6 to 1.7 times that of placebo. The causes of death were varied. Use of these medications for dementia-related symptoms decreased especially in the nursing homes as the federal regulations require appropriate documentation, minimal effective dose, and attempts at gradual dose reduction. The residents should be free from unnecessary medications, excessive dosages, and duration. Further studies on antipsychotics and mortality have provided additional information. Some studies confirmed an increased mortality risk, and others did not (Table 1). Of note, additional studies have focused on specific factors that may be confounding variables for the mortality risk as detailed below.

Kales *et al*[46] in an outpatient study comparing the mortality risk of different psychotropics suggested that haloperidol had the highest risk in the first 30 d and quetiapine the lowest. Additionally, the highest mortality risk for risperidone, olanzapine, quetiapine, and valproate is in the first 120 d of use. Lopez *et al*[26] in a long-term study adjusted the covariates and found that neither the nursing home admission nor mortality were linked to the use of antipsychotic medications. However, the presence of the psychiatric symptoms-including psychosis and agitation, was associated with increased mortality and nursing home admission. A study by Gardette *et al*[47] suggests that dementia severity played an important role, and antipsychotic use was not an independent risk factor for mortality when cognitive status was included in the multivariate analyses. In a large prospective study, Arai *et al*[48] presented their initial findings which showed no statistical difference on mortality among patients receiving antipsychotics and not receiving antipsychotics. Studies which either support or negate the mortality risk of antipsychotics are included in the table (Table 1).

An algorithm based on the recommendations below has been included (Figure 1). The algorithm describes the critical elements in the diagnostic assessment of Alzheimer's disease with psychosis and behavioral disturbances, through various interventions, and facilitates understanding of the management of this condition.

As discussed, the decision to start a patient on medication for behavioral and psychological symptoms of AD is based on a judicious consideration of risks and benefits. Although, not a scope of this article, we must emphasize that nonpharmacological interventions must be attempted first, and medications be used only if these measures are unsuccessful or the symptoms are too severe. Potential benefits have to be weighed against the risk of serious adverse effects. Appropriate documentation of the potential danger to self or others helps in the decision to start psychotropic medications. Moreover, it is also important to discuss with the patients and/or family, when possible, about the risks, benefits,

Table 1 Comparison of studies supporting or negating the mortality risk of antipsychotic medications[49]

Ref.	Type	Population	Comment
Schneider *et al*[50]	Meta-analysis; *n* = 5110	Mixed	Analyses of survival and causes of death needed; MR increased
Suh *et al*[51]	Prospective 1-yr study; *n* = 273	NH patients	MR not increased
Raivio *et al*[52]	Prospective 2-yr study; *n* = 254	NH patients	Very frail patients; restraints increased risk of mortality; MR not increased
Ballard *et al*[53]	Randomized, placebo-controlled, 1-yr study; *n* = 165	NH patients	MR increased
Gardette *et al*[47]	Prospective cohort 3.5-yr study; *n* = 534	Outpatients	Medications not independent predictor for mortality when adjusted for dementia severity; MR increased
Gisev *et al*[54]	Population-based cohort 9-yr study; *n* = 332	Outpatients	Highest risk in patients with baseline respiratory disease; MR increased
Huybrechts *et al*[55]	Population-based cohort 180-d study; *n* = 75445	NH patients	MR increased
Kales *et al*[46]	Retrospective cohort 180-d study; *n* = 33604	Outpatients	Highest risk with haloperidol; MR increased
Langballe *et al*[56]	Retrospective cohort 6-yr study; *n* = 26940	Outpatients	Limited adjustment in analysis; diagnosis based on prescription of antidementia drugs; MR increased
Lopez *et al*[26]	Prospective cohort 22-yr study with 4.3-yr follow-up; *n* = 957	Outpatients	Psychiatric symptoms increases risk of mortality; MR not increased
Arai *et al*[48]	Prospective cohort 10-wk study; *n* = 6000	Mixed	Preliminary finding; MR not increased

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goals, and alternatives of treatment. It is useful to document this discussion along with any comments or apprehensions. Medications should be started at low doses and titrated slowly and carefully.

For mild to moderate symptoms in the absence of psychosis, we recommend a trial of antidepressants (citalopram or sertraline) or cholinesterase inhibitors (donepezil, rivastigmine, galantamine). Mirtazapine and gabapentin have lesser degree of evidence, with positive results based on open-label studies and case reports. Though carbamazepine has shown efficacy, it is not recommended as a first line treatment because of its tolerability profile. Valproate has conflicting data supporting its efficacy and comes with significant side effects, though it remains widely used.

For moderate to severe symptoms, or in the presence of psychosis, antipsychotics may be used. Atypical antipsychotics are preferred as the initial choice. Risperidone is the most studied option, studies also support the use of olanzapine, quetiapine, and aripiprazole.

The choice of the agent should be guided by a thorough understanding of its pharmacologic properties and safety profiles, concomitant medications, and concurrent medical conditions. Drug interactions should be carefully considered. Parameters should be monitored, including chemistry panel, lipid profile, glycosylated hemoglobin, body mass index and waist measurements, electrocardiogram, and therapeutic blood levels when appropriate. Patients may be followed within a week to a month of starting treatment in the nursing home setting, or more often as needed.

Behavioral and psychological symptoms of AD typically wax and wane and attempts to taper medications is recommended. However, in patients with severe symptoms who responded to antipsychotics, withdrawal of medications should be done with careful consideration as it may associated with the risk of relapse[31].

CONCLUSION

Behavioral and psychological symptoms are common in patients with AD. These symptoms can be difficult to manage. Thorough assessment is needed with careful consideration of the risks and benefits of medication treatment. Nonpharmacological intervention should be attempted first. Where symptoms are mild to moderate, antidepressants, cholinesterase inhibitors, and mood stabilizers may be used. For severe symptoms or with psychosis, atypical antipsychotics are preferred. Medications come with significant potential for adverse effects. Regular assessments for possible tapering and discontinuation are recommended. Further studies are needed for investigating better options in the pharmacological management of these symptoms and the safety concerns.

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REVIEW

Memantine: New prospective in bipolar disorder treatment

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Abstract

We review preclinical and clinical evidences strongly suggesting that memantine, an old drug currently approved for Alzheimer's dementia, is an effective treatment for acute mania and for the prevention of manic/hypomanic and depressive recurrences of manic-depressive illness. Lithium remains the first line for the treatment and prophylaxis of bipolar disorders, but currently available treatment alternatives for lithium resistant patients are of limited and/or questionable efficacy. Thus, research and development of more effective mood stabilizer drugs is a leading challenge for modern psychopharmacology. We have demonstrated that 21 d administration of imipramine causes a behavioural syndrome similar to a cycle of bipolar disorder, *i.e.*, a mania followed by a depression, in rats. Indeed, such treatment causes a behavioural supersensitivity to dopamine D2 receptor agonists associated with an increase sexual activity and aggressivity (mania). The dopamine receptor sensitization is followed, after imipramine discontinuation, by an opposite phenomenon (dopamine receptor desensitization) and an increased immobility time (depression) in the forced swimming test of depression. Memantine blocks the development of the supersensitivity and the ensuing desensitization associated with the depressive like behavior. On the basis of these observations we have suggested the use of memantine in the treatment of mania and in the prophylaxis of bipolar disorders. To test this hypothesis we performed several naturalistic studies that showed an acute antimanic effect and a long-lasting and progressive mood-stabilizing action (at least 3 years), without clinically relevant side effects. To confirm the observations of our naturalistic trials we are now performing a randomized controlled clinical trial. Finally we described the studies reporting the efficacy of memantine in manic-like symptoms occurring in psychiatric disorders other than bipolar. Limitations: A randomized controlled clinical trial is needed to confirm our naturalistic observations.

Conclusion: We believe that this review presents enough pharmacological and clinical information to consider the administration of memantine in the treatment of bipolar disorders that no respond to standard mood stabilizers.

Key words: Memantine; Bipolar disorder; Depression; Mood stabilizer; Manic symptoms

Core tip: Memantine, blocks the development of the supersensitivity of dopamine receptors caused by antidepressants and the ensuing desensitization associated with the depressive like behavior. On the basis of these observations we have suggested the use of memantine in the treatment of mania and in the prophylaxis of bipolar disorders. To test this hypothesis we performed several naturalistic studies that showed an acute antimanic effect and a long-lasting and progressive mood-stabilizing action (at least 3 years), without clinically relevant side effects. To confirm the observations of our naturalistic trials we are now performing a randomized controlled clinical trial. Finally we described the studies reporting the efficacy of memantine in manic-like symptoms occurring in psychiatric disorders other than bipolar.

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INTRODUCTION

Mood disorders are one of the leading causes of morbidity, disability and premature mortality[1] contributing for about 50% of the non-fatal burden of mental disorders[2]. Bipolar disorder (BD) has a lifetime prevalence of approximately 5%. Eighty-three percent of BD cases are classified as "seriously severe" and 17.1% as "moderately severe"[3].

Prophylaxis of manic-depressive illness aimed at preventing recurrences of the various phases is a leading clinical and research challenge for contemporary psychopharmacotherapy. With the exception of lithium, it has been difficult to find robust evidences for effective and long-term mood-stabilization in patients with bipolar disorder treated with currently approved mood-stabilizers such as lamotrigine, aripiprazole, olanzapine and quetiapine[4]. Most antipsychotic drugs and the anticonvulsants carbamazepine and valproate, are currently used for acute manic or mixed-states but lack regulatory approval for long-term prophylaxis. Antidepressants lack evidence of substantial long-term preventive effects[4-6].

All of these treatments, as well as others sometimes used on an empirical or "off-label" basis, appear to remain incompletely effective, alone or in combinations and patients with bipolar disorder remain unwell in approximately half of their time even with currently available treatments[4,7]. Moreover, approximately three-quarters of this unresolved morbidity is depressive, dysthymic, or dysphoric[4,7].

These considerations highlight the urgent need for more effective treatments that can provide long-term protective effects in patients with bipolar disorder, especially for depressive phases of the disorder that are closely associated with disability, substance abuse, and premature mortality.

MEMANTINE

Memantine is a NMDA receptor blocker in clinical use since 1982. Its pharmacological profile is well known and has been extensively described[8-16].

DOPAMINE AND THE NEUROBIOLOGY OF BIPOLAR DISORDER

In 1965 Schildkraut[17] proposed the first neurobiological hypothesis of depression, suggesting that depression could be due to a dysregulation of serotonin and noradrenaline function, but not dopamine.

The first observation suggestive of an involvement of dopamine in the mechanism of action of antidepressants and in the pathogenesis of mood disorders has been reported by Serra *et al*[18]. A great deal of pharmacological evidence and clinical observations, confirming the important role of dopamine in the therapeutic effect of antidepressants and in the pathogenesis of mood disorders, has been reported in the last decades[19-22].

Moreover, a large body of clinical evidences has been accumulated indicating that antidepressant treatments can induce episodes of mania/hypomania, not only in bipolar but also in unipolar patients[23,24]. In a recent meta-analytic review Tondo *et al*[25] reported a rate of antidepressant-induced switching of 12.5%.

Early reports of a possible link between this effect of antidepressants and the induction of a rapid cycling course of bipolar disorders were made by Kukopulos *et al*[26] and Wehr *et al*[27]. The term rapid-cycling bipolar disorder was coined by Dunner *et al*[28] in 1974 to identify lithium non-responders (further research has confirmed that rapid cycling is a factor of poor prognosis). Although some controversies exist[29], it is now accepted that antidepressants can induce mania/hypomania[25] and rapid-cycling bipolar disorder[30]. In keeping with these observations Ghaemi[30] suggests viewing antidepressants as "mood destabilizers". Since 1990 we and other groups re-evaluated the effect of chronic antidepressants on dopamine receptor sensitivity and observed that chronic antidepressant treatments sensitize dopamine D2 receptors selectively in the dopaminergic reward system, supporting the hypothesis that an increase activity of this system could underlying both the therapeutic effect and the ability to cause mania/hypomania of antidepressants[31-41].

Thus, the dopamine receptor sensitization induced by antidepressant should be considered a useful animal model of mania. In fact, it fulfils the McKinney *et al*[42] criteria to validate a human mental disorder animal model: it resembles the condition it models in its aetiology, biochemistry, symptomatology and treatment. The model is induced by the same treatment that can induce mania in humans, is associated with an increase dopaminergic transmission and, like other models of mania, with an increase protein kinase C (PKC) activity[43], which appear to be associated with mania. The animal behaviour showed an increase sexual activity[44,45] and aggressivity (unpublished results), manic symptoms that can be easy observed also in rats. Finally it is sensitive to treatments that seem to have an antimanic effect in humans.

ANTIDEPRESSANTS INDUCE A "BIPOLAR-LIKE" BEHAVIOR

According with clinical observations[46] D'Aquila *et al*[47,48] recently reported that the supersensitivity of dopamine receptors induced by antidepressants is followed, after 4 wk of imipramine discontinuation, by a reduced sensitivity of these receptors and a behavioural syndrome that mimics depression in humans.

Antidepressant induced manic episodes in humans[38,41,49,50] and dopamine receptor sensitization should be considered not a mere iatrogenic phenomenon but the intensification of a spontaneous underlying hypomanic process. In fact, the conversion from unipolar to bipolar course induced by antidepressants persists also after the discontinuation of antidepressant treatment, suggesting that these drugs anticipate a natural phenomenon.

FAILURE OF LITHIUM, CARBAMAZEPINE AND VALPROATE TO PREVENT DOPAMINE D2 RECEPTOR SENSITIZATION

As observed in numerous studies in humans for mania[25], we observed that currently used mood-stabilizers does not block the behavioural supersensitivity to quinpirole induced by antidepressants in rats[51-53].

THE ROLE OF NMDA GLUTAMATE RECEPTORS IN THE SENSITIZATION PHENOMENON AND ANIMAL MODELS OF MANIA

The stimulation of the NMDA glutamate receptor is required in the reverse tolerance (or sensitization) to psychostimulants that results in manic-like behaviors in animals and humans, particularly for amphetamine[54-59], methylphenidate[60], cocaine[61-64], apomorphine[65,66] and other dopamine mimetics[67,68], nicotine[69], morphine[70,71] and ethanol[72-74], and some kind of stress[58,75].

Incidentally, it is worthy to recall that the sensitization (also called reverse tolerance) to psychostimulants (amphetamine-cocaine) result in manic-like behaviors in animals and in manic-like syndromes in humans (indeed, the so called "amphetamine psychosis" considered for a long time as "paranoid schizophrenia", can be considered, according with the more recent nosography, a manic episode with psychotic symptoms).

ANTIDEPRESSANT-INDUCED DOPAMINE D2 RECEPTOR SENSITIZATION REQUIRES NMDA RECEPTOR STIMULATION

The effects of antidepressant treatments on dopamine receptors are antagonized by MK-801, a non competitive NMDA receptor blocker[76-78], suggesting that such phenomenon is mediated by NMDA receptor stimulation.

These findings led to hypothesize that the blockade of NMDA receptor could be effective in the treatment of mania and in the prevention of the recurrences of bipolar disorder[79].

MEMANTINE FOR BIPOLAR DISORDER: PHARMACOLOGICAL RATIONALE

Memantine prevents not only, like MK-801, the increased sensitivity to the selective Dopamine D2 receptor stimulants observed after 21 d of imipramine administration, but also the following desensitization and the associated depressive-like behavior[80]. A reduction of manic-like behaviour in animals has been observed also by Gao *et al*[81].

Moreover, Memantine, among the NMDA receptor blockers, posses the unique ability to prevent the excitotoxic effect of glutamate NMDA receptor stimulation without interfere with the normal synaptic activity. Indeed, by blocking the extracellular NMDA receptor without affecting those inside the synapse, memantine antagonizes the excitotoxic effect due to the excessive stimulation of the NMDA receptor, preserving the normal synaptic function. This effect results in a very potent neurotrophic action and makes memantine the most promising neurotrophic drug[82].

Thus, memantine may act as antimanic and mood-stabilizer by: (1) Preventing dopamine receptor sensitization (mania) and the ensuing desensitization (depression); and (2) Blocking extracellular NMDA receptors. The NMDA receptor blockage should not only suppress mania but also prevent the excitotoxic effect due to their excessive stimulation associated with mania[83] and, as a result, the cellular loss and/or atrophy, which seems to underlying the depressive phase of the disorder[84].

The prevention of neurodegeneration, the increased expression of neurotrophic factors and the promotion of adult neurogenesis are considered to play a key role in the clinical effect of lithium, the gold standard antimanic and mood-stabilizer drugs.

Interestingly, memantine and lithium share a number of pharmacological actions at different physiological levels, that today are considered important targets (such as neuroprotective/neurotrophic action[85,86], promotion of neurogenesis[86], increased brain-derived neurotrophic factor[87], Inhibition of PKC[88] and glycogen synthase kinase-3[89]) for the development of antimanic and mood-stabilizing drugs. A detailed description of the shared pharmacological effects of lithium and memantine is beyond the aim of this review.

On the basis of the latter observation it may be suggested that lithium and memantine might have a synergistic effect. Thus, we are planning a randomized, controlled clinical trial to confirm the efficacy, safety and tolerability of the combination of lithium and memantine in bipolar patients resistant to lithium prophylaxis.

Our hypothesis is in contrast with the prevalent idea that suggest the NMDA receptor antagonist as antidepressant[90], *i.e.*, having an acute antidepressant effect. However, we recently found that memantine failed to reduce immobility time in the forced swimming test after chronic treatment, and to sensitize dopamine receptors[80], as observed with virtually all antidepressant treatments.

On the other hand, clinical studies aimed at evaluate the possible acute antidepressant effect of memantine have provided contrasting/negative results[11,12].

MEMANTINE IN TREATMENT-RESISTANT BIPOLAR DISORDER: CLINICAL EVIDENCES

Growing evidences show that memantine might be effective at preventing recurrences of both phases of bipolar disorder and in reducing the manic-like symptomatology associated with several neurological and psychiatric conditions[11,12,91]. Memantine monotherapy was reported to show evidence of antimanic effects at well-tolerated daily doses (20-50 mg) in a three-week open-label trial in 33 acutely manic patients[92]. Our group found suggestive evidence of mood-stabilizing actions in 40 BD patients in two unblinded, 6 and 12-mo open label trials when memantine was added to stable, ongoing but inadequately effective treatments[93,94]. Memantine as a monotherapy also has been reported to show beneficial effects in a few individual patients with bipolar disorder, including after discontinuation of lithium treatment[95-98]. Another short-term study found memantine to be more effective than placebo when added to lamotrigine for four weeks to treat acute bipolar depression in a randomized, controlled trial, but this effect was no longer significant at 8 wk[99]. A recent 12-wk trial found little overall difference in effects of small doses of memantine (5 mg/d; $n = 62$) *vs* placebo added to valproate in bipolar II disorder patients for 12 wk[100]. Finally, we just reported the results of a three-year naturalistic study of adding memantine to 30 treatment-resistant bipolar patients[91]. In this study memantine showed a long-term and progressive ability to prevent depressive and mania/hypomania recurrences, in patients who had been resistant to standard treatments for more than 3 years. Memantine decreases the duration of illness, the duration of new episodes, recurrence frequency and symptomatology severity.

Finally, it has been recently reported that memantine improves cognitive dysfunctions and increases hippocampal volume in euthymic bipolar patients[101].

MEMANTINE IN "MANIC SYMPTOMS" IN PSYCHIATRIC SYNDROMES OTHER THAN BIPOLAR DISORDER: USE OF FORMAL PSYCHOLOGICAL ASSESSMENT

Mood symptoms, irritability, aggressiveness and abnormal manic-like behaviors are widely presented among juvenile and adult patients suffering from diverse neurological and psychiatric disorders[102]. These category of symptoms are often the main cause for disability, unresolved morbidity and stress for care-givers[102].

To review the clinical reports on the effect of memantine in manic symptoms in psychiatric syndromes other than bipolar disorder, we use a new methodological approach: Formal Psychological Assessment (FPA)[103-105]; From a theoretical-mathematical perspective, FPA jointly applies two theories from mathematical psychology: The Knowledge Spaces Theory (KST)[106-108] and in the Formal Concept Analysis (FCA)[109,110].

The FPA provides a strong methodological approach based on the construction of a Boolean matrix that relates the so-called objects and attributes. The objects, from a psychological point of view, may be or the items of one or more questionnaires, or a set of clinical disorders. The attributes, which describe them, generally correspond to the decomposition of the diagnostic criteria of a particular clinical disorder. All this can derive from both the diagnostic and statistical manual of mental disorders-5 (DSM-5) and/or representative theories and review of the literature about it.

The procedure that characterizes it consents to give a great help in overcoming the problems of the traditional assessment in various ways. First of all, allows relating the items of a questionnaire to the diagnostic criteria of the disorder it investigates, and then go to see the strengths and weaknesses of both questionnaires and diagnostic criteria of a specific disorder. A second important use of FPA is the construction of new tools for clinical evaluation in an adaptive and effective way. The formal details of FPA are beyond the aims of this paper and can be found in the cited papers about KST, FCA and especially FPA. Third, the FPA gives the possibility to compare all the symptoms of a specific disorder with other disorders, and it help both in differential diagnoses and in the selection of pharmacological therapies that are going to affect not only on the disorder in its entirety but

Table 1 The analysis of relations between the diagnostic criteria of Manic Episode and other specific disorders

Manic episode →	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14	A15	A16	A17	A18	A19	A20	A21	A22	A23	A24	A25
Other clinical disorders																									
D-1			x			x		x						x				x	x					x	x
D-2			x			x								x				x	x					x	
D-3								x				x										x	x		
D-4												x										x	x		
D-5								x				x	x									x	x	x	
D-6	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
D-7																							x		
D-8			x						x					x				x	x			x			
D-9			x						x					x				x	x						
D-10	x		x				x	x	x	x	x	x	x	x		x	x	x	x			x			
D-11			x																						
D-12			x						x					x											
D-13			x						x					x											
D-14			x						x					x				x	x						
D-15			x						x					x											
D-16													x												
D-17			x																						
D-18																								x	x
D-19			x						x					x				x	x		x				
D-20			x						x					x											
D-21			x																	x				x	x
D-22																				x					
D-23			x																	x					x
D-24			x																	x					x
D-25			x														x								
D-26						x			x									x	x						
D-27	x	x	x		x	x			x	x	x		x			x		x	x						
D-28			x											x											
D-29			x						x																
D-30						x												x	x						
D-31	x														x			x	x						
D-32									x									x	x						
D-33			x						x					x											x
D-34			x	x																x					x
D-35			x											x				x	x					x	x
D-36														x										x	
D-37														x								x			
D-38														x											
D-39																									x
D-40								x														x			
D-41			x	x																x				x	x
D-42			x																		x	x		x	x
D-43																	x				x				
D-44			x				x	x																	

D-6: It can have all the symptoms of Manic Episode; D-11: It can have many symptoms manic episode and dysthymia.

may act in some symptoms positively changing the course of certain illness; the latter case is what we used in this paper, but there are other papers that demonstrate the validity of this methodological approach in the other two fields described above. For the purposes of this paper, each clinical disorder is a defined object. Each object can be described on the basis of a given theoretical framework. The elements characterizing the objects are named attributes. Attributes are the decomposition of the diagnostic criteria of Manic Episode from DSM-5 and review of the literature about Mania. Each selected disorder may investigate one or more attributes and each attribute can characterize one or more clinical disorders. The "Clinical Context" is the result that we can get from the analysis of relations between the diagnostic criteria of Manic Episode and other specific disorders visible in the formal representation of the matrix (Table 1). The attributes of Manic Episode are placed in the columns of the matrix and all other clinical disorders (in this case are objects) in rows. In this way we can see the similarities and make logical inferences.

Summarizing, this part of the paper is aimed at identifying all clinical disorders that contain Manic Episode symptoms using a well-organized approach. This procedure has a great clinical relevance because it allows us making important associations that can then pour in the therapeutic treatment that psychiatrists play in order to improve the condition of people suffering from certain clinical disorders.

Table 2 contains all the attributes of manic episode. These attributes are derived from the decomposition of the diagnostic criteria for manic episode DSM-5 and a review of the literature on the Mania. Table 3 lists all of the disorders described in the DSM-5, which contain one or more manic symptoms. Table 1, which is also the most explanatory, relates the attributes of the Manic Episode with various clinical disorders with manic symptoms and specific to each disorder in Table 3 which attributes contain of Table 2. Tables 1, 2 and 3 show the results of the matrix summarizing juvenile and adult psychiatric disorders presenting manic symptoms among their diagnostic criteria.

Accordingly, a systematic review of the literature was performed aiming at identifying the effect of memantine in reducing isolated or clustered manic symptoms.

There is large consensus reporting that memantine is highly effective, compared to placebo, in treating and preventing behavioral symptoms of agitation, aggression, delusions and irritability in moderate to severe Alzheimer's Disease[111-113]. Larsson *et al*[114] reported that patients with dementia treated with memantine were less physically active during sleep than patients treated with placebo. Also a large two-year follow-up French study reported a temporal relationship between the onset of memantine treatment and the stabilization of psychotropic drug use in elderly patients[115].

Memantine improves compulsive buying[116] and attenuates kleptomania symptomatology[117].

The combination of memantine and risperidone in the treatment of children with autistic disorders reduces the associated manic-like symptomatology[118].

Recent reports found memantine might be effective in reducing symptoms of juvenile and adult attention-deficit/hyperactivity disorder (ADHD). On the basis of the results of an open-label 8-wk trial with memantine in 6-12 years old outpatients with ADHD combined type, it has been suggested the use of memantine in children with ADHD[119]. Memantine was also associated with a statistically significant improvement in the global symptomatology, inattentive and hyperactive symptoms as measured with the Adult ADHD Investigator Symptom Report in a sample of adult ADHD patients. A total of 44% of subjects showed Clinical Global Impression ratings of much or very much improved[120,121].

Moreover, memantine was reported to be clinically relevant in reducing anxiety symptoms and improving sleep quality when used to treat anxiety disorders[122].

Finally, memantine have been shown to be effective in a number of catatonia cases resistant to lorazepam and/or electroconvulsive therapy[123-130].

CONCLUSION

We have reviewed the preclinical and preliminary clinical evidence strongly suggesting that memantine, a safe and well tolerated drug, may be considered a new option for the treatment and long-term prophylaxis of bipolar patients, who failed to respond to standard treatments.

Moreover, we have underscored that memantine seems to be efficacy also in manic symptoms occurring in psychiatric disorders other than in manic episode of bipolar disorder.

In order to confirm our naturalistic clinical observation, we are now starting a randomized controlled, multicenter, clinical trial comparing mood stabilizing effect of memantine *vs* lamotrigine as adjunctive agents in Bipolar Type I patients who have been resistant to lithium and other current standard treatments.

Table 2 Attributes of manic episode derived from the decomposition of the diagnostic criteria for manic episode DSM-5 and a review of the literature on the manic symptomatology

Attribute	Explanation
A1	Elevated mood
A2	Expansive mood
A3	Irritable mood and Aggressiveness
A4	Increased goal-directed activity
A5	Increased energy
A6	Hyperactivity
A7	Inflated self-esteem
A8	Grandiosity and bizarre ideas
A9	Decreased need for sleep or sleep disturbance
A10	More talkative than usual
A11	Pressure to keep talking
A12	Flight of ideas
A13	Subjective experience that thoughts are racing
A14	Distractibility
A15	Increased sociability
A16	Increased work or school activity
A17	Increased sexual activity or inappropriate sexually
A18	Psychic agitation
A19	Motor agitation
A20	Excessive involvement in activities with high potential for painful consequences
A21	Theatrically and exaggerated expression of emotion
A22	Psychotic features
A23	Catatonia
A24	Disinhibited behavior
A25	Impulsivity

Table 3 Clinical disorders with manic symptoms

Disorders	Abbreviation
Attention-deficit/hyperactivity disorder	D-1
Autism spectrum disorder	D-2
Brief psychotic disorder	D-3
Schizophreniform disorder	D-4
Schizophrenia	D-5
Schizoaffective disorder	D-6
Catatonia	D-7
Major depressive episode	D-8
Cyclothymic disorder	D-9
Depressive episode, with mixed features	D-10
Disruptive mood dysregulation disorder	D-11
Persistent depressive disorder (dysthymia)	D-12
Premenstrual dysphoric disorder	D-13
Recurrent brief depression	D-14
Generalized anxiety disorder	D-15
Obsessive-compulsive disorder	D-16
Reactive attachment disorder	D-17
Disinhibited social engagement disorder	D-18
Posttraumatic stress disorder	D-19
Acute stress disorder	D-20
Conduct disorder	D-21
Pyromania and kleptomania	D-22
Oppositional defiant disorder	D-23
Intermittent explosive disorder	D-24
Alcohol intoxication	D-25
Alcohol withdrawal	D-26
Caffeine intoxication	D-27
Caffeine withdrawal	D-28
Cannabis withdrawal	D-29
Sedative, hypnotic, or anxiolytic withdrawal	D-30
Stimulant intoxication	D-31
Stimulant withdrawal	D-32
Tobacco withdrawal	D-33
Gambling disorder	D-34
Alzheimer disorder	D-35
Fronto-temporal neurocognitive disorder	D-36
Lewy bodies disorder	D-37
Vascular neurocognitive disorder	D-38
General personality disorder	D-39
Schizotypal personality disorder	D-40
Antisocial personality disorder	D-41
Borderline personality disorder	D-42
Histrionic personality disorder	D-43
Narcissistic personality disorder	D-44
Paraphilic disorders	D-45

Diagnostic and statistical manual of mental disorder-5 containing one or more manic symptom.

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REVIEW

Development of alexithymic personality features

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Abstract

The purpose of this paper is to review the current literature regarding the development of alexithymic personality features. Modern brain imaging technologies provide interesting data on the associations of alexithymia with different aberrations in brain function related to emotion regulation; however, the development of these deviations is poorly understood. A notable amount of research covers the relation of alexithymia to different environmental factors. Many of these associations, for example, with low socio-economic status and general psychopathology in childhood, are well established. However, the retrospective and cross-sectional designs commonly used in these studies, as well as the use of self-report measures, hinder the ability to firmly establish causality. Certain individual developmental factors, such as lagging speech development and congenital cardiac malformations in childhood, have been associated with the development of alexithymia. Regarding the stability of alexithymia, a systematic review of the literature was conducted for this paper. In addition to being characterized as a personality feature in the general population, alexithymia also clearly has a state-like dimension that results in increases and decreases in alexithymic features in conjunction with mental disorder symptoms. An essential question is whether the alexithymic features in adulthood are, in fact, infantile features of a restricted ability to identify and describe emotions that simply persist in individuals through adolescence to adulthood. To firmly establish the roots of alexithymia development, longitudinal studies, particularly in younger populations, are needed. Furthermore, multifaceted study settings are encouraged.

Key words: Alexithymia; Development; Emotion; Personality; Stability

Core tip: This review summarizes the current literature regarding the development of alexithymic personality features. The subject is covered from several perspectives: neurobiological, environmental, developmental, and the stability of the core alexithymic features. Regarding the stability of alexithymia, the paper includes a systematic review of the literature. On this basis, both essential issues regarding the development of alexithymia and directions for future studies are raised.

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INTRODUCTION

The concept of alexithymia was introduced 40 years ago and signifies a personality construct representing difficulties in identifying and expressing feelings, a scarce imagination, and an externally oriented way of thinking[1]. Although first observed in psychosomatic patients, a major factor that contributes to the keen interest in alexithymia is its association with both mental and somatic illnesses. Alexithymia has repeatedly been shown to be related to mental disorders, such as depression[2], anxiety disorders[3], eating disorders[4], and substance misuse[5]. It has also been related to somatic illnesses, including essential hypertension[6], diabetes mellitus[7], and psoriasis[8]. Alexithymic features are not limited to different patient populations; in contrast, alexithymia has been shown to be a relatively common personality characteristic in the general population. In studies conducted in the general population, the prevalence of clinically significant alexithymia in adults has been approximately 10%, and it is somewhat more common in males[9-11].

Although the introduction of the concept dates back four decades, prospective studies have been scarce. This scarcity is partly explained by the lack of reliable methods for measuring alexithymia. The current gold standard in the measurement of alexithymia is the 20-item Toronto Alexithymia Scale (TAS-20)[12,13]. This scale consists of three subscales that measure the different dimensions of alexithymia: Difficulty Identifying Feelings (DIF), Difficulty Describing Feelings (DDF) and Externally Oriented Thinking (EOT). The scale has been criticized for its lack of a limited imagination dimension and the lack of reliability of the EOT subscale; however, the wide use of the instrument supports its application. Because of these limitations, other instruments have also been developed; the most notable self-report measure is the Bermond-Vorst Alexithymia Questionnaire (BVAQ)[14]. This instrument aims to form a more complete picture of the individual's alexithymic features, for example, regarding the emotional component of alexithymia lacked by the TAS-20. The BVAQ is a psychometrically reliable and valid instrument, that correlates reasonably well with the TAS-20 scale[15].

Measures based on self-observation have obvious limitations. Because the labeling and describing of emotions is difficult for individuals with ample alexithymic features, it has been questioned if these individuals are able to correctly assess themselves using self-reporting instruments[16]. Furthermore, the divergent validity of the scales is easily limited. For example, alexithymic features and depressive symptoms appear to be intertwined at least to some extent[17]. As a result of these limitations, interview-based methods of assessment have also been developed, such as the Observer Alexithymia Scale[18] and the Toronto Structured Interview for Alexithymia (TSIA)[19]. The TSIA is a semi-structured interview method; it appears to correlate well with the TAS-20 scale[19], and it is a psychometrically sound instrument[20]. However, compared with self-assessment methods, interviews are time consuming, which limits the use of this type of instrument.

The development of feasible measures has provided the opportunity for quantitative research and thus, a marked increase in alexithymia studies. However, similar to all personality characteristics, alexithymia is clearly a dimensional (not categorical) concept. A common finding in clinical settings is that individuals reaching equal TAS-20 scale scores are far from homogenous. Thus, it has been suggested that different subtypes of alexithymia exist. Based on the TAS-20 scores, four subtypes of alexithymia have been suggested: general-high alexithymia, which is characterized by high scores on all three dimensions, introvert-high alexithymia, which is characterized by high DIF and DDF scores and low EOT scores, extrovert-high alexithymia, which is characterized by high EOT scores and normal DIF and DDF scores, and non-alexithymia, which is characterized by low scores on all dimensions[21]. Furthermore, based on the BVAQ scores, two subtypes of alexithymia can be distinguished: type I alexithymia, which is characterized by both low emotional experience and, consequently, poorly developed cognitions that accompany the emotions, and type Ⅱ alexithymia, which is characterized by low emotionality, but well-developed emotional cognitions[14]. Although providing interesting standpoints for research, the evidence that supports the existence of these subtypes has been so far limited and somewhat controversial[22].

Despite the extensive research on the associations of alexithymia with different variables, several questions regarding the development of alexithymia remain. In the present paper, we aim to comprehensively review the current scientific research on the development of alexithymic personality features. We further discuss the extent to which the current literature supports the perspective of alexithymia as a personality trait and raise several questions that concern the understanding of the development of these features.

GENETIC BACKGROUND

Heiberg *et al*[23] (1977) were the first investigators to suggest the inheritance of alexithymic characteristics. However, the method used to measure alexithymia in their twin study is not comparable with the current standards. Over two decades later, Valera *et al*[24] (2001) published another twin study in which they demonstrated that the EOT dimension was associated with genetic factors; however, their study sample was rather small. Several years later, Jørgensen *et al*[25] (2007) conducted

a similar study in a large twin sample (n = 8785) and confirmed the association of both the TAS-20 total score and all alexithymia dimensions with genetic factors.

Gene polymorphisms that are potentially associated with alexithymia have also been studied. Ham *et al*[26] (2005) suggested a connection between alexithymia and the catechol-O-methyltransferase Val108/158 Met gene polymorphism, but this association was challenged in a subsequent study[27]. In separate studies, alexithymia has been associated with functional variants of the brain-derived neurotrophic factor and DRD2/ANKK1 gene polymorphism[28] as well as a polymorphism in the serotonin (5-hydroxytryptamine) transporter-linked promoter region[29].

NEUROBIOLOGICAL FACTORS

Regarding the neurobiological correlates of alexithymia, the primary foci have been regions of the central nervous system (CNS) that are vital for emotion regulation, such as the frontal lobe and limbic system. Soon after the introduction of the alexithymia concept, "split-brain" patients were observed to have alexithymic features[30]. "Split-brain" represents the outcome of cerebral commissurotomy, where the corpus callosum is either completely or partially cleaved, leading to reduced transfer between the two brain hemispheres. This led to a hypothesis that alexithymia is a manifestation of a defect in the interhemispheric transfer. However, commissurotomy has primarily been used to treat epilepsy, and the significance of this illness alone for alexithymia has not been evaluated. Furthermore, more recent studies disagree on this issue; observations that alexithymia is both related to facilitated transcallosal inhibition[31] and reduced transcallosal inhibition exist[32].

In addition to the previously described deficit in interhemispheric communication, there have been two central attempts to model the neurobiological correlates of alexithymia: hemispheric lateralization and dysfunction in specific regions of the CNS associated with emotional regulation, such as the prefrontal cortex and the amygdala. Regarding hemispheric lateralization, alexithymia has been associated with functional asymmetry and, in particular, left hemisphere dominance[33-35]. The hypothesis is largely based on the finding that many brain functions, such as the processing of verbal or emotional information, predominantly occur in only one hemisphere[36,37]. Traditionally, emotional processing has been located in the right hemisphere, whereas logical processing is, for the most part, located in the left hemisphere[37]. Therefore, left hemisphere dominance in alexithymia would be convenient. In contrast, increased activity in the right hemisphere has also been associated with alexithymia[38]. A core problem in this model is that recent research has identified little evidence for this type of crude distribution of hemispheric functions. The human brain is a plastic organ, and it is plausible that although some brain functions tend to occur in one side of the brain, individuals do not actually possess left- or right-sided brain networks[39].

The amygdala is a central part of the limbic system that has an essential role in the processing of emotional stimuli; thus, it is understandably a point of interest for alexithymia studies. It is also heavily involved in facial expression recognition; indeed, alexithymia has been associated with lower activity in the amygdala when processing facial emotion (in particular the DIF and DDF dimensions)[40,41]. The dysfunction of both the amygdala and fusiform gyrus, a structure that also plays a central role in the early stages of facial expression processing[42], may have a significant role in the deficits of emotional awareness and social function that are related to autism spectrum disorders (ASD)[43,44]. These findings also lead to a hypothesis that these dysfunctions are the potential link between the theory of mind deficits that are typical for ASD and associated with severe cases of alexithymia. The relationship between ASD and alexithymia is discussed further in the Developmental considerations section.

The anterior cingulate cortex (ACC) is a region in the corpus callosum that, in addition to regulating autonomic and endocrine functions, is very active in emotional functioning and goal-directed behaviors[45]. In several studies, abnormal ACC function has been observed in alexithymic individuals, for example, during the perception of facial expression or the stimulation of different emotional states[35,46,47]. An interesting finding in one particular study was that while the activation of the ACC was lower in alexithymic individuals when processing emotional stimuli, the motor and somatosensoric cortices were more active[47]. This finding may be related to the known liability of alexithymic individuals to somatization[47]. Interestingly, a recent study suggests that specifically the cognitive, but not affective, component of alexithymia is associated with deficits in emotional attention and recognition[48]. Thus, while several studies suggest that alexithymia alters the way individuals perceive emotions, the specific effects on emotion regulation remain uncertain[44,48].

ENVIRONMENTAL FACTORS

The association of alexithymia with sociodemographic and familial factors has been extensively studied. Of the sociodemographic factors, the relation of alexithymia with low educational level, low socio-economic status and living in a rural area have been firmly established[9,11,49]. Previous research also indicates that a lack of social support is associated with alexithymia, both in adults[50,51] and adolescents[52]. However, these studies are scarce, and the causality is difficult to establish. Low social support may promote the emergence of alexithymia; however, alexithymic features may also impede the ability to build supportive relationships or the ability to utilize them.

Familial factors, such as a mother's low education level, parental divorce, or being an unwanted child, have been associated with alexithymia[49,53]. Maternal alexithymia and

general psychopathology in the family while growing up have been associated with the development of alexithymic features[54]. Inadequate parenting and childhood adversities have been repeatedly shown to impair the development of emotion regulation and are thus likely to have a significant impact on the development of alexithymic features[5,55-57]. However, it has been observed that even if one parent exhibits an optimal parenting style, this may very well prevent the development of alexithymia in the child[58].

In a recent study, the degree of alexithymia was significantly associated with early neglect[59]. Although this study was also based on self-assessment, the association was very strong; thus, the authors suggested that alexithymia could be categorized into "neglect" and "non-neglect" subtypes. For alexithymic individuals with a history of emotional neglect, there appeared to be a lower acceptance for one's own emotions and problems in the regulation of emotional states. In two other recent studies, previous traumatic experiences were significantly associated with alexithymia[60,61]. However, the cross-sectional design in all of these studies limits the generalization of the results. Overall, parental care during childhood, or rather, the lack of it, has also been associated with alexithymic features. In two separate studies, low experienced parental care has been associated with difficulties in the identification and verbalization of emotions[62,63]. However, some studies found no direct relation between reported parental care and the development of alexithymia[52,64]. In addition, there are studies that indicate that parental, in particular maternal, overprotection may have an effect on later alexithymia[52,65]. In both of these studies, maternal overprotection was associated with the dimensions of difficulties in identifying and describing feelings. This finding leads to a hypothesis that an overprotective, and hence restrictive and intrusive, mother denies psychological autonomy, which may lead to difficulties in sharing feelings with others.

However, the assessment of childhood experiences, such as traumatic experiences and parental attitudes, is difficult in cross-sectional settings because of the subjective nature and because the assessment often concerns experiences that date back several decades. As Kooiman *et al*[64] (1998) note, it is questionable whether the victims of parental neglect and abuse are suitable subjects for studies that use self-reporting instruments because they are prone to use primitive defense mechanisms.

DEVELOPMENTAL CONSIDERATIONS

Individual developmental factors associated with alexithymia have scarcely been studied. In one particular study, congenital cardiac malformations have been associated with a risk for alexithymic features[66]. This is due to the relationship between congenital cardiac malformations and neurodevelopmental morbidities that affect social cognition. In longitudinal studies, both Kokkonen *et al*[67] (2003) and Karukivi *et al*[68] (2012) reported the associations of alexithymia with lagging speech development in childhood. Kokkonen *et al*[67] (2003) demonstrated that the ability to speak at the age of one year was negatively associated with adult alexithymia, in particular, with the dimension of externally oriented thinking. Karukivi *et al*[68] (2012) studied the association between various developmental factors assessed at the age of five and alexithymia in late adolescence. They determined that in males, deficit in speech development at 5 years was associated with later alexithymia.

Previous research indicates that children with impaired speech development often have difficulties in various social situations and face problems in creating gratifying peer relationships, because of their lack of communication and regulation skills[69-71]. A central hypothesis is that these children struggle with interpreting both vocal and facial emotional cues[72,73], and thus, the association is similar to that of adults with alexithymia. It has been suggested that alexithymic individuals have adequate vocabulary to depict their feelings, but because these feelings are poorly differentiated, it is difficult for these individuals to itemize and verbalize them[74,75]. The hypothesis that children lacking language skills would have a higher risk of developing alexithymia because of their struggles in social situations is suggestible, but the limited research does not enable firm conclusions. Nevertheless, this association would only explain alexithymia in adults to a small extent.

An interesting standpoint is the connection between alexithymia and ASD. Because impaired recognition and expression of feelings are intrinsic features of ASD, it is not surprising that an association between alexithymia and autistic syndromes has been hypothesized. Indeed, an overlap of some extent between alexithymia and Asperger syndrome[76,77] has been observed. It has also been reported that clinically significant alexithymic features in the parents of children with ASD are more common than on average[78]. One hypothesis for this overlap is similar deficits in the theory of mind in both ASD and alexithymia[79]. However, the overall prevalence of ASD is approximately 1%-2%[80]; thus, a vast majority of individuals who present clinically significant alexithymic features do not fall in this category. Therefore, although the theory of mind deficit is an attractive hypothesis, it only explains alexithymia to a limited extent. Indeed, alexithymia and ASD are considered to be different constructs, but alexithymic features appear to be an idiosyncratic trait in many individuals with ASD[81].

Alexithymia has also been associated with certain irregularities in the autonomic nervous and immune systems. For example, aberrant immune responses have led Guilbaud *et al*[82] (2003) to suggest that individuals with significant alexithymic features may suffer from unnoticed chronic stress. Furthermore, dysregulation of the autonomic nervous system has been hypothesized to be related to alexithymia[83,84]. Particularly, the affective component of alexithymia has been suggested to be of importance in the regulation of sympathetic responses[85]. However, the overall results regarding the

associations with the autonomic nervous system are discordant[86,87]. Taking into account that, for example, depression has been associated with aberrations in the immune system[88], this is one possibility how alexithymia is connected to mental disturbances. Additionally, it has been suggested that alexithymia may be linked to somatic illnesses through an over-activation of the hypothalamic-pituitary-adrenal axis[89]. Although an interesting issue to debate, the current evidence for the causality between these aberrations and the development of alexithymia is practically non-existent.

As previously discussed, the prevalence of alexithymia in adults is around 10%[9-11]. From a developmental standpoint, the most interesting questions concern the age at which the prevalence settles at this level. In studies conducted in adolescent populations, the prevalence of alexithymia has varied from 7.3%[90] to 23.5%[49]. On average, the prevalence is approximately the same as in adults[91-93]. One interesting finding is that to date, in contrast to adults, no gender difference regarding the prevalence has been identified in adolescents. In two studies, different age groups of adolescents were compared, and the prevalence of alexithymia was significantly higher in younger adolescents[90,93]. However, Parker *et al*[94] (2010) have questioned the measurement of alexithymia using the TAS-20 scale in adolescents, particularly in younger age groups, because of readability issues.

Previous research has shown that owing to their lack of cognitive capacity and adequate emotion regulation skills, children typically present psychosomatic symptoms when they face anxiety-provoking circumstances[95]. Therefore, it can be hypothesized that alexithymic characteristics are normal in childhood, at least to some extent. This would explain the finding that younger adolescents appear to be somewhat more alexithymic than older adolescents. The later development of emotion regulation skills facilitates the proper identification and verbalization of emotions. Thus, it is likely that developmental stages have a significant impact on the prevalence of alexithymic features.

The major question is whether alexithymia simply persists in alexithymic individuals from childhood or if it actually develops *de novo* in later phases. Soon after the concept of alexithymia was introduced, Freyberger[96] (1977) introduced the concepts of primary and secondary alexithymia, of which the first was defined as a disposition factor, and the latter as a defense mechanism. Several subsequent studies suggested that alexithymia might develop in response to overwhelming stress to avoid experiencing agonizing and unbearable emotions[97,98]. During the previous two decades, this "state or trait" issue has been assessed in several studies discussed in the next section. Overall, the contemporary view is that alexithymia is a multifaceted construct that often includes trait and state components alike.

STABILITY OF ALEXITHYMIC FEATURES

To comprehensively assess the current scientific evidence for the stability of alexithymia as a personality trait, a systematic review of the literature was conducted. The inclusion criteria for the studies were as follows: (1) a longitudinal design with a non-clinical or patient sample; (2) the assessment of the stability of alexithymia as a personality trait (absolute and/or relative stability); (3) the use of a validated instrument to measure alexithymia; (4) written in English; and (5) not a review.

A systematic search was conducted using the PubMed database. The period ranged from September 1, 1995, to September 1, 2014. Using the search terms [("alexithymia" OR "alexithymic") AND ("stability" OR "trait" OR "reliability")], 304 papers were identified. In the next phase, the search term was complemented by adding ("longitudinal" OR "prospective" OR "follow" OR "test-retest" OR "change"), which resulted in 87 studies. The studies were inspected manually, and 34 papers met the inclusion criteria. The studies are presented in Table 1.

In terms of stability, it is vital to differentiate the absolute and relative stabilities of alexithymia. Absolute stability refers to potential changes in individual alexithymia scores over time, whereas relative stability refers to potential relative differences among individuals. Overall, a vast majority of the studies have been conducted in patient populations, and only a few studies have assessed the stability of alexithymia in non-clinical populations. Regardless of the studied sample, most studies indicate a rather high relative stability for alexithymia, which is typical for a personality-like feature. However, as some authors have noted, there are unanswered questions regarding the relative stability of alexithymia in patient populations[103,128]. Marchesi *et al*[103] (2014), for example, state that because alexithymic features decrease simultaneously with mental disorder symptoms, we do not know if they return to the level that preceded the mental disorder.

The few studies conducted with non-clinical populations also indicate high absolute stability, whereas in clinical samples, significant sample-wise changes in the scores over time weaken the absolute stability. It is plausible that this effect is related to an association between the alexithymic features and mental disorder symptoms. Factors beyond mental disorders can weaken the absolute stability of alexithymia: the studies conducted in populations with, for example, previous myocardial infarction[126], breast cancer[114] or service as peacekeepers[107] indicate that other stressful events may cause significant changes in absolute stability over time. Overall, understanding the stability of personality features over time is difficult. For example, personality disorders have typically been perceived as chronic and treatment-resistant; however, recent longitudinal studies indicate that they remit more often and faster than typically assumed[131]. Thus, personality features may be more flexible than we originally assumed.

Although other methods of alexithymia assessment exist, the studies that assess the stability of alexithymia have been conducted almost invariably with the TAS-20 scale. Regarding the TAS-20 scale, the stability of alexithymia appears to vary depending on the studied dimension. In previous studies, EOT has been reported

Table 1 Studies that assessed the stability of alexithymia in patient and non-clinical populations

Ref.	Country	Sample	*n*	Age group and gender	Measure	Type of stability assessed	Follow-up period	Outcome
Misterska *et al*[99]	Poland	Patients with idiopathic scoliosis undergoing brace treatment	36	Adolescent females	TAS-26	Absolute and relative	12 mo	Low absolute stability, high relative stability
Karukivi *et al*[100]	Finland	Non-clinical	315	Adolescent males and females	TAS-20	Absolute and relative	4 yr	High absolute stability, high relative stability
de Haan *et al*[101]	The Netherlands	Patients with substance use disorders	101	Adult males and females	TAS-20	Absolute and relative	3 wk	Low absolute stability, moderate to high relative stability
Zunhammer *et al*[102]	Germany	Non-clinical	142	Adult males and females	TAS-20	Absolute and relative	Not available	Moderate to high absolute stability, high relative stability
Marchesi *et al*[103]	Italy	Pregnant panic disorder patients (n = 21) and healthy controls (n = 256)	277	Adult females	TAS-20	Absolute and relative	Not available	Low absolute stability, moderate relative stability
de Haan *et al*[104]	The Netherlands	Patients with substance use disorders	187	Adult males and females	TAS-20	Absolute and relative	3 mo	Low absolute stability, moderate relative stability
Porcelli *et al*[105]	Italy	Patients with cancer (half received a psychological intervention)	104	Adult males and females	TAS-20	Absolute and relative	6 mo	Low absolute stability, high relative stability
Tolmunen *et al*[106]	Finland	Non-clinical	755	Adult males	TAS-26	Absolute and relative	11 yr	High absolute stability, high relative stability
Larsson *et al*[107]	Sweden	Non-clinical peacekeepers	104	Adult males	TAS-20	Absolute and relative	6 mo	Low absolute stability, moderate relative stability
Meganck *et al*[108]	Belgium	Patient sample (n = 201) and non-clinical (n = 264)	465	Adult males and females	OAS	Relative	2 wk	High relative stability
Seo *et al*[109]	South Korea	Non-clinical	22	Adolescent males and females	TAS-20	Relative	4 wk	High relative stability
Spek *et al*[110]	The Netherlands	Patients with sub-threshold depression	119	Adult males and females	TAS-20	Absolute	12 mo	Low absolute stability
Marchesi *et al*[111]	Italy	Patients with major depression (n = 16), sub-threshold depression (n = 21) and without depression (n = 112)	149	Adult females	TAS-20	Absolute and relative	Not available	Low absolute stability, high relative stability
Grabe *et al*[112]	Germany	Patients admitted to psychotherapeutic treatment	297	Adult males and females	TAS-20	Absolute and relative	8-12 wk	Low absolute stability, high relative stability
de Timary *et al*[113]	Belgium	Patients with alcohol-dependence undergoing treatment	70	Adult males and females	TAS-20	Absolute and relative	14-18 d	Moderate absolute stability, high relative stability
Luminet *et al*[114]	France	Breast cancer patients	122	Adult females	TAS-20	Absolute and relative	6 mo	Low absolute stability, high relative stability
Moriguchi *et al*[115]	Japan	Non-clinical	196	Adult females	TAS-20	Relative	11 wk	Moderate relative stability
Säkkinen *et al*[93]	Finland	Non-clinical	769	Adolescent males and females	TAS-20	Relative	5 wk	High relative stability
Rufer *et al*[116]	Switzerland	Patients with obsessive-compulsive disorder	42	Adult males and females	TAS-20	Absolute and relative	6 yr	Low absolute stability, high relative stability
de Vente *et al*[117]	The Netherlands	Patients with work-related stress (n = 69) and a non-clinical sample (n = 62)	131	Adult males and females	TAS-20	Absolute and relative	16 wk	Low to moderate absolute stability, moderate relative stability
Salminen *et al*[118]	Finland	Non-clinical	901	Adult males and females	TAS-20	Absolute and relative	5 yr	High absolute stability, moderate to high relative stability
Saarijarvi *et al*[119]	Finland	Patients with major depression	116	Adult males and females	TAS-20	Absolute and relative	5 yr	Low absolute stability, high relative stability
Picardi *et al*[57]	Italy	Non-clinical	115	Adult males and females	TAS-20	Absolute and relative	1 mo	High absolute stability, high relative stability

Berthoz *et al*[120]	United Kingdom	Patients with autism spectrum disorder (n = 19) and healthy controls (n = 29)	48	Adult males and females	TAS-20 BVAQ-B	Relative	4-12 mo	TAS-20: high relative stability BVAQ-B: moderate relative stability
Yao *et al*[121]	China	Non-clinical	34	Adult females and males	OAS	Relative	2 wk	High relative stability
De Gucht *et al*[122]	The Netherlands	Patients with medically unexplained symptoms (n = 313) and a non-clinical sample (n = 698)	1011	Adult males and females	TAS-20	Relative	6 mo	High relative stability
Rufer *et al*[123]	Germany	Patients with obsessive-compulsive disorder	42	Adult males and females	TAS-20	Absolute and relative	Not available	High absolute stability, high relative stability
De Gucht[124]	The Netherlands	Patients with somatization	318	Adult males and females	TAS-20	Absolute and relative	6 mo	High absolute stability, high relative stability
Porcelli *et al*[125]	Italy	Patients with functional gastrointestinal disorders	112	Adult males and females	TAS-20	Absolute and relative	6 mo	High absolute stability, high relative stability
Kojima *et al*[126]	Canada	Patients with previous myocardial infarction	1443	Adult males and females	TAS-20	Absolute and relative	3-6 mo	Moderate absolute stability, low relative stability
Luminet *et al*[127]	Belgium	Patients with major depression	46	Adult males and females	TAS-20	Absolute and relative	14 wk	Low absolute stability, high relative stability
Honkalampi *et al*[128]	Finland	Non-clinical	1584	Adult males and females	TAS-20	Absolute and relative	12 mo	Low absolute stability, high relative stability
Honkalampi *et al*[129]	Finland	Patients with major depression	169	Adult males and females	TAS-20	Absolute	6 mo	Low absolute stability
Bressi *et al*[130]	Italy	Non-clinical	180	Adult males and females	TAS-20	Relative	2 wk	High relative stability

n: Number of subjects; TAS-20: 20-item Toronto Alexithymia Scale; OAS: Observer Alexithymia Scale; BVAQ-B: Bermond-Vorst Alexithymia Questionnaire, version B.

to be the most constant subscale in the TAS-20[113,119]. It has been suggested that this stability reflects the developmental nature of this particular subscale. It is suggested that the DIF and DDF subscales fluctuate more with mood. However, there appears to be some variation in the reported findings, and in some studies, DDF has been suggested as the most stable subscale[100,114]. Nevertheless, the differences are small, and it is difficult to draw firm conclusions. Additionally, regarding the different dimensions of alexithymia, the TAS-20 does not enable the assessment of the stability of limited imagination.

CONCLUSION

Despite the substantial amount of research regarding alexithymia, how and why alexithymic features develop in an individual remain inadequately understood. Although several distinct theories have been suggested from different standpoints, no comprehensive understanding has been established.

One core difficulty in research on the development of alexithymic characteristics is the heterogeneity of the determinants. The current evidence indicates that alexithymia is a personality feature in the general population that is characterized by a variety of emphases in the symptom dimensions, and it is not a categorical concept confined to a group of "alexithymics"; thus, alexithymic features are prevalent. Furthermore, to some extent, alexithymic features appear to intertwine with psychiatric symptoms, such as depression[17], or other personality variables, such as negative affectivity[132]. These findings reflect the measurement of alexithymia, where it is difficult to achieve strong divergent validity with feasible self-report measures. Despite these limitations, the extensive alexithymia research strives to systematically identify additional details of this process.

Data from the few twin studies that have been conducted suggest that alexithymia is, to some extent, inherited, and certain genetic aberrations have been reported. Modern brain imaging technologies have led to an increasing amount of data on the neurobiological correlates of alexithymia. During recent years, for example, the abnormal function of the anterior cingulate cortex in alexithymia has been identified and a notable number of studies point to alterations in the perception of emotions on the neurobiological level. However, the research evidence has been obtained, for the most part, from studies based on comparisons of brain function between alexithymic and non-alexithymic

individuals in specific situations. Thus, these studies provide only limited information on the development of these aberrant dysfunctions and their clinical manifestations.

Regarding the development of alexithymic features, the most substantial amount of research covers the relation of alexithymia to different environmental factors. Many of these associations, for example, with low socio-economic status and general psychopathology in childhood, are quite well established. However, the retrospective and cross-sectional designs commonly used in these studies, as well as the use of self-report measures, hinder the ability to firmly establish causality. Aside from the methodological problems, one central issue is the relevance of these potential risk factors to alexithymia. The factors are very similar to the factors that affect common mental disorders and other psychosocial problems; thus, specific risk factors for alexithymia are difficult to break down.

Specific individual developmental factors, such as lagging speech development and congenital cardiac malformations in childhood, have been associated with later alexithymia. However, to more profoundly understand the development of alexithymia, further research in this area is needed. Several studies have assessed the stability of alexithymia. Overall, in addition to its characterization as a personality feature in the general population, alexithymia clearly also has a state-like dimension that results in increases and decreases in alexithymic features in conjunction with, for example, mental disorder symptoms. The divergent stability of the different dimensions of alexithymia must also be considered.

According to the current knowledge, the true path for the development of alexithymia remains an unanswered question. The central question that arises is to what extent infantile features of restricted ability to identify and describe emotions simply persist in alexithymic individuals throughout adolescence and adulthood. Because the roots of developmental alexithymia appear to lie in the stages that precede adulthood, more studies that assess the development of alexithymia in younger age groups are needed. Additional longitudinal studies that prospectively assess the mechanisms of the development of alexithymia and the subsequent predisposition to mental and somatic illnesses are also needed. Studies that combine different standpoints, such as neurobiological and familial factors, are potentially fruitful.

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REVIEW

Peptides from adipose tissue in mental disorders

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Abstract

Adipose tissue is a dynamic endocrine organ that is essential to regulation of metabolism in humans. A new approach to mental disorders led to research on involvement of adipokines in the etiology of mental disorders and mood states and their impact on the health status of psychiatric patients, as well as the effects of treatment for mental health disorders on plasma levels of adipokines. There is evidence that disturbances in adipokine secretion are important in the pathogenesis, clinical presentation and outcome of mental disorders. Admittedly leptin and adiponectin are involved in pathophysiology of depression. A lot of disturbances in secretion and plasma levels of adipokines are observed in eating disorders with a significant impact on the symptoms and course of a disease. It is still a question whether observed dysregulation of adipokines secretion are primary or secondary. Moreover findings in this area are somewhat inconsistent, owing to differences in patient age, sex, socioeconomic status, smoking habits, level of physical activity, eating pathology, general health or medication. This was the rationale for our detailed investigation into the role of the endocrine functions of adipose tissue in mental disorders. It seems that we are continually at the beginning of understanding of the relation between adipose tissue and mental disorders.

Key words: Adiponectin; Leptin; Visfatin; Resistin; Omentin; Adipsin; Eating disorders; Schizophrenia

Core tip: New approach to adipose tissue as endocrine organ developed new research fields in psychiatry. Several papers linked the well-known adipokines like leptin, adiponectin and resistin with mental disorders. But there are still a hundreds of recently discovered adipokines with possible role in mental disorders.

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INTRODUCTION

This year is the twenty-year anniversary of a new approach to adipose tissue. Since the discovery of leptin[1] in 1994, adipose tissue has been recognized as an endocrine organ and an important source of biologically active peptides called adipokines.

There is growing body of clinical evidence that adipokines play a role in various mental disorders including schizophrenia, mood disorders, anxiety disorders, post-traumatic stress disorder, eating disorders (EDs), sleep disorders, autism spectrum disorders (ASDs), attention deficit hyperactivity disorder and some neurodegenerative disorders such as Alzheimer's disease (AD)[2-6]. Research on adipokines has looked at the effects of drugs used to treat mental disorders on the plasma level of adipokines, the role of adipokines in the etiology of mental disorders and mood states and their impact on other aspects of the health status of psychiatric patients. One of the most interesting and challenging areas of research is the role of adipocytes in the etiology of mental disorders. Recently clinical research has been corroborated by novel studies in animal models. Use of animal models enables us to develop a more sophisticated causal model of the role of adipocytes in normal and pathological psychological functioning. Several types of adipocyte receptor have been found in several central nervous system areas, and have been shown to affect brain function through neuroplastic processes[7-9]. These findings in depth the immune theory of psychiatric diseases[10,11]. Also some hypotheses tiding etiology of mental disorders and addictions in adults with disturbed adipocyte development in childhood were formulated[10-12]. There are other possible mechanisms by which adipocytes may be involved in the etiology of mental disorders[13,14]. At present the evidence is inconsistent, and raises new questions and suggests new topics for research[15]. Understanding the role of adipocytes in the etiology of mental disorders might lead to new treatments and approaches to managing mental health problems[16-19]. On the other side research on the role of adipokines in mental health reflects significant changes in perception of adipose tissue. Methodological problems with research in this area continue to be reflected in inconsistent results[20-27]. In attempting to synthesize the findings of the various studies it is essential to consider interactions among factors such as patient age, sex, socioeconomic status, smoking habits, level of physical activity, eating pathology, general health and medication. More research is needed, particularly into the ways in which adipokines circulate around the various body fluids and compartments[10]. This review discusses research linking selected adipokines with mental disorders.

ADIPONECTIN

Adiponectin is a 244-amino acid peptide produced in adipose tissue by mature adipocytes and is classed as an adipokine. Adiponectin was discovered independently in four different laboratories in 1995; it is also known as adipoQ, adipocyte complement-related protein with mass = 30 kDa, gelatin binding protein with mass = 28 kDa and adipose most abundant gene transcript 1 (apM1)[28]. Native adiponectin creates homotrimers that may form dimers, trimers and high molecular weight (HMW) complexes[29]. Adiponectin interacts with adiponectin receptors (AdipoR1 and AdipoR2) and is homologous to C1q subunits and globular domains of type X and Ⅷ collagens[30]. Both receptors are expressed in white and brown adipose tissue[31]. AdipoR1 is expressed mainly in skeletal muscles but is also found in endothelial cells. It has high affinity for globular adiponectin and low affinity for full-length adiponectin[32]. The complex of AdipoR1 with adiponectin activates AMP-activated protein kinase (AMPK) and promotes lipid oxidation[32]. AdipoR2 is highly expressed in the liver and has intermediate affinity for both globular and full-length adiponectin. It increases peroxisome-proliferator-activated receptor ligand activity by reducing steatosis and enhancing insulin sensitivity through activation of AMPK[24]. T-cadherin, an adiponectin-binding protein with high affinity for HMW adiponectin multimers is mainly expressed in the endothelium and smooth muscle[33].

BIOLOGICAL ROLE OF ADIPONECTIN

The biochemical effect of adiponectin partly depends on the relative high concentration of this peptide in the blood, as compare to the remaining adipokines[34,35]. Adiponectin accounts for approximately 0.01% of all plasma protein[36]. Adiponectin is mainly involved in energy homeostasis. It is exclusively secreted by adipocytes and is linked to glucose and lipid regulation[37]. Adiponectin stimulates fatty acid oxidation, suppresses hepatic gluconeogenesis and also inhibits monocyte adhesion, macrophage transformation, proliferation and migration of smooth muscle cells into blood vessels[29]. These metabolic and anti-inflammatory actions are closely associated with activation of AMPK and modulation of nuclear factor-B. AdipoR1 and AdipoR2 are expressed widely both in peripheral tissues and in the brain[38]. Adiponectin plays a crucial role in several metabolic diseases. It has strong insulin-sensitizing and anti-inflammatory effects. Multiple metabolic abnormalities such as obesity, diabetes and atherosclerosis have been associated with decreased adiponectin levels[39]. In several animal models treatment with adiponectin was shown to reverse these abnormalities, resulting in increases in fatty acid oxidation, insulin sensitivity and reductions in glucose and lipid levels[40].

ADIPONECTIN IN MENTAL DISORDERS

Adiponectin activity is strongly associated with metabolic disorders and energy expenditure interactions, but it has also been associated with various mental disorders such as mood disorders, anxiety disorders, eating and sleep

disorders and neurodegenerative disorders.

Decreased serum adiponectin levels have been also reported in major depressive disorders, panic disorders and schizophrenia[41-43]. Serum levels of adiponectin were significantly lower in elderly patients with major depressive disorders than in non-depressed controls[44,45]. Adiponectin also plays an important role in depression-related behaviors. Circulating adiponectin levels were decreased in a chronic social defeat stress model of depression; they were also inversely correlated with the social interaction ratio. Adiponectin insufficiency increased susceptibility to stress-induced depressive behaviors and impaired function of hypothalamic-pituitary-adrenal axis[46]. Expression of AdipoR1 and AdipoR2 was high in areas of the brain involved in depressive disorders and intra-cerebral administration of adiponectin elicited antidepressant-like behavioral effects in normal-weight mice and obese diabetic mice[47].

Reduction in circulating adiponectin levels has been correlated with social withdrawal, which is common in psychiatric disorders such as depression and post-traumatic stress disorder. The mechanisms underlying the reduction in circulating adiponectin levels induced by social defeat are still not known, however very recent research has shown that glucocorticoid stress hormones inhibit adiponectin gene expression and secretion *in vitro* and *in vivo*[48,49]. It seems reasonable to speculate that a social defeat-induced decrease in plasma adiponectin levels may be connected to a stress-induced surge in glucocorticoids[47].

The data on adiponectin levels in anorexia nervosa (AN) patients are inconsistent. It has been reported that adults with AN have decreased[20], increased[21,22] or unchanged[23] adiponectin levels. Earlier research showing that obese patients have lower total adiponectin levels suggested that adiponectin levels might be negatively correlated with body mass index (BMI)[29]. A later study assessing levels of specific isoforms of adiponectin found that percentage HMW was lower in the AN group than in controls, whereas percentage low molecular weight (LMW) was higher in the AN group. HMW and LMW were positively and negatively correlated with the BMI respectively in the sample as a whole. The observation that the level of total adiponectin was similar in the AN group and control group suggests that AN may be associated with upregulation of adiponectin production, because these patients with AN appear to have produced a similar amount of adiponectin to controls despite having fewer fat cells[50].

Assessments of adiponectin levels in patients with schizophrenia suggest that they are dependent on nutritional status. Elevated adiponectin levels were observed in normal-weight, drug-naïve, first-episode schizophrenia patients. In schizophrenia upregulated secretion of adiponectin has been correlated with levels of pro-inflammatory mediators[13]; it has been suggested that inflammation is not the only reason for the increase in adiponectin secretion in schizophrenia.

Although adiponectin is involved in sleep regulation and the pathomechanism of seizures normal levels have been reported in normal-weight patients with mild sleep disorders such as parasomnia and epilepsy[51]. Only in patients with severe sleep disorders such as obstructive sleep apnea hypopnea syndrome (OSAHS) have decreased levels of adiponectin been found, but OSAHS is associated with more serious hypoxia-related changes in the brain and frequently co-occurs with obesity[51].

Adiponectin abnormalities have been implicated in various metabolic disorders and may also be risk factors for the development of neurodegenerative disorders such as AD[52].

To date few studies have investigated the potential relationship between adiponectin and AD. One recent clinical study demonstrated that some AD patients have elevated levels of adiponectin in plasma and cerebrospinal fluid[53], which suggests that adiponectin may play an important role in mediating AD progression, possibly through its effects on peripheral or brain metabolism. Recent studies have shown that the adiponectin receptors AdipoR1 and AdipoR2 are expressed throughout the central nervous system[54]. But there is still controversy as to whether adiponectin crosses the blood-brain barrier[24,25]. It is likely that both adiponectin and adiponectin pathways could be targets for a new, effective treatment for AD[16].

LEPTIN

Leptin, a 146-amino acid peptide, is a product of the *Ob*(*Lep*) gene and is mainly synthesized by adipocytes. Leptin has also been extracted from placentae, stomach mucosa, enterocytes, liver and bone marrow[55]. Leptin was identified in 1994 and takes its name from the Greek *leptos*, meaning slim, fit. It functions as a "satiety signal" and is released by fat tissue and regulate food intake regarding to total fat tissue storage[7]. Leptin plays an important role in peripheral signaling, providing information about accumulated energy stores and thus playing a role in long-term regulation of the amount of food ingested[7]. This adipose tissue-derived hormone modulates a complex hypothalamic network of several cooperating orexigenic and anorexigenic neuropeptides to reduce food intake and increase energy expenditure[56]. The arcuate nucleus (ARC) is an important leptin-sensitive hub. Other hypothalamic and thalamic nuclei including the paraventricular nucleus, dorsomedial nucleus, ventromedial nucleus and lateral hypothalamic area are also direct targets of leptin[57].

BIOLOGICAL ACTIONS OF LEPTIN

Leptin plays a critical role as a negative regulator of food intake through specific neuronal receptors localized in hypothalamic nuclei. Leptin stimulates anorexigenic neurons expressing pro-opiomelanocortin and inhibits orexigenic pathways releasing neuropeptide Y and the melanocortin antagonist Agouti-related peptide[58]. Leptin

serum concentrations are maintained in direct proportion to the fat tissue mass. In several animal models lack of leptin causes hyperphagia and obesity whereas leptin administration decreases body mass and increases energy expenditure[59]. However in humans 90%-95% of obese people have elevated leptin serum levels[60]. This suggests that obesity may be associated with problems with leptin signaling or dysregulation of the leptin-brain axis. Low serum leptin acts as a signal of lack of energy storage for hypothalamic regions; this function may have evolved as a defense against generalized metabolic debilitation[61]. In women a body fat percentage below 10%-15% is associated with cessation of menstruation and relative lack of leptin or leptin receptor dysfunction[62]. In adolescent girls and boys leptin stimulates higher release of hypothalamic gonadoliberin and-*via* specific receptors in the pituitary gland-follicle-stimulating hormone and luteinizing hormone (LH)[8]. Leptin also plays a crucial role in many physiological processes including angiogenesis, inflammation, immune function and reproduction[63].

LEPTIN AND MENTAL DISORDERS

In humans, both high and low levels of leptin have been associated with psychopathology. Leptin resistance accompanying obesity is supposed to influence disorders such as anxiety, depression and may affect neurocognitive functions[64]. At present it is commonly believed, although there is no definitive proof, that appetite modulators also affect non-homeostatic cognitive, emotional and reward factors involved in regulation of food intake[65,66]. The most common disorders associated with disturbance of metabolic state regulators are AN and bulimia nervosa (BN). AN and BN are classified as EDs of complex and still unknown etiology. AN is characterized by low leptin levels. Data on leptin levels in leptin in the BN are inconsistent; it is possible that leptin levels may be vary according to the phase of the disease or the severity of symptoms (overeating, compensatory behaviors)[67]. In underweight AN patients levels of leptin in plasma and cerebrospinal fluid are significantly lower than normal and correlated with BMI[68,69]. Leptin levels were similar in restrictive and binging/purging AN, suggesting that cachexia plays an important role in leptin changes in anorexia[70].

Hypoleptinemia is believed to be the primary signal for initial somatic and behavioral adaptations to starvation[71]. Recent research has focused on the potential influences of leptin and other hormones, severe life events and chronic stress in the onset and the course of EDs[46]. Leptin influences energetic balance but it also regulates processing of the hedonic and motivational components of rewards[72]. It is widely recognized that anhedonia, the inability to experience pleasure, is a key symptom of EDs[73,74]. Data from animal models has shown that food abundance increasing body weight as well as leptin levels suppress reward-related behaviors. Conversely caloric restriction and body mass reduction resulted in a decrease in leptin levels and an increase in reward-related behaviors[75]. Thus in line with these animal studies, similar observations have been recognized in chronically fasting patients with AN. The modulatory effect of leptin on reward-related behaviors has also been postulated to play a role in excessive exercising in AN patients[67]. Low leptin levels have been shown to correlate with hyperactivity in starved animals[76]. Amenorrhea, which is one of the most common symptoms of AN in female patients, is probably secondary to the decrease in adipose tissue, but may be directly associated with very low serum leptin levels[77]. It has been shown that a serum leptin level less than 1.85 mcg/L predicts amenorrhea and subnormal serum levels of LH in AN[78]. Weight restoration therapy does not reverse amenorrhea in all patients and it has been reported that in these cases leptin levels remain lower than in healthy controls[79]. Comorbid depressive symptoms are another characteristic of AN. Evidence indicates that there is a bidirectional relationship between depression and metabolic dysregulation[80,81]. Leptin receptors have been found in the limbic system, and leptin also has been shown to affect hippocampal and cortical structures through its effects on neurogenesis, axon growth, synaptogenesis and dendritic morphology. Low levels of leptin are associated with depressive behaviors and exposure to chronic stress decreases serum leptin. A recent study of therapy for AN reported a reduction in depressive symptoms measured with Beck Depression Inventory and Hamilton depression Rating Scale following increases in BMI and leptin serum levels. This suggests that there may be a direct association between leptin concentration balance and depressive symptoms[9]. Leptin may serve as biomarker for depression in general, or in depressed patients with altered metabolic function[82].

Modern research on the importance of leptin in EDs has explored its wider role, focusing on the critical role that appetite regulation and weight regulation mechanisms play in weight loss and maintenance of lean body mass in AN[83]. This research is aimed at understanding the ways in which leptin is transported to the brain and subsequent alterations in hypothalamic expression of leptin receptors and downstream signaling pathways[14]. Research into early epigenic encoding of leptin-receptor interactions[84] is another promising new area of investigation.

Early research on the role of leptin in schizophrenia explored the impact of treatment with antipsychotics on leptin levels[85]. The relationship between leptin level and weight gain associated with neuroleptic drugs has also be investigated[86]. There have been many reports of altered levels of leptin in schizophrenic patients; some studies reported decreased serum leptin levels in schizophrenic patients, but others have found increased serum leptin levels in antipsychotic-naïve female patients with schizophrenia[26,27]. The neurobiological basis of schizophrenia is not fully understood but dopamine abnormalities in this disease have been extensively investigated[87,88]. On animal model there is postulated theory of increased dopamine level in nucleus accumbens

in schizophrenic rats. Leptin may modulate dopaminergic activity through leptin receptor-expressing neurons in the mesolimbic pathway[89]. It has been reported that leptin reduces mesolimbic dopaminergic activity and decreases dopamine levels in the nucleus accumbens[90,91]. This is consistent with studies which have reported a negative correlation between leptin levels and severity symptoms in schizophrenia[85] and may indicate that leptin is involved in negative feedback to counteract increased dopamine activity in the brain[91]. However other study noted higher plasma levels of leptin in schizophrenic patients than in healthy controls[92].

RESISTIN

Resistin was discovered in 2001; it is a peptide and is also known as adipose tissue-specific secretory factor or C/EBP-epsilon-regulated myeloid-specific secreted cysteine-rich protein (XCP1). It is considered a pro-inflammatory factor and is thought to be responsible for resistance to insulin[93]. Adipocytes are the main source of resistin in the human body, but expression of resistin is also high in mononuclear blood cells.

Recently researchers suggested that there is an association between inflammatory agents produced by adipose tissue and risk of depression[11]. Some studies have reported a positive correlation between resistin concentration in the blood and atypical, melancholic subtypes of major depressive disorders[94,95]. This association may be related to the reduction in intrasynaptic concentration of monoamines by resistin *via* inhibition of release of norephinephrine and dopamine in the hypothalamus[96].

It has been suggested that resistin is involved in the pathogenesis of bipolar disorder (BD). Insulin resistance is one of the main etiological factors in BD. Resistin activates enzymes involved in gluconeogenesis and increases glycogenolysis, thereby contributing to hepatic insulin resistance by decreasing the expression of GLUT 4. A recent study reported increased levels of resistin in patients with BD, the specific role of resistin in the pathogenesis of the illness is still unknown[97]. Reduced concentration of resistin have been observed in patients with obsessive compulsive disorder[98], similarly lower levels of serum resistin have been observed in patients with ASDs[99] and EDs[100]. Low resistin levels in EDs could be due to downregulation of mononuclear macrophage levels and/or a reduction in pro inflammatory processes[100].

OTHER ADIPOKINES

The well-known adipokines are discussed above, but there are over 600 less well-known adipokines which are extensively involved in human physiology and pathology. Some adipokines are involved in the regulation of metabolism (*e.g.*, dipeptyl peptidase 4, vaspin, visfatin, chemerin), others in the immune response [*e.g.*, adipsin, ASP, SAA3, interleukin (IL)-17D, colony-stimulating factors], inflammation (*e.g.*, IL-1β, IL-6, IL-8, IL-10, C-reactive protein, monocyte chemoattractant protein-1, osteopontin, progranulin, chemerin), hypertension (*e.g.*, angiotensinogen), cell adhesion (*e.g.*, plasminogen activator inhibitor-1), adipogenesis and bone morphogenesis (*e.g.*, bone morphogenetic protein-7), cell or tissue growth (*e.g.*, insulin-like growth factor-1, transforming growth factor beta, fibronectin, fibroblast growth factor 21, vascular endothelial growth factor) and many others functions[101-108]. Some adipokines have multidirectional actions or interplay with other molecules in a variety of functions. These data urgent to define their function and potential clinical relevance in health and disease, also in mental disorders.

Few attempts have been already done. There was no significant association between the concentration of circulating visfatin and presence of EDs[109,110]. Recent studies have shown reliance between starvation and decrease plasma level of adipsin, which suggests possible role of this peptide in etiology of AN[111]. Serum levels of omentin were normal in drug-naive patients with major depression[112]. These negative results should not dissuade researchers from investigating the role of adipokines in mental disorders.

CONCLUSION

The studies discussed here provide evidence that disturbances in adipokine secretion are important in the pathogenesis, clinical presentation and outcome of mental disorders. There is a consensus that leptin and adiponectin are associated with symptoms of depression. Changes in the physiology of appetite modulators in EDs play a pivotal role in motivated behaviors, reward processes and energy balance. Sometimes, as in AN, secondary downregulation of adipokines has a significant impact on the symptoms and course of a disorder. A better understanding of the endocrine function of adipose tissue would have a significant impact on understanding of mental disorders and would lead to more rational therapies for these diseases. There is a lack of research into the role of adipokines in different mental disorders; this is an area which warrants further research. Detailed investigation of links between adipokines and mental disorders is still a new topic in psychiatric research.

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REVIEW

Eating disorders and psychosis: Seven hypotheses

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Abstract

Psychotic disorders and eating disorders sometimes occur in the same person, and sometimes, but not always, at the same time. This can cause diagnostic confusion and uncertainty about treatment. This paper examines seven ways in which symptoms of both conditions can co-exist. The literature on this topic consists to a large extent of case reports, so that firm conclusions cannot be drawn from their examination. There is no consistent sequence in the co-occurrence of the two conditions-eating disorders sometimes precede, and sometimes follow the onset of psychosis. The advent of the psychosis, and sometimes the treatment of the psychosis can cure the eating disorder, but it can sometimes aggravate it. Psychosis is not necessarily a mark of severity in the course of an eating disorder, and food refusal can occur independent of severity in psychotic illness, but it can be a cause of death. There is some genetic association and some overlap of physiologic, cognitive and brain structure deficits in the two types of disorder. The connection between the two, however, remains speculative. The area of comorbidity and overlapping symptoms in psychiatry requires more research. Clinical recommendations include attention to the different individual ways in which these two disparate conditions often overlap.

Key words: Psychosis; Anorexia; Bulimia; Eating disorder; Comorbidity

Core tip: Eating disorder symptoms and psychotic symptoms may co-exist and may serve individual psychological purposes. When planning treatment, the whole person needs to be kept in mind, lest curing one symptom exacerbates another. Effective treatment requires attention to overlapping dimensions of illness.

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INTRODUCTION

Working in an outpatient clinic for women with psychotic illness, the author encountered many patients with concurrent problems in eating that made it difficult to decide which symptoms to treat first.

Case example 1

A 25-year-old woman being treated with antipsychotic medication for schizophrenia [Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria] appeared, over a three-month period, to be losing considerable weight. Questions about her eating habits yielded the following answers: "I can't eat much." "The medication upsets my stomach." "If I eat too much, I vomit." On physical exam, her weight was below norms for her height. Heart rate was slowed but regular, and blood pressure was low. Her skin appeared dry.

The treating team entertained the following questions: is the patient suffering only from schizophrenia, or from

an eating disorder as well? Will the eating problems disappear once the psychosis is adequately treated? Should treatment focus more on the eating problems than on the schizophrenia, since self-starvation can lead to acute heart problems and even death, while schizophrenia is a chronic condition?

Case example 2

Another young woman in her mid-twenties who had previously been treated elsewhere for anorexia nervosa (DSM-Ⅳ criteria), developed delusions about being followed and exhibited eccentric public behavior that brought her to the attention of police, and, hence, to the psychosis clinic. Her case raised the following questions among the treating team: could the psychosis be a result of undernutrition? Could the patient be suffering from two separate disorders, anorexia nervosa plus an affective disorder with psychotic features, or possibly schizophrenia? Which of her symptoms should take precedence with respect to treatment?

To help answer the questions of the mental health team, the search terms "eating disorders", "anorexia", and "bulimia" plus "psychosis", "schizophrenia", "delusion" and "hallucination" were entered into the PubMed and Google Scholar databases, with subsequent searching for further references in all relevant articles, many of which turned out to be case descriptions.

Perusal of the literature led to seven potential hypotheses about the comorbidity of psychotic illness (schizophrenia or the presence of delusions or hallucinations in the context of an affective disorder), and eating disturbance. The hypotheses, and the predictions to which they lead, will first be outlined, and subsequently explored in greater detail. Many are contradictory. They are meant only to provoke discussion.

Hypothesis 1: Eating disorders and psychoses are entirely separate disorders that can, by chance, occur in the same person.

Two epidemiologic predictions follow from this hypothesis: (1) The incidence of psychotic disorder among those with eating disorder will be the same as it is in the general population; and (2) The incidence of eating disorder among individuals with psychotic disorder will be the same as it is in the general population.

Hypothesis 2: As a result of starvation, electrolyte, and metabolic imbalance, transient psychotic symptoms can develop in patients with a primary eating disorder. The direction of effects could be in the opposite direction. Patients with a primary psychotic illness (*e.g.*, schizophrenia or delusional depression for instance) can stop eating due to delusions related to food-*e.g.*, the food is poisoned; the food is contaminated, and subsequently develop an eating disorder.

Since the secondary condition depends upon the presence of the first, the prediction here would be that effective treatment of the primary condition would abolish both.

Hypothesis 3: Control of food intake provides a sense of mastery, achievement, and self-control to individuals whose sense of self-efficacy is low, as is the case of individuals at risk for psychosis. Control of food can, thus, be conceptualized as an attempt to ward off acute psychosis. The opposite direction of causality is also possible, namely that apathy, for instance, a negative symptoms of schizophrenia, reduces the urge to purge and diet in anorexia/bulimia-prone individuals.

If hypothesis 3 were true, recovery from one disorder would, in distinction to hypothesis 2, make the other worse.

Hypothesis 4: Because of body image distortions, eating disorders are delusional-*e.g.*, psychotic disorders.

If hypothesis 4 were true, a family history of psychosis should be present in patients with eating disorders, and a family history of eating disorders in patients with schizophrenia and other psychotic illness. The biochemical, cognitive, and anatomical deficits found in one condition should be present in the other. Moreover, as in hypothesis 2 and contrary to hypothesis 3, the successful treatment of one condition would also cure the other.

Hypothesis 5: An eating disorder is an early sign (prodrome) of an impending psychosis or, conversely, psychotic symptoms can herald the beginning of an eating disorder.

If this were the case, one disorder would precede the other and fade into the background once the primary condition surfaced.

Hypothesis 6: Antipsychotics used to treat psychosis lead to weight gain and, thus, induce eating disorder. Conversely, antidepressants used to treat eating disorder can trigger psychosis.

The prediction here is that the second disorder will disappear once the offending treatment is stopped.

Hypothesis 7: Psychotic symptoms are a marker of severity in eating disorders, while food refusal signals a severe and dangerous stage of psychotic illness.

This hypothesis lends itself to two predictions: (1) Patients diagnosed with an eating disorder who exhibit psychotic symptoms will display illness acuity markers-*e.g.*, low body mass index (BMI), electrolyte imbalance, severe depression, high levels of food restriction and purging, suicide attempts, long duration of illness, treatment resistance and a high mortality rate; and (2) Patients diagnosed with a psychotic illness who exhibit food refusal will similarly show markers of illness severity-*e.g.*, poor response to treatment, a large number of psychotic symptoms and signs, frequent hospitalization, involuntary hospitalization, high suicide rate, and a high mortality rate.

TESTING THE HYPOTHESES

Eating disorders and psychoses are entirely separate disorders

Conceptualizing eating disorders and psychotic disorders as falling into two separate, distinct DSM categories is the usual way of thinking about these disorders. The logical extension to acceptance of this belief is that the incidence of psychotic disorders such as schizophrenia for instance, among individuals with eating disorder, reflects their rate in the general population, and the incidence of eating disorders such as anorexia nervosa, for instance, among individuals with psychotic disorder, is on a par with their occurrence in the general population.

Early studies of eating disorder suggested a disproportionally high rate of associated psychotic illness. For instance, in a survey of 1017 eating disorder patients admitted to Danish psychiatric institutions during the period 1968-1986, Møller-Madsen *et al*[1] found that, among those who were rehospitalized during the same time period (which was true for 22%), the diagnosis was changed to psychosis in as many as 6%.

Belief in a disproportionate incidence rate in no longer credible. Once diagnostic criteria were more clearly specified and reliable interview instruments more widely used, the incidence of psychotic illness in the context of eating disorder was shown to be low. In an authoritative review that included 119 separate studies published in the English and German literature prior to 2002 (covering 5590 patients diagnosed with anorexia nervosa), Steinhausen[2] found that a concurrent diagnosis of schizophrenia was, indeed, rare. More recently, Miotto *et al*[3] found no cases of co-morbid schizophrenia among 112 female patients with DSM-IV eating disorders. Schizophrenia was found to be more prevalent, however, among men with eating disorder. Of 98 male veterans with eating disorder, 27 (28%) in one study received a concurrent diagnosis of schizophrenia or other psychosis[4]. This was over three times the rate of psychosis in male veterans who did not have an eating disorder and also over three times the rate of female veterans with eating disorder. One potential explanation for the gender difference is expectation. Clinicians generally do not expect to see eating disorder in men, so that the cognitive distortions and food phobias that accompany eating disorders, while interpreted as overvalued ideas in women, are seen as delusions in men, and therefore considered to indicate psychotic illness.

Although current literature considers full-fledged psychosis to be relatively rare, individual psychotic symptoms are not infrequent in the context of eating disorder. Miotto *et al*[3] found more 'paranoid ideation' and "psychoticism" on the Symptom Checklist-90-Revised[5] symptom checklist in eating disorder patients than in non-psychiatric controls of similar age. Earlier workers[6] had reported that 17 of 130 patients (14%) with eating disorder showed some signs of psychosis. Blinder *et al*[7] however, studying 2436 female inpatients with eating disorder (ED) in 2006, found psychotic symptoms in only 0.4%, (mostly in the restricting anorexia nervosa type of ED), a lesser percentage than the reported rate of psychotic symptoms in the general population[8,9].

Despite these findings, various reviews have reported the incidence of schizophrenia in patients with eating disorders to be between 3%-10%[10] and the incidence of transient psychotic episodes to be 10%-15%[11]. There seems to be no good evidence for such conclusions. Overall, the incidence of psychosis in eating disordered patients is approximately that of the population at large.

Looking at the question the other way around (the incidence of eating disorder in the context of psychosis), Götestam *et al*[12] studied 19000 Norwegian psychiatric patients using a staff report questionnaire and found that, among inpatient males with schizophrenia, 1.71% suffered from eating disorders. The figure was 2.88% for women. When outpatients were included, the percentage came down to 1.6% for males, but rose to 3.8% for females. This suggests that disordered eating occurs much less frequently in association with schizophrenia in men but, in women, more frequently in association with the kind of psychiatric problems (mostly depression and anxiety) found in outpatient clinics. The general population lifetime prevalence of anorexia nervosa, bulimia nervosa, and binge-eating disorder is estimated to be 0.3%, 0.9%, and 1.6% respectively[13]. Considering that community rates of ED are always much higher than rates derived from medical care settings (because most people with ED do not seek medical help), the Götestam *et al*[12] rates of ED in schizophrenia patients are, thus, substantially higher than expected in both men and women.

More recently, Fawzi *et al*[14] in Egypt found that the prevalence of disordered eating [defined by a score of $\geqslant$ 30 on the Eating Attitudes Test (EAT40)[15]] was 30% in 50 antipsychotic-naïve men and women with schizophrenia, compared to 12% in non-psychiatric controls. The patients also had significantly higher EAT40 mean scores than the controls.

The question, therefore, of whether eating disorders and psychotic disorders belong in separate categories of disease and occur together only by chance is unsettled. Perhaps because of help seeking and referral patterns (psychosis being of more clinical concern than ED), patients suffering from both disorders are more in evidence in psychosis services, such as the one to which the two cases described above belonged, than they are in ED services.

Symptoms of eating disorders lead to psychosis, and vice versa

ED patients may suffer from starvation, electrolyte, and metabolic imbalance, conditions that can provoke transient psychotic symptoms. Equally, patients with psychosis may suffer from food-related delusions-*e.g.*, the food is poisoned; the food is contaminated, that lead to food refusal.

If this were the case, one would expect the secondary condition to disappear once the trigger (starvation or

food delusion) were removed.

There are several case reports in the literature of psychosis following starvation caused by anorexia nervosa[16]. Mavrogiorgou *et al*[17] report the case of a 37-year-old woman with anorexia who, for four years, suffered acute paranoid-hallucinatory psychosis at the tail end of fasting episodes. During these four years, psychotic symptoms could not be elicited either before or after the fasting periods, which suggests a cause and effect relationship between the fasting and the psychotic decompensation. The authors hypothesize that the fasting led to acute hyperactivity of the dopaminergic system, giving rise to subsequent psychosis. It has been suggested that starvation is especially psychotogenic when it occurs during adolescence, a critical period for brain structural, neurochemical, and molecular changes[18] that are specifically critical in the regulation of dopamine pathways[19]. Starvation during early adolescence, more than in any other time period, may have a particularly damaging effect on the brain[20]. The duration and severity of starvation-induced psychosis, and ultimately how it is diagnosed and treated, may thus depend on the patient's age at the time of the starvation episodes[21].

On the converse side, patients with schizophrenia develop delusions about food that can subsequently lead to food refusal[22]. What starts as a delusion about food can progress to a condition that meets all the criteria of an ED.

Symptoms of one condition can, thus, act as risk factors for the other condition.

Symptoms of one condition protect against the other condition

The prediction here is opposite to that of hypothesis 2. Control of food intake provides a sense of mastery, achievement, and self-control to individuals who may be at risk for psychosis. The increase in feelings of self-efficacy can then help to ward off the psychosis. It is also possible that a symptom of psychosis, such as apathy for instance, can ward off an eating disorder.

If this were the case, then, in some individuals, recovery from ED would precipitate psychosis and recovery from psychosis would trigger an ED.

Deckelman *et al*[23] present four cases where schizophrenia and bulimia coexist and where the negative symptoms of schizophrenia appear to diminish the drive to restrict eating or the impulse to binge and purge. There are also case reports of psychosis that first manifests after a person has recovered from an ED[24]. Case reports are, of course, not evidence for or against a hypothesis. They merely demonstrate that reciprocal relationships, such as the ones described above, can and do occur. They were first suggested by David *et al*[25] and illustrated by a clinical case in which EAT40 scores[15] rose when psychosis was contained and declined when psychosis was at its peak. Hugo *et al*[26] presented four cases that showed the same reciprocal relationship. They argued that disordered eating can be used as a defense against a more fragile, disintegrated state such as psychosis. Yet again, in a review of male cases, Bou Khalil *et al*[27] conclude that, in general, symptoms of ED diminish when psychotic episodes flare and recur when psychotic episodes go into remission.

It is interesting to speculate why this reciprocal relationship might make sense. The pre-psychotic state is often accompanied by a distorted sense of agency and a loss of control[28,29] that can be initially counteracted by exerting control over eating. For example, Yamashita *et al*[30] reported the case of a 14-year-old girl whose anorexia nervosa, present for about two years, abruptly shifted after two weeks of hospitalization to an acute psychosis characterized by persecutory delusions and auditory hallucinations. All traces of the eating disorder disappeared, as if control over eating no longer served a purpose. Rojo-Moreno *et al*[31] recently reported two cases that followed a similar trajectory. There are several potential interpretations of these cases. The ED might protect against psychosis. It could also be argued that the ED was a prodrome of psychosis. Another possibility is that the antipsychotics used to treat the psychosis also cured the ED[32-35].

Eating disorders and psychotic disorders are marked by similar cognitive distortions, perceptual defects, genetic markers, physiologic and anatomical abnormalities

It can be argued that eating disorder and psychotic disorder are different expressions of the same illness, the distorted thoughts about eating being a form of delusion[36] (Mountjoy). Interestingly, auditory hallucinations, the hallmark of psychotic conditions, also occur in anorexia nervosa[23,31,37,38]. Depersonalization and derealization, too, are common symptoms of both disorders[11], as are overvalued ideas[39,40].

If the two conditions were different aspects of the same illness, family medical history should be positive for both disorders and successful treatment of one condition should cure the other as well. In addition, biochemical, cognitive, and anatomical deficits found in one condition should also be present in the other.

Data from the National Survey of American Life show an association between having a first-degree relative with schizophrenia and the lifetime development of bulimia, among other disorders[41]. Among other possibilities, this association could be the result of shared genes. The genetics of ED was recently reviewed by Trace *et al*[42]. They found that dopamine receptor D2 polymorphisms were significantly associated with anorexia nervosa, as they have been in genome-wide association studies in schizophrenia[43]. Significant associations have been shown between the Val158Met polymorphism of the catechol-O-methyl transferase gene and anorexia nervosa, and schizophrenia[44]. It is not unusual in modern psychiatric genetics to find that risk genes cross traditional diagnostic boundaries[45], suggesting the importance of epigenetic factors in the determination of specific psychiatric syndromes. In both ED and psychotic disorders, dopamine genes have been found to be dysregulated as a result of epigenetic influences[46].

With respect to treatment response, Wenokur *et al*[38]

present a case where an eating disorder and a psychotic disorder disappeared together in response to one treatment. Patients with ED co-morbid with psychosis have been reported to do well on drugs that act on the dopaminergic system[47,48]. Both disorders have been linked to altered dopamine activity, manifested in anorexia nervosa mainly by hyperactivity[49,50] and, in psychotic illness, mainly by delusions and hallucinations. Altered dopamine activity in ED is present even after recovery, suggesting that it is more than a sequela of undernutrition[51].

Many brain alterations are associated with anorexia nervosa and tend to be distributed across the same brain structures implicated in schizophrenia[52]. Studies have found abnormal functioning in ED in the frontal, limbic, occipital, striatal and cerebellar regions, deficits that sometimes persist after the patient has recovered, which suggests that the dysfunction is not merely a consequence of poor nutrition[53].

Many of the cognitive and social dysfunctions found in ED are reminiscent of those seen in psychotic disorders. A basic lack of trust leading to social isolation, poor therapeutic alliance, and poor treatment adherence is common to both disorders[54,55]. The ability to put oneself in the mindset of the other person (theory of mind) is deficient in both disorders[56], as are difficulties in shifting sets or rapidly being able to pass from one mode of thinking to another[57]. Similarity in these dimensions of illness is not, of course, limited to eating disorders and psychotic disorders.

While most of the work in these areas is new, the idea that ED and schizophrenia patients suffer from similar cognitive impairment had been suggested earlier by Yamashita *et al*[30].

The symptoms of one disorder can herald the onset of the other disorder

An ED can be the early sign of an impending psychosis, or psychotic symptoms can signal the beginning of an ED.

If such were the case, one disorder would precede the other and disappear when the other emerged.

Historically, at the beginning of the 20th century, French psychiatrists considered anorexia nervosa to be a prodrome for schizophrenia[58], and this idea subsequently entered British psychiatry[59,60]. As recently as 2013, a study of 11067 youth found that those who later developed a psychotic disorder (n = 21) had reported more ED symptoms at age 16 than those who remained free of psychosis[61].

The case against eating symptoms serving exclusively as a prelude to psychosis is made by case reports illustrating the fact that ED sometimes arises in the midst of an existing psychotic illness[10,17,21,62]. Even when ED does start first, in these cases it does not go away when psychosis appears, so it cannot be considered a prodrome. Sometimes, eating disorders occur very late in the course of schizophrenia. Stein *et al*[63] describe four elderly patients suffering from a chronic form of schizophrenia who, for the first time, developed eating disorders late in life. The schizophrenia, however, did not disappear when the ED emerged.

Erin Hawkes, who suffers from schizophrenia and has written an insightful book about her experience with this illness[64], writes about bulimia as a response to schizophrenia symptoms. The order of onset of eating disorder *vs* psychosis in those who eventually suffer from both conditions is so variable that neither can justifiably be considered a prodrome of the other. Shiraishi *et al*[65] convincingly illustrated this variability by graphing their eight cases.

The treatment of one disorder is responsible for the onset of the other

Antipsychotics used to treat psychosis instigate weight gain that subsequently induces eating disorder. By the same token, antidepressants used to treat eating disorders can precipitate psychosis.

If this were the case, the second disorder would disappear once treatment for the first were stopped.

Hawkes[66] writes that her bulimia worsened after treatment with olanzapine: "I was put on olanzapine. Terrible mistake: I was, within two months, 137 pounds of (in my opinion) fat. My purging went wild…. Olanzapine gave me a ravenous appetite…. Thus, purging became all-important".

There have been several reports of medication-induced bingeing resulting from treatment of eating disorder with antipsychotic agents[67-71]. A 2013 meta-analysis of 8 randomized trials of the use of the newer antipsychotic agents (six olanzapine, one risperidone, one amisulpride) for eating disorders concludes that, compared with placebo, their use was associated with a nonsignificant increase in BMI that exerted a nonsignificant effect on the drive for thinness and on body dissatisfaction[72], in other words, affording no reason to believe that treatment with antipsychotics worsened eating disorders. The doses prescribed were relatively low, however, (4.2 mg-10 mg for olanzapine), lower than would have been prescribed had the target been psychosis. The other potential explanation for the negative finding is that only two of the eight studies covered in the meta-analysis controlled for medication adherence. Many of the patients may not have taken their prescribed doses. The jury is still out, therefore, on the possibility that antipsychotic treatment can induce eating disorder.

With respect to treatments for ED that might precipitate psychosis, antidepressants, often used in the treatment of eating disorders, are known to sometimes result in psychosis[73,74].

Psychosis may be a severity marker in eating disorder. Conversely, not eating may be a severity marker for psychotic illness

If that were the case, then ED patients with psychotic symptoms might be more severely ill than other ED patients along a number of parameters such as duration of illness, treatment resistance and mortality rate. By the same token, food refusal could be a marker of severity in

psychosis patients. If so, it would be associated with non-response to treatment and a high mortality rate.

Other than the acknowledgement that three domains need to be considered to ascertain severity in ED-the psychological (*e.g.*, depression), the behavioral (*e.g.*, eating and purging behaviors), and the physical (*e.g.*, BMI; hyperactivity; electrolyte imbalance), there is no agreed upon severity scale for these disorders[75]. Early on, Lasegue[76] delineated three phases of "hysterical anorexia" as he called it, the first marked by an "uneasiness and fullness" after eating, with consequent reductions in food intake, the second marked by severe restriction, increased activity levels and an "intellectual perversion" resulting in a complete denial of the illness, and the third marked by "extreme emaciation, laborious exercise and general debility"[77]. Currently, the markers of severity are usually BMI, physical risk, and illness duration (not psychosis)[78]. The literature does not support a correlation of psychosis with severity in ED.

Nor is there any evidence to suggest that food refusal in the context of psychosis is an indicator of severity of psychotic illness, although not eating can aggravate psychotic symptoms[79,80] and, if left untreated, lead to death by starvation.

Both ED and psychotic disorders have a high mortality rate from suicide, substance abuse and medical complications. In ED, cardiovascular complications arise from malnutrition, dehydration, and electrolyte abnormalities, precipitating death by inducing heart failure or fatal arrhythmias. In psychotic disorders, the cardiovascular system is compromised by obesity and the metabolic complications of antipsychotic drugs[81-83]. Deliberate starvation can lead to death in persons with long standing psychosis but is not generally viewed as a marker of severity in psychotic illness.

CONCLUSION

The combination of eating disorder and psychotic illness is more often seen in services for psychotic disorders than in eating disorder services, probably because psychotic symptoms take precedence in terms of referral. The "doubly disordered" risk being undertreated in schizophrenia services because the ED may appear trivial in comparison to the more flagrant psychotic symptoms and may worsen insidiously due to the effects of weight gain induced by antipsychotic medication. Clinicians need to be aware of the fact that, because of undernutrition, ED can precipitate a state that looks like psychosis, but that is usually transient. During adolescence, however, when the developing brain is exquisitely vulnerable to insult, acute starvation may kindle a psychosis that takes on a life of its own. It is also the case that the delusions of a primary psychotic condition can lead to food aversions and initiate dangerous eating behavior. Some have argued that ED symptoms can protect against the development of psychosis and psychotic symptoms can protect against ED. This may be true for some individuals, and clinicians need to be alert to this possibility. Some dimensions of illness are common to both conditions and research in this area is accelerating. Also clinically interesting is the phenomenon of eating disorders serving as a prodrome or early stage of psychosis, and eating disorders emerging as a result of the treatment of psychosis. Reports of such cases have been relatively prevalent; phenomena of this sort need to be documented and better studied.

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REVIEW

Antecedents and sex/gender differences in youth suicidal behavior

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Abstract

Suicide is the second leading cause of death in youth globally; however, there is uncertainty about how best to intervene. Suicide rates are typically higher in males than females, while the converse is true for suicide attempts. We review this "gender paradox" in youth, and in particular, the age-dependency of these sex/gender differences and the developmental mechanisms that may explain them. Epidemiologic, genetic,

neurodevelopmental and psychopathological research have identified suicidal behaviour risks arising from genetic vulnerabilities and sex/gender differences in early adverse environments, neurodevelopment, mental disorder and their complex interconnections. Further, evolving sex-/gender-defined social expectations and norms have been thought to influence suicide risk. In particular, how youth perceive and cope with threats and losses (including conforming to others' or one's own expectations of sex/gender identity) and adapt to pain (through substance use and help-seeking behaviours). Taken together, considering brain plasticity over the lifespan, these proposed antecedents to youth suicide highlight the importance of interventions that alter early environment(s) (*e.g.*, childhood maltreatment) and/or one's ability to adapt to them. Further, such interventions may have more enduring protective effects, for the individual and for future generations, if implemented in youth.

Key words: Suicide; Attempted suicide; Sex; Gender; Child; Adolescent; Review

Core tip: Previous research has demonstrated clear and consistent sex-/gender-specific patterns in the continuum of suicidal behaviour. Here, we review epidemiologic, genetic, neurodevelopmental and psychopathological research to identify and discuss explanations for these findings. We propose antecedents to youth suicide and highlight the importance of early intervention. Understanding the mechanisms underlying sex/gender differences in youth suicidal behaviour could help identify strategies to reduce suicide risk across the lifespan.

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INTRODUCTION

Problem

Suicide is the second leading cause of death among young people globally with substantial social and economic costs[1]. While youth suicide rates vary widely across and within countries[2,3], in developed countries, with good-quality vital registration data[1], rates are at least 2 to 3 times higher in boys than girls[4,5]. Suicide rates have declined in boys since the 1990s, but there is concern that in some countries, rates have increased for girls[6] and the downward trend in boys, is now reversing[7]. However, it is unclear how best to intervene to reduce suicide risk in youth[8]-a problem that may be resolved, in part, by addressing sex/gender differences in suicidal behaviours.

Gender paradox

Herein, the "gender paradox"-higher suicide attempt rates in females but higher suicide rates in males-merits attention[9]. In particular, this paradox is age dependent. For suicide attempt rates, the sex/gender difference (F > M) increases with age peaking in mid adolescence[10-13], whereas for suicide rates, the sex/gender difference (M > F) steadily climbs until early adulthood[1]. Although suicide attempt data are self-reported, hospital presentation data reveal the same pattern[14-17] and suicide misclassification seems an unlikely explanation[18]. Why do these changes occur and could this knowledge help us reduce suicide risk in boys and girls?

Purpose of this review

We build on developmental perspectives of youth suicidal behaviours[2,19] to advance our understanding of the mechanisms underlying the gender paradox, which may help focus approaches to youth suicide prevention. In the following sections, we examine the continuum of suicidal behaviours in boys and girls, synthesizing findings from epidemiologic, genetic, neurodevelopmental and psychopathology research to propose key mechanisms. We then highlight how these mechanisms operate within the sex/gender developmental contexts in which youth live, which if modified, may reduce their suicide risk.

Terminology

"Boys" and "girls" refer to youth ages 10 to 24 years[20]. "Sex/gender" is used rather than "sex" or "gender" to signify the complex interplay of social and biological determinants[21]. Most findings are limited by dichotomous measures of sex/gender[22], and to Western cultures. We defined suicidal ideation, attempts and suicide according to standard nomenclature[23]. Hereafter, hospital presentation data on self-inflicted injuries and poisonings are referred to as "hospital presentations" or when admitted, "hospital admissions". For both, unless otherwise noted, suicidal intent was unspecified.

SEX/GENDER DIFFERENCES IN THE CONTINUUM OF SUICIDAL BEHAVIOUR

In this section, we review the epidemiologic evidence for a proposed continuum from suicidal ideation to behaviours, with those attempting and dying by suicide experiencing a greater burden of risk[24-26].

Suicide attempts

Several factors complicate our understanding of suicide attempts in boys and girls as they age. First, knowledge from community-based samples (*i.e.*, school or household surveys) may be slanted to girls because girls have a higher past year[27-30] and lifetime prevalence[25,29,31,32] of suicidal ideation and attempts than boys between the ages of 12

to 24. Second, depending on the study design, younger youth may not be well-represented given the prevalence of suicide attempts is highest in mid adolescence, and the lifetime recall of suicide attempts is inconsistent, particularly at early ages[33]. Third, community-based surveys tend to represent more common, but less lethal behaviours. For example, although 8.0% of United States students (grades 9 to 12) reported a past year suicide attempt, the proportion reporting their attempt was treated by a doctor or nurse was only 2.7% (higher in girls than boys, 3.6% *vs* 1.8%)[28]. The sex/gender difference in youth suicide attempts (F > M) only diminishes among hospital presentations in medically serious suicide attempts (largely self-poisonings)[34] and reverses (M > F) with increased lethality of methods (*e.g.*, hanging and firearms)[35,36].

With these caveats, we review prospective community-based studies where the temporal ordering between potential predictors of suicide attempts is less ambiguous, to illustrate cumulative risks and potential causal chains in boys and girls as they age. Suicidal ideation, tied to depression[10,37], is a predictor of a later attempt[24,37,38]; but more for girls than boys[10,26]. Further, when depression and suicide attempts were compared by age in girls, suicide attempts declined in older girls (narrowing the F > M difference) but depression did not[10], raising the question what accounted for this decline and its relevance to suicide prevention?

Other longitudinal studies have shown that suicide attempt risk is predicted by early adverse environments and early psychiatric morbidity. However, it remains unclear whether boys' and girls' pathways differed. For example, in a New Zealand birth cohort study[39], after adjusting for predictors collected prior to ages 15 to 16: lower socio-economic status (SES) at birth, parental alcohol problems, childhood sexual abuse and poor parental attachment along with predictors collected at ages 15 to 16: neuroticism and novelty seeking, the initially higher risk of a suicide attempt in girls compared to boys between the ages of 15 to 21 was attenuated (RR = 1.73 to 1.17). While tentative, this attenuation of risk hints that the F > M difference in suicide attempts is mediated by one or more of these predictors. Also, this study noted that the predictors' effects were later largely mediated by mental disorders and stressful life events, except for low SES at birth, neuroticism and novelty seeking. That is, the predictive power of early adverse environments on suicide attempts was reduced as youth aged, mediated, in part, by psychiatric morbidity and stressful life events.

Further research indicated that for youth who attempted suicide, psychiatric morbidity was evident earlier than age 15, coinciding with environmental effects. In a study of kindergarten students[40] teacher-rated trajectories of anxiousness and/or disruptiveness (between the ages of 6 to 12) predicted lifetime suicide attempts by age 15 to 24. Sex/gender (along with childhood sexual abuse before age 18 and a family history of suicide attempts) remained predictive. Potential sex/gender differences in these pathways and possible mediators of sex/gender differences were difficult to interpret, though, as the study attrition in boys was 50% and the temporal sequence of events, uncertain. Notably, boys were overrepresented among students with disruptiveness or both trajectories by age 12; however, girls with both trajectories were most likely to report a suicide attempt at ages 15 to 24[40].

Suicide

We now consider how boys and girls differ along the continuum from suicide attempts to suicide as they age. Given suicide rates are higher in boys and increase with age, samples may be slanted more towards older males. Because youth suicide is rare[1], information from studies of community-based samples often comes from retrospective "psychological autopsies". Such studies typically have small samples and rely on informants' recall, usually family members. Informants may have difficulties reporting on more personal or distant aspects of the decedent's life (*e.g.*, childhood sexual abuse or a suicide attempt). Differential reporting may be overcome by interviewing similar informants for both controls and decedents but problems of statistical power preclude testing some associations. Suicide attempts and suicides share many predictors, including early adverse environments[2]; however, the temporal sequencing between predictors, and by sex/gender, has been harder to discern for suicide.

A prior suicide attempt is one of the strongest known predictors of youth suicide[2], but potential sex/gender differences overall, and by age of onset are unclear. Prospective hospital presentation data confirm these youth have a higher suicide risk (about 10 times) than their peers[41]. Suicide risk is strongest in the year after the presentation, but remains elevated in subsequent years[42]. However, these risks likely differ by age and method. Unlike older samples where a hospital admission with a more lethal method (*vs* self-poisoning) predicts suicide in men and women[43], in youth aged 10 to 18, a hospital presentation for self-cutting (*vs* self-poisoning) is more predictive of suicide[42], a method of lower lethality[44,45], associated with repetition[42]. Repeat (*vs* single) hospital presentations are more strongly associated with suicide, particularly in girls[46]. However, self-poisonings, usually medication overdoses in Western cultures[14], are the most common hospital presentation among youth[3] and sex/gender differences in lethality are not evident here[44].

In a case-control study of suicidal behaviour under age 25, youth who died by suicide and those who made a medically serious suicide attempt shared most predictors, including a prior suicide attempt[35], and only two predictors discriminated these youth: sex/gender and a current mood disorder. Compared to youth who made a medically serious suicide attempt, youth who died by suicide were more likely to be male (81.7% *vs* 45.6%) but were less likely to have a current mood disorder (30.0% *vs* 71.2%). Differential reporting of mood symptoms by the informants seemed less likely given the severity of the events being compared. Supplementary analyses revealed

that the higher proportion of boys among youth who died by suicide was explained by their lower prevalence of a current mood disorder and greater prevalence of a highly lethal method. The possibility that younger age, early adverse environments (*e.g.*, childhood sexual abuse) and dimensional measures of psychiatric morbidity (*e.g.*, impulsive aggression, defined below) might predict more lethal methods was unexplored. Compared to peers, childhood sexual abuse was associated with a medically serious suicide attempt (OR = 7.4) as well as a current substance use disorder (OR = 3.1). However, such comparisons with peers were not reported for youth who died by suicide. While not explicitly tested, a lifetime history of antisocial behaviour (26.7% *vs* 36.8%) or of care for mental health problems (50.0% *vs* 68.8%) appeared less prevalent in youth who died by suicide than among those with a medically serious suicide attempt.

In keeping with the findings on youth suicide attempts[40], a Finnish birth cohort study[47] found parent and teacher ratings of anxiety and/or conduct disorder at age 8 predicted later hospital admissions and/or suicides among boys aged 8 to 24. Yet, measures of psychopathology at age 8 were not predictive in girls, implying different pathways and timing of effects in boys and girls.

Collectively, these studies demonstrate important differences between boys and girls in the prevalence and lethality of suicidal behaviours; however, the reasons for these differences and the timing of their effects, critical for prevention efforts, have seldom been studied. Nevertheless, community-based studies support a model of youth suicide attempts whereby their onset is predicted by early adverse environments in concert with differing, early psychiatric morbidity (*i.e.*, neuroticism, anxiousness *vs* novelty seeking, disruptiveness). Past suicidal ideation (and concurrent depression) may be more predictive of suicide attempts in girls than boys, and among girls, most predictive in mid adolescent *vs* older girls. With respect to suicide, the effect of a prior suicide attempt may differ in boys and girls, dependent on the method's lethality and care for mental health problems. Community-based and hospital presentation studies indicate that the proportion of boys (*vs* girls) with a suicide attempt increases with the attempts' lethality and at this end of the continuum, factors other than a current mood disorder seem significant. However, what these factors are (*e.g.*, early adverse environments and/or other types of psychiatric morbidity) and how they may differ in boys and girls with age, influencing mental health care is uncertain. In the following sections, we turn to other lines of evidence to improve our understanding of the inter-relationships between early environments, psychiatric morbidity, help-seeking and the gender paradox.

SEX/GENDER DIFFERENCES IN GENETIC VULNERABILITIES AND SUICIDAL BEHAVIOUR

Suicidal behaviours aggregate within families after controlling for familial transmission of mental disorders (unlike suicidal ideation) and this transmission does not seem to be explained by imitation effects[48]. Further, there is some evidence that the elevated risk of suicide among offspring exposed to a parent's suicide is highest among youth who were under the age of 17 when exposed. Impulsive aggression, (*i.e.*, reacting with hostility or aggression to frustration or provocation)[48], may mediate the familial transmission, and stem from genetic vulnerabilities and/or adverse early environments[49]. It has been hypothesized that vulnerabilities to suicide arise from gene/environment interactions occurring during critical windows of brain development. Identifying sex/gender developmental differences may help focus targets for intervention[50,51].

More specifically, there is evidence that early adverse life events, particularly childhood maltreatment (physical or sexual abuse, neglect), have an enduring impact on the brain both through genetic vulnerabilities (*e.g.*, variation in single nucleotide polymorphisms) and telomere erosion making some individuals more vulnerable to brain changes and through "epigenetics"[52-56]: changes in gene expression mediated by altered chromatin without modifying the DNA sequence[57]. While the genetic structure (genotype) transmitted to offspring from their parents at conception is unchanged, offspring gene expression may be modified by environmental exposures. Several epigenetic mechanisms have been proposed, which could in theory, influence sex/gender differences in psychopathology, (*e.g.*, sex hormone induced differences and/or differential exposures to environmental risk factors, including drugs of abuse and child maltreatment)[54,58]. There is an ongoing debate about parent-to-child transmission of epigenetic effects[59].

Youth who die by suicide experience child maltreatment more often than their peers and at an earlier age than their peers-in one study the respective proportions were: 60.0% *vs* 18.0% by age 9 and 77.0% *vs* 34.0% by age 14[60]. Thus, it seems that for many youth who die by suicide, their neurodevelopment was affected, and dependent on their age, may have had an enduring impact, creating a "diathesis"[61] affecting their ability to flourish cognitively, emotionally and behaviourally in their environments[40,53]. We highlight childhood sexual abuse, as it has been found to be associated with suicide attempt(s), independently of other forms of child maltreatment in cross-sectional studies among youth. Further, the magnitude of this association is stronger in boys than girls[62,63]. Yet, this sex/gender difference is not evident in adults[64] implying the nature and timing of the abuse differs for boys and girls. In fact, there is some evidence that for boys, childhood sexual abuse typically occurs prior to puberty; is more forceful and usually perpetrated by another male. However, boys are less likely than girls to disclose the abuse. The lack of this sex/gender difference in adults may be explained, in part, by differential reporting and/or selection biases, including mortality[62,64].

Given that brain plasticity lessens in adulthood, interventions that alter environment(s) and/or an individual's

adaptations to it, may have more enduring protective effects (*i.e.*, for those individuals and future generations) if first implemented in youth. In the next section, we describe how neurodevelopmental disruptions may give rise to different types of psychopathology in boys and girls which may then, contribute to the gender paradox.

SEX/GENDER DIFFERENCES IN NEURODEVELOPMENTS AND PSYCHOPATHOLOGY

Increasingly, psychopathology is viewed within a neurodevelopmental lens[58,65,66]. However, current nosology systems [*e.g.*, the Diagnostic and Statistical Manual (DSM) for Mental Disorders and the International Classification of Diseases] are based on categorical clusters of signs and symptoms which lack neurobiological substrates. Thus, mental disorders are defined and measured relying heavily on how signs and symptoms are communicated and considered abnormal within cultures. Lack of knowledge, stigma and discrimination may prevent disclosing symptoms. Suicidal behaviours are still illegal in some countries[1]. It is only recently, (*i.e.*, within DSM 5), that suicidal behaviours have been identified separately from mental disorders, (*i.e.*, not presumed to be fully explained by a mental disorder)[67]. Increasingly, research is employing dimensional systems, including biological measures, to better capture sub threshold conditions and changes over time. Categorical systems have been criticized for producing somewhat arbitrary boundaries, possibly confusing temporal sequences and shared/unique etiologies. Nonetheless, standard diagnostic criteria across time and place provide useful "phenotypic" information which can be refined, iteratively, as knowledge grows about etiological substrates "ranging from environmental disruptions to genetically determined syndromes"[65]. These paradigm shifts may be particularly helpful for youth suicide prevention efforts, improving early detection. More specifically, although nearly 90% of youth who died by suicide were identified as having a mental disorder in psychological autopsy, up to 40% under age 15 did not meet diagnostic thresholds[2]. Further, many of the youth diagnosed with mental illness after death, may have been previously undiagnosed and untreated for mental illness.

In recent years, structural and functional magnetic resonance imaging studies have illustrated normal and abnormal brain development in youth. Puberty begins around age 8 to 11 for girls and for boys, on average, one year later[68]. During puberty, the brain is more "plastic", allowing youth to explore and master changing environments requiring greater autonomy. Over time, grey matter peaks and then declines while white matter increases (myelination), reflecting the brain's organizational changes where the most frequently used connections are strengthened and preserved. Disrupting these processes can influence the onset of mental disorder. For example, accelerated grey matter loss has been found in youth who transition to psychosis[69]. With maturation, the prefrontal cortex becomes increasingly involved in modulating responses to novel or rewarding events. Exogenous behaviours (automatic responses to external stimuli – one definition of impulsivity)[70]-tend to become balanced by more endogenous, goal directed, planning behaviors[68,71]. Indeed, engagement in "risky" behaviours seems to peak during adolescence but then decline[72,73], not unlike the age-suicide attempt distribution evident in girls[10]. Given sex-by-age interactions occur in cortical development, including faster myelination in girls than boys[74], disruptions in neurodevelopment, prior to or during this time may solidify with maturation contributing to the onset of different psychopathologies in boys and girls.

The way youth exert cortical control in response to threats and rewards depends upon the subcortical brain. Indeed, heightened behavioural inhibition has been posited to place youth at greater risk for mood and anxiety disorders[75]. It is noteworthy then, that the amygdala is highly connected to both cortical and subcortical brain regions and is one of the few regions known to contain sex hormone receptors. Thus, dependent on early social and biological environmental exposures, which may vary by sex/gender, amygdala development seems critical in how boys and girls appraise and respond emotionally and behaviourally to their environments. The amygdala is involved in face processing (social cues), fear learning and extinction and can modulate HPA activity (the fight or flight stress response). The rate of amygdala growth is related to pubertal development in boys and girls[76,77]. Girls tend to have larger left amygdala volumes than boys (aged 10 to 22 years)[78]. Further, a recent longitudinal study found that increased amygdala growth from ages 12 to 16 years was associated with onset of depression in girls (ages 12 to 18) but not boys[79]. Reduced amygdala activity has been linked to callous-unemotional traits, such as reduced responses to other's fear, mediating proactive (*vs* reactive) aggression in conduct disordered youth[80]. The above neurodevelopmental findings have some consistencies with knowledge about sex/gender differences in youth mental disorders. In the following section, we review sex/gender differences in the general population of youth and then, among youth who die by suicide.

SEX/GENDER DIFFERENCES IN TYPES OF MENTAL DISORDERS AND SUICIDE

Prospective and retrospective studies confirm that 50%-70% of adults with a mental disorder had one in their youth[81]. In particular, disruptive or "externalizing" disorders: Attention Deficit Disorder with Hyperactivity (ADHD), Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), are more prevalent in boys than girls, and internalizing disorders: Depression, Anxiety, including Post-Traumatic Stress Disorder, more prevalent in girls than boys[82,83]. ADHD declines with age, whereas

depression and substance use disorders increase[84]. Anxiety disorders tend to precede depression (with some continuing to co-occur with depression)[75]. Externalizing disorders (rather than internalizing ones) seem to precede adult substance use disorders and there is continuity between youth and adult substance use disorders[81]. Substance use disorders may be more prevalent in boys than girls[82].

A puzzling question pertaining to sex/gender differences in psychopathology is why do seemingly different psychopathologies, internalizing and externalizing, co-occur? Population-based research indicates that ODD is linked to such co-occurrences, not CD or ADHD[85]. Further, the ODD link seems to be explained by irritability and has been posited as a mood disorder variant[85,86], newly captured in DSM 5 as Disruptive Mood Dysregulation Disorder[87]. Still, the need to better characterize irritability and its persistence over time is recognized given that irritability may precede and/or be better explained by other disorders (*i.e.*, personality and/or bipolar spectrum disorders often not identified in population-based studies of youth[88,89] but may vary in age of onset and by sex/gender)[90,91].

For example, there is some evidence that when externalizing behaviours (especially those before age 13) precede depression, youth are more likely to experience an irritable depression at age 18[92]. Further, among depressed youth, those most likely to be depressed and irritable (*vs* depressed, not irritable) were boys (OR = 4.26). Notably, depressed boys did not differ from depressed girls on non-episodic irritability but rather, "a change in the child's usual liability to be precipitated into anger"[93]. In contrast, when girls were depressed and irritable, they exhibited more CD (but not ODD symptoms) than boys. Most of the depressed youth (70%), stayed in the same depression-irritability group into adulthood (ages 19 to 21)[93], implying that reactive (*vs* proactive) aggression persisted among depressed and irritable boys (*vs* girls). Aggression, (intent to hurt or harm another) is more likely physical in boys and indirect (relational) in girls[94]. Instrumental or proactive aggression has been related to psychopathy, whereas, reactive aggression is thought to arise from difficulties regulating emotional responses to threats[95].

As noted earlier, nearly all youth who died by suicide were identified in studies as having a mental disorder. The most common, strongest risk factors were prior mood, substance-use and disruptive disorders. Combinations of these disorders lead to higher risks. Given mental disorders, particularly mood and substance use disorders, are more common in suicides among older youth[96-98], disruptive disorders would seem implicated in younger youth, consistent with studies on youth suicide attempts[39,40,47]. Compared to girls, boys' suicides more often include prior disruptive and substance use disorders. In contrast, girls' suicides are more likely to include prior mood or eating disorders[2,97-100]. Schizophrenia, though rare, is also a strong risk factor. Still, it may be more common in boys than girls, due to earlier onset in boys[101,102].

Few studies of youth suicide have employed dimensional measures of psychiatric morbidity. In one, dimensional measures of harm avoidance (correlated with anxiety and mood disorders) and irritability (correlated with substance abuse) and aggressive acts (correlated with CD) distinguished youth who died by suicide from their peers[103]. Another study (all ages), found that measures of impulsivity and aggression were associated with a younger age at suicide, independent of mental disorders[104]. It is well established that substance use disorders are associated with suicide in older youth, particularly males, but less so in older adults[104]. However, there has been less study of the acute effects of alcohol consumption on suicide among youth[105,106]. Alcohol may proximally enable suicidal acts, by decreasing arousal or fear and/or inhibitions to act (*i.e.*, decrease anxiousness but increase impulsivity). Studies examining alcohol concentrations among those who died by suicide indicate about one third were intoxicated at the time of their death. In fact, alcohol (at any level) was higher among males than females and younger persons[107,108].

SEX/GENDER DIFFERENCES IN PERCEIVED THREATS AND LOSSES

Sex/gender differences in adverse early environments not only shape early risks, but may be compounded by social expectations or norms, arising in subsequent developmental contexts, influencing not only how youth perceive threats or losses, but how they adapt to them. Gender has been described as a relational concept, something that is performed, which may be relatively stable in some contexts but not others[109]. While youth are not passive, their micro and macro level social contexts may model and reinforce conformity to expected "masculine" or "feminine" perceptions, emotions and behaviours[110], *via* differential monitoring, rewards/punishments[109,111]. The degree of monitoring and rewards/punishments likely varies across cultures and within social networks but may be differentially directed to boys or girls and developmentally conditioned.

Conflicts arise when youth are unable to meet their own or other's sex/gender expectations, hopes or aspirations, and specific developmental contexts may be particularly adverse or threatening. Feelings of defeat/humiliation or entrapment (*i.e.*, inability to escape), with low levels of social support may increase risk of a suicide attempt[112]. The transition to adulthood is accompanied by numerous changes, challenging youth's sense of self or identity. Perceived pubertal timing (earlier in girls, later in boys) has been found to prospectively predict youth suicide attempts[37]. In addition to the biological and physical changes of puberty, youth face varying sex/gender expectations to master transitions to adulthood, including: academic performance; entering the labour force; forming new social networks/peers outside the family, including romantic partner(s) and possibly, having children/parenting.

Younger youth may be influenced more by adults (parents, teachers); whereas, older youth, by their peers[76].

Among youth who died by suicide, interpersonal stressors have been associated with suicide and vary with age. Before age 16, family conflicts were apparent; whereas, in older youth, conflicts occurred within a romantic relationship[98]. Media exposures (*e.g.,* TV, movies, online/social media) may act as a "super peer" by modeling values and behaviours[113]. Indeed, there is concern about how the growing use of less regulated, more interactive media among youth contributes to suicidal behaviours[114]. Knowledge of and access to lethal methods is socially scripted[109], and knowledge of a peer (but not necessarily a friend) who died by suicide is prospectively associated with a suicide attempt in youth[115].

Before we highlighted how early adverse environments, in particular child maltreatment, may differ for boys and girls, increasing their suicide risk. As youth age and their social environments expand, they may face new, adverse or threatening environments which vary by sex/gender and developmental context. For example, peers may discriminate against sexual minorities and/or promote unrealistic expectations such as an idealized physical appearance. Bullying involves an imbalance in power, is intentional and repeated, occurring online and offline. Both bullies and those who are bullied are more likely to experience suicidal ideation and attempt suicide. Although the association with being bullied (peer victimization) and suicidal ideation does not seem to differ by sex/gender, it is unclear whether is true for suicidal behaviour[116]. However, as mentioned, boys and girls differ in how they express aggression, which is related to how they bully[117,118]. Intimate partner violence contributes to suicide attempts, an association most evident in girls[119]. Sexual minority youth are known to be at a greater risk of suicide attempts. Not only do they encounter bullying from their peers, but they may also face rejection, maltreatment and discrimination from family and others during a critical time in their development[120-123].

It has been postulated for boys beginning to define themselves as adult men. It may be especially difficult to attain "masculine" norms of personal autonomy and attainment. Such ideals may be discrepant with actual achievements and/or broader socio-economic realities, undermining the "human need to belong and form lasting significant personal relationships"[124]. Men have been found to have greater mental health risks than women during acute economic downturns, (*i.e.*, increased unemployment). In particular, European men aged 15 to 24 were most affected by the 2008 global economic recession, with an 11.7% increase in suicide rates[7].

Qualitative studies illustrate how micro environments may reinforce masculine norms of personal autonomy and attainment as youth age. Mac An Ghaill *et al*[125] 2012 described how British pre-adolescent boys were confused and unhappy with treatment from teachers. For example, teachers praised girls for being good pupils, and physically separated boys from "their mates" encouraging isolation and competition between them. Further, among their peers, boys learned not to speak of being scared by "real things" to avoid exclusion[125]. In another study, Irish men (aged 18 to 30 years) seen in hospital after attempting suicide identified that their lower educations limited their opportunities, including moving out of their environments[126]. Given their backgrounds, they did not recognize their experience as connected to mental illness, nor did they see treatment as relevant. Some spoke of being unable to "come out" as gay. (A problem inherent in suicide risk determination in psychological autopsy studies[127] but also in inferences about major causes of mortality)[128]. Instead, men tried to mask their "pain" through alcohol and/or drugs to project strength. When their "pain" worsened, including sleeplessness, they did not tell others as they feared being rejected by their peers for being weak and burdening their partners, who might leave them.

These experiences not only mirror "thwarted belongingness and perceived burdensomeness"[129], but also neuroimaging studies demonstrating pain networks are activated when social exclusion is perceived[130]. Also, according to this Interpersonal Theory[129], the acquired ability for suicide comprises habituation to pain. Still, most research on pain sensitivity has examined non-suicidal self-injury rather than suicidal behaviours in youth[112]. Denying or suppressing pain has been posited as more common in male youth, of relevance to the gender paradox[131].

SEX/GENDER DIFFERENCES IN ADAPTATIONS TO PAIN

Fearful youth may avoid some contexts given heightened sensitivity to non-rewarding cues. Self-disclosure may be viewed as potentially harmful[110,132,133]. Further, if youth are oppositional and/or aggressive, they may be unwantedly or unexpectedly rejected by their peers. Affiliation with more "deviant" peers may be rewarding, provided such peers can be found and are more tolerant. However, isolation may be reinforced, and the impact of threats or loss, stronger[110]. Affiliating with delinquent or substance abusing peers has been associated with a suicide attempt among youth[134,135] and contributes to adjustment difficulties among youth exposed to childhood sexual abuse[136].

Substance use

Given "masculine" norms of personal autonomy, boys may try managing pain through substance use. In some contexts, including birth cohorts, alcohol use is more socially acceptable and males provided more drinking opportunities[137,138]. Further, given opportunities to drink alcohol, youth with a history of childhood sexual abuse are more likely to do so[138] and boys (but not girls) with a history of sexual abuse tend to binge drink more than their peers[139]. While alcohol may be used to self-medicate[140], binge drinking is associated with

Table 1 Proposed sex/gender antecedents of youth suicide

Genetic vulnerabilities and sex/gender differences in early adverse environments affect neurodevelopment and sex/gender differences in:
Early internalizing and externalizing (co)morbidity where ODD ± anxiety symptoms or disorders precede:
Irritable depression with more reactive or "impulsive" aggression in boys
Irritable depression with more proactive or "planned" aggression in girls
Substance misuse
Mood and/or substance use disorders (not necessarily diagnosed or treated)
Sex/gender differences in perceived threats and losses
Sex/gender differences in adaptations to pain (*e.g.*, disclosure, and to whom) and suicide attempt methods

ODD: Oppositional Defiant Disorder.

a temporary increase in depression which improves after 2 to 4 wk abstinence. Thus, if drinking is stopped or controlled, it may not be perceived as problematic. However, if it continues, intake will likely increase contributing to social isolation/exclusion, *e.g.*, through academic/work difficulties and/or aggressive acts[19,141,142]. Notably, an interpersonal loss, (*e.g.*, a romantic breakup), has been found to independently increase the risk of suicide for boys (under age 20 years), but not girls, possibly because girls had more confidants[143]. Further, such interpersonal loss has been more strongly associated with youth suicide in the presence of substance abuse and the absence of conduct disorder (but not influenced by depression)[144,145].

Help-seeking

Masculine norms of personal autonomy may also prevent boys from seeking help. Youth help-seeking preferences have been examined in relation to: the source of help (*i.e.*, informal: family and friends or formal: health professionals), the type of problem and timing. Surveys of high school students suggest that the developmental trends differ in boys and girls. That is, over the course of high school, girls increasingly identify friends and professionals as likely sources for help with personal-emotional problems, with less dependence on family. Although boys also report seeking out family members less, they do not compensate with friends or professional help as much as girls[146]. Others have examined help-seeking attitudes in boys and girls. In a self-report attitude survey (in six high schools) on managing suicidal behaviour and depression, boys were more likely to endorse items consistent with avoidant strategies (including not telling others). In contrast, girls, scored higher on approach strategies[147]. Further, while both boys and girls tended to connect suicide with adverse life experiences rather than mental disorder, this was truer for boys than girls[148]. Such a stance may reinforce the desire for self-management. In a study among university students who screened positive for depression, alcohol use or prior suicide attempt, the main reason for not seeking professional help was their problems were minor or transient, most apparent among heavy alcohol users[140]. In sum, youths' interactions with others in specific contexts may not only contribute to perceived threats and losses and pain and but also, how youth adapt to these experiences.

CONCLUSION

The age-dependent gender paradox observed in youth may be explained by several factors that vary according to genetic vulnerabilities and the contexts boys and girls are born into and interact with as they age. In this final section, we return to the premise, introduced earlier, that given brain plasticity lessens in adulthood, interventions that alter environment(s) and/or a youth's abilities to adapt to them, may have more enduring protective effects (*i.e.*, for those individuals and future generations) if first implemented in youth. Integrating findings on sex/gender differences in the continuum of suicidal behaviour with genetic, neurodevelopment, psychiatric (co)morbidity and social contexts that shape sex/gender perceived threats and losses and adaptations to pain, we propose the following antecedents to youth suicide (Table 1) which, if acted on, may reduce suicide risk in boys and girls.

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MINIREVIEWS

Racial disparities in psychotic disorder diagnosis: A review of empirical literature

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Abstract

Psychotic disorder diagnoses are common in the United States and internationally. However, racial disparities in rates of psychotic disorder diagnoses have been reported across time and mental health professions. This literature review provides an updated and comprehensive summary of empirical research on race and diagnosis of psychotic disorders spanning a 24-year period. Findings reveal a clear and pervasive pattern wherein African American/Black consumers show a rate of on average three to four higher than Euro-American/White consumers. Latino American/Hispanic consumers were also disproportionately diagnosed with psychotic disorders on average approximately three times higher compared to Euro-American/White consumers. In addition, a trend among international studies suggests that immigrant racial minority consumers receiving mental health services may be assigned a psychotic disorder diagnosis more frequently than native consumers sharing a majority racial background. Potential explanations for this phenomenon are discussed, including possible clinical bias and sociological causes such as differential access to healthcare and willingness to participate in mental health services. Directions for future research should include the exploration of disproportionate diagnoses according to race through qualitative interviewing as well as empirical investigation.

Key words: Race; Ethnicity; Psychosis; Diagnosis; Review

Core tip: An updated review of empirical research related to race and diagnosis of psychotic disorders is provided. This manuscript concludes with addressing potential causes of racial diagnostic disparities with implications for future research. Although the topic of race and diagnosis has received increasing attention in the professional literature, a full review of empirical studies is needed to summarize patterns among research results. Due to the broad consumer implications of psychotic disorder-related misdiagnosis (*e.g.*, social stigma, hospitalizations, psychotropic medications, relational and employment discrimination, and increased risk of suicide) better understanding of this phenomenon is clearly warranted.

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INTRODUCTION

Cultural sensitivity is imperative when providing services to consumers in the field of healthcare, especially mental health care given the priority placed on valuing diversity, objectivity, and the ethical principles of beneficence and nonmaleficence[1,2]. The importance of being a culturally competent and sensitive clinician is necessitated by the mental health field when working with consumers. In particular, mental health professionals have the obligation to ensure cultural sensitivity and objectivity when providing a differential diagnosis. Assigning a mental disorder diagnosis primarily influenced by personal perceptions of or stereotypes about consumers' ethnicity or culture risks inadvertently harming consumers psychologically or socially through misdiagnosis. According to professional standards of care, mental disorders should be characterized by maladaptive patterns of clinically significant disturbances in an individual's cognitions, psychological or emotional states, or behaviors resulting in prominent distress or disability in social, occupational or other important areas of functioning[3]. It is important to note that deviant behaviors, that is behaviors which a clinician deems unusual or out of the norm either statistically or from their own perspective, do not constitute mental disorders. Moreover, a culturally expectable or acceptable pattern of cognitions, psychological or emotional states, or behaviors does not warrant a mental disorder diagnosis[3]. Clinicians therefore have the obligation to utilize updated diagnostic criteria, test their subjective judgments, and clearly document both clinically significant distress or disability associated with a maladaptive disturbance as well as specific symptomatology before assigning a mental disorder diagnosis[4]. As Adeponle *et al*[5] explain misdiagnosis may include identifying a disorder when none is present (overdiagnosis), or mistaking the diagnosis for another condition (misidentification), particularly when culturally normative behavior is mistaken for psychopathology. This risk is most acute when clinicians fail to elicit crucial and accurate diagnostic information because of insufficient attention to cultural and contextual factors that shape maladaptive behaviors.

Increasing attention by consumers, clinicians, researchers, and policy makers has focused on cultural disparities in healthcare over the past several decades. In particular, the President's New Freedom Commission on Mental Health[6] formulated goals for eliminating mental health-related disparities. Relatedly, during its evolution the Diagnostic and Statistical Manual of Mental Disorders has placed increasing emphasis on cultural sensitivity regarding accurate differential diagnoses[7]. The most recent version highlights cultural issues, stressing that psychopathology varies across cultures for specific types of behaviors. Diagnostic and Statistical Manual of Mental Disorders-5[3] explains that clinical significance depends on cultural norms, and "awareness of the significance of culture may correct mistaken interpretations of psychopathology...". The inclusion of cultural information within a diagnostic formulation is critical because a diagnostic judgment leading to a potential misdiagnosis can have several lasting negative effects for consumers, ranging from having an inaccurate healthcare record and complications related to insurance coverage, to being misprescribed psychotropic medications and potential death resulting from self-stigma-induced suicide. Diagnosis is considered to be the springboard of triage and treatment decisions. As one of the first clinical decisions a mental health professional must make, diagnosis can greatly influence the future of a consumer's healthcare, including participation in and trust of the healthcare system generally[8]. Unfortunately, despite widespread calls for cultural sensitivity and culturally formulated updates to diagnostic manuals, decades of research has shown that racial disparities continue to exist regarding the types of mental disorder diagnoses assigned to consumers of difference races.

One of the most consistent research findings related to race and diagnosis is the disproportionately high rate of psychotic disorder diagnoses among consumers of color, specifically African Americans. This phenomenon has been documented despite the absence of genetic evidence indicating a true increase in prevalence in this population[9]. For example, research shows that African Americans are almost five times more likely to be diagnosed with Schizophrenia compared with Euro-Americans admitted to state psychiatric hospitals[10]. Surprisingly, clinicians' own race appears not to alter this diagnostic trend[11]. Although a vast array of race and diagnostic trend-related studies have been conducted, very few literature reviews have complied information for future research or practice purposes.

For example, Neighbors *et al*[12] gave a review suggesting that race influenced the process of diagnostic classification and reported how many psychiatric epidemiologists apply diagnostic instruments developed in Euro-American samples to African American consumers, assuming these instruments measured the same construct. Some studies in the review supported the proposal that African Americans and Euro-Americans differed in presentation of clinical symptoms while others concluded the opposite leading them to believe the contradiction was due to a lack of systematic research on racial differences in presenting complaints. Two contradictory assumptions were described by Neighbors *et al*[12]: (1) African Americans and Euro-Americans display symptomatology essentially the same with diagnostic errors resulting from clinician stereotypes; and (2) African Americans and Euro-Americans display psychopathology differently and diagnosticians incorrectly assume it is the same with diagnostic errors resulting from clinicians being unaware of or insensitive to cultural differences in how the same disorder can be displayed differently according to race. The authors propose having a more structured interviewing procedure compared to one that is unstructured, which is more likely to be influenced by unsubstantiated clinical impressions.

Since the Neighbors *et al*[12] literature review was completed the vast majority of race and diagnosis-related research studies were undertaken. In addition, diagnostic

criteria for psychotic disorders have changed. Thus, Garb[13] completed another literature review, including studies until 1996 in part focused on race and diagnosis however specifically from a racial bias perspective. As an overall conclusion Garb explained that "African-American and Hispanic (Puerto Rican) patients are...more likely to be diagnosed as having Schizophrenia, even when measures of psychopathology do not indicate that a diagnosis of Schizophrenia is justified". Seven citations are provided as a basis for this conclusion. More recently Chien *et al*[14] described literature reflecting racial differences in Schizophrenia. These authors explain that while epidemiological accounts of Schizophrenia suggest a similar prevalence across races, research has shown that Schizophrenia is repeatedly diagnosed at a higher rate in the African American population. Because prior literature reviews in this area were undertaken some time ago, additional research has been completed after the completion of past reviews, diagnostic criteria for psychotic disorders have changed recently, and cultural and professional norms have advanced in contemporary society, an updated literature review is warranted. The purpose of the present review is to provide a fully updated and comprehensive summary of race and diagnosis-related empirical studies, highlighting trends and drawing data-driven conclusions for future research and clinical guidance.

LITERATURE REVIEW SEARCH STRATEGY

We used three separate academic search engines to conduct this review: PsycINFO, Psychology and Behavioral Sciences Collection, and Medline. Because the purpose of this review focused on empirical studies related to race and diagnosis, key terms for all search engines included "psychosis or psychotic or Schizophrenia or schizophrenic" and "race or ethnicity or culture" and "research or study or investigate". Results displayed the following quantity of primary hits for each search engine: PsycINFO, n = 1073; Psychology and Behavioral Sciences Collection, n = 254 results; Medline, n = 725. All initial results were then reviewed for peer-reviewed empirical studies published in journals (dissertations and book chapters excluded) until saturation was achieved. Twenty-six articles over a 24 year period were determined to be representative in discussing the affect of race on diagnosis in psychotic disorders. Interestingly, there appears to be a pattern regarding years and number of empirical studies in this area over time. Between 1989 and 2001 five studies were completed. Perhaps due to these studies highlighting an important issue with real-world consumer implications, the 2001 United States Surgeon General's[15] report on mental health and race, and public policy focusing on race and mental health (*e.g.*, the 2003 President's New Freedom Commission on Mental Health), additional studies were then conducted. Between 2003 and 2008 13 different studies were completed. Perhaps due to the breadth of research over this short period of time, along with generally consistent findings, empirical research was then continued but at a comparative reduced pace. Between 2009 and 2013 eight studies were completed. These representative studies are summarized here.

REVIEW OF AMERICAN RESEARCH ON RACE AND DIAGNOSIS OF SCHIZOPHRENIA

The preponderance of literature clearly shows how African Americans are more frequently misdiagnosed than Euro-Americans, with research findings initially gaining momentum since the early 1980's[16]. In particular, African Americans are disproportionately diagnosed with Schizophrenia with estimates ranging from three to five times more likely in receiving such a diagnosis. Eack *et al*[9] conducted a study with 752 participants and found that even after controlling for other significant demographic and clinical characteristics, African Americans were more than three times as likely to be diagnosed with Schizophrenia than Euro-Americans. Additionally, Eack *et al*[9] reported that after interviews, clinician-perceived honesty was lower for African American consumers, a factor found to be a significant correlate of increased Schizophrenia diagnoses among African Americans. Conversely, increased distrust and a poorer clinical relationship were reported by African American consumers. Barnes[10] researched 2311 persons having a single admission to a state psychiatric hospital with a Schizophrenia diagnosis during an eight-year period. The researcher found that African Americans were four times more likely than Euro-Americans to receive a Schizophrenia diagnosis. Four years later, Barnes[17] explored 2404 persons admitted to Midwestern state psychiatric hospitals, finding that race was the strongest predictor of an admission diagnosis of Schizophrenia after controlling for the influence of other demographic variables. Interestingly, Barnes showed that Schizophrenia subtypes were not equally distributed by race, with African American consumers significantly more likely to receive a diagnosis of Schizophrenia-paranoid subtype or Schizophrenia-undifferentiated subtype than Euro-American consumers.

In hopes of applying semi-structured diagnostic interviews to eliminate racial disparities in diagnosis, Neighbors *et al*[18] analyzed data of 665 African American and Euro-American psychiatric inpatients with results showing that race was related to diagnoses even when utilizing standardized diagnostic criteria and interviewing procedures. The authors reported that African Americans showed a higher percentage of Schizophrenia (44%) diagnoses compared to the Euro-Americans (32%), with a statistically significant relationship between race and the hospital's admitting diagnosis. In comparison to researchers' primary diagnosis and its relationship to race,

Neighbors *et al*[18] showed there was also a statistically significant clinician relationship with showing that African Americans had a higher percentage (33%) of Schizophrenia diagnoses compared to Euro-Americans (24%). These findings show how clinicians perceive symptoms differently by consumer race, particularly when assigning a diagnosis of Schizophrenia.

When looking at Latino American patients, Minsky *et al*[19] speculated that because African Americans were diagnosed with Schizophrenia spectrum disorders at a higher rate, then the same may be true for Latino Americans. To our knowledge these researchers conducted the first systematic study comparing the diagnostic and symptom severity patterns of Latino Americans with those of African Americans and Euro-Americans. With 19219 participants Minsky *et al*[19] showed that African Americans were more likely than Latino Americans or Euro-Americans to be diagnosed as having psychotic disorder (mainly Schizophrenia) by clinicians. However, Minsky et al reported that Latino Americans scored highest on psychosis subscales, as well as self-reported clinical severity. Similarly, Blow *et al*[20] looked at ethnic differences in diagnostic patterns between Latino Americans, African Americans, and Euro-Americans of 134523 veterans while controlling for possible confounding variables. They found that race most strongly predicting a Schizophrenia diagnosis. Results concluded that Latino Americans where more than three times more likely to be diagnosed with Schizophrenia than Euro-Americans. However, Minsky *et al*[19] explained that African Americans continued to reflect being most strongly diagnosed with schizophrenia, which is four times more likely than Euro-Americans.

To date, there are no empirically verified explanations determining why African Americans are overrepresented in having a Schizophrenia diagnosis, although researchers speculate about different possibilities. Some have argued that clinician bias may be an unconscious process stemming from stereotypes and biases resulting in mis-diagnosis[21,22]. Others speculate that the underdiagnosis of Major Depressive Disorder and Bipolar Disorder in African Americans could contribute to the overdiagnosis of Schizophrenia[17]. Another possibility proposed is clinicians' own race contributing to diagnostic bias. For example, Trierweiler *et al*[11] examined clinician race differences in diagnostic practices with 292 adult inpatients predominantly from an African American community using a sample distribution of 72% African Americans and 28% non-African Americans. Their results unexpectedly showed no differences between diagnosing Schizophrenia *vs* not-Schizophrenia disorders according to clinicians' race, suggesting equal diagnostic dissemination between the two races. However, Trierweiler *et al*[11] suggested that clinicians of difference races may apply diagnostic criteria differently. For example, they reported that non-African American clinicians generally associated negative symptoms of Schizophrenia (*i.e.*, blunted affect, anhedonia, motor retardation) with a Schizophrenia diagnosis, while African American clinicians associated positive symptoms (*i.e.*, hallucinations, delusions) with a diagnosis of Schizophrenia. Trierweiler *et al*[11] discussed how this shows how diagnostic assignment can be attributed to differences between clinicians' race on a more micro or symptom conceptualization level. While the majority of research explored racial bias in psychiatric diagnoses during hospital admissions, Sohler *et al*[8] investigated whether diagnostic racial bias is influenced by a person being discharged from their first psychiatric hospitalization. Using a sample size of 528 participants after a six month and two year follow-up period, no evidence indicated that a racial bias influenced a Schizophrenia diagnosis. However, Sohler *et al*[8] stated that African American consumers were more often discharged without a definitive diagnosis (*i.e.*, psychosis not otherwise specified) compared with Euro-Americans, with a substantial amount of African Americans meeting criteria for Schizophrenia (which could be a result of clinician difficulty in assigning a conclusive diagnosis).

REVIEW OF AMERICAN RESEARCH ON RACE AND DIAGNOSIS OF OTHER PSYCHOTIC DISORDERS

Given that Schizophrenia is one of several specific psychotic disorders demonstrating race-specific diagnostic disparities, it is important to also consider whether a similar pattern exists among other psychotic disorders. Disorders with psychotic features range from Schizophrenia, more complex disorders such as Schizoaffective Disorder, shorter duration disorders such as Schizophreniform Disorder, disorders with more narrow symptomatology such as Delusional Disorder, and mood disorders with psychotic features[3]. It has been shown that Schizophrenia is disproportionately diagnosed among African Americans, but does the same hold true with race affecting the diagnosis of psychotic disorders in general? Schwartz *et al*[22] conducted a study from a 10-county community mental health agency with 1648 participates, finding that African Americans were significantly more likely to receive a psychotic disorder diagnosis than Euro-Americans. They reported that 27% of all African American consumers assessed were diagnosed with psychotic disorders compared with only 17% of all Euro-American consumers. Schwartz *et al*[22] discussed how African American consumers' symptoms may be more associated with disruptive or socially deviant behavior patterns in arriving at such conclusions. Regarding forensic psychiatric inpatient consumers known for deviant behaviors, Perry *et al*[23] used data from 129 randomly selected evaluations in a pre-trial correctional psychiatric facility and found that Euro-Americans were 78% less likely to be diagnosed with a psychotic disorder than African Americans. The authors reported how high levels of education were associated with decreased odds of being diagnosed with psychotic disorder while length

of stay in the forensic psychiatric facility increased those odds. According to Perry *et al*[23] the predicted probability that African Americans in the forensic psychiatric facility where diagnosed with a psychotic disorder is 56% compared to only 21% for Euro-Americans. They go on to state how behavioral hospitalizations may also be strongly associated with an increased likelihood of being diagnosed with a psychotic disorder. Boa *et al*[24] collected information from 269 inpatient health care facilities, including 102201 consumer discharges, and investigated differences in behavioral inpatients between African Americans and Euro-Americans. Their results showed that African Americans were more than three times as likely to be hospitalized with a primary psychotic diagnosis compared to Euro-Americans. In addition, African Americans accounted for over 50% of all behavioral hospitalizations with a primary psychotic disorder compared to only 23% of Euro-Americans. Perry *et al*[23] go on to state how behavioral discharges of African Americans were twice as likely to reflect a primary psychotic diagnosis compared to Euro-Americans.

Similar to Schizophrenia, there appears to be a relationship between Latino American consumers and racial disparities among psychotic diagnoses. Kales *et al*[25] explored 23758 elderly persons in the VA medical centers identifying how Euro-Americans, Latino Americans, and African Americans compare by rate of diagnosis. Their results showed that Latino American (24%) and African American (25%) persons had significantly higher rates of psychotic disorders in all hospital units compared to Euro-Americans (18%). Even among minors (*i.e.*, those under 18 years of age) in psychiatric emergency centers, Muroff *et al*[26] reviewed 2991 child and adolescent Latino American, African American, and Euro-American records and found that African American and Latino American children and adolescents were twice as likely to receive a psychotic disorder diagnosis compared to Euro-Americans. This confirms the conjecture that Latino American consumers share in experiencing racial disparities of psychotic disorder diagnoses with African Americans.

Psychotic symptoms are more common and milder within the general population compared to meeting full criteria for diagnosis of a psychotic disorder. However, psychotic symptoms usually are illuminating signs of a potential precursor to psychotic disorders. Cohen *et al*[27] looked at a sample of 16423 participants to determine the prevalence of psychotic symptoms among ethnic groups. Results showed that Latino Americans (13%) and African Americans (15%) had a higher lifetime rate of psychotic symptoms than Euro-Americans (9%) and Asians (9%). Additionally, Latino Americans reported more lifetime symptoms than other groups after controlling for other factors according to Cohen and Marino. Similar to Schizophrenia, the prospect of clinician race influencing diagnostic decisions may be a factor in racial disparities of psychotic disorders. Arnold *et al*[28] conducted the first study to our knowledge using blinded evaluations by expert diagnosticians to evaluate ethnicity effects on the assessment of psychotic symptoms. Their results from 193 persons meeting specific criteria showed no significant differences in diagnoses between ethnic groups. However, African American men with psychosis who presented for inpatient hospitalization exhibited significantly higher scores for total psychotic symptoms than Euro-American men, which interestingly did not increase the rate of a Schizophrenia diagnoses even when evaluated by ethnically blinded raters according to Arnold *et al*[28]. They discussed how their findings indicate that psychotic symptom presentation should be evaluated in the context of other symptoms in diagnostic assessments to prevent a misdiagnosis of Schizophrenia.

REVIEW OF INTERNATIONAL RESEARCH ON RACE AND DIAGNOSIS OF PSYCHOTIC DISORDERS

The vast majority of empirical literature related to race and diagnosis of psychotic disorders has included consumer samples and clinicians from the United States. Nevertheless, could the same diagnostic patterns be found internationally? Alexandre *et al*[29] reviewed medical records of 977 patients in Portugal, where 82% of the immigrants were from African Portuguese-speaking countries and only 3.3% from Eastern Europe countries. The term Black is widely used in Portugal and refers to patients of African origin while not suggesting any racial prejudice, according to Alexandre *et al*[29]. Their results showed that Black inpatients where significantly more frequently diagnosed with Schizophrenia and acute and transient psychosis. By contrast, in the Netherlands, Vinkers *et al*[30] examined 21857 pre-trial psychiatric reports comparing Dutch natives with what they termed Black and minority ethnic groups (BME), and Whites from other Western countries (mostly born in Europe). These researchers found that mandated psychiatric hospital admissions were more frequently recommended for BME persons (19.8%) and Whites from other Western countries (19.3%) compared to Dutch natives (9.2%).

According to Vinkers *et al*[30] these findings show how immigrants may encounter an increased risk of psychotic disorders diagnoses and hospital admissions, perhaps related to misunderstanding of or biases about symptomatology.

In Canada, Adeponle *et al*[5] examined 323 persons referred to a cultural consultation service (CCS) to determine factors associated with change in the diagnosis of psychotic disorders *via* the CCS as compared to that of the referring clinician. Results showed that 49% of consumers referred with a psychotic disorder diagnosis were changed to a nonpsychotic disorder diagnosis after CCS assessment. These consumers were significantly more likely to be residing in Canada ten years or less. Surprisingly, Black patients represented the largest

Table 1 Summary of empirical research results of disproportionate diagnoses and race

Ref.	Disproportionate diagnoses found	Disproportionate diagnoses not found
American studies showing diagnosis and race in schizophrenia		
Neighbors *et al*[18]	X	
Minsky *et al*[19]	X	
Sohler *et al*[8]		X
Barnes[10]	X	
Blow *et al*[20]	X	
Barnes[17]	X	
Schwartz *et al*[22]	X	
Eack *et al*[9]	X	
American studies showing diagnosis and race in non-schizophrenia psychotic disorders		
Kales *et al*[25]	X	
Arnold *et al*[28]	X	
Boa *et al*[24]	X	
Muroff *et al*[26]	X	
Cohen *et al*[27]	X	
Perry *et al*[23]	X	
International Studies showing diagnosis and race in schizophrenia or other psychotic disorders		
Al-Saffar *et al*[7]	X	
Alexandre *et al*[29]	X	
Vinkers *et al*[30]	X	
Adeponle *et al*[5]	X	

[1]Disproportionate diagnosis of psychotic disorders among immigrant consumers who were not Black.

percentage (44%) of those patients who had no change of a psychotic disorder diagnosis after CCS assessment. Conversely, only 5% of persons referred with a non-psychotic disorder diagnosis received a final diagnosis of a psychotic disorder. These findings unexpectedly show that prior diagnoses of psychotic disorders were significantly more likely to be changed among persons who are not black. Black consumers in this study were recent immigrants or refugees from Africa or the Caribbean, whereas black samples included in most studies from the United States include more indigenous African American populations and fewer immigrants. This may suggest that misdiagnosis, or more specifically overdiagnosis, of psychotic disorders occurs more frequently with immigrant and refugee patients from all racial-ethnic backgrounds. To possibly better explain this phenomenon, Al-Saffar *et al*[7] in Sweden attempted to describe the distribution of differing ethnic groups in psychiatric outpatient services and the influence of ethnicity on diagnosis. An investigation of 839 persons revealed that Black citizens, a relatively new ethnic group in Swedish society, had a higher rate of receiving a psychotic disorder diagnosis as compared to other ethnic groups. These findings are similar to the previously stated study by reflecting a potential relationship between psychotic disorders with those who are immigrant patients. International studies therefore show a trend toward ethnicity having a strong impact on how diagnoses are given in cross-cultural settings.

CONCLUSION

This review demonstrated how race and ethnicity has in fact influenced the diagnosis of Schizophrenia. Table 1 shows a comprehensive summary of empirical studies over a 24-year period that did and did not report disproportionate psychotic disorder or Schizophrenia diagnoses according to consumer race. Research showed a clear pattern wherein African Americans continued to display a long-term increased rate of Schizophrenia diagnoses, often three to four times as high compared to Euro-Americans. As speculated by previous researchers, Latino Americans were also disproportionately diagnosed at a more than three times higher rate than Euro-Americans with a Schizophrenia diagnosis. In consideration of a psychotic disorder diagnosis more generally, African Americans were more likely to be diagnosed than Euro-Americans. Latino Americans and African Americans both showed an increased lifetime rate of psychotic symptoms in comparison to Euro-Americans and Asians, as reported by clinicians. Even African American and Latino American minor consumers under the age of 18 were twice as likely to be diagnosed with a psychotic disorder as Euro-American youth. Interestingly, one study showed that no differences were found in a diagnosis of Schizophrenia by persons discharged after their first psychiatric hospitalization, although African Americans were discharged more often with an upspecified diagnosis such as psychosis not otherwise specified compared to Euro-Americans (Table 1).

Internationally, there appears to be a similar pattern of racial disparity, but when inspected closely, evidence revealed a different and intriguing dynamic. In Sweden, mental health consumers of African descent compared to other ethnic groups had an increased risk of receiving a psychotic disorder except for Schizophrenia. Dutch psychiatric consumers in the Netherlands were less likely mandated for psychiatric hospitalization compared to BME, and even Whites from other Western countries. This shows that both BME and White consumers from other Western countries are equally mandated

for psychiatric hospitalization when compared to native mental health consumers in the Netherlands. Correspondingly, African immigrants in Portugal were more frequently diagnosed with Schizophrenia. In Canada, immigrants from Africa or the Caribbean that were referred to a CCS determining diagnosis showed the highest percentage of maintaining a psychotic disorder diagnosis and also the lowest percentage of later replacing their initial psychotic disorder diagnosis to a non-psychotic diagnosis. These international trends may suggest how misdiagnosis of psychotic disorders more commonly transpire with immigrant ethnic minority consumers receiving mental health services compared to consumers from communities sharing a majority racial and ethnic background.

Implications for further research include exploring some of the potential explanations that have been suggested in the literature to clarify how race affects the diagnosis of psychotic disorders. Understandably, when considering racial bias in diagnostic disparities, one would likely presume that clinician race would interfere with clinical judgment leading to diagnostic prejudice, but this has been proven inconclusive. Instead, it was suggested in prior literature that diagnostic criteria could be applied differently depending upon clinician race. Some authors suggested that misinterpretation of more socially deviant and disruptive behaviors often associated with African Americans were factors related to misdiagnosis. Other rationales for the long-term trend noted above included unconscious clinician biases and the underdiagnosis of Major Depressive Disorder and Bipolar Disorder among African Americans in favor of a psychotic disorder diagnosis. As Feisthamel *et al*[31] explain, "Most authors assert that the cause involves racial diagnostic bias, which refers to clinicians making unwarranted judgments about people on the basis of their race". They provide a potential pathway for this circumstance, one that would need to occur regardless of treatment setting or professional affiliation given the broad scope of the trends found in prior research. Feisthamel *et al*[31] also propose a different, albeit not uncontroversial hypothesis, that a sociocultural pattern may exist for consumers of color themselves related to a combination of less access to healthcare, more distrust in mental health professionals and systems, higher social stigma associated with mental illness, and more culture-specific methods of addressing personal distress. This pattern may result in increased symptomatology once consumers of color do access mental health treatment, and ultimately more severe (*e.g.*, psychotic disorder) diagnoses by clinicians.

Although it may be difficult to identify concrete contributing factors explaining how race affects a psychotic disorder diagnosis, importantly clinicians and future researchers should be aware of this longstanding and pervasive trend. It should also be noted that although clear evidence supports a longstanding trend in differential diagnoses according to consumer race, this trend does not imply that one race (*e.g.*, African Americans) actually demonstrate more severe symptoms or higher prevalence rates of psychosis compared with other races (*e.g.*, Euro-Americans). Because clinicians are the diagnosticians and misinterpretation, bias or other factors may play a role in this trend caution should be used when making inferences about actual rates of psychosis among ethnic minority persons. Given the fact that similar race-related diagnosis results have been found in empirical studies across time and location indicates that the underlying reasons for the phenomenon should be investigated. A literature review has demonstrated that thus far little empirical research has been devoted to understanding whether clinician racial bias, clinician misinterpretation of symptomatology, or another factor altogether is responsible for this pattern. Or perhaps as Feisthamel *et al*[31] suggest as one possibility, the trend described here may be indicative of real differences in symptomatology presented by consumers of different races. Additional empirical research may help the field get closer to a proven interpretation of these findings resulting in appropriate education for clinicians and consumers that is necessary in combating this persistent phenomenon.

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ORIGINAL ARTICLE

Factors associated with hopelessness in epileptic patients

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Abstract

AIM: To investigate factors related to hopelessness in a sample of epileptic patients, including measures of depression and quality of life (QOL).

METHODS: Sixty-nine participants were administered the following psychometric instruments: Beck Depression Inventory-Ⅱ, Beck Hopelessness Scale (BHS), and QOL in Epilepsy (QOLIE)-89. Patients were dichotomized into two categories: those affected by epilepsy with generalized tonic-clonic seizures *vs* those having epilepsy with partial seizures.

RESULTS: The groups differed on the QOLIE Role Limitation/Emotional dimension. Patients with generalized seizures reported more limitations in common social/role activities related to emotional problems than patients with other types of epilepsy (89.57 ± 25.49 *vs* 72.86 ± 36.38; t_{63} = -2.16; P < 0.05). All of the respondents reported moderate to severe depression, and 21.7% of patients with generalized seizures and 28.6% of patients with other diagnoses had BHS total scores ⩾ 9 indicating a higher suicidal risk. The study did not control for years of the illness.

CONCLUSION: Patients with generalized seizures reported more limitations in common social/role activities related to emotional problems compared to patients with other types of seizures. Patients at increased suicide risk as evaluated by the BHS were older than those who had a lower suicidal risk. Future studies are required to further investigate the impact of hopelessness on the outcome of epileptic patients.

Key words: Epilepsy; Hopelessness; Suicide risk; Emotional problems; Social/role activities

Core tip: The present study assessed factors associated with hopelessness, depression, and quality of life in a sample of 69 epileptic patients using standardized psychometric instruments. All of the participants reported moderate to severe depression, and 25% of the patients had Beck Hopelessness Scale total scores ⩾ 9 indicating a higher suicidal risk. Although the study did not control for years of the illness which may limit the generalizability of findings, patients with generalized seizures experienced more limitations

in common social/role activities due to emotional problems than those with other types of seizures.

Pompili M, Serafini G, Innamorati M, Montebovi F, Lamis DA, Milelli M, Giuliani M, Caporro M, Tisei P, Lester D, Amore M, Girardi P, Buttinelli C. Factors associated with hopelessness in epileptic patients. *World J Psychiatr* 2014; 4(4): 141-149 Available from: URL: http://www.wjgnet.com/2220-3206/full/v4/i4/141.htm DOI: http://dx.doi.org/10.5498/wjp.v4.i4.141

INTRODUCTION

Epilepsy is associated with a substantial economic burden, significant mortality and a dramatic decline in work productivity[1]. Epilepsy affects approximately 3 million people in the United States, with 140000 new cases[2,3] diagnosed every year. In European countries, epilepsy affects approximately 0.9 million children and adolescents (estimated prevalence: 4.75 per 1000) with 1.9 million cases reported in Europeans aged 20-64 years (estimated prevalence: 6 per 1000) and 0.6 million in those with 65 years and higher (estimated prevalence: 7 per 1000)[4]. A recent report in Europe[5] calculated an estimated 2.6 million individuals affected by epilepsy, costing 13.8 billion Euros in the year 2010.

Several studies have suggested that epilepsy is a severely disabling brain condition. Ding *et al*[6] calculated the Years Lived with Disability (YLD) according to a prevalence survey of epilepsy in 66393 individuals recruited in rural Chinese provinces and epilepsy mortality data. Epilepsy accounted for 1.41 lost years of life and 0.67 YLDs per 1000 in the population. The population of rural China, therefore, lost 2.08 per 1000 Disability Adjusted Life Years related to epilepsy. Leonardi *et al*[7] argued that the global burden of epilepsy should be recognized as a fundamental public health need since epilepsy was responsible for approximately 0.5% in terms of the global diseases burden worldwide in the year 2000.

One third of individuals with epilepsy have more than one seizure per month, and a satisfactory control of seizures is achieved in no more than 65%-70% of cases. Individuals who report being "seizure free" are usually those without medical and psychiatric comorbidities[4] and/or with a high quality of life (QOL)[8,9]. One of the most relevant challenges for clinicians is improving the QOL in epileptic patients. In the effort to reduce the subjective burden of this disorder and the associated psychosocial impairment, most of research has focused on patients suffering from refractory seizures[10-14]. QOL and its predictors among patients with different types of epilepsy have been widely analyzed only by a few studies.

Several biological and psychosocial variables may influence QOL and subjective well-being. It has been suggested that hopelessness is closely related to depression, and hopelessness has been frequently reported in studies as strongly associated with suicidal behaviors[15-17] as well as with medical illnesses, particularly terminal cancer[18-21].

Table 1 Sociodemographic characteristics of the sample (n = 69)

	n (%)
Men	44.9%
Age (mean ± SD)	38.86 ± 15.99
Epilepsy	
Generalized seizures	35.4%
Partial seizures	64.6%

Hopelessness predisposes patients with psychiatric disorders to suicidal behavior and has been identified as a relevant risk factor for suicide, particularly in individuals with serious mental disorders[16,22-24]. The QOL may be significantly altered by hopelessness and negatively influenced by poor psychosocial adjustment[25-27], resulting in increased suicidal risk. Therefore, hopelessness represents a critical risk factor and may be predictive of perceived lower QOL[28-30].

Attitudes toward epilepsy and self-efficacy have been found to be independent predictors of depressive symptoms. However, it has been suggested that the reduced self-efficacy related to seizure management may not influence the association between attitudes towards epileptic patients and depressive symptoms[31]. As previous studies reported that hopelessness is a predictor of future suicide behaviors in patients with mood disorders[32,33] and poor QOL[34,35] in epileptic patients, the present study was designed to evaluate the role of risk factors associated with hopelessness on the QOL in a sample of epileptic patients.

MATERIALS AND METHODS

Participants

Individuals were volunteers for the study and provided written informed consent. The hospital's Institutional Review Board approved the study. Sixty-nine consecutive patients with epilepsy (31 men and 38 women) were admitted to the Department of Neurological Science, Neurological Unit, Sant'Andrea Hospital of Rome (Italy) between January 2010 and December 2010. The main socio-demographic and clinical characteristics of the sample are summarized in Table 1. The mean age of participants was 38.86 ± 15.99 years (36.65 ± 16.25 for men and 40.66 ± 15.76 for women; $t_{67} = 1.04$; $P = 0.30$). The majority of the patients was affected by partial seizures (64.6%) while 35.4% of them suffered from generalized tonic-clonic seizures.

Patients had to meet the following inclusion criteria: (1) they had a clinically established diagnosis of epilepsy with generalized tonic-clonic or partial seizures; (2) they were admitted consecutively as outpatients over a 12-mo period at the Department of Neurological Science, Neurological Unit, Sant'Andrea Hospital of Rome (Italy); (3) they were older than 18 years of age; and (4) they gave signed voluntary consent to participate in the research.

Exclusion criteria were: (1) a diagnosis of dementia or delirium; (2) positive psychotic symptoms (delusions

and hallucinations); (3) illiteracy or inability to perform the evaluation; and (4) an inability to provide informed consent.

Measures

The patients were administered the Beck Depression Inventory-Ⅱ (BDI-Ⅱ), the Beck Hopelessness Scale (BHS), and the QOL in Epilepsy Inventory-89 (QOLIE-89).

BDI-Ⅱ: The BDI-Ⅱ is a 21-item self-report instrument evaluating the presence/severity of depressive symptoms during the previous 14 d[36]. Each item is scored from 0 to 3 in order to evaluate symptom severity, with total scores ranging from a 0 to 63. A score of ⩾ 14 is suggestive of mild depression, while a score of ⩾ 20 is suggestive of moderate to severe depression. Internal consistency and concurrent validity have been documented in clinical/non-clinical samples[23,37].

BHS: The BHS is a 20-item self-report scale assessing hopelessness/negative attitudes concerning coming events[15]. The scale evaluates feelings about the future, loss of motivation, and expectations for the future. Subjects are requested to endorse a pessimistic sentence or deny an optimistic sentence. Research has documented an association between the BHS total score and depressive symptoms, suicidal intent, and suicidal ideation. Furthermore, Beck *et al*[23] conducted a follow-up study on 1958 outpatients and reported that those with higher BHS total scores (⩾ 9) were 11 times more likely to complete suicide than the outpatients with lower BHS total scores. Thus the BHS seems to be a useful predictor of eventual suicidal behavior. An Italian version of the BHS has been validated by Pompili *et al*[37]. The present study used the cutoff score of ⩾ 9 to distinguish those patients at high risk for suicide.

QOLIE-89: The QOLIE-89 was developed based on the Epilepsy Surgery Inventory-55 and the Medical Outcomes Health Survey Short Form-36. It has 89 items assessing the following 17 dimensions of Health Related QOL (HRQOL): Health Perceptions, Overall QOL, Physical Functions, Role Limitations due to Physical Problems, Role Limitations due to Emotional Problems, Pain, Work/Driving/Social Functions, Energy/Fatigue, Emotional Well-Being, Attention/Concentration, Health Discouragement, Seizure Worry, Memory, Language, Medication Effects, Social Support, and Social Isolation. There are three additional items concerning sexual relations, changes in health, and overall health. Each subscale score was converted into a scale of 0-100 points, with higher scores indicative of a better level of functioning and higher QOL[38,39].

Statistical analysis

Statistical analyses were carried out with SPSS 17.0 for Windows. Differences between the groups of patients with different severity of hopelessness and different diagnoses were evaluated using t-tests for dimensional variables and one-way Fisher exact tests for 2 × 2 contingency tables. Significant variables at the bivariate analyses were then included in a logistic regression model as potential predictors. The groups of patients with different levels of hopelessness were included in the analysis as the dependent variable. The associations between variables are described as OR with confidence intervals and significance levels.

RESULTS

Differences between diagnostic groups

Table 2 presents the differences between those patients with generalized seizures *vs* those patients with partial seizures (including those who had secondarily generalized seizures). The two groups differed only on the QOLIE Role Limitation/Emotional dimension. Patients with generalized seizures reported more limitations in common social/role activities related to emotional problems as compared to patients with other diagnoses (89.57 ± 25.49 *vs* 72.86 ± 36.38; t_{63} = -2.16; $P < 0.05$). All of the respondents reported moderate to severe depression, and more than 20% (21.7% and 28.6%, respectively for patients with generalized seizures and patients with partial seizures) reported scores on the BHS ⩾ 9, indicating a higher suicide risk.

Differences between high-risk group vs low-risk group

On the BHS, 28.6% of the patients with partial seizures and 21.7% of those generalized seizures had a score ⩾ 9. Differences between the two groups of patients were categorized by hopelessness severity (*i.e.*, high *vs* low BHS total scores) are presented in Table 3. Patients with high BHS: (1) were older (50.53 ± 15.36 *vs* 35.04 ± 14.37; t_{67} = -3.80; $P < 0.001$); (2) reported more severe depressive symptoms on the BDI-Ⅱ (38.24 ± 8.53 *vs* 27.46 ± 5.88; t_{67} = -4.84; $P < 0.001$); (3) had lower scores on the QOLIE Health Perception subscale (55.64 ± 20.14 *vs* 72.52 ± 18.93; t_{67} = 3.14; $P < 0.01$); (4) had lower scores on the Overall QOL (54.85 ± 14.10 *vs* 70.25 ± 17.03; t_{67} = 3.69; $P < 0.001$); (5) had lower scores on the Role Limitation Physical subscale (57.65 ± 37.34 *vs* 78.08 ± 31.25; t_{67} = 2.23; $P < 0.05$); (6) had lower scores on the Role Limitation Emotional subscale (52.94 ± 39.96 *vs* 86.92 ± 26.83; t_{67} = 3.27; $P < 0.01$); (7) had lower scores on the Pain subscale (64.56 ± 31.24 *vs* 81.88 ± 22.92; t_{67} = 2.46; $P < 0.05$); (8) had lower scores on the Energy/Fatigue subscale (48.53 ± 21.05 *vs* 66.22 ± 20.13; t_{67} = 3.11; $P < 0.01$); (9) had lower scores on the Emotional Wellbeing subscale (49.41 ± 18.27 *vs* 73.08 ± 17.64; t_{67} = 4.76; $P < 0.001$); (10) had lower scores on the Memory subscale (55.08 ± 26.84 *vs* 71.43 ± 25.39; t_{67} = 2.27; $P < 0.05$); (11) had lower scores on the Social Isolation subscale (71.18 ± 27.59 *vs* 88.65 ± 17.60; t_{67} = 2.45; $P < 0.05$); (12) had lower scores on the Changes in Health subscale (48.53 ± 25.72 *vs* 67.31 ± 27.36; t_{67} = 2.49; $P < 0.05$); and (13) had lower scores on the Overall Health subscale (55.63 ± 15.04 *vs* 72.50 ± 19.29; t_{67} = 3.21; $P < 0.01$).

Table 2 Differences between diagnostic groups (generalized seizures *vs* partial seizures)

		Mean	SD	*t*-tests (DF: 67)	Significance
Age	Partial seizures	40.81	15.09	1.06	0.30
	Generalized seizures	36.35	18.35		
Men (%)	Partial seizures	35.7%	-		0.09
	Generalized seizures	56.5%	-		
BHS	Partial seizures	6.86	4.05	1.27	0.21
	Generalized seizures	5.52	4.04		
BHS ≥ 9	Partial seizures	28.6%	-	-	-
	Generalized seizures	21.7%	-	-	-
BDI-Ⅱ	Partial seizures	31.07	8.67	1.12	0.27
	Generalized seizures	28.70	7.16		
BDI-Ⅱ ≥ 21	Partial seizures	100%	-	-	-
	Generalized seizures	100%	-	-	-
QOLIE-89					
Health Perception	Partial seizures	68.55	19.63	0.45	0.66
	Generalized seizures	66.12	23.07		
Overall QOL	Partial seizures	64.09	17.16	-1.67	0.10
	Generalized seizures	71.74	18.47		
Physical function	Partial seizures	85.48	22.14	0.24	0.81
	Generalized seizures	84.13	21.19		
Role limitations due to physical problems	Partial seizures	74.29	31.94	0.54	0.59
	Generalized seizures	69.57	37.11		
Role limitations due to emotional problems	Partial seizures	72.86	36.38	-2.16	0.05
	Generalized seizures	89.57	25.49		
Pain	Partial seizures	81.79	23.09	1.72	0.09
	Generalized seizures	70.33	29.96		
Work/driving/social function	Partial seizures	84.18	13.94	0.06	0.96
	Generalized seizures	83.99	11.37		
Energy/fatigue	Partial seizures	59.72	20.06	-0.9	0.37
	Generalized seizures	64.78	24.56		
Emotional wellbeing	Partial seizures	63.62	21.98	-1.85	0.07
	Generalized seizures	72.70	17.04		
Attention/concentration	Partial seizures	74.22	23.97	-1.77	0.08
	Generalized seizures	82.58	14.18		
Health discouragement	Partial seizures	77.38	21.98	-0.08	0.94

BHS: Beck Hopelessness Scale; BDI-Ⅱ: Beck Depression Inventory-Ⅱ; QOL: Quality of life; QOLIE-89: Quality of life in Epilepsy-89; DF: Degree of freedom.

In order to assess those factors associated with higher hopelessness when controlling for the effect of other variables, variables significant at the bivariate level were included as predictors in a logistic regression model with patients having higher hopelessness *vs* those with lower scores on the BHS serving as the dependent variable (Table 4). Given that the diagnostic groups were associated with different levels of limitations in common social/role activities related to emotional problems, we also included the interaction between these variables in the model.

The multivariate model fits the data well ($\chi^2_{14} = 45.89$; $P < 0.001$), explaining 76% of the variability (Nagelkerke $R^2 = 0.76$). Patients with higher BHS scores (compared to those with lower BHS scores): (1) were 1.23 times more likely to be older ($P < 0.05$); (2) were 1.27 times more likely to have lower scores on the Overall score QOL of the QOLIE-89 ($P < 0.05$); (3) were 1.26 times more likely to report higher scores on the Energy/Fatigue subscale ($P < 0.05$); and (4) were 1.18 times more likely to report lower scores on the Emotional Wellbeing subscale ($P < 0.05$). It is important to note that depression severity failed to reach statistical significance when controlling for the effect of other variables (OR = 1.34; $P = 0.07$). Thus, higher hopelessness is associated with some dimensions of QOL and age, while depressive symptomatology, as measured by the BDI-Ⅱ, does not have an effect on hopelessness.

DISCUSSION

In the present study, patients with higher hopelessness scores, as assessed by BHS, were older and reported more severe depression on the BDI-Ⅱ as compared to those with lower hopelessness scores. Moreover, after multivariate analyses, the patients with higher scores on the BHS were more likely to have lower scores on the Overall QOL score of the QOLIE-89, more likely to report higher scores on the Energy/Fatigue and Emotional Wellbeing subscales, and more likely to be older compared to those with lower hopelessness scores. Contrary to our expectations, depression severity failed to reach statistical significance in the prediction of hopelessness when controlling for the effects of other variables. This non-significant finding is most likely related to the fact that all the patients reported moderate to severe depression.

An association between epilepsy and major depression

Table 3 Differences between patients with scores of 9 or higher on the Beck Hopelessness Scale and patients with lower scores

		Mean	SD	*t*-tests (DF: 67)	Significance
Age	Lower hopelessness	35.04	14.37	-3.80	0.001
	Higher hopelessness	50.53	15.36		
Men (%)	Lower hopelessness	50.0%	-	-	0.11
	Higher hopelessness	29.4%			
Generalized seizures	Lower hopelessness	37.5%			0.39
	Higher hopelessness	29.4%	-		
BDI-Ⅱ	Lower hopelessness	27.46	5.88	-4.84	0.001
	Higher hopelessness	38.24	8.53		
QOLIE-89					
Health Perception	Lower hopelessness	72.52	18.93	3.14	0.01
	Higher hopelessness	55.64	20.14		
Overall QOL	Lower hopelessness	70.25	17.03	3.69	0.001
	Higher hopelessness	54.85	14.10		
Physical function	Lower hopelessness	87.31	20.47	1.73	0.09
	Higher hopelessness	76.77	25.86		
Role limitations due to physical problems	Lower hopelessness	78.08	31.25	2.23	0.05
	Higher hopelessness	57.65	37.34		
Role limitations due to emotional problems	Lower hopelessness	86.92	26.83	3.27	0.01
	Higher hopelessness	52.94	39.96		
Pain	Lower hopelessness	81.88	22.92	2.46	0.05
	Higher hopelessness	64.56	31.24		
Work/driving/social function	Lower hopelessness	84.39	13.32	0.25	0.81
	Higher hopelessness	83.48	13.45		
Energy/fatigue	Lower hopelessness	66.22	20.13	3.11	0.01
	Higher hopelessness	48.53	21.05		
Emotional wellbeing	Lower hopelessness	73.08	17.64	4.76	0.001
	Higher hopelessness	49.41	18.27		
Attention/concentration	Lower hopelessness	79.29	21.80	0.86	0.39
	Higher hopelessness	74.25	18.25		
Health discouragement	Lower hopelessness	81.35	17.49	1.47	0.16
	Higher hopelessness	69.41	31.91		
Seizure worry	Lower hopelessness	63.33	22.50	1.99	0.051
	Higher hopelessness	51.23	19.23		
Memory	Lower hopelessness	71.43	25.39	2.27	0.05
	Higher hopelessness	55.08	26.84		
Language	Lower hopelessness	79.69	23.12	1.63	0.11
	Higher hopelessness	69.18	22.88		
Medication effects	Lower hopelessness	78.21	25.58	-0.43	0.67
	Higher hopelessness	81.21	22.77		
Social support	Lower hopelessness	75.24	20.448	1.73	0.09
	Higher hopelessness	64.71	25.76		
Social isolation	Lower hopelessness	88.65	17.60	2.45	0.05
	Higher hopelessness	71.18	27.59		
Change in health	Lower hopelessness	67.31	27.36	2.49	0.05
	Higher hopelessness	48.53	25.72		
Sexual relations	Lower hopelessness	63.73	28.86	1.50	0.14
	Higher hopelessness	51.47	29.94		
Overall Health	Lower hopelessness	72.50	19.29	3.21	0.01
	Higher hopelessness	55.63	15.04		

BDI-Ⅱ: Beck Depression Inventory-Ⅱ; QOL: Quality of life; QOLIE-89: Quality of life in Epilepsy-89; DF: Degree of freedom.

has often been reported, and epileptic patients frequently show depressive symptoms, but a recent systematic review and meta-analysis of nine studies including 29891 patients with epilepsy[40] reported a global prevalence of actual/past-year depression of only 23.1%. The high prevalence of depression found in our patients could be due to the fact that depression was diagnosed using a self-report instrument rather than clinical assessment. Significant heterogeneity in the results of ascertaining depression using different methods has been reported[40].

Overall, the current findings were only partially in line with those of Jehi *et al*[41], who analyzed data from 1931 subjects affected by drug-resistant and medically-controlled epilepsy during one year of follow-up and found that depression, together with seizure severity, was a major predictor of QOL in epileptic patients. Likewise, Lehrner *et al*[42] reported that depression significantly predicted QOL in 56 patients with temporal lobe epilepsy. Boylan *et al*[43] found that in a sample of 122 patients with refractory epilepsy, scores on the BDI were able to explain 51% of the total variance of the the QOLIE-31 scores, and only depression significantly predicted QOL. Gilliam *et al*[44] reported that depression severity and adverse effects related to antiepileptic

Table 4 Logistic regression model (patients with Beck Hopelessness Scale scores < 9 as reference)

	Beta	SE	Wald	DF	Significance	OR	95%CI for OR	
							Lower	Upper
Age	0.21	0.09	50.02	11	0.05	1.23	1.03	1.47
BDI-Ⅱ	0.30	0.16	30.38	11	0.07	1.34	0.98	1.84
Health Perception	-0.02	0.04	0.25	11	0.61	0.98	0.90	1.06
Overall QOL	-0.23	0.12	30.97	11	0.05	0.79	0.63	1.00
Role limitations due to physical problems	-0.01	0.03	0.08	11	0.77	0.99	0.94	1.04
Role limitations due to emotional problems	0.00	0.02	0.01	11	0.93	1.00	0.96	1.04
Pain	-0.08	0.05	20.97	11	0.09	0.92	0.85	1.01
Energy/fatigue	0.23	0.11	40.65	11	0.05	1.26	1.02	1.55
Emotional wellbeing	-0.16	0.08	40.38	11	0.05	0.85	0.74	0.99
Memory	-0.09	0.05	20.88	11	0.09	0.92	0.83	1.01
Social isolation	0.10	0.05	30.24	11	0.07	1.10	0.99	1.22
Change in health	-0.01	0.03	0.23	11	0.63	0.99	0.93	1.04
Overall health	-0.07	0.05	10.83	11	0.18	0.93	0.84	1.03
Diagnosis by role limitations due to emotional problems	0.02	0.02	0.75	1	0.39	0.98	0.95	1.02

QOL: Quality of life; SE: Standard error; DF: Degree of freedom.

medications were independent predictors of health status in a study of 205 outpatients with controlled and uncontrolled seizures. Luoni *et al*[45] found that depressive symptoms were powerful predictors of HRQOL in patients with pharmacoresistant epilepsy. Many other studies have documented that depression is a significant predictor of QOL in epileptic patients[12-14,43,46-52].

Consistent with the present findings, occasional researchers have found depressive symptoms to be unrelated to epilepsy. For example, Attarian *et al*[53] did not find an association between depression severity and seizure rate in 143 epileptic outpatients.

In our study, patients with higher BHS total scores were more likely to have significant limitations and impairments in QOL as reported on the QOLIE-89. It is possible that poorly controlled seizures and their medical consequences may contribute to hopelessness that may reduce QOL and increase the risk for suicide in patients with epilepsy. In keeping with the findings from Jehi *et al*[41], definitive conclusions concerning the eventual bidirectional association between hopelessness/depression and epilepsy are not easy to be drawn given the existence of spurious correlations from potential third variables. For example, both hopelessness/depression and epilepsy may be associated with reduced neurotrophic factors activity and altered signalling pathways related to neurotoxic effects such as hippocampal atrophy and memory/learning impairment[54].

After multivariate analyses, the results indicated that those patients in our study who had generalized seizures reported more limitations in common social/role activities related to emotional problems compared to those patients with other types of seizures. This is consistent with the results of the study by Luoni *et al*[45] who found that generalized seizures negatively predicted the "seizure worry" score according to the validated Italian version of the QOLIE-31. Tracy *et al*[14] reported that, in a sample of 435 patients with predominant (56%) generalized seizures, the BDI-Ⅱ score was the single reliable predictor of Emotional Well-Being subscale scores, explaining 37% of its variance in a general linear model.

In our study, 21.7% of the patients with generalized seizures and 28.6% of the patients with other diagnoses reported BHS total scores ⩾ 9, indicating a higher suicidal risk. We have also found in a previous study that 26% of the total sample of patients affected by temporal lobe epilepsy had high levels of hopelessness as well as an elevated risk of committing suicide[37]. Furthermore, Pompili *et al*[55,56], in a meta-analytic analysis of research, found that suicide is more frequent both in epileptic patients and in those with epilepsy who have been surgically treated compared to the general population. Clearly, suicide in epilepsy is a significant and frequent event. This underlines the importance of identifying factors that increase suicide risk in an effort to reduce the risk. Interestingly, it has been reported that suicide mortality among epileptic patients is roughly the same as mortality due to epilepsy, suggesting that deaths by suicide are typically not included in global mortality epilepsy rates[57]. Mortality rates in subjects with epilepsy are, therefore, presumably underestimated if they do not include deaths related to suicide.

In the present study we also found that older patients with epilepsy are at higher suicide risk when compared to younger patients. We hypothesize that epileptic patients develop higher hopelessness as they grow older about their current status and future life. However, older patients have been exposed to the illness for a longer period of time compared to younger patients. Our study did not control for years of illness limiting our ability to speculate about the association between the age of the patients with epilepsy and their hopelessness levels.

Limitations

One limitation of the present study is that we did not control for seizure severity. Subjects who are "seizure-free" often report having high QOL that resembles that of the general population[8,9] although, in some of these individuals, comorbid mental disorders, in particular depression impair subjective wellbeing[47,51,58,59]. Several

researchers[60,61] have reported a negative association between seizure severity and QOL, and patients in whom seizures are controlled effectively using antiepileptic drugs/surgery may be more likely to experience an improvement in health-related QOL. Seizure severity and other seizure-related variables have been found to be strong predictors of psychiatric comorbidity and depression[14,42,47,48,50].

Furthermore, the two groups of patients (those affected by epilepsy with generalized tonic-clonic seizures *vs* those having epilepsy with partial seizures) are not similar and a healthy control group was not available.

Other limitations include the small size of the present sample and the scarcity of information concerning seizure refractoriness, the number of psychoactive medications being taken, and seizure frequency. Further additional studies, including larger samples of patients with epilepsy, are required to investigate the complex relationship between depression, hopelessness, and QOL in epileptic patients. In addition, we were not able to ascertain the specific cause of the epilepsy (there are epilepsy subtypes that may be induced by external stimuli such as fever, toxin exposure, psychological distress).

In addition, we had insufficient information concerning seizure severity, seizure frequency, age at onset of seizures, duration of the illness, or number/type of psychotropic drugs, and so we were not able to evaluate the impact of these disease-variables on levels of hopelessness and QOL scores.

The patients were administered self-report measures that were not validated using an additional psychiatric examination, exposing the present findings to possible recall bias. In addition, the cross-sectional nature of this research further limits the generalization of the present findings. Lastly, all respondents reported moderate-severe depression, and this high prevalence of depression may indicate that the sample was highly selective and not representative of patients with epilepsy in general. However, the questionnaires were completed when the patients were admitted as outpatients for a seizure with no intervening period between seizure occurrence and mood evaluation.

Given the methodology which was used in the present study, a causal interpretation of the association between variables is not possible. Prospective follow-up studies using more advanced methodologies are required in order to make causal inferences about directional and developmental pathways underlying the variables involved in epilepsy.

Despite the limitations of the study, the current findings are consistent with existing results in the literature suggesting that, among patients with epilepsy, patients with higher hopelessness are more likely to have impairments in QOL compared to those with lower levels of hopelessness. Hopelessness in individuals with epilepsy needs to be identified as soon as possible in order to improve the QOL and reduce the burden of the disease. Prevention efforts to address recognized risk factors for suicidality are also needed for patients with epilepsy. Further prospective studies, including larger samples, should be carried out to investigate the complex nature of the relationship between hopelessness and the QOL in patients with epilepsy.

COMMENTS

Background

Epilepsy is a disabling illness associated with psychosocial impairment and significant mortality. Improving the quality of life (QOL) in epileptic patients is one of the most important goals associated with a general reduction of the subjective burden of this disease. Multiple variables such as hopelessness may influence QOL and subjective wellbeing in patients with epilepsy.

Research frontiers

Previous studies have reported that hopelessness is a predictor of future suicide behaviors in patients with mood disorders and with a poor QOL in epileptic patients. However, the impact of hopelessness on the outcome of patients with epilepsy needs to be further elucidated.

Innovations and breakthroughs

An association between epilepsy and major depression has been commonly reported, and depression and seizure severity are major predictors of the QOL in epileptic patients. Patients with generalized seizures reported more limitations in common social/role activities related to emotional problems compared to patients with other types of seizures. Suicide is frequent in epileptic patients, and those patients with higher Beck Hopelessness Scale (BHS) scores are more likely to die by suicide than those with lower BHS scores. In this study, patients at increased suicide risk as evaluated by the BHS were older than those who had a lower suicidal risk.

Applications

Clinicians should carefully screen epileptic patients for limitations in common activities due to emotional problems, as well as the presence of hopelessness, in order to identify those patients with poor outcomes.

Terminology

The Beck Depression Inventory-Ⅱ is a 21-item self-report instrument evaluating the presence/severity of depressive symptoms during the previous two weeks. The BHS is a 20-item self-report measure assessing hopelessness/negative attitudes about the future. Specifically, this instrument evaluates feelings about the future, loss of motivation, and negative expectations. The QOL in Epilepsy Inventory-89 (QOLIE-89) assesses specific domains regarding life in patients with epilepsy. The QOLIE-89 measures approximately 17 dimensions of the Health Related QOL, including individual's common social/role activities.

Peer review

The manuscript is well-written, interesting and useful for physicians.

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CASE REPORT

Polydipsia, hyponatremia and rhabdomyolysis in schizophrenia: A case report

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Abstract

The prevalence of polydipsia among patients with schizophrenia is 6%-20%. Around 10%-20% of patients with polydipsia may develop hyponatremia and even complicated with rhabdomyolysis. Here we presented a 40-year-old man with schizophrenia, who had received paliperidone 15 mg/d for more than one year, and polydipsia was noted. In Jan, 2014, he developed hyponatremia (Na 113 mEq/L) with consciousness disturbance. After 3% NaCl (500 cc/d) intravenous supplement for three days, the hyponatremia was corrected, but rhabdomyolysis developed with a substantial elevation in the level of creatine kinase (CK) to 30505 U/L. After hydration, the CK level gradually decreased to 212 U/L. Both the hyponatremia itself and quick supplementation of NaCl can cause rhabdomyolysis. If rhabdomyolysis is not recognized, insufficient hydration or water restriction for polydipsia may further exacerbate the rhabdomyolysis with a lethal risk. In this case, we highlight the possible complication of rhabdomyolysis with polydipsia-induced hyponatremia. In addition to monitoring the serum sodium level, the monitoring of CK is also important; and switching of antipsychotic may improve the polydipsia.

Key words: Schizophrenia; Polydipsia; Hyponatremia; Rhabdomyolysis; Quetiapine

Core tip: We present a 40-year-old man with schizophrenia who had polydipsia for more than one year and later had hyponatremia related consciousness disturbance. Though the association of polydipsia with schizophrenia and/or neuroleptic treatment is already discussed in the literature, there were no articles as detailed as our article. It reviewed the possible mechanism associated with hyponatremia and rhabdomyolysis, the choice of antipsychotics, and the reasons of polydipsia in schizophrenia patient at a time.

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INTRODUCTION

Polydipsia was prevalent in patients with psychiatric disorder, especially in chronic schizophrenia patient. The resulting complication of hyponatremia and rhabdomyolysis were also recorded in some case reports. Regarding the possible lethal risk of acute kidney injury, the management of polydipsia and the choice of antipsychotics should be concerned.

CASE REPORT

This 40-year-old single man was diagnosed with schizophrenia with the presentation of auditory hallucination, persecutory delusions and disturbing behavior, self-talking, poor self-hygiene, and wandering out, when he was 21-year-old. He had a medical history of chronic hepatitis B. Due to poor family support he stayed in a nursing home for years. He had been prescribed paliperidone 12 mg/d since November 2012, and polydipsia (more than 3 L/d) was noted. In December 2013, the dose of paliperidone was titrated to 15 mg/d due to persistent auditory hallucination.

On Jan 24, 2014, he was observed to have disturbed consciousness by the staff at the nursing home, and was sent to the emergency room immediately. The initial laboratory evaluations showed hyponatremia (Na 113 mEq/L), and creatine kinase (CK) of 247 U/L. The Glasgow Coma Scale was E4V1M4, with normal vital signs and unremarkable results for other laboratory exams. The patient was treated with 3% NaCl (500 cc/d) for three days. His consciousness became clear on the second day, and on the third day, the follow-up sodium level was 132 mEq/L. He was transferred to the acute psychiatric ward on the fourth day (Jan 27, 2014) in stable condition.

However, the follow-up data at psychiatric admission showed elevated levels of CK (30505 U/L), serum alanine (ALT, 102 U/L) and aspartate aminotransferase (AST, 457 U/L). To prevent acute kidney injury causing by rhabdomyolysis, he was given 1000 CC NaCl 0.9% from the 4th to the 13th day. On the 7th day, the CK level decreased to 1081 U/L, and on the 16th day, CK was reduced to 212 U/L, and liver enzymes returned to a normal range. After admission, the patient was prescribed paliperidone 6 mg/d initially for his psychotic symptom, and polydipsia was still noted with total water intake of 4000 CC/d, although the behavior modification was done. On the 15th day, the antipsychotic was switched to quetiapine, and gradually titrated to 1200 mg/d. Polydipsia was not noted beginning the 21st day, and the patient was discharged on the 31st day. Polydipsia was still not noted at three months after hospitalization, and the psychiatric condition remained stable now.

DISCUSSION

The clinical definition of polydipsia is water intake over 3 L/d. The prevalence of polydipsia among patients with schizophrenia is 6%-20%[1,2]. The possible mechanism may be related to the dry mouth side effect of anticholinergic drugs, compulsive behavior, or stress reduction[3-7]. It is also suggested the supersensitivity of the dopamine receptor induced by the long-term use of antipsychotic may stimulate the thirst center[4,8]. Previous studies showed 10%-20% of subjects with polydipsia may develop hyponatremia[7]. The complication of hyponatremia includes changes in consciousness, coma, seizure, and rhabdomyolysis. The exact etiology of rhabdomyolysis secondary to hyponatremia is unclear, but several mechanisms have been proposed. First, because of the lower osmolality of the extracellular fluid, acute hyponatremia resulted in cells swelling, and after hours of the extrusion of intracellular potassium which lowered the transmembrane potential but cause the release of CK and myoglobin[9-11]. Second, the decreased extracellular sodium may disturb the Na-Ca exchange pumps. Calcium level increased inside the cell because of reduced of the sodium outside the cell to be exchanged which led to the cell death by releasing proteases and lipase[12-14]. To conclude, creatine kinase may elevate after 48-96 h of hypomatremia because of the lowered sodium level itself or the rapid correction of hyponatremia[9,13,15,16]. In our case, we assumed that hyponatremia was corrected rapidly by the supplement of 3% saline which led to the delayed rise of CK, ALT, and AST.

With regard to the possible relationship of polydipsia with the supersensitivity of the dopamine receptor induced by long-term use of antipsychotics[8,17], risperidone, with a high affinity to D2 receptor blockade, has been reported to be associated with polydipsia[18,19]. There was also a case report discussing about olanzapine which caused the elevation in CK value[20]. Clozapine and quetiapine are weaker D2 antagonists, and have been suggested to be promising treatments for patients with polydipsia related to high potency antipsychotics[18,21-23]. Although two cases reported quetiapine-induced CK elevation in a neuroleptic-naïve patient[24]. In this case, the patient's polydipsia improved soon after switching paliperidone to quetiapine, not only in the acute psychiatric ward setting, but also after discharge and for three months in the nursing home (up to this writing).

In conclusion, both the hyponatremia itself and quick supplementation of NaCl can cause rhabdomyolysis. If rhabdomyolysis is not recognized, insufficient hydration or water restriction for polydipsia may further exacerbate the rhabdomyolysis with a lethal risk. In this case, we highlight the possible complication of rhabdomyolysis with polydipsia-induced hyponatremia. In addition to monitoring the serum sodium level, the monitoring of CK is also important; and switching of antipsychotic may improve the polydipsia.

COMMENTS

Case characteristics

An 40-year-old male with diagnosis of chronic schizophrenia.

Clinical diagnosis

Psychogenic polydipsia, schizophrenia, hyponatremia.

Treatment

Quetiapine 1200 mg.

Experiences and lessons

The authors highlight the possible complication of rhabdomyolysis with polydipsia-induced hyponatremia.

Peer review

The case report is interesting.

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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Patent (list all authors)

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