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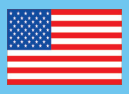

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REVIEW

Catatonia: Our current understanding of its diagnosis, treatment and pathophysiology

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Abstract

Catatonia is a psychomotor syndrome that has been reported to occur in more than 10% of patients with acute psychiatric illnesses. Two subtypes of the syndrome have been identified. Catatonia of the retarded type is characterized by immobility, mutism, staring, rigidity, and a host of other clinical signs. Excited catatonia is a less common presentation in which patients develop prolonged periods of psychomotor agitation. Once thought to be a subtype of schizophrenia, catatonia is now recognized to occur with a broad spectrum of medical and psychiatric illnesses, particularly affective disorders. In many cases, the catatonia must be treated before any underlying conditions can be accurately diagnosed. Most patients with the syndrome respond rapidly to low-dose benzodiazepines, but electroconvulsive therapy is occasionally required. Patients with longstanding catatonia or a diagnosis of schizophrenia may be less likely to respond. The pathobiology of catatonia is poorly understood, although abnormalities in gamma-aminobutyric acid and glutamate signaling have been suggested as causative factors. Because catatonia is common, highly treatable, and associated with significant morbidity and mortality if left untreated, physicians should maintain a high level of suspicion for this complex clinical syndrome. Since 1989, we have systematically assessed patients presenting to our psychiatry service with signs of retarded catatonia. In this paper, we present a review of the current literature on catatonia along with findings from the 220 cases we have assessed and treated.

Key words: Catatonia; Schizophrenia; Benzodiazepines; Electroconvulsive therapy; Extrapyramidal disorders

Core tip: Catatonia is a complex clinical syndrome occurring in more than 10% of patients with acute psychiatric illnesses, and it is associated with multiple life-threatening complications. In the last several decades, renewed interest in this syndrome has led to a great deal of research and debate regarding its

diagnosis and treatment. In this paper, we present a review of the current literature on catatonia along with findings from the 220 cases we have assessed and treated since 1989. Catatonia itself is readily treated using low-dose lorazepam, and it also has important implications for how other underlying psychiatric conditions should be treated.

Rasmussen SA, Mazurek MF, Rosebush PI. Catatonia: Our current understanding of its diagnosis, treatment and pathophysiology. *World J Psychiatr* 2016; 6(4): 391-398 Available from: URL: http://www.wjgnet.com/2220-3206/full/v6/i4/391.htm DOI: http://dx.doi.org/10.5498/wjp.v6.i4.391

INTRODUCTION

Catatonia is a clinical syndrome characterized by a distinct constellation of psychomotor disturbances. Two subtypes have been described: Retarded and excited. Catatonia of the retarded type is associated with signs reflecting a paucity of movement, including immobility, staring, mutism, rigidity, withdrawal and refusal to eat, along with more bizarre features such as posturing, grimacing, negativism, waxy flexibility, echolalia or echopraxia, stereotypy, verbigeration, and automatic obedience[1-3]. Excited catatonia, on the other hand, is characterized by severe psychomotor agitation[4], potentially leading to life-threatening complications such as hyperthermia, altered consciousness, and autonomic dysfunction. This so-called "malignant" or "lethal" catatonia can be rapidly fatal if not appropriately treated[5,6]. The relative prevalence and diagnostic significance of catatonic signs differ among studies and patient populations, but there is general agreement that catatonia occurs in 9%-17% of patients with acute psychiatric illnesses[1,2,7] and that retarded catatonia is the more frequently observed subtype[4,8-10].

The catatonic syndrome is associated with other disorders, underscoring the necessity of rapid diagnosis and treatment. In particular, catatonia appears to be a risk factor for the development of neuroleptic malignant syndrome[11-13], which has a mortality rate of approximately 10%[14] and may be clinically indistinguishable from malignant catatonia[15,16]. This has important implications for the treatment of catatonia in the context of psychosis, which will be discussed later in this review. Additionally, the immobility and refusal to eat or drink associated with catatonia can give rise to potentially serious medical complications, including dehydration[17], malnutrition[18,19], deep vein thrombosis and pulmonary embolism[20,21], pneumonia and other infections[17], pressure ulcers[19], and muscle contractures[18,19]. The very nature of catatonia can make it challenging, if not impossible, to carry out patient interviews and examinations, thereby interfering with the recognition of underlying diagnoses. These complications of catatonia highlight the importance of recognizing the syndrome and quickly initiating treatment.

Overall, it is clear that catatonia is a common and serious problem that often remains unrecognized. Despite a renewed interest in the disorder over the last several decades[22], a number of questions remain regarding its causes and treatment. In this paper, we review the current understanding of the diagnosis, treatment, and pathophysiology of catatonia, and we identify several areas of uncertainty where further research is required.

DIAGNOSIS

Clinical features

While catatonia has long been considered a subtype of schizophrenia or a clinical feature of other medical and psychiatric conditions, the earliest descriptions by Kahlbaum *et al*[23] in fact suggested a unique entity with a distinct clinical course. This proposal was not universally accepted, however, and a great deal of debate has ensued regarding the most appropriate classification of catatonia. Largely due to the influence of Emil Kraepelin, catatonia eventually came to be "officially" seen as a type of schizophrenia[24]. Early descriptions of catatonia in both the diagnostic and statistical manual of mental disorders (DSM) and international classification of diseases included it only under the category of schizophrenia, and this view persisted for many years. Things began to change in the 1970's, when multiple reports indicated that catatonia is more closely associated with affective disorders than schizophrenia[4,25]. More recently, it has been proposed that catatonia is also relatively common in patients diagnosed with autism[26]. In 1994, catatonia was recognized in the DSM-Ⅳ as a disorder that could either complicate general medical conditions or be a specifier in mood disorders. At the same time, there were continued arguments in support of catatonia being its own distinct diagnostic category[7,27].

A number of different criteria have been proposed for the diagnosis of catatonia. In our own ongoing assessment and treatment of consecutively referred patients with catatonia who present to either our acute-care inpatient psychiatric unit or to the consultation-liaison service, we diagnose patients based on the presence of at least four of the catatonic signs originally described by Karl Kahlbaum in 1874[1]. These signs, along with their frequency in our patient series, are presented in Table 1. As we originally reported in 1990[1], immobility and mutism are the most common signs, each present in over 90% of patients. In keeping with this finding, the diagnostic criteria proposed by Taylor *et al*[27] include immobility and mutism (along with stupor) as core criteria for catatonia. A systematic effort to identify the catatonic signs with the best diagnostic performance was conducted by Peralta *et al*[2]. Immobility and mutism were again identified as the most common signs, observed in 90.6% and 84.4% respectively of catatonic patients. Rigidity was also common in their

Table 1 Frequency of various catatonic signs in our series of 220 consecutive catatonic cases

Sign	% of patients
Immobility	97
Mutism	97
Withdrawal and refusal to eat	91
Staring	87
Negativism	67
Posturing	58
Rigidity	54
Waxy flexibility/catalepsy	27
Stereotypy	25
Echolalia or echopraxia	14
Verbigeration	14

sample, observed in 75.0% of catatonic patients. The use of 4 or more catatonic signs as a diagnostic criterion resulted in 100% specificity, but also led to a small number of catatonic patients failing to be identified. As a result, Peralta *et al*[3] suggest the use of three or more catatonic signs as a diagnostic criterion for catatonia, and this recommendation has been supported by more recent work from the same group[3]. The DSM-Ⅴ defines catatonia as the presence of three or more of the following: Catalepsy, waxy flexibility, stupor, agitation, mutism, negativism, posturing, mannerisms, stereotypies, grimacing, echolalia, and echopraxia[28]. A number of scales have been developed to quantify catatonic signs[29]. While these scales may prove useful for research, we have not found them to be necessary for clinical purposes.

The most important step in the diagnosis of catatonia is recognition of the syndrome's characteristic clinical signs. Immobility and mutism are particularly common, and the appearance of either of these signs in the absence of another explanatory condition should raise the clinical suspicion of catatonia, at which point the presence of other catatonic signs can be determined. In our experience, patients are often incontinent, disheveled, and cachectic depending on the duration of illness. The lack of meaningful responses to external stimuli in these patients should not be interpreted as a lack of awareness of their surroundings. Indeed, many of the patients we have treated reported being completely aware and were able to recall their catatonic state in detail after they recovered.

Differential diagnosis

A number of neurological conditions may appear similar to catatonia, and may even have substantial overlap with respect to pathophysiological mechanisms. The following is a partial list of conditions that, in our experience, have considerable clinical overlap with catatonia and should be carefully considered.

Extrapyramidal side-effects: Extrapyramidal side-effects are commonly associated with both typical and atypical antipsychotic drugs[30,31], so they are of special concern in patients with psychiatric illness. Like patients with catatonia, patients with drug-induced parkinsonism may present with immobility, staring, and rigidity. On numerous occasions we have been asked to see a patient with a tentative diagnosis of catatonia who in fact had antipsychotic-induced parkinsonism. This distinction is an important one to make, since the benzodiazepine medication used to treat catatonia may exacerbate the postural instability that is often associated with parkinsonism. One notable difference between the syndromes is that parkinsonian patients are typically cooperative and interactive, in contrast to catatonic patients who are often withdrawn and negativistic. Also, tremor, which is often present in patients with parkinsonism, is not a feature of catatonia. Unusual features like echophenomena and posturing are typically absent in parkinsonism. We have, however, seen parkinsonian patients whose freezing was mistaken for posturing. Additionally, some patients treated with antipsychotic drugs may develop signs consistent with both catatonia and parkinsonism[32]. Other extrapyramidal side-effects may also resemble some aspects of catatonia. For example, the posturing and immobility of catatonic patients can be mistaken for dystonia, while the psychomotor agitation of excited catatonia can appear similar to akathisia. In patients being treated with antipsychotic medication, care must be taken in assessing these clinical features to ensure diagnostic accuracy.

Neuroleptic malignant syndrome: Neuroleptic malignant syndrome is a life-threatening reaction to antipsychotic treatment (including treatment with atypical antipsychotics[33]) in which patients develop rigidity, mutism, and delirium accompanied by diaphoresis, hypertension, tachycardia, and fever[34,35]. Autonomic instability helps to distinguish this syndrome from uncomplicated catatonia, but it may sometimes be indistinguishable from malignant catatonia except for the precipitating factor of antipsychotic treatment. Cessation of antipsychotic medication, along with supportive therapy, is often sufficient to treat these patients, but additional pharmacological treatment or electroconvulsive therapy (ECT) may be indicated.

Nonconvulsive status epilepticus: Nonconvulsive status epilepticus can be clinically indistinguishable from catatonia. In both cases, patients can be immobile, mute, rigid, and unable to eat, drink, or cooperate with an examination. Although electroencephalogram (EEG) findings in nonconvulsive status epilepticus can be highly variable, these investigations are nonetheless crucial to making the correct diagnosis[36,37].

Abulia or akinetic mutism: Disorders of diminished motivation exist on a spectrum including abulia (moderate) and akinetic mutism (severe)[38]. In the extreme case, neurological dysfunction results in a complete lack of spontaneous speech or movement due to a lack of motivation or drive. Patients are fully aware and visual

tracking is preserved. Overt signs of catatonia such as negativism and echophenomena may differentiate the two disorders, but more subtle presentations can make the two conditions difficult to distinguish[39]. In such cases, a trial of lorazepam may be helpful in identifying catatonia.

Locked-in syndrome: Locked-in syndrome is usually associated with ventral pontine lesions, and results in near complete paralysis, while blinking and vertical eye movements are spared[40]. Patients are aware and, unlike catatonic patients, generally eager to communicate through blinking. However, it should be noted that some patients with locked-in syndrome are unable to blink or move their eyes. As with catatonic patients, EEG investigations are often normal. Abnormalities identified using magnetic resonance imaging (MRI) or brainstem evoked potentials help to identify patients with the locked-in syndrome.

Vegetative state: The vegetative state is characterized by a complete lack of awareness of the self or surroundings, often secondary to a severe cerebral injury[41]. The patient makes no voluntary responses to stimuli, and does not visually track objects, but sleep-wake cycles are preserved. Although this definition of the persistent vegetative state is reasonably clear, confidently assessing a lack of awareness can be problematic. EEG and MRI techniques have been used to demonstrate awareness in a disturbing number of patients who otherwise met criteria for a vegetative state[42,43]. Unlike the normal EEG of catatonia, the EEG in vegetative states is almost always abnormal[44].

Stiff person syndrome: Stiff person syndrome is an autoimmune disorder frequently presenting with low back and lower extremity stiffness and spasms, as well as exaggerated lumbar lordosis[45], which can be mistaken for posturing. Like catatonia, the condition can render patients immobile. Episodes are typically triggered when patients are startled or experience emotional stress. In contrast with what is observed in patients with catatonia, patients with stiff person syndrome are not mute and will often indicate that they are in great pain as a result of the muscle spasms. Since most patients are GAD65 antibody seropositive[45], antibody testing may be helpful if there is diagnostic uncertainty. The syndrome generally improves in response to benzodiazepine treatment, perhaps supplemented by adjunctive immunotherapy where appropriate.

INVESTIGATIONS

All patients suspected of having catatonia should have EEG testing as a screen for other neurological conditions. This will typically show epileptiform activity in nonconvulsive status epilepticus and slowing in cases of encephalopathy. The EEG in catatonia is typically normal unless there is a concurrent condition that may be causing the abnormality[1,9,46]. Given that catatonia can develop in the context of a wide array of neurological conditions, brain imaging, preferably by MRI, is recommended[1,47]. In cases of retarded catatonia, immobility generally allows these investigations to be conducted easily. Laboratory investigations should include a complete blood count, blood urea nitrogen, creatinine, muscle and hepatic enzymes, thyroid function tests, electrolytes, blood glucose, and urinalysis to assess for comorbid conditions, causes, or complications of catatonia. Marked dehydration is not uncommon in catatonic patients, and must be attended to. Vital signs should be assessed frequently, as hypertension and fever (often accompanied by elevated creatine phosphokinase, decreased serum iron, and leukocytosis) may herald the onset of malignant catatonia or neuroleptic malignant syndrome if the patient has received antipsychotic agents[35,48-50]. When possible, a careful review of the patient's recent medications and any changes should be conducted. It is important to determine whether or not a patient has been receiving antipsychotic agents or benzodiazepines, as we have reported, and continue to see, the development of catatonia following abrupt discontinuation of benzodiazepines[51,52].

Unfortunately, the nature of catatonia makes some aspects of a physical and neurological exam impossible. Components of the neurological exam that can usually be assessed include the pupillary reaction, ocular movements, corneal reflex, reaction to pain, the presence of drooling, blink response to threat, reaction to light or sound, frontal release signs, assessment of tone, deep tendon reflexes, and the plantar response.

TREATMENT

A characteristic feature of catatonia is its striking responsiveness to benzodiazepine treatment. We recommend an initial dose of 1-2 mg lorazepam, administered sublingually or intramuscularly. The ability to administer lorazepam intramuscularly is a major advantage, since many catatonic patients refuse to eat or take medication by mouth. A lower lorazepam dose is preferable in patients who are young, elderly, or medically compromised, especially when there is a diagnosis or high likelihood of sleep apnea. If the initial dose is ineffective, it should be repeated in 3 h and again after another 3 h. We have analyzed treatment response in 153 patients treated with lorazepam. In this group, we have observed a response in 132 (85.7%), 90 of whom experienced complete recovery within 3 h. This robust response to low-dose lorazepam has also been reported by others[46,53], but higher doses may be necessary in some cases[54,55]. If a patient responds adequately to benzodiazepine treatment, they should continue on the same dose (provided that this dose is not overly sedating or causing any other problematic side-effects) until treatment of any underlying disorder is underway. Relapse into a catatonic state can occur

Table 2 Rates of response to lorazepam treatment in catatonic patients with various underlying diagnoses

Diagnosis	Patients responding (%)
Bipolar disorder (n = 31)	97
Unipolar depression (n = 30)	93
Other psychoses (n = 24)	92
Medical/neurological condition (n = 11)	82
Schizophrenia (n = 22)	59

if benzodiazepines are discontinued before this. In our experience, a subset of patients may develop catatonia whenever attempts are made to discontinue lorazepam, and these patients may require long-term maintenance treatment[56]. This phenomenon has also been reported by others[57].

It should be noted that patients with long-standing catatonia may not respond as robustly or as rapidly to benzodiazepine treatment as those with acute catatonia[54,58]. We have reported the cases of two brothers, one of whom had been catatonic for 2 wk prior to treatment, while the other had been hospitalized with catatonia for 5 years[59]. The first brother recovered completely in 2 wk on a lorazepam dose of 3 mg/d. The second brother, on the other hand, showed only gradual improvement on lorazepam 4 mg/d before being discharged from hospital a year after treatment initiation.

An underlying diagnosis of schizophrenia may be associated with a less robust response to benzodiazepine treatment[53]. We have observed a response rate of only 59.1% in patients with schizophrenia, compared with a response rate of over 90% in patients with other psychiatric diagnoses (Table 2). The poorer treatment response in patients with schizophrenia may be related to the chronicity of symptomatology, or it may suggest a distinct underlying pathophysiology, perhaps reflecting the prominence of psychosis affecting their motor behaviour. Nevertheless, benzodiazepines can be effective for treating catatonia in many patients with schizophrenia, and a therapeutic trial is warranted. This is especially the case given the overall safety of benzodiazepine medication.

ECT is another highly effective option for the treatment of catatonia[9,60], and even patients who do not respond to benzodiazepines are likely to respond to ECT[61,62]. Despite its effectiveness, ECT has an important drawback: It requires clear consent. Catatonic patients are unable to discuss ECT or consent to its administration, and consent from a substitute decision maker is often difficult to obtain. Because of these problems, and because benzodiazepines are easily administered and have a high margin of safety, we recommend that benzodiazepines be used as the first line of treatment. ECT should be considered in patients who fail to respond to benzodiazepines after several days and surrogate consent should be sought. The exception to this strategy is the patient with malignant catatonia, for whom ECT should be administered early, since the condition has a high rate of mortality if it is not rapidly and effectively treated[6,49].

Of the catatonic patients we have assessed, 77.7% later reported having experienced psychotic symptoms during the catatonic episode. This raises a difficult problem in treatment, since antipsychotic medications may be associated with an increased risk of neuroleptic malignant syndrome in patients with catatonia. White *et al*[12] identified 17 consecutive patients with neuroleptic malignant syndrome, all of whom exhibited catatonic signs prior to antipsychotic exposure. In our own patients, we have observed that 3.6% of catatonic patients treated with antipsychotic medications developed neuroleptic malignant syndrome[63]. This is in contrast to an incidence of 0.07%-1.8% in all patients treated with antipsychotic drugs[64,65]. Raja *et al*[11] identified 3 cases of neuroleptic malignant syndrome in a series of consecutive patients presenting to the psychiatric emergency service, all 3 of whom demonstrated catatonic signs and low serum iron prior to the onset of neuroleptic malignant syndrome. The relationship between catatonia and neuroleptic malignant syndrome is not limited to patients treated with typical antipsychotics, as clozapine has also been reported to be a precipitating factor[13]. Although more research is required in order to identify which patients are most susceptible to neuroleptic malignant syndrome, we feel that the existing evidence is sufficient to recommend the avoidance of antipsychotic drugs in acutely catatonic patients. In our experience, once catatonic symptoms have been treated by benzodiazepines or ECT and patients are eating, drinking, and walking, antipsychotic treatment can be initiated safely.

Although lorazepam and ECT have long been recognized as effective treatments for patients with catatonia, other options have been suggested. Several case reports have described patients effectively treated with zolpidem[66,67], which, like typical benzodiazepines, may treat catatonia through interactions with GABA-A receptors[68]. As well, amantadine and memantine, which act as NMDA antagonists but also interact with a number of other neurotransmitter systems, have shown efficacy in a small number of patients[69,70]. It is not yet clear whether these options are likely to be helpful in the small fraction of patients who do not respond to either lorazepam or ECT.

PATHOPHYSIOLOGY

While the pathophysiology of catatonia is still unclear, several theories have been proposed based on the available data. One possible interpretation of catatonia is that the syndrome is an outward manifestation of intense anxiety[22,71]. The majority of catatonic patients we have treated reported feeling extremely anxious before and during their catatonic episode, to the extent that some believed they were about to die, had already died, or that they needed to remain immobile

in order to avoid threats from others. Benzodiazepines reduce anxiety by enhancing chloride conductance through GABA-A receptor ion channels, and may treat catatonia through this mechanism. However, a number of our patients - particularly those with schizophrenia - reported little anxiety during their catatonic episode. This observation does not exclude the possibility that anxiety is an important component of catatonia, but suggests that it is not an essential component for all patients with the syndrome.

A second interpretation of catatonia is that it is essentially a movement disorder similar to parkinsonism. As noted previously, the clinical features of catatonia overlap with those of parkinsonism, which is understood to be caused by dysfunction of the basal ganglia. Since most projection neurons in the basal ganglia are GABAergic, it is plausible that benzodiazepines could treat catatonia by influencing GABA signaling in the basal ganglia. Functional imaging studies have shown that catatonia is associated with altered activity in orbitofrontal, prefrontal, parietal, and motor cortical regions[72], suggesting that these cortical structures may also play a role in the pathophysiology of catatonia. This interpretation is reinforced by observations that GABA-A binding is reduced in cortical regions of catatonic patients, motor and affective symptoms are correlated with these abnormalities in GABA-A binding, and cortical abnormalities in catatonic patients are normalized following exposure to lorazepam[72].

Whatever the pathophysiology of catatonia may be, it is clear that a wide variety of underlying disorders can be associated with the emergence of catatonic signs. These include mood disorders, nonaffective psychotic disorders, a number of medical and neurological conditions, and genetic disorders[73]. How - or if - these diverse etiologies converge upon a final common pathway causing catatonia is unknown, and it is possible that variations in the clinical presentation of catatonia represent distinct underlying mechanisms that would respond preferentially to different treatments. For instance, future research may allow physicians to identify patients who are unlikely to respond to lorazepam treatment and should receive ECT or another pharmacological treatment as a first line option.

CONCLUSION

The syndrome of catatonia encompasses a wide range of psychomotor abnormalities, none of which are present in all patients. Immobility and mutism are especially common, and the presence of these signs should prompt physicians to actively assess other markers of catatonia. The differential diagnosis of catatonia is complex, and catatonia itself can arise from a diverse array of psychiatric and medical etiologies, complicating the investigation of these patients. Affective disorders are the most common underlying psychiatric diagnoses. Fortunately, most catatonic patients rapidly respond to low-dose lorazepam. Some patients, particularly those with long-standing catatonia or schizophrenia, may respond more gradually or not at all to lorazepam, and may require ECT or other pharmacological treatments. We feel that the use of antipsychotics should generally be avoided until the acute catatonic episode has resolved in order to avoid precipitating neuroleptic malignant syndrome. The pathophysiology of catatonia is still poorly understood, and it is unclear whether different constellations of clinical signs might represent distinct underlying mechanisms. Recognizing and treating catatonia usually results in rapid resolution of the syndrome, whereas failing to recognize it may lead to potentially fatal complications including infection, neuroleptic malignant syndrome, and pulmonary embolism. Because of this, physicians should maintain a high level of suspicion for the catatonic syndrome, especially in patients experiencing an acute psychiatric illness.

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REVIEW

Treatment-adherence in bipolar disorder: A patient-centred approach

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Abstract

About half of the patients diagnosed with bipolar disorder (BD) become non-adherent during long-term treatment, a rate largely similar to other chronic illnesses and one that has remained unchanged over the years. Non-adherence in BD is a complex phenomenon determined by a multitude of influences. However, there is considerable uncertainty about the key determinants of non-adherence in BD. Initial research on non-adherence in BD mostly limited itself to examining demographic, clinical and medication-related factors impacting adherence. However, because of inconsistent results and failure of these studies to address the complexities of adherence behaviour, demographic and illness-related factors were alone unable to explain or predict non-adherence in BD. This prompted a shift to a more patient-centred approach of viewing non-adherence. The central element of this approach includes an emphasis on patients' decisions regarding their own treatment based on their personal beliefs, life circumstances and their perceptions of benefits and disadvantages of treatment. Patients' decision-making processes are influenced by the nature of their relationship with clinicians and the health-care system and by people in their immediate environment. The primacy of the patient's perspective on non-adherence is in keeping with the current theoretical models and concordance-based approaches to adherence behaviour in BD. Research over the past two decades has further endorsed the critical role of patients' attitudes and beliefs regarding medications, the importance of a collaborative treatment-alliance, the influence of the family, and the significance of other patient-related factors such as knowledge, stigma, patient satisfaction and access to treatment in determining non-adherence in BD. Though simply moving from an illness-centred to a patient-centred approach is unlikely to solve the problem of non-adherence in BD, such an approach is more likely to lead to a better understanding of non-adherence and more likely to yield effective solutions to tackle this common and distressing problem afflicting patients with BD.

Key words: Non-adherence; Bipolar disorder; Attitudes; Health-beliefs; Treatment-alliance; Familial influences; Knowledge; Stigma

Core tip: Treatment non-adherence in bipolar disorder (BD) is a complex phenomenon determined by a multitude of influences, but its critical determinants are yet to be identified with certainty. Demographic and illness-related factors have not been able to explain or predict non-adherence in BD. On the other hand, patient-centred variables such as attitudes and beliefs regarding medications, treatment-alliance, family attitudes, knowledge, stigma and access to treatment may be the more seminal influences on medication-taking in BD. A move from an illness-centred to a patient-centred approach is more likely to lead to a better understanding and more effective solutions for non-adherence in BD.

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INTRODUCTION

To write prescriptions is easy, but to come to an understanding with people is hard. A country doctor: Franz Kafka, 1917.

Bipolar disorder (BD) is a commonly prevalent and enduring condition characterized by recurrent episodes and often followed by residual symptoms. The high rates of comorbidity, suicide and functional impairment in BD also ensure that it is a common cause of disability as well as economic and social burden[1,2]. Pharmacological treatments are efficacious in both acute and long-term treatment of BD in clinical trials of these medications. Nevertheless, the effectiveness of medication treatments, particularly long-term treatment with medications is less impressive in day-to-day practice. Inadequate treatment-adherence is the single most important hurdle in translating efficacy in research settings into effectiveness in clinical practice[3]. In common with other chronic medical conditions with intermittent symptoms and delayed effects of discontinuing treatment, non-adherence is widespread in BD and is associated with several adverse consequences. Apart from undermining the usefulness of treatment and leading to poor outcomes, non-adherence also increases the risk of relapse, re-hospitalization and suicide several folds[2,4]. Non-adherence in individuals with BD leads to greater utilization of health-care services and increased mental health expenditures[5-7]. Finally, the poorer quality of life, stigmatization and functional impairment which accompany non-adherence lead to added burden on the family and society as a whole[8].

HOW COMMON IS NON-ADHERENCE IN BD?

Adherence has been defined as "the extent to which a person's behaviour, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"[9]. Studies of BD have largely focused on medication non-adherence rather than other aspects of treatment-adherence. Not surprisingly, there is a considerable variation between the rates of such non-adherence ranging from universal adherence in some studies to more or less universal non-adherence in others[10-12]. Much of this variability in rates can be attributed to methodological differences across studies. Adherence has been defined and assessed differently in different studies. Studies also differ in the settings in which they have been conducted (*e.g.,* clinics or community), in their designs (*e.g.,* cross-sectional or longitudinal), in the patient samples included, and in the phase of illness or the duration during which non-adherence has been estimated[13-17]. Extremely high or low rates have usually been obtained from studies with small patient samples and from specialized settings, or from randomized controlled trials of medication efficacy[10-12,18-20]. If these extremes are ignored most studies report non-adherence rates from 20% to 50%, with a few reporting rates from 60% to 70% for all patients with BD[21-23]. This is very similar to the estimates of several reviews on the subject, which conclude that on the average about 40% to 50% of patients with BD (range 9%-66%) do not take their medications regularly[2,4,24-28]. These rates are essentially the same regardless of whether patients are on mood stabilizers or antipsychotics. Moreover, rates of non-adherence seem to have remained unchanged or even increased over the years despite the introduction of several new medications[1,4,13,26,29]. The fact that about half of patients with BD become non-adherent during long-term treatment puts it on par with several other chronic psychiatric and medical disorders[4,9,30-32]. Moreover, a large part of this commonly prevalent non-adherence remains undetected in real-world treatment of BD as well; clinicians appear to be particularly likely to underestimate non-adherence among their patients[17,33-36]. However, the blame for lack of detection in day-to-day practice cannot be entirely laid at the clinician's door, because it is notoriously difficult to predict who is likely become non-adherent. Non-adherence is obviously a complex phenomenon determined by a multitude of influences. However, despite best efforts it is still unclear as to which of these factors is most critical in determining non-adherence in BD[4,13,26].

DEMOGRAPHIC AND ILLNESS-RELATED DETERMINANTS OF NON-ADHERENCE IN BD

In a seminal article about 40 years ago Jamison *et al*[37] proposed four mutually interacting domains to explain non-adherence to prescribed lithium among patients with BD. These included factors related to

the patient (*e.g.*, demographic characteristics), the illness (*e.g.*, severity), the effect of medications (*e.g.*, side effects) and characteristics of the clinicians (*e.g.*, relationship with patients). These determinants have been subsequently adopted by others working in the field, but some significant additions have been made in each category. For example, patient-related factors have come to include personal attitudes and beliefs about medication-taking in addition to demographic factors. Clinician-related factors has been broadened to include an environmental domain, which encompasses the influence of clinician-patient interactions and health-system related factors on adherence, as well as the influence of the family and significant others in the patient's life[13,25,28,38,39].

In the 1980s and 1990s research on treatment non-adherence amongst those diagnosed with psychiatric disorders including BD mostly limited itself to examining demographic, clinical and medication-related factors impacting adherence[2,17,38,40]. The exclusive focus on these factors appeared to be driven by biologically and medically orientated conceptualizations of the illness, although the primacy of the biological approach had been the object of criticism for long. Unfortunately, these efforts to predict non-adherence on the basis of demographic and illness-related factors were not very successful[40-44]. This failed quest could be due to several reasons, the principal one being the equivocal and inconsistent results obtained from different studies[40,45,46]. For example, although certain demographic correlates have emerged as likely determinants in some studies[4,26,27,42], several other studies have found no association between demographic variables and non-adherence in BD[17,47-51]. Among individual demographic attributes there has been some evidence for an association of non-adherence in BD with younger age[13,27,39,52,53], minority ethnicity[7,54-58], and social disadvantage[27,34,52,56,57,59], but the evidence for such links is either limited or often contradictory[2,4,34,38,48,49,60]. The role of clinical factors in determining non-adherence in BD seems to have been similarly inconsistent and ambiguous[42,61]. Overall severity of the illness in terms of symptom-burden, greater number of episodes and prior hospitalizations appeared to influence non-adherence in some[25,27,28,35,62], but not all studies[2,16,47,51,59]. A majority of studies among patients with BD found that poor insight and denial of the illness was associated with non-adherence[4,24,26,38,63-65]. However, though it might be difficult for a patient to be adherent without a basic level of insight, simply having insight may not be sufficient to ensure adherence[1,16,36,65,66]. The presence of comorbid disorders, particularly substance use disorders has also emerged as a consistent correlate of non-adherence in BD[26,28,39,42,46], but the evidence for associations with most other clinical variables has been either scarce or inconsistently replicated[35,62,67-70]. Among medication-related factors the role of the efficacy-tolerability balance in determining adherence has been the focus of most studies in BD. A large number of studies have found that treatment side effects negatively influenced adherence in BD[7,35,46,59,70], though many of these have exclusively investigated the side effects of lithium[34,67,71-74]. On the other hand, an almost equally large number of studies and patient surveys have revealed that side effects are not associated with non-adherence in BD[2,4,26,27,39,75]. It appears that fear or concerns regarding side effects rather than their actual prevalence may be more important in determining non-adherence in BD[17,26,41,45,76,77]. The influence of treatment-efficacy on adherence has been examined less often, though some studies suggest that medications alleviating depressive symptoms are more likely to promote adherence[7,51,78-80].

The uncertain influence of clinical and demographic factors on adherence in BD could also be due to the fact that many of the studies examining this association have failed to take into account complex interactions between several such variables, which could eventually determine the risk of non-adherence in BD[28]. For example, the higher prevalence of non-adherence during manic episodes could well be due to a lack of insight or the presence of cognitive impairment during such episodes[1,4,41]. Similarly, the greater risk of non-adherence in men could be related to the more frequent use of substances among them[81,82]. Additionally, the simple and dichotomous categorizations of demographic, clinical and treatment-related factors adopted by these studies ignored the subjective experience of medication-taking and the importance of factors such as attitudes and health-beliefs, which might underlie the link between demographic and clinical factors and non-adherence[28,81,83]. Accordingly, there is ample evidence to suggest that variables such as age, gender, severity of illness, effects of substance use, side effects and other treatment-related factors may impact adherence through their effects on subjective patient experiences such as their attitudes to medications, their knowledge of the illness and the availability of social support[2,19,51,84-88]. Moreover, while certain demographic and clinical variables such as young age, symptom-severity, substance use comorbidity and lack of insight may be useful in delineating groups at high risk for non-adherence, they do not accurately predict non-adherence at the level of the individual patient[11,40,41,45]. Finally, because many of these factors may not be amenable to change they do not provide opportunities for adherence enhancement through targeted psychosocial interventions[48,49]. These limitations of attempting to predict and target non-adherence based on demographic and illness-related factors indicates the need for an alternative perspective on treatment-adherence. The newer perspective lays greater emphasis on the patient's point of view of medication-taking, while acknowledging that problems with adherence are likely to be determined by complex interactions between the patient, the illness, its treatment and the wider socio-cultural environment in which such treatment takes

place[11,27,41,61].

A PARADIGM SHIFT TO A PATIENT-CENTRED APPROACH TO ADHERENCE IN BD

As with other chronic medical conditions, research on predictors of non-adherence in BD over the last two decades has undergone a gradual shift in thinking from an illness-centred to a patient-centred approach[40,89]. In this patient-centred paradigm, adherence is viewed as a dynamic rather than a static process which is influenced by many factors within and outside the patient[2,13,26,42,43]. At the core of this process lie the patients' abilities to make decisions about their own treatment[11,27,90]. Patients are the "final decision-makers" who have a right to choose whether or not continue treatment based on their own beliefs, personal circumstances and their perceptions of benefits and disadvantages of treatment. This right of patients to have a say in their treatment is acknowledged and prioritized in the patient-centred approach to medication-taking[2,7,27,32,50,90]. The emphasis on the patient's decision-making prompts a shift in the patient-clinician relationship to one in which both are equal and active collaborators. This approach is in keeping with the move away from earlier compliance-based models to those that place emphasis on concordant relationships between patients and clinicians[1,4,32,50,89,90]. While compliance-based paradigms treated patients as passive recipients of treatments and ignored the centrality of their viewpoints, the currently prevalent adherence- and concordance-based approaches place greater stress on the need for an agreement on decisions regarding treatment between patients and clinicians. The cornerstone of the concordance approach rests on open discussions of mutual views about taking medications, and a shared decision-making alliance between patients and clinicians while retaining the primacy of patients' choices. This shift in paradigms has been further propelled by the formulation of a number of health-behaviour models, which have been used to explain non-adherence in BD with a certain degree of success[11,41,45,76,90,91]. Though consisting of divergent social, cognitive and behavioural perspectives on adherence, they give central importance to the very same elements such as patients' attitude and health-beliefs, the treatment-alliance and factors in patients' immediate environments influencing adherence. Finally, the move from illness-related determinants to patients' perspectives on adherence has aided the development of several adjunctive psychosocial interventions to enhance medication-adherence in BD. These treatments, which use the framework of a collaborative alliance with patients and families to address non-adherence through educative, cognitive and behavioural means have had some success in optimizing adherence in BD[2,4,26,28,38,61].

PATIENT-CENTRED DETERMINANTS OF NON-ADHERENCE IN BD

Attitudes and beliefs regarding medications

In the research on adherence a distinction is often made between unintentional and intentional non-adherence. Unintentional non-adherence arises from personal or environmental restrictions which hamper medication-taking, while intentional non-adherence arises from patients' views on medications which affect their willingness to take them[92,93]. In an influential study, Horne and Weinman[94] categorized patients' beliefs about medications into general beliefs related to the intrinsic nature of medicines and ways in which medicines are used by doctors, and specific beliefs comprised of the perceived necessity of taking medications coupled with concerns about their adverse consequences. Both general health-beliefs and specific beliefs (attitudes) regarding medications have been examined among patients with BD. Barring a few exceptions[10,27,74,80,95], the majority of such studies of patients with BD have found that both health-beliefs and attitudes to medications are associated with non-adherence in BD[2,4,13,26,28]. Some of the studies have actually concluded that adverse attitudes and health-beliefs among patients have a much greater influence on non-adherence than demographic, illness or treatment-related factors such as side effects[17,26,45,51,76]. In other studies attitudinal factors such as doubts about the need for medications, as well as concerns about their adverse effects have been found to account for a substantial proportion of variance in intentional non-adherence[11,19,37,41,87,96]. All kinds of negative attitudes have been found in these studies though the commonest ones appear to be fear of side effects and harm caused by medications[17,19,37,51,75,97], denial of severity of illness and the need for treatment[11,41,46,86,98,99], the negative impact of long-term medications on daily routines and competing priorities of life[37,85,86,98,100,101], perceived ineffectiveness of medications[19,51,69,46,98,102], fears regarding dependence, being controlled or stigmatized by taking medications[35,37,60,75,103], and missing the pleasure experienced during manic episodes because of the mood-controlling effects of medications[37,44,101,104,105]. On the other hand, some patients perceive medications to be helpful and seem to realize the necessity of taking medications to prevent relapses, hospitalizations and other negative consequences[11,69,79,98,106,107]. Attitudes towards medications among patients might be relatively independent of their demographic and clinical characteristics[50,51,108,109], or they might differ according to age and illness-related factors such as the severity of the illness and its course, comorbid substance use and side effects of medications[85,100,110-113]. Additionally, patients' attitudes are more likely to be influenced by their knowledge of the illness, attitudes among their family members and ethno-cultural groups, the clinician-patient relationship and the overall quality of life among patients[35,60,84,101,103,114]. However, regardless of the

substantial evidence in favour of attitudes and health-beliefs influencing adherence behaviour in BD, the number of studies is relatively small. Moreover, because of the cross-sectional designs and the small numbers of patients in most studies it is not possible to make any inferences about causality[41,86].

Treatment alliance

Apart from attitudes and health-beliefs the other principal influence on non-adherence in BD is the treatment-alliance between the doctors or clinicians and patients. The concept of the treatment-alliance as a collaborative and affective bond between clinicians and patients has its origin in psychoanalytic and psychotherapeutic literature[115,116]. In keeping with the research-evidence on treatment-alliance in psychotherapy and other psychiatric disorders such as schizophrenia[115-117], an effective alliance appears to have a significant influence on treatment-adherence in BD as well. Though research on the influence of treatment-alliance on adherence is relatively scarce, the more or less unequivocal finding from several studies is that a strong therapeutic alliance is associated with improved adherence among patients with BD[18,58,91,114,118-120]. A strong alliance appears to enhance treatment-adherence in BD in several ways such as fostering more positive attitudes to treatment and enhancing the acceptance of treatment among patients[1,2,13,14,26,78]. The importance of a genuinely collaborative alliance in determining adherence is also in accord with the current emphasis on the active involvement of patients in decision-making and concordance-based approaches to understanding adherence in BD[1,13,52,78,121]. Moreover, a patient-centred approach and a collaborative clinician-patient alliance appear to be essential ingredients of all psychosocial interventions designed to enhance adherence in BD[1,7]. Definitions of therapeutic alliance in psychotherapy have three common elements including the collaborative nature of the relationship, the affective bond between patients and therapists, and the patient's and therapist's ability to agree on treatment goals and tasks[115]. Research among patients with BD indicates that the very same components of treatment-alliance are intimately related to adherence behaviour. Forging a successful treatment-alliance in BD begins with a two-way, reciprocal communication between the patient and the clinician[18]. There are a number of studies among patients with BD showing that not only do clinicians tend to overestimate the degree of adherence among patients, but there is also considerable discrepancy between clinicians and their patients regarding the reasons for non-adherence as well as the meaning of non-adherence[3,24,43,76,96]. Clinicians might also fail to acknowledge the patient's concern or distress about long-term treatment. Therefore, clinicians first need to create an atmosphere in which patients are able to freely discuss their problems about taking medications. Clinicians also need to play an active role in attempting to understand the patient's views on illness and medication-taking. To further this open and active stance clinicians must not only listen more effectively, but also learn to value this communication with patients in order to forge effective links with them[18,26,107,122]. Empathy, compassion and skilful counselling are much valued by patients and positively associated with adherence in BD[120,123]. This bi-directional communication also forms the vehicle for imparting information about the illness and its treatment since patients frequently express the need for such information[75,106,122]. Moreover, information can be used to effectively dispel incorrect beliefs about medications, reduce feelings of stigma and foster positive attitudes to treatment among patients[50,114]. The other necessary component of an effective treatment-alliance is a genuinely collaborative relationship between the patients and clinicians. This collaborative relationship is built on respect for patients' rights to decide about their own treatment and a shared decision-making process with patients and clinicians as active and equal partners[8,18,121]. Evidence suggests that patients place substantial emphasis on this interactional component of the treatment-alliance and that the degree of agreement between clinicians and patients on decisions regarding treatment is a high priority for patients[18,122]. Adherence is also enhanced when both patients and clinicians agree on their roles and responsibilities within the alliance. Patients also want this interactional relationship to be flexible and responsive to changes in clinical status and their treatment needs[18]. Feelings of trust also help in building a strong treatment-alliance as studies have found that trust in medication, trust in the clinician and absence of negative treatment expectations are all associated with adherence in BD[85]. Other elements of importance are regular contacts and reviews by clinicians, ongoing support and the long-term stability of the clinician-patient relationship[49,58,106,114,124]. Finally, factors such as attitudes of patients about the illness and its treatment, their perception of the clinician, ethnic and cultural backgrounds of patients, expectations of patients and the extent to which these have been met, and personality attributes such as locus of control have emerged as some of the more significant influences on the treatment-alliance[60,86,114,118,125,126].

Knowledge about the illness and its treatment

Another potential determinant of adherence in BD is the knowledge about the illness and its treatment among patients. Lack of such knowledge is widespread and a prevailing source of dissatisfaction among patients with BD[75,101,106,113,127,128]. Patients appear particularly unhappy with the lack of information provided on side effects and other aspects related to medication-treatment[75,86,127-129]. Although enhancing knowledge should improve adherence among patients, results of studies in BD have been somewhat equivocal in this regard. While several studies have found that inadequate knowledge of the illness among patients appears to affect treatment-adherence[19,75,80,95,102,128], quite a few others have concluded that patients' level of knowledge is not

associated with adherence in BD[10,34,51,84,118,130]. Similarly, psychosocial interventions imparting information in an effort to reduce non-adherence have met with mixed success[38,90,109,126,131,132]. There could be several reasons for these unexpected results including factors such as old age and longer duration of treatment, which influence the levels of knowledge and may act as potential confounders[10,19,84,86,130,133]. Insufficient knowledge could be due to insufficient efforts and ineffective means of imparting information by clinicians, as well as cognitive impairments, lack of insight and motivation among patients[127,128,134]. Patient's perceptions about their need for information and the extent to which these are met also have some bearing on adherence. Provision of information is more likely to be effective only if it is tailored to the specific needs of patients[128].

The role of the family and significant others

Families influence patients' medication-adherence in several ways. A disorganized or dysfunctional family environment has been associated with higher prevalence of non-adherence in BD[101,135,136]. A disturbed family atmosphere often leads to non-adherence by reducing the social support available to the patient[108,137]. Such an outcome would be more likely among patients who are more dependent on family members. This probably explains why a number of studies have found that patients with a greater external locus of control are more likely to become non-adherent[50,83,95,126]. Perceived criticism, negative affective responses and stigmatization or rejection within the family are also associated with non-adherence among patients with BD[75,138]. Finally, attitudes and health-beliefs of family members and their knowledge of the illness and treatment have been shown to have a significant influence of the patient's own beliefs and attitudes. Accordingly, negative attitudes and improper understanding of the illness among family members may affect the patient's decision whether or not to continue treatment[2,4,75,91,101,138].

Stigma, patient satisfaction and system-related factors

For many people with BD the stigma of having a chronic mental illness and needing to take long-term treatment for it may deter adherence. Consequently, studies among patients with BD have found their perceived sense of stigma to be associated with non-adherence[75,100,135,139]. Feelings of stigma regarding BD and its treatment also appear to promote negative attitudes towards treatment and adversely affect the treatment-alliance[114]. Patient satisfaction with various aspects of treatment has been found to be a determinant of non-adherence in BD. Dissatisfaction with the efficacy of treatment, with lack of information, with clinicians and with the treatment-alliance have all been found to adversely affect adherence in BD[59,80,106]. On the other hand, patients who are contended with their own lives are more likely to adhere with treatment[28,103,140]. Access to treatment and affordability of treatment also constitute significant barriers to continued adherence in BD. Bhugra *et al*[141] have suggested that only about half of the patients receive appropriate treatment BD because of systemic barriers to gaining access to appropriate care. This has been endorsed by the results of a number of other studies[38,49,80,101,119]. Finally, further elaboration of the concepts of shared decision-making, personal recovery and integrated or collaborative care are being increasingly applied to understand treatment-adherence in chronic medical disorders[142]. However, as of now these concepts have been only sparingly used to explain treatment-adherence in psychiatric disorders such as schizophrenia and depression. They have not yet been widely applied to BD. A discussion of the importance of these factors is thus beyond the scope of this brief review.

CONCLUSION

This brief examination of the literature on treatment-adherence in BD clearly suggests that research in this area is in the process of making a decisive shift towards the patient's perspective on non-adherence. Given the failure of demographic, illness and treatment-related factors to explain and predict non-adherence in BD, greater emphasis on factors such patients' attitudes and health-beliefs, the clinician-patient relationship and the impact of the immediate environment on treatment-adherence, certainly appears to be more appropriate. Moreover, such a stance is congruent with the current theoretical perspectives of adherence and concordance-based models of adherence. However, non-adherence continues to be rife in BD and simply adopting a patient-centred approach is unlikely to be a panacea for the problem. Nevertheless, it seems to be the only way forward for both research and clinical practice. Research focusing on non-adherence from the viewpoint of patients is more likely to lead to a greater understanding of this complex phenomenon in BD. A patient-centred approach also encourages clinicians to improve their understanding of the critical elements of adherence behaviour, to enhance their sensitivity to their patients' needs and to develop a collaborative and trusting relationship with them while attempting to tackle the problem of non-adherence. Thus, while there is no looking back to an earlier era of considering non-adherence to be only a patient's problem, we can only hope that adopting a patient-centred approach will lead us to find effective solutions to this common and distressing problem of non-adherence in BD.

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ORIGINAL ARTICLE

Basic Study

Reasoning and Rehabilitation cognitive skills programme for mentally disordered offenders: Predictors of outcome

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Abstract

AIM

To investigate factors predicting treatment completion and treatment outcome of the Reasoning and Rehabilitation Mental Health Programme (R&R2MHP) cognitive skills programme for mentally disordered offenders.

METHODS

Secondary analysis of data previously obtained from 97 male patients who were sectioned and detained under the United Kingdom Mental Health Act in low, medium and high security hospitals and who had completed R&R2MHP. Predictors of treatment completion included background variables and five outcome measures: Four self-reported measures of violent attitudes, social problem-solving skills, reactive anger and locus of control and an objective measure of behaviour on the

ward that was completed by staff. Completion of the 16 session programme, which was delivered on a weekly basis, was classified as ⩾ 12 sessions.

RESULTS

It was found that the R&R2MHP is appropriate for delivery to participants of different ages, ethnic background, and at different levels of security without the completion rate or treatment effectiveness being compromised. Participants taking oral typical psychotropic medication were over seven times more likely to complete the programme than other participants. Behavioural disturbance on the ward prior to commencing the programme predicted non-completion (medium effect size). As far as treatment completion was concerned, none of the background factors predicted treatment effectiveness (age, ethnic background, level of security, number of previous convictions and number of previous hospital admissions). The best predictor of treatment effectiveness was attitude towards violence suggesting that this should be the primary outcome measure in future research evaluating outcomes of the R&R2MHP cognitive skills program.

CONCLUSION

The findings suggest that a stable mental state is a key factor that predicts treatment completion.

Key words: Treatment; Completion; Outcomes; Mentally disordered offenders; Reasoning and Rehabilitation Mental Health Programme; Cognitive skills program

Core tip: This study adds important new information to understanding factors that predict treatment completion of the Reasoning and Rehabilitation Mental Health Programme cognitive skills programme for mentally disordered offenders. Out of 97 male patients, 76 (78.4%) completed the programme. There were two factors that predicted treatment completion, low level of behavioural disturbance on the ward prior to treatment commencing, and most importantly patients currently being on oral typical psychotropic medication, which increased over seven times the likelihood that they would compete the programme. The findings suggest that a stable mental state is a key factor that predicts treatment completion.

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INTRODUCTION

An increasing number of mentally disordered offenders (MDOs), who have severe mental illness, are at far greater risk of committing violent offences and within these populations of MDOs recidivism is high. In the United Kingdom, within 5 years of release 15% of MDOs re-offend, 3% of whom commit serious violent offences[1]. In a large longitudinal cohort study of 47326 Swedish prisoners, Chang *et al*[2] reported that up to 20% of violent reoffending in men and 40% in women was attributable to the diagnosed psychiatric disorders.

There are well-recognised predicators of recidivism in MDOs, with examples including beliefs and attitudes supporting a criminal lifestyle and poor social problem-solving skills[3-4]. Consequently, there is a rising demand for evidence-based treatments designed to minimise antisocial behaviour in MDOs and manualised programmes have been developed in an attempt to reduce the rates of offending through cognitive skills training[5]. The most widely applied programme is the 36 session "Reasoning and Rehabilitation" (R&R) programme, which employs a cognitive-behavioural paradigm and is accredited for use by the correctional services[5]. R&R aims to encourage self-control, meta-cognition, social skills, interpersonal cognitive problem-solving skills, creative thinking, critical reasoning, social perspective-taking, values enhancement, emotional management and helper therapy[6]. While R&R has previously been shown to be effective in reducing recidivism rates in young offenders and juveniles, completion rates may be poor[7,8].

In an attempt to be more responsive to the needs of offenders, Young *et al*[9] developed a revised version of the original R&R, referred to as "Reasoning and Rehabilitation Mental Health Programme" (R&R2MHP), which specifically focuses on helping offenders with serious mental health problems (*e.g.,* psychosis) and has substantially fewer sessions (*i.e.,* 16 *vs* 36). While the original R&R had been shown to be effective in reducing offending in both institutional and community settings with moderate effect sizes[10], it was not considered sufficient to meet all the needs of special offender groups, including those with mental disorders[9].

In their multi-site controlled trial using the R&R2MHP, Rees-Jones *et al*[11] found that 52 out of 67 (78%) of participants completed the programme (*i.e.,* completing 80% or more of the sessions). C-Y Yip *et al*[12] found a completion rate of 80% in a maximum secure unit setting. A completion rate of 92% was found among patients with intellectual disability[13]. These studies have reported a number of positive outcomes relating to attitudes towards violence, social-problem solving skills, reactive anger, locus of control and behaviour on the ward.

In spite of the high completion rate of the R&R2MHP, it is nevertheless important to identify factors that may either facilitate or hinder successful completion of the programme. Young *et al*[14] found that most non-completers were from maximum security, suggesting that the institution's level of security is a possible factor. No other predictors of non-compliance were examined

in this study. Rees-Jones *et al*[11] found that there were no significant differences between the completers and non-completers in age, previous convictions, previous admissions, and motivation to engage in treatment. The only difference was that non-completers had significantly better problem-solving skills at baseline than the completers (Cohen's d = -0.65, medium effect size), which seems counter-intuitive. C-Y Yip *et al*[12] found no significant difference between completers and non-completers in age, number of previous convictions or admissions, but the non-completers were rated by informants to be significantly more behaviourally disordered (Cohen's d = -0.88, large effect size) as measured by the Disruptive Behaviour and Social Problem Scale (DBSP)[15]. This provides strong evidence that participants who are rated by nursing staff as behaviourally disturbed prior to the commencement of the R&R2MHP are more likely than other participants to not complete the programme.

The purpose of the current study is to combine data from the Rees-Jones *et al*[11] and C-Y Yip *et al*[12] studies, which include all three levels of security (low, medium, maximum), in order to answer the following research questions: (1) what factors predict treatment completion/non-completion; and (2) what factors predict treatment outcome among those completing the programme.

The variables we investigated in the current study include the age of the participant, ethnic background ("white" *vs* "other"), level of security (*i.e.*, low, medium and high), number of previous convictions, number of previous hospital admissions, medication status, and the scores on typical psychometric outcome measures at baseline (*i.e.*, prior to the commencement of the programme) relating to attitudes towards violence, social-problem solving skills, reactive anger, locus of control and behaviour on the ward. Of particular interest is type and form of administration of the psychotropic medication the patient is prescribed at the time of the programme, because deteriorating mental state is an important factor that leads to non-completion[16]. The distinction drawn in this study is between the "First" and "Second" generation antipsychotic drugs and whether they are prescribed orally or by a depot injection. We also analysed differences between completers and non-completers in the outcome measures at baseline.

MATERIALS AND METHODS

Participants

Participants were a mixed sample of 97 males who were sectioned and detained under the United Kingdom Mental Health Act (1983) in either a low, medium or high secure hospital setting [*n* = 25 (25.8%), 42 (43.3%), 30 (30.9%) respectively] in 13 secure forensic facilities across the United Kingdom (three low secure, nine medium secure and one high secure). These settings differ in their staffing arrangements and physical security measures. Patients are stratified based on whether they present a serious danger to themselves and others and have potential to abscond, hence reside within a graded care system relative to their individual needs.

All patients participated in the treatment condition (R&R2MHP) and inclusion criteria included an age range of 19-63, history of severe mental illness (*e.g.,* schizophrenia, schizoaffective disorder, bipolar disorder), no previous experience of participating with R&R2, and proficiency in the English language. Exclusion criteria included intellectual disability, patients who were mentally unstable (*e.g.,* experiencing serious current psychotic symptoms), and/or who posed a risk of violence to the researcher.

Intervention

R&R2MHP[9] is a structured, manualised CBT programme comprised of sixteen 90-min sessions, delivered on weekly basis, and developed for antisocial youths and adults with mental health problems. The programme is a revised version of the original 36 session Reasoning and Rehabilitation programme, initially developed for use in correctional facilities[5]. The aim of the programme is to reduce anti-social behaviour and attitudes and improve pro-social thinking, emotional and behavioural control and problem-solving skills. R&R2MHP consists of five treatment modules: (1) a neurocognitive model which introduces techniques to increase attention control, impulse control, memory, and constructive planning; (2) a problem-solving module which encourages problem identification, generation of multiple alternative solutions, and consequential thinking; (3) an emotional control module which involves management of anxiety, anger, and conflict; (4) a social skills module which aims to increase awareness of the thoughts and feelings of others; and (5) a critical reasoning module which aims to develop skills in the assessment and evaluation of information, *e.g.,* evaluating options and effective behavioural skills. The programme offers a novel approach by allowing participants to engage in both individual and group therapy, with the latter being achieved by the inclusion of a mentoring paradigm whereby a member of staff meets with the patient between group sessions to assist the participant to transfer skills learned in the group into their daily lives. Mentors receive written guidance about how to structure each mentoring session and received training and on-site supervision from programme facilitators. As a structured, manualised programme, R&R2MHP fosters consistency in delivery and programme integrity. A steering committee, attended by site principal investigators and clinical staff, met regularly to maintain a consistent approach to research and treatment.

Treatment completion

A cut-off of $\geqslant$ 12 sessions was used to classify patients as completers, in line with the methodology

and recommendation provided by Cullen *et al*[7] thus representing at least 80% attendance of the programme. Hence, non-completers were classified as those attending < 12 sessions.

Baseline assessments

Demographic data (*e.g.,* age, and ethnic background), psychiatric diagnosis, medication status, and index offence information were obtained from clinical file review at the beginning of the study. Medication status at the time of study was categorised into the following groups according to the type of medication and method of delivery (*i.e.,* oral *vs* depot injection): (1) currently on oral typical psychotropic medication; (2) currently on oral atypical psychotropic medication; (3) currently on depot typical psychotropic medication; (4) currently on depot atypical psychotropic medication; (5) currently on antidepressant psychotropic medication; and (6) currently on mood stabilisers psychotropic medication.

The "typical" psychotropic medication' category included: Haloperidol, Thioridazine, Thiothixene, Fluphenazine, Trifluoperazine, Perphenazine, Molindone, Loxapine and Prochlorperazine.

The "atypical" psychotropic medication category included: Risperidone, Olanzapine, Quetiapine, Clozapine, Ziprasidone, and Aripiprazole.

Outcome measures

The following outcome measures were administered at baseline (Time 1) and repeated at post group (Time 2) to assess the violent attitudes and social problem-solving skills, reaction to provocation (anger), and disruptive behaviour and social functioning. All measures are self-reported with the exception of the DBSP which is rated by an informant.

Maudsley Violence Questionnaire[17,18]: Is a 56-item true/false questionnaire with a score range of 0-56. The Maudsley Violence Questionnaire (MVQ) measures cognitive style in relation to violence attitudes and is designed for use across a spectrum of violent offenders and non-violent individuals. Following factor analysis the 56 items can be stratified into two factors: *Machismo* - endorsing stereotypical expectations of men as strong and tough (42 items based on this factor) and *Acceptance* - accepting and enjoying violent behaviour (14 items based on this factor). The MVQ has high internal consistency (Cronbach's α ranges from 0.76 to 0.91) and validity[17].

Social Problem-Solving Inventory-Revised Short[19]: Is a 25-item questionnaire with a 5-point Likert-type response format. The Inventory is comprised of five subscales: Two of which measure problem-solving orientation (positive and negative problem orientation) whilst the remaining three assess problem-solving style (rational problem-solving, impulsivity/carelessness, and avoidance) (scores range between 0 and 20 for each domain). An adjusted total score was obtained (score range = 0-20) with higher scores reflecting better problem-solving ability. The measure is reported to have high test-retest reliability (0.68-0.91) and internal consistency (Cronbach's α ranged from 0.69 to 0.95).

The Novaco Anger Scale and Provocation Inventory: Reaction to Provocation/Personal Affect Questionnaire[20]: Was used to assess cognitive, arousal, and behavioural domains of anger experience. Forty-eight items, each rated on a 3-point Likert-type format scale, provide these domains with higher scores indicating higher anger levels (score range between 16 and 48 for each domain); a total score can also be obtained by summing the domain scores (score range from 48-144). The Reaction to Provocation/ Personal Affect Questionnaire (NAS-PI) has been shown to have good reliability (test-retest coefficients ranged from 0.78 to 0.91) and internal consistency of 0.92[21,22].

The Locus of Control Scale[23]: Was used to assess the extent to which participants believe events to be internally or externally controlled. The Locus of Control Scale (LoC) is a 40-item yes/no questionnaire with a high score indicating that the person perceives events as externally controlled, whereas a low score indicates that a person believes they control events internally (score range from 0-40). The scale has been found to have varied level of internal consistency, ranging from 0.37 to 0.86[24].

The Disruptive Behaviour and Social Problem Scale[15]: Is an informant-rated questionnaire consisting of 14 statements rated on a 7-point Likert-type format scale relating to a person's behaviour and social interactions over the past month (score range of 14-98) in their current environment (*i.e.*, in this study, this was completed by a member of the healthcare staff who knew the patient well and rated their behaviour on the ward). The scale consists of two factors: (1) disruptive behaviour, for example, whether the participant is difficult to manage; if they are verbally aggressive or attention seeking (score range 8-56); and (2) social and psychological functioning, for example, insight into behaviour, feelings of guilt, and positive social interactions with others (score range of 6-42). Higher scores indicate a greater degree of problems. Both factors have good internal consistency in male offenders (Cronbach's α 0.92 and 0.84, respectively).

Procedure

We combined the existing data bases from the Rees-Jones *et al*[11] and C-Y Yip *et al*[12] studies. The two studies included 67 and 30 male participants in the treatment group, respectively. Both studies involved non-randomised controlled trials. For treatment effectiveness we relied on differences in the outcome measures between baseline and end of treatment for

those participants who completed the programme. In controlled trials the failure to complete the programme reduces the real differences between the treatment and control groups[25].

Statistical analysis

Descriptive statistics summarised demographics, clinical and forensic baseline characteristics. To assess differences between groups t-tests were performed on continuous data and χ^2-tests on categorical data. Change scores in the outcome measures between baseline (Time 1) and end of treatment (Time 2) were measured in two ways: (1) change in mean scores over time and use of a paired *t* test (Cohen's d was calculated by the mean difference score over the standard deviation of the difference); and (2) by categorising an improvement of one or more points on each test as an "improvement" and no change or a worse score as "no improvement". A binary logistic regression was used to investigate which of the outcome measures best predicted completion *vs* non completion.

We ran a binary logistic regression for each of the outcome measures with improvement between Time 1 and Time 2 being the independent variable and predictors being participants' age, ethnic background ("black" *vs* "other"), oral typical psychotropic medication (yes *vs* no), and level of security (low/medium *vs* high).

RESULTS

Patient demographics and baseline characteristics

The sample were of mixed ethnicity; White (*n* = 52, 53.6%), Black Caribbean (*n* = 13, 13.4%), Black African (*n* = 11, 11.3%), Black Other (*n* = 12, 12.4%), Asian (*n* = 2, 2.1%), Mixed Race (*n* = 4, 4.1%) or Other (*n* = 2, 2.1%). These were reclassified as "White" (*n* = 52, 53.6%) and "Other" (*n* = 44, 45.4%). The age range of participants was 19-63 with an average age of $\bar{X}$ = 35.31, SD = 9.16. All participants had a history of severe mental illness, most commonly psychotic disorders (*n* = 87, 89.7%), as well as mood disorders (*n* = 9, 9.3%) and developmental disorders (*n* = 1, 1%).

The majority of index offences were violence related (*n* = 85, 73.9%), for example homicide and assault; other index offences for current admission included financial (*n* = 6, 5.2%), drug (*n* = 4, 3.5%), sexual (*n* = 12, 10.4%), arson (*n* = 7, 6.1%) and other (*n* = 1, 0.9%).

Treatment completion rate

The average number of sessions attended was 13.22, SD = 3.84; 78.4% (*n* = 76) participants completed R&R2MHP and 21.6% (*n* = 21) did not (*i.e.,* they did not complete the minimum of 12 sessions). Information on the reason for drop out was only available for 10.3% (*n* = 10) of cases: These were due to non-compliance (*n* = 6), poor mental state (*n* = 1) and "other unknown reason" (*n* = 3).

Table 1 Differences in medication status of completers and non-completers

	Completers *n* (%)	Non-completers *n* (%)	χ^2 df = 1	OR (95%CI)
Currently on oral typical psychotropic medication	22 (29.7)	1 (5.3)	4.86[1]	7.62 (0.97-60.62)
Currently on oral atypical psychotropic medication	39 (52.7)	13 (68.4)	1.51	0.51 (0.18-1.50)
Currently on depot typical psychotropic medication	10 (13.5)	3 (15.8)	0.65	0.83 (0.21-2.38)
Currently on depot atypical psychotropic medication	6 (8.1)	0 (0)	1.65	0.91 (0.86-0.98)
Currently on antidepressant psychotropic medication	16 (21.6)	2 (10.5)	1.2	2.34 (0.49-11.2)
Currently on mood stabilisers psychotropic medication	20 (27.0%)	5 (26.3)	0.01	1.04 (0.33-3.25)

[1]$P < 0.05$.

Factors predicting treatment completion

Background measures: There was no significant age difference (*t* = 1.0) between the completers (mean = 35.8, SD = 9.4) and non-completers (mean = 33.5, SD = 8.0).

The completion rates for the three levels of security (low, medium, high) were 76.0% (*n* = 19), 78.6% (*n* = 33) and 89.0% (*n* = 24), respectively. The difference was not significant (χ^2 = 0.131, df = 2).

Similarly there was no significant difference between the number of "White" (*n* = 43, 82.7%) and "Other" (*n* = 32, 72.7%) ethnic participants who completed the programme. This difference was not significant (χ^2 = 1.39, df = 1).

There was no significant difference (*t* = -0.32, df = 86, ns) in the number of previous convictions between the completers (mean = 8.34, SD = 14.88) and non-completers (mean = 8.45, SD = 9.62).

No significant difference (*t* = -0.85, df = 82, ns) was found in the number of previous hospital admissions between the completers (mean = 3.89, SD = 3.86) and non-completers (mean = 4.79, SD = 4.60).

Table 1 shows the differences in the medication status between completers and non-completers. Out of the six medication categories only "Currently on oral typical psychotropic medication" showed a significant difference between the two groups (χ^2 = 4.86, df = 1, OR = 7.62, 95%CI: 0.97-60.62).

Baseline measures: Out of the five baseline psycho-

Table 2 Differences in the baseline scores of completers and non-completers on the Maudsley Violence Questionnaire, Social Problem-Solving Inventory-Revised Short, Novaco Anger Scale and Provocation Inventory, Locus of Control Scale and: Disruptive Behaviour and Social Problem Scale

	Completers Mean (SD) (*n*)	Non-completers Mean (SD) (*n*)	*t* value (df)	Cohen's d
MVQ (total)	15.8 (12.2) (76)	17.4 (13.3) (21)	-0.52 (95)	0.05
SPSI-RS	11.8 (3.0) (76)	12.6 (3.3) (21)	-1.15 (95)	0.22
NAS-PI	81.0 (19.9) (76)	80.3 (18.4) (21)	0.14 (95)	0.01
LoC	16.77 (5.4) (52)	13.93 (4.4) (15)	1.85 (65)	0.57
DBSP	35.2 (11.4) (63)	43.1 (14.6) (15)	-2.27 (76)[1]	0.60

[1]$P < 0.05$. MVQ: Maudsley Violence Questionnaire; DBSP: Disruptive behaviour and social problem scale; NAS-PI: Novaco Anger Scale and Provocation Inventory; LoC: Locus of Control Scale; SPSI-RS: Social problem-solving inventory-revised short.

metric measures, only the DBSP discriminated significantly between completers and non-completers (see Table 2). Completers had a significantly lower score (t = -2.27, df = 76, Cohen's d = 0.60). A further analysis of the DBSP showed that the Disruptive Behaviour subscale (t = -2.19, df = 76, $P < 0.05$, Cohen's d = 0.59) differentiated better between the completers and non-completers than the Social Problem subscale (t = -1.36, df = 76, ns, Cohen's d = 0.38).

Factors predicting treatment outcome among completers

Background predictors of therapeutic outcome: The binary logistic regression for each of the outcome measures showed that none of the predictors (age, ethnic background, oral typical psychotropic medication, and level of security) predicted therapeutic outcome (categorical measure).

Outcome predictors of therapeutic outcome: Table 3 shows the difference in the outcome measured between Time 1 and Time 2. There was a significant improvement over time on four of the outcome measures: MVQ, SPSI-RS, NAS-PI and DBSP with the effect sizes (Cohen's d for a paired sample) being 0.43, 0.27, 0.23, and 0.27, respectively. No significant improvement was found for LoC.

DISCUSSION

The findings suggest that R&R2MHP can be used with participants of different ages, ethnic background, and at different levels of security without the completion rate or treatment effectiveness being compromised.

Two specific findings are relevant to the completion rate, namely psychotropic medication and ward behaviour. The medication status of the participants appears to influence the completion rate. Those participants who were on oral typical psychotropic medication at the time of the study were over seven times more likely to complete the programme. Yet being on oral typical psychotropic medication did not predict treatment effectiveness on any of the five outcome measures. The implication is that this type of medication helped participants complete their required sessions, but it did not have any additional benefit relevant to treatment effectiveness. Participation in cognitive skills group programmes of this type require a reasonably stable mental state, however none of the other types of medication predicted completion. There is evidence that atypical antipsychotics do not offer clinical superiority over typical antipsychotics (with the exception of clozapine)[26,27], and we have found that those patients on oral route of typical antipsychotics are more likely to complete the programme. Oral medication may provide greater flexibility to cope with changes in mental state and prevent deterioration. Furthermore patients who are on an oral route of antipsychotic administration rather than depot are likely to be more clinically stable in terms of insight and attitude towards treatment, and this is likely to translate into better compliance with psychological treatment[28]. This is a novel finding and merits further research.

At baseline the completers had a significantly lower total score on a measure of ward behaviour rated by staff (the DBSP) than the non-completers with a medium effect size. The disruptive behaviour subscale was a much better predictor of non-completion than the social and psychological functioning subscale (Cohen's d 0.59 *vs* 0.38). This suggests that patients whose behaviour is often disruptive on the ward are at much greater risk of non-completion than other patients. The implication is that their behavioural disturbance on the ward needs to be addressed before they are able to participate fully in a cognitive skills intervention. Future research should investigate the causal and contributory factors to behavioural disturbance in the ward setting and this may relate to a range of problems, including poor mental state[29] and symptoms of attention deficit hyperactivity disorder[30].

As far as treatment effectiveness is concerned, the MVQ performed much better in terms of effect size than the other outcome measures. The two main violent attitudes measured by the MVQ, which have implications for treatment targets, are the use of violence to defend or enhance vulnerable self-esteem and the general acceptance that violence is justified as a way of life. Typically, controlled treatment trials compare the treatment group with a control group with the former including outcome measures of those who did not complete the programme ("Intention to Treat"; "ITT"), which in fact reduces the effect size where there is a poor completion rate[25]. This may bias the apparent effectiveness of specific outcome measures. The answer is either to delete the non-completers from the group differences comparison (*i.e.,* conduct a per-protocol analysis) or control for factors that may cause drop-out. The latter is methodologically sounder than the former[31].

Table 3 Differences between pre and post measures on the psychometric tests

Measure	*n*	(pre)	SD (pre)	Mean (post)	SD (post)	*t*(df)	Cohen's d
MVQ (total)	76	15.78	12.19	12.23	9.61	3.75 (75)[2]	0.43
SPSI	76	11.73	3.00	12.54	3.04	-2.33 (75)[1]	0.27
NAS-PI	76	80.99	19.89	77.09	15.86	2.09 (75)[1]	0.23
LoC	52	16.77	5.42	16.32	5.39	1.91 (51)	0.08
DBSP	63	35.21	11.40	32.57	11.32	2.16 (62)[1]	0.27

[1]$P < 0.05$; [2]$P < 0.01$. MVQ: Maudsley violence questionnaire; DBSP: Disruptive behaviour and social problem scale; NAS-PI: Novaco anger scale and provocation inventory; LoC: Locus of control scale; SPSI-RS: Social problem-solving inventory-revised short.

Everitt and Pickles (2004) outline six factors that influence treatment adherence, including completing all the sessions: (1) the amount of time and inconvenience; (2) the perceived importance of the procedure; (3) the potential health benefits *vs* potential risks; (4) the amount of discomfort caused by the treatment; (5) the amount of effort required; and (6) the number and type of side effects caused by the treatment[31]. They point to a number of factors that may improve treatment adherence, including short treatment trials, close supervision (*e.g.,* inpatient settings), and staff maintaining a positive attitude during the trial. Future research should investigate the effects of these six factors. Reducing the sessions of the original R&R has clearly improved treatment completion; completion in institutional settings may be better than programmes delivered in the community[32,25].

LoC showed no significant treatment effects in the current study. It failed to distinguish between completers and non-completers, using a categorical measure of improvement. In addition, it showed no significant difference between the Time 1 (baseline) and Time 2 (end of treatment) measures, unlike the four other outcome measures. Rees-Jones *et al*[11] (2012) found no difference in LoC between Time 1 and Time 2 for males in low and medium security, but there was a significant improvement at Time 3 (at three month follow-up). In contrast, Jotangia *et al*[16] (2013), investigating females in low and medium security, found an improvement on the LoC scale both at Time 2 and Time 3. This suggests two possibilities. Firstly, LoC is more effecting in measuring treatment improvement in females than males. This possibility merits further research. Secondly, LoC may take longer than the other measures to show treatment effects; this has been found for other outcome measures[25].

The main limitations of the study are the lack of documented reasons for the non-completion, the relatively low number of participants in the non-completion group, which resulted in limited power, the lack of information about institutional factors that may have influenced non-completion, and the fact that the participants were a convenience sample from previously published studies. In addition, the effects of gender could not be ascertained and this should be investigated in future studies.

This is a cross-sectional study that investigates associations rather than causation, nevertheless, this study has added important new information to understanding factors predicting treatment completion/non-completion among MDOs. For patients who were on oral typical psychotropic medication, this very significantly improved completion. In contrast, disturbed ward behaviour prior to commencing treatment was significantly associated with non-completion. No background factors were found to predict treatment outcome among those who completed the programme but among outcome measures attitudes towards violence was the best predictor of treatment effectiveness suggesting that this should be the primary outcome measure in future research.

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COMMENTS

Background

Cognitive skills programmes have been found to be effective in reducing offending through reduced violent attitudes and improved social problems skills. It is important to understand the factors that best predict completion of programmes, as well as those predicting a successful treatment outcome among those who completed the programme. The factors that best predict completion may not be the same factors as those that predict treatment outcome.

Research frontiers

Identification of the variables that predict treatment completion and treatment outcome will lead to more personalised treatment and better use of resources.

Innovations and breakthroughs

No previous research has investigated the effects of typical *vs* atypical psychotropic drugs as predictors of treatment completion and treatment outcome among mentally disordered offenders. The findings show that typical psychotropic drugs, administered orally, increased seven-fold the likelihood of the patients completing the programme, whereas it had no effect on treatment effectiveness. This is a novel finding.

Applications

The mental state of patients engaging in cognitive skills programmes needs to

be carefully assessed and continually reviewed during the programme as well as their medication status. In addition to mental state, this includes the behaviour of the patient on the ward. The fact that the age of the patient, ethnic background, number of previous convictions, number of hospital admissions, and level of security did not predict treatment completion or treatment outcome shows that the Reasoning and Rehabilitation Mental Health Programme (R&R2MHP) can be applied to most patients at different levels of security provided their mental state is stable.

Terminology

A typical medication comprised the first generation of psychotropic drugs, followed by the atypical (second generation) drugs.

Peer-review

This is, in summary, an interesting research paper aimed to investigate factors predicting treatment completion and treatment outcome of the R&R2MHP cognitive skills programme in a sample of 96 mentally disordered offenders.

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ORIGINAL ARTICLE

Retrospective Study

Infectious, atopic and inflammatory diseases, childhood adversities and familial aggregation are independently associated with the risk for mental disorders: Results from a large Swiss epidemiological study

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Abstract

AIM

To examine the associations between mental disorders and infectious, atopic, inflammatory diseases while adjusting for other risk factors.

METHODS

We used data from PsyCoLaus, a large Swiss Population Cohort Study (n = 3720; age range 35-66). Lifetime diagnoses of mental disorders were grouped into the following categories: Neurodevelopmental, anxiety (early and late onset), mood and substance disorders. They were regressed on infectious, atopic and other inflammatory diseases adjusting for sex, educational level, familial aggregation, childhood adversities and traumatic experiences in childhood. A multivariate logistic regression was applied to each group of disorders. In a complementary analysis interactions with sex were introduced *via* nested effects.

RESULTS

Associations with infectious, atopic and other chronic inflammatory diseases were observable together with consistent effects of childhood adversities and familial aggregation, and less consistent effects of trauma in each group of mental disorders. Streptococcal infections were associated with neurodevelopmental disorders (men), and measles/mumps/rubella-infections with early and late anxiety disorders (women). Gastric inflammatory diseases took effect in mood disorders (both sexes) and in early disorders (men). Similarly, irritable bowel syndrome was prominent in a sex-specific way in mood disorders in women, and, moreover, was associated with early and late anxiety disorders. Atopic diseases were associated with late anxiety disorders. Acne (associations with mood disorders in men) and psoriasis (associations with early anxiety disorders in men and mood disorders in women) contributed sex-specific results. Urinary tract infections were associated with mood disorders and, in addition, in a sex-specific way with late anxiety disorders (men), and neurodevelopmental and early anxiety disorders (women).

CONCLUSION

Infectious, atopic and inflammatory diseases are important risk factors for all groups of mental disorders. The sexual dimorphism of the associations is pronounced.

Key words: Neurodevelopmental disorders; Mental disorders; Substance abuse; Childhood diseases; Infectious diseases; Atopic diseases; Chronic inflammatory diseases; Risk factors

Core tip: This study adds to the evidence that infectious, atopic and inflammatory diseases make up an important group of risk factors for neurodevelopmental and common mental disorders. They contribute independently of further major risk factors such as childhood adversities, traumatic experiences and familial aggregation. Each group of mental disorders (neurodevelopmental, early and late anxiety, mood, substance) attracts different combinations of risk factors. The sexual dimorphism of the associations is pronounced. The hypothesized biological mechanism that acts as a common denominator in this group of risk factors involves imbalances, *e.g.*, within the development of the immune system interfering with critical stages of brain development.

Ajdacic-Gross V, Aleksandrowicz A, Rodgers S, Mutsch M, Tesic A, Müller M, Kawohl W, Rössler W, Seifritz E, Castelao E, Strippoli MPF, Vandeleur C, von Känel R, Paolicelli R, Landolt MA, Witthauer C, Lieb R, Preisig M. Infectious, atopic and inflammatory diseases, childhood adversities and familial aggregation are independently associated with the risk for mental disorders: Results from a large Swiss epidemiological study. *World J Psychiatr* 2016; 6(4): 419-430 Available from: URL: http://www.wjgnet.com/2220-3206/full/v6/i4/419.htm DOI: http://dx.doi.org/10.5498/wjp.v6.i4.419

INTRODUCTION

There is an increasing awareness that infectious diseases, atopies and inflammatory conditions contribute to the risk for neurodevelopmental disorders (ND) and common mental disorders (CMD). A great number of the empirical results documented below underline the eminent role of the immune system. Nevertheless considerable scepticism abounds. Among other things, it is not clear how immunological risk factors are balanced against other risk factors in ND and CMD. The main aim of this study was, therefore, to assess the associations of infectious, atopic and inflammatory diseases with ND and CMD while adjusting for socio-demographic characteristic, familial aggregation, traumatic experiences and childhood adversities. A simple vulnerability-trigger model will serve to introduce the state of empirical research, thus reducing the potential variability of single and multiple hit models to a minimal general form.

Associations related to triggering mechanisms

The most intuitive example of a triggering factor in CMD is a postinfectious condition such as fatigue[1]. Infectious mononucleosis, *i.e.*, typically an Epstein Barr virus (EBV) infection in adolescence or adulthood, is a well known cause of postinfectious fatigue. However, also several other pathogens are also able to upregulate psychiatric symptoms, such as persistent pathogens: Borna disease virus, herpes simplex virus (HSV)-1, varicella zoster virus, and *Chlamydophila trachomatis*[2]. Apart from the first attack, a reactivation of an endogenous infection can increase the risk of depression[3].

It is noteworthy that the reciprocal causal direction also exists[4,5]. Generally speaking, it is not only the case that pathogens can trigger psychiatric illness, but, conversely, that psychiatric disorders can lead to an increased risk of infection. The two should not be confounded, keeping in mind that the causal direction is not always clear[6]. The examples above illustrate a trigger mechanism of ND and CMD, *i.e.*, the second part of conventional vulnerability-trigger (or, by analogy, diathesis-stress) models.

Associations related to vulnerability mechanisms

The first part of the vulnerability-trigger model are vulnerability factors occurring very early in life: Infections, atopic and inflammatory processes that establish, apart from their immediate effects, a lasting, possibly life-long vulnerability for CMD. A well known example of an early vulnerability is comprised in the pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) model. This model has been applied in attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and tic disorders such as the Gilles de la Tourette Syndrome[7,8]. It suggests that some persons with ND or CMD might actually suffer from an autoimmune disorder due to autoantibodies directed against basal ganglia tissue and appearing after infections with group A streptococci.

Evidence for associations between early infections and ND and CMD goes far beyond PANDAS and other autoimmune processes such as NMDA receptor encephalitis[9]. A compelling example is the link between EBV infections in childhood and risk of psychotic experiences in adolescence demonstrated in the ALSPAC cohort[10]. In a similar vein, studies from the Goodwin group which suggested that respiratory diseases in childhood and severe infections requiring the use of antibiotics in the first year of life increase the risk for several mental disorders such as depression, anxiety disorders and oppositional defiant disorder (ODD) later on in life[11,12].

The temporal sequence between pathogens and CMD may apply later in life as well. For instance, Danish record linkage studies have shown that individuals hospitalized because of an infection, particularly a bacterial infection, were more likely to develop schizophrenia later in life[13]. Apart from studies demonstrating a temporal sequence, many cross-sectional antibody based studies have pointed at associations between ND and CMD and selected pathogens. Serological studies have been particularly proliferative in psychosis research by implicating a broad spectrum of viral, bacterial and protozoan pathogens. For illustrative purposes, these are: (1) herpes viridae (cytomegalovirus[14], human herpesvirus-6[15], HSV-1[16,17], EBV[18]); (2) Toxoplasma gondii[14,19-23]; (3) Chlamydia infections: trachomatis[23,24], psittaci and pneumoniae[25,26]; (4) Mycoplasma pneumoniae (case study)[27]; (5) *Helicobacter pylori*[28]; and (6) gastrointestinal pathogens[29,30].

Associations related to parallel mechanisms

Not only were pathogens shown to precede psychotic experiences but also atopic diseases such as asthma and atopic dermatitis[31]. Similarly, the first occurrence of atopic dermatitis was reported to precede major depressive disorder and anxiety disorders[32] or ADHD[33]. Also other atopic diseases preceded ADHD[34]. However, evidence for the converse temporal sequence between atopic diseases and ND and CMD was also found with ND and CMD occuring first[35,36].

Again, the number of cross-sectional comorbidity studies providing evidence for a simple link between ND and CMD on the one hand and atopic diseases on the other is much greater than those focusing on temporal succession. They involve in particular asthma[37-44], hay fever[45], and eczema[46]. The association between atopic dermatitis and ADHD has gained particular attention since it emerges typically in the first years of life[33,47,48].

Beside atopies, chronic or relapsing inflammatory diseases have been shown to be linked to a great variety of CMD, and both theoretically qualify as triggers and as vulnerability markers. Skin diseases such as acne[49,50], psoriasis[51] and rosaceae[52] also contribute to the list of associations. Moreover, this list includes gastric inflammatory diseases[53-56], and gastrointestinal diseases/syndromes: Irritable bowel syndrome[57,58], Crohn's disease[59], interstitial cystistis[60,61] as well as recurrent cystitis[62], autoimmune diseases[63-65] and others[51]. This is only a small selection of associations, and the list could be extended with ease.

Aims of the analysis

To summarize, the complex picture of associations entails any variant of temporal sequences and almost any combination between groups of somatic diseases and groups of ND and CMD. Thus, in so far as infectious, atopic and chronic inflammatory diseases precede ND and CMD or share a mutual vulnerability with them, the relevant mechanisms cannot be determined on the level of single pathogens. Taken together, the literature provides important pieces of a larger puzzle with, however, still blurred contours. Comprehensive analyses enabling a broader understanding of these links are still missing. The present study takes advantage of a

large epidemiological data base from the PsyCoLaus study[66] to further investigate whether major groups of infectious, atopic and inflammatory diseases are associated with major groups of mental disorders.

MATERIALS AND METHODS

The Colaus/PsyCoLaus study

The data used in this analysis stem from CoLaus/PsyCoLaus[66,67], a cohort study designed to study mental disorders and cardio-vascular risk factors in the community and to determine their associations. The sample was randomly selected from the residents of the city of Lausanne (Switzerland) from 2003 to 2006 according to the civil register. Sixty-seven percent of the 35 to 66 years old participants of the physical baseline exam (n = 5535) also accepted the psychiatric evaluation, which resulted in a sample of 3720 individuals who underwent both the somatic and psychiatric exams.

Measures

A French version of the semi-structured Diagnostic Interview for Genetic Studies (DIGS)[68] was used in the PsyCoLaus study to assess a broad spectrum of lifetime DSM-IV Axis I criteria. The French version has shown excellent inter-rater and adequate test-retest reliability for major mood and psychotic disorders[69] as well as for substance use disorders[70]. Moreover, the DIGS allowed for gathering additional information on the course and chronology of comorbid features[66]. However, the brief phobia section of the DIGS was replaced by the corresponding sections from the Schedule for Affective Disorders and Schizophrenia - Lifetime Version (SADS-L)[71] in the current study. The anxiety sections of the French version of the SADS-L also revealed satisfactory reliability[72]. All diagnoses were lifetime diagnoses.

Grouping of mental disorders

We considered the following major groups of mental disorders based on the typical age of onset and common classifications: (1) neurodevelopmental diseases [typically starting during childhood: Tic disorders, ADHD, conduct disorder (CD), ODD]; (2) early-onset anxiety disorders (typically starting during childhood: separation anxiety disorder, overanxious disorder, animal phobias, social phobia); (3) late-onset anxiety disorders [typically starting after adolescence: Generalized anxiety disorder (GAD), panic, agoraphobia, specific phobias (excl. animal phobias[73])]; (4) mood disorders (typically starting after adolescence: major depressive disorder, dysthymia, bipolar disorders); and (5) substance use disorders (typically starting after adolescence: alcohol, cannabis, other illicit drug abuse/dependence).

Disorders with low frequencies (schizophrenia, schizoaffective disorders) or inadequately fitting in with the major groups (OCD, personality disorders, eating disorders) were not included in the analyses.

Assessment of infectious, atopic and inflammatory diseases

The information on infectious diseases and related conditions was derived using an extended version of the medical history parts of the DIGS and the SADS-L and was based on self-reporting. In the interview participants were asked questions about ever having been diagnosed with various infectious diseases, diseases of the nervous system, cardiovascular, respiratory, gastrointestinal, metabolic and dermatological conditions as well as allergies and hormonal problems. For each disease, a screening question was asked and followed up in the case of an affirmative response.

In the current analyses the infectious diseases and related conditions were selected: (1) diseases typically related to streptococcal infections of the respiratory tract (scarlet fever, tonsillitis, rheumatic fever); (2) measles/mumps/rubella (MMR); the age range of the sample implies that most participants had not received an MMR vaccine in childhood, as routine measles and later MMR vaccinations schedules were only introduced by the Swiss government only in the 1960s; (3) urinary tract infections (UTIs) (cystitis, pyelitis, pyelonephritis, other nephritis, urethritis, prostatitis); (4) irritable bowel syndrome; (5) peptic ulcer/gastritis; (6) asthma and atopic diseases; (7) acne; and (8) psoriasis.

Covariates

We adjusted the analysis for the following variables which might account for the relationship between infectious diseases and mental disorders: (1) sex; (2) education level (low: Basic school and apprenticeship level; medium: Pre-university and high-level technical schools; high: University); (3) familial aggregation assessed by the semi-structured Family History - Research Diagnostic Criteria[74,75] which includes information on first and second degree relatives; subtypes parallelized to the groups of mental disorders mentioned above; dichotomized into any *vs* none; (4) childhood adversities dichotomized into any *vs* none if one of the following questions was confirmed: Did your parents fight frequently amongst themselves (interparental violence)?; Did your parents ever do anything that frightened you (like lock you in a closet)? (fear of maltreatment by parents); Did any of the following occur before your 16th birthday: .... put in foster care? (foster care); Overall, how would you characterize your childhood (N/A, happy, either happy not unhappy, unhappy, very unhappy)? categorized as yes, if unhappy or very unhappy (unhappy children); and (5) traumatic experiences in childhood below the age of 10 (serious accident or disaster, victim of violent attacks (self or loved ones), witnessed homicide or other forms of violent deaths; the age limit was chosen in order to focus on experiences mostly generating a vulnerability for mental disorders instead of acting as a trigger

themselves); the questions were taken from the French version of the SADS-LA (see above) and dichotomized into any *vs* none.

Statistical analysis

The data were analyzed using binary logistic regression and displaying odds ratios (OR) and 95%CI. The regression analysis was redone for men and women separately before including interaction effects. In order to better figure out the source of sex-specific divergences - either men or women - the interaction effects were modeled *via* nested effects, *i.e*., by nesting each infectious, atopic and inflammatory variable in men and in women. All analyses were carried out using SAS version 9.3. The statistical analysis was reviewed by Viktor von Wyl from the Epidemiology, Biostatistics and Prevention Institute of the University of Zürich.

RESULTS

Table 1 shows the overall and sex-specific prevalence estimates for five major groups of mental disorders (neurodevelopmental, early-onset anxiety, late-onset anxiety, mood and substance disorders) together with education level, familial aggregation, trauma below the age of 10, childhood adversities and various infectious and atopic/inflammatory diseases. In bivariate analyses, mental disorders were consistently associated with familial aggregation, trauma and childhood adversities. Trauma showed distinct sex-specific associations in early disorders and in substance abuse. The associations of ND and CMD with infectious, atopic and inflammatory diseases spread across the whole table in a less consistent way. Moreover, they displayed more sex-specific divergencies. Therefore, and since some variables, *e.g*., UTI, are skewed by sex, an additional look at the sex-specific associations was necessary in multivariate analyses.

In multivariate analysis (Table 2), the associations with familial aggregation and childhood adversities remained relatively stable across all five models for each group of mental disorders (ORs up to 3). The effect of trauma clearly diminished. Each group of ND /CMD displayed associations with any of the infectious, atopic and inflammatory diseases included in the analysis. Many associations occurred at trend level, thus suggesting more in-depth analyses either related to sex-specific associations or to the level of specific disorders.

Analyses involving interaction effects by nesting infectious, atopic and inflammatory diseases within sex (Table 3) uncovered further hetereogenity. In detail, ND disorders were associated with streptococcal infections specifically in men (OR = 1.98, 95%CI: 1.08-3.66) but not in women. Peptic ulcer/gastritis was significant only in the men model (OR = 1.95, 95%CI: 1.08-3.53), and showed a similar tendency in women. The opposite applies for UTI, where only women (OR = 1.68, 95%CI: 1.11-2.54) reached the conventional significance level.

Early-onset anxiety disorders showed associations with MMR, which were similar in both groups; again only women (OR = 1.46, 95%CI: 1.01-2.10) reached the conventional significance level. Another shared issue is irritable bowel syndrome with a strong impact in men (OR = 3.15, 95%CI: 1.58-6.28) and a trend level impact in women. Associations found specifically in men comprise peptic ulcer/gastritis (OR = 1.85, 95%CI: 1.13-3.05), psoriasis (OR = 2.02, 95%CI: 1.20-3.39) and, at trend level, acne. Moreover, associations with UTI emerged specifically in women (OR = 1.44, 95%CI: 1.16-1.79), at trend level also with atopic disease, but not in men.

In late-onset anxiety disorders, UTI (OR = 2.13, 95%CI: 1.19-3.82) were predictive not in women but in men. The significant predictors in women comprise MMR (OR = 1.81, 95%CI: 1.12-2.90) and peptic ulcer/gastritis (OR = 1.60, 95%CI: 1.02-2.51), whereas irritable bowel syndrome and atopic disease remain significant at the trend level.

Mood disorders were associated with UTI in women (OR = 1.47, 95%CI: 1.19-1.81) and in men (OR = 1.63, 95%CI: 1.00-2.65). Also the impact of peptic ulcer/gastritis is apparent in both groups (in women: OR = 1.58, 95%CI: 1.02-2.46, and in men: OR = 1.98, 95%CI: 1.26-3.09). Acne (1.96, 95%CI: 1.35-2.85) predicts mood disorders in men, whereas irritable bowel syndrome (OR = 2.25, 95%CI: 1.35-3.76) and psoriasis (OR = 2.02, 95%CI: 1.14-3.58) contribute in women.

Finally, substance abuse/dependence did not yield any relevant associations in women. In men, it was linked with peptic ulcer/gastritis (OR = 1.88, 95%CI: 1.18-2.99) and with acne (OR = 1.74, 95%CI: 1.17-2.59).

As a side effect of the analysis involving interaction effects, the sex main effect in early and late anxiety disorders disappeared and greatly diminished in mood disorders. The models proved to be stable even when the strongest predictors in each model were omitted. Preliminary analyses on a more detailed level focusing on specific ND and CMD revealed a heterogeneity of results that clearly surpassed the findings presented in this study (results not shown).

DISCUSSION

This is the first study to apply a comprehensive epidemiological perspective on the associations of major groups of ND and CMD with infectious, atopic and inflammatory diseases. It adds to the evidence that infectious, atopic and inflammatory diseases make up an important group of risk factors. The main outcome was the great range of associations although the statistical models had been adjusted for trauma, childhood adversities, familial aggregation and education. Provided that the analyses were carried out on grouped CMD and somatic diseases, the results reported in this study represent only the tip of an iceberg. In addition,

Table 1 Groups of mental disorders and risk factors in the PsyCoLaus study: Frequencies and crude odds ratios (with 95%CI), overall and by sex

	n (%)	Education level low	Education level medium	Education level high	Familial aggregation[6]	Trauma below age of 10	Childhood adversities[7]	Streptococcal diseases[8]	MMR	Peptic ulcer/ gastritis	Irritable bowel syndrome	Atopic diseases	Acne	Psoriasis	Urinary tract infections[9]
Total *n* (%)															
All	3720 (100.0)	1965 (53.4)	916 (24.9)	798 (21.7)	2071 (55.7)	160 (4.3)	1013 (27.2)	230 (6.2)	3033 (86.7)	317 (6.5)	187 (3.8)	2129 (43.8)	474 (9.7)	220 (4.5)	844 (22.7)
Males	1750 (47.0)	888 (51.3)	366 (21.1)	477 (27.6)	876 (50.1)	45 (2.6)	417 (23.8)	87 (5.0)	1353 (83.2)	159 (7.0)	52 (2.3)	895 (39.6)	191 (8.4)	108 (4.8)	86 (4.9)
Females	1970 (53.0)	1077 (55.3)	550 (28.2)	321 (16.5)	1195 (60.7)	115 (5.8)	596 (30.3)	143 (7.3)	1226 (89.6)	158 (6.1)	135 (5.2)	1234 (47.4)	283 (10.9)	112 (4.3)	758 (38.5)
Odds ratios															
Neurodevelop-mental disorders[1]															
All	308 (8.3)	1 (ref)	1.17 (0.89-1.55)	0.94 (0.69-1.29)	1.75 (1.26-2.42)	1.93 (1.22-3.05)	2.93 (2.31-3.71)	1.67 (1.11-2.50)	1.18 (0.83-1.67)	1.68 (1.14-2.49)	1.74 (1.07-2.83)	0.98 (0.78-1.24)	0.87 (0.59-1.29)	1.07 (0.63-1.80)	1.13 (0.86-1.48)
Males	189 (10.8)	1 (ref)	1.39 (0.96-2.00)	0.85 (0.58-1.24)	1.98 (1.27-3.10)	1.28 (0.53-3.06)	3.10 (2.27-4.23)	2.65 (1.57-4.48)	1.35 (0.87-2.08)	1.52 (0.89-2.57)	2.18 (1.03-4.61)	1.15 (0.85-1.56)	0.88 (0.50-1.53)	1.09 (0.57-2.08)	1.36 (0.73-2.56)
Females	119 (6.0)	1 (ref)	1.03 (0.67-1.57)	0.93 (0.54-1.58)	1.75 (1.08-2.85)	2.98 (1.72-5.12)	3.22 (2.21-4.69)	1.05 (0.52-2.11)	1.13 (0.63-2.04)	1.94 (1.08-3.49)	1.86 (0.97-3.58)	0.89 (0.62-1.30)	0.97 (0.55-1.72)	0.93 (0.37-2.35)	1.94 (1.34-2.82)
Early anxiety disorders[2]															
All	951 (25.6)	1 (ref)	0.98 (0.82-1.17)	0.93 (0.77-1.12)	2.75 (2.36-3.21)	1.96 (1.41-2.71)	1.85 (1.58-2.17)	1.51 (1.13-2.00)	1.43 (1.12-1.81)	1.33 (1.01-1.76)	2.42 (1.74-3.37)	1.23 (1.06-1.43)	1.32 (1.05-1.66)	1.41 (1.03-1.94)	1.90 (1.61-2.24)
Males	327 (18.7)	1 (ref)	1.03 (0.76-1.41)	1.06 (0.80-1.41)	2.48 (1.93-3.20)	2.01 (1.06-3.82)	2.01 (1.55-2.61)	1.71 (1.05-2.78)	1.27 (0.89-1.80)	1.75 (1.15-2.66)	2.84 (1.53-5.27)	1.03 (0.81-1.31)	1.59 (1.08-2.32)	2.22 (1.42-3.48)	1.25 (0.74-2.11)
Females	624 (31.7)	1 (ref)	0.90 (0.72-1.13)	1.01 (0.77-1.32)	2.76 (2.26-3.36)	1.65 (1.13-2.42)	1.65 (1.35-2.02)	1.29 (0.91-1.84)	1.35 (0.96-1.88)	1.11 (0.77-1.61)	1.97 (1.33-2.92)	1.25 (1.03-1.51)	1.11 (0.83-1.47)	1.01 (0.64-1.59)	1.51 (1.24-1.83)
Late anxiety disorders[3]															
All	554 (14.9)	1 (ref)	0.96 (0.77-1.20)	0.82 (0.64-1.04)	2.15 (1.67-2.76)	1.64 (1.12-2.42)	1.92 (1.59-2.32)	1.38 (0.98-1.94)	1.44 (1.07-1.95)	1.66 (1.21-2.27)	2.30 (1.59-3.32)	1.34 (1.12-1.61)	1.13 (0.85-1.49)	1.13 (0.75-1.69)	1.49 (1.22-1.82)
Males	200 (11.4)	1 (ref)	1.14 (0.78-1.67)	1.22 (0.87-1.72)	1.96 (1.24-3.08)	0.97 (0.38-2.48)	1.60 (1.16-2.20)	1.01 (0.51-1.99)	1.03 (0.68-1.56)	1.32 (0.77-2.25)	2.04 (0.97-4.31)	1.19 (0.89-1.61)	1.56 (0.99-2.46)	0.70 (0.33-1.47)	2.68 (1.60-4.49)
Females	354 (18.0)	1 (ref)	0.84 (0.65-1.11)	0.64 (0.45-0.92)	2.06 (1.53-2.79)	1.67 (1.08-2.57)	2.02 (1.59-2.55)	1.47 (0.98-2.20)	1.75 (1.11-2.75)	1.93 (1.29-2.86)	2.14 (1.39-3.29)	1.35 (1.07-1.69)	0.88 (0.61-1.27)	1.56 (0.95-2.56)	1.06 (0.83-1.34)
Mood disorders[4]															
All	1765 (47.4)	1 (ref)	1.21 (1.03-1.41)	0.99 (0.84-1.16)	2.14 (1.87-2.45)	1.90 (1.37-2.63)	2.07 (1.79-2.40)	1.05 (0.80-1.38)	1.18 (0.97-1.44)	1.71 (1.32-2.22)	2.31 (1.63-3.26)	1.27 (1.11-1.44)	1.29 (1.05-1.59)	1.45 (1.07-1.96)	2.19 (1.87-2.56)
Males	628 (35.9)	1 (ref)	1.43 (1.11-1.84)	1.26 (1.00-1.59)	1.93 (1.57-2.37)	1.91 (1.05-3.44)	1.85 (1.48-2.31)	1.01 (0.51-1.69)	1.15 (0.88-1.52)	1.70 (1.17-2.47)	1.65 (0.91-3.00)	1.29 (1.06-1.57)	1.76 (1.27-2.45)	1.38 (0.91-2.09)	2.04 (1.32-3.14)
Females	1137 (57.7)	1 (ref)	1.00 (0.82-1.24)	1.02 (0.79-1.31)	2.08 (1.73-2.50)	1.52 (1.02-2.27)	2.12 (1.72-2.60)	1.01 (0.72-1.43)	0.93 (0.70-1.26)	1.83 (1.25-2.69)	2.25 (1.44-3.52)	1.09 (0.91-1.30)	0.93 (0.71-1.23)	1.79 (1.12-2.85)	1.47 (1.22-1.77)
Substance abuse/ dependence[5]															
All	576 (15.5)	1 (ref)	0.77 (0.61-0.96)	0.89 (0.71-1.12)	2.10 (1.62-2.72)	1.22 (0.81-1.84)	1.82 (1.51-2.19)	0.89 (0.56-1.40)	0.90 (0.69-1.17)	1.55 (1.13-2.12)	1.26 (0.83-1.92)	0.97 (0.81-1.16)	1.17 (0.89-1.54)	1.42 (0.98-2.06)	0.78 (0.61-0.98)
Males	429 (24.5)	1 (ref)	0.82 (0.62-1.09)	0.66 (0.51-0.87)	2.65 (1.87-3.75)	1.00 (0.50-1.98)	1.94 (1.52-2.47)	0.98 (0.59-1.62)	0.98 (0.73-1.33)	1.62 (1.09-2.41)	1.79 (0.96-3.35)	1.12 (0.90-1.40)	1.64 (1.15-2.33)	1.24 (0.78-1.97)	1.36 (0.84-2.18)
Females	147 (7.5)	1 (ref)	0.80 (0.53-1.21)	1.00 (0.63-1.59)	2.11 (1.35-3.29)	2.48 (1.46-4.24)	2.60 (1.85-3.65)	0.82 (0.41-1.65)	1.58 (0.82-3.06)	1.53 (0.86-2.74)	1.64 (0.88-3.07)	1.06 (0.75-1.48)	0.89 (0.52-1.53)	1.66 (0.84-3.28)	1.41 (1.01-1.98)

[1]Tics, attention deficit hyperactivity disorder, conduct disorder, oppositional defiant disorder; [2]Separation anxiety disorder, overanxious disorder, specific phobias (animals), social phobia; [3]Generalized anxiety disorder, panic, agoraphobia, specific phobias (excl. animals); [4]Major depression disorder, dysthymia, bipolar disorders; [5]Alcohol, cannabis, other illicit drugs abuse/dependence; [6]Overall figures; Ns relating to each subgroup of mental disorders: 382 (neurodevelopmental), 1110 (early anxiety), 386 (late anxiety), 1446 (mood), 349 (substances); OR's were based on subgroup specific information; [7]Interparental violence, fear of maltreatment by parents, growing up in a children's home, unhappy childhood; [8]Tonsillitis, scarlet fever, rheumatic fever. MMR: Measles/mumps/rubella; [9]cystitis, pyelitis, pyelonephritis, other nephritis, urethritis, prostatitis.

Table 2 Mental disorders regressed on infectious, atopic and inflammatory diseases, odds-ratios and 95%CI derived from logistic regression models

	Model 1 Neurodevelopmental disorders	Model 2 Early anxiety disorders	Model 3 Late anxiety disorders	Model 4 Mood disorders	Model 5 Substance abuse/ dependence
Sex	0.38 (0.27-0.52)	1.60 (1.33-1.94)	1.50 (1.19-1.87)	2.05 (1.74-2.41)	0.19 (0.14-0.24)
Education level					
Low	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medium	0.91 (0.66-1.24)	1.24 (1.01-1.52)	1.11 (0.87-1.41)	0.86 (0.72-1.04)	1.19 (0.92-1.54)
High	1.10 (0.78-1.56)	1.08 (0.87-1.34)	1.07 (0.83-1.39)	0.88 (0.72-1.06)	1.27 (0.98-1.66)
Familial aggregation of CMD	1.55 (1.07-2.23)	2.54 (2.14-3.01)	1.75 (1.34-2.29)	1.77 (1.52-2.06)	2.12 (1.59-2.82)
Trauma below age of 10	1.43 (0.84-2.44)	1.07 (0.73-1.57)	1.12 (0.73-1.71)	1.11 (0.76-1.62)	1.36 (0.84-2.20)
Childhood adversities	2.74 (2.09-3.60)	1.51 (1.25-1.81)	1.89 (1.53-2.33)	1.87 (1.57-2.23)	1.81 (1.45-2.27)
Streptococcal infections	1.29 (0.79-2.10)	1.11 (0.80-1.55)	1.22 (0.84-1.78)	0.80 (0.59-1.10)	0.80 (0.51-1.25)
Mumps, measles, rubella	1.37 (0.91-2.06)	1.36 (1.04-1.77)	1.33 (0.97-1.83)	1.07 (0.86-1.34)	1.15 (0.85-1.54)
Peptic ulcer/gastritis	1.72 (1.11-2.68)	1.23 (0.89-1.71)	1.47 (1.03-2.11)	1.74 (1.27-2.39)	1.58 (1.09-2.29)
Irritable bowel syndrome	1.30 (0.71-2.36)	1.81 (1.24-2.64)	1.74 (1.15-2.62)	1.87 (1.26-2.79)	1.70 (1.06-2.73)
Atopic diseases	0.95 (0.73-1.25)	1.11 (0.94-1.31)	1.24 (1.01-1.51)	1.06 (0.91-1.24)	1.02 (0.83-1.26)
Acne	0.83 (0.53-1.30)	1.10 (0.85-1.43)	1.02 (0.74-1.39)	1.23 (0.97-1.57)	1.27 (0.92-1.76)
Psoriasis	1.22 (0.69-2.16)	1.45 (0.99-2.11)	1.05 (0.66-1.69)	1.59 (1.11-2.28)	1.41 (0.91-2.19)
Urinary tract infections	1.51 (1.06-2.14)	1.37 (1.12-1.67)	1.06 (0.83-1.35)	1.49 (1.22-1.80)	1.20 (0.88-1.64)

CMD: Common mental disorders.

Table 3 Mental disorders regressed on infectious, atopic and inflammatory diseases, odds-ratios and 95%CIs derived from logistic regression models with nested effects

		Model 1 Neurodevelopmental disorders	Model 2 Early anxiety disorders	Model 3 Late anxiety disorders	Model 4 Mood disorders	Model 5 Substance abuse/ dependence
Sex		0.41 (0.23-0.72)	0.79 (0.54-1.15)	1.08 (0.68-1.69)	1.56 (1.08-2.26)	0.34 (0.21-0.54)
Education level						
Low		1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medium		1.09 (0.79-1.49)	0.79 (0.65-0.98)	0.89 (0.70-1.13)	1.15 (0.96-1.38)	0.83 (0.64-1.08)
High		0.88 (0.62-1.25)	0.91 (0.73-1.14)	0.92 (0.71-1.20)	1.12 (0.92-1.36)	0.77 (0.59-1.01)
Familial aggregation of CMD		1.53 (1.06-2.21)	2.53 (2.14-3.00)	1.78 (1.36-2.33)	1.77 (1.52-2.06)	2.14 (1.60-2.86)
Trauma below age of 10		1.47 (0.86-2.50)	1.08 (0.73-1.58)	1.11 (0.73-1.71)	1.12 (0.76-1.64)	1.40 (0.86-2.27)
Childhood adversities		2.78 (2.12-3.65)	1.52 (1.26-1.83)	1.91 (1.55-2.36)	1.89 (1.59-2.25)	1.83 (1.46-2.29)
Streptococcal infections	Women nested	0.69 (0.29-1.67)	1.15 (0.76-1.73)	1.32 (0.84-2.07)	0.91 (0.60-1.36)	0.87 (0.42-1.82)
	Men nested	1.98 (1.08-3.66)	1.08 (0.60-1.92)	1.04 (0.51-2.09)	0.67 (0.40-1.12)	0.78 (0.44-1.39)
Mumps, measles, rubella	Women nested	1.16 (0.58-2.32)	1.46 (1.01-2.10)	1.81 (1.12-2.90)	0.97 (0.70-1.35)	1.62 (0.79-3.29)
	Men nested	1.47 (0.88-2.45)	1.29 (0.88-1.91)	0.96 (0.62-1.49)	1.12 (0.83-1.52)	1.04 (0.74-1.46)
Peptic ulcer/gastritis	Women nested	1.72 (0.88-3.34)	0.97 (0.63-1.49)	1.60 (1.02-2.51)	1.58 (1.02-2.46)	1.19 (0.61-2.35)
	Men nested	1.95 (1.08-3.53)	1.85 (1.13-3.05)	1.25 (0.67-2.35)	1.98 (1.26-3.09)	1.88 (1.18-2.99)
Irritable bowel syndrome	Women nested	1.23 (0.56-2.70)	1.48 (0.95-2.30)	1.60 (0.99-2.57)	2.25 (1.35-3.76)	1.63 (0.84-3.16)
	Men nested	1.74 (0.70-4.36)	3.15 (1.58-6.28)	1.97 (0.86-2.48)	1.33 (0.67-2.62)	1.80 (0.90-3.61)
Atopic diseases	Women nested	0.74 (0.48-1.12)	1.19 (0.96-1.47)	1.28 (0.99-1.66)	0.97 (0.79-1.18)	1.02 (0.69-1.49)
	Men nested	1.14 (0.80-1.61)	1.02 (0.77-1.34)	1.19 (0.86-1.66)	1.22 (0.97-1.53)	1.05 (0.81-1.35)
Acne	Women nested	0.75 (0.39-1.47)	0.94 (0.68-1.31)	0.82 (0.55-1.23)	0.90 (0.66-1.24)	0.74 (0.40-1.37)
	Men nested	0.92 (0.50-1.67)	1.47 (0.96-2.25)	1.52 (0.92-2.51)	1.96 (1.35-2.85)	1.74 (1.17-2.59)
Psoriasis	Women nested	0.84 (0.29-2.43)	1.05 (0.60-1.82)	1.48 (0.83-2.66)	2.02 (1.14-3.58)	1.70 (0.77-3.73)
	Men nested	1.44 (0.73-2.86)	2.02 (1.20-3.39)	0.60 (0.25-1.42)	1.33 (0.82-2.17)	1.30 (0.76-2.21)
Urinary tract infections	Women nested	1.68 (1.11-2.54)	1.44 (1.16-1.79)	0.94 (0.72-1.22)	1.47 (1.19-1.81)	1.30 (0.89-1.89)
	Men nested	1.26 (0.63-2.51)	0.99 (0.55-1.76)	2.13 (1.19-3.82)	1.63 (1.00-2.65)	1.04 (0.61-1.79)

CMD: Common mental disorders.

many associations were sex-specific. Intriguingly, accounting for interaction effects of infectious, atopic and inflammatory diseases with sex had different consequences for ND and CMD. In early and late anxiety disorders the sex main effect came down to one, meaning that the sex ratio in these disorders was fully determined by sex-specific associations with these risk factors.

Challenges

In view of the broad spectrum of results, the discussion will not focus on particular pathogens or findings as was done in the introduction, but will attempt to systematize them. Their interpretation encounters several basic challenges. First, the general heterogeneity of the associations between ND/CMD and infectious/atopic/ chronic inflammatory diseses is enormous. The extent

and heterogeneity of associations require appropriate, *i.e.*, neither universal nor parsimonious explanatory approaches. This methodological argument also applies also for the surprising sexual dimorphism of associations between ND/CMD and infectious, atopic and inflammatory diseases: There must be several mechanisms inducing sex-specific differences in rates of ND/CMD. Not least, this also applies to the different ages when CMD risk factors may emerge. While much attention has been paid to prenatal and perinatal events[76-78], the impact of MMR or scarlet fever in the current results shows that the age range can vary broadly. In brief: The same infectious disease or immune system imbalance could yield different vulnerability outcomes, depending on the age when it occurs.

Interpretation approaches

On a formal level the interpretation of the findings can follow three basic pathways (see, for example)[47]: (1) infectious, atopic and inflammatory diseases induce a risk for ND and CMD; (2) ND and CMD increase the risk for infectious, atopic and inflammatory diseases; and (3) both ND/CMD and infectious, atopic and inflammatory diseases share the same intermediate mechanisms or etiopathogenetic processes. These pathways will be used in the following to categorize and interpret the results.

Most of the current results point to the pathways one and three. In instances such as childhood infectious diseases the interpretation seems to be relatively unambiguous. Childhood infections lend themselves to the first pathway since they mostly precede other disorders or diseases. The range of potentially relevant pathogens, that figure as risk factors for mental disorders extends beyond well investigated prenatal infections (in the first place those summarized under the label TORCH - toxoplasmosis, rubella, cytomegalovirus, herpes)[79,80] and the PANDAS model (related to group A streptococcal infections in early childhood)[81]. In the current analysis it includes viral pathogens (MMR) in addition to streptococcal diseases. Moreover, the brief list of infectious diseases involved is to be understood as a preliminary compilation. More specific analyses, for example on anxiety disorders[82], would contribute additional links. In addition, several frequently occurring infectious agents in childhood cannot be adequately assessed by self-report data (*e.g.*, Haemophilus influenzae, respiratory syncytial virus, influenza).

Similar reasoning about the sequence of events also applies to atopic diseases. They often start in childhood and adolescence, *i.e.*, mostly before mood disorders (men) and late anxiety disorders (women). Thus, atopic diseases also seem to contribute to CMD rather than the other way round. However, atopic diseases represent a different type of immune system imbalance than infectious childhood diseases. It is a puzzling finding that the same disorder can be associated with risk factors which represent different, partly even antagonistic or competing immune system responses, such as Th1 *vs* Th2 or Th17 *vs* Treg[83].

This phenomenon can be perceived in associations related to chronic inflammatory diseases which represent pathway 3 above. For example, acne[84] and psoriasis[85] are assumed to be Th1/17 related skin diseases, whereas atopic eczema or the irritable bowel syndrome[57] are considered to have mainly[86] a Th2 related background.

Pathways 1 and 3 suggest that immunological processes are the common denominator of the related risk factors of ND/CMD. The immunological hypothesis in ND and CMD has many direct contributors, such as the TORCH (Toxoplasma gondii, rubella virus, cytomegalovirus, and herpes simplex virus)[80] and PANDAS models in ND disorders, serological studies, for example in schizophrenia (see above), leucocyte counts in depression[87], gastrointestinal inflammation in psychosis[29], the autoantibodies link[88], the inflammation topic in mood disorders[89], and, finally, evidence for upregulated proinflammatory mediators such as IL-1β, IL-6 and TNF-α[90]. However, in some instances such as UTI or ulcer the categorization of immune processes is less clear and may involve different basic mechanisms.

Hypotheses regarding the neurophysiological background mechanisms

The basic assumption of the immunological hypothesis within a two or three hit model (*i.e.*, a vulnerability-trigger model) of CMD is that immune system imbalances impact brain development during critical stages. Animal models referring to neonates have shown that bacterial infections may have an impact both on brain development and on the programming of the immune system[91-93]. While this research is based on *E. coli* models, the implications might generalize to other microbes, including streptococci, as well. It has been suggested that this pathway relies on the impact of cytokines on microglia, which in turn crucially influence brain development at different stages of life by influencing cell proliferation, synaptogenesis and immune processes in exchange with astrocytes, neurons and oligodendroglia[94,95]. An interesting perspective that has emerged recently is that mast cells are able to activate microglia[96].

In agreement with epidemiological research, the microglia pathway offers new perspectives for the understanding of the sex-ratios in mental disorders. Microglia numbers in males and females are differently skewed at different age stages. In early childhood, more microglia can be discerned in various brain regions of males, whereas in adolescence and adulthood, there are more microglia in the brains of females[97]. If more frequent, microglia are at the same time more "active"[94].

Limitations

While the promise of this study relies on a comprehensive epidemiological approach not feasible in most other subdisciplines in psychiatry, the study also has several limitations. First, all information is based on

the self-reporting of study subjects, which implies a substantial recall bias, both regarding mental problems and infectious diseases. Provided that infectious diseases remain asymptomatic in many instances and that underreporting is the most probable biasing effect regarding adverse experiences and stigmatized issues, our results represent rather conservative approximations of the "real" associations. Second, herpes as well as measles, mumps and rubella infections were presumably reported more frequently by subjects with a more severe or an exanthematic appearance of the infection. Thus, while these infections were underreported in this study, their frequencies implicitly provide a measure of disease severity. A similar limitation also applies to UTI and streptococcal infections. Third, the age of onset in streptococcal infections, herpes infections and in UTI could not be reliably assessed, the first two because of the inclusion of related diseases and late sequels, the latter because of the large proportion of undiagnosed or asymptomatic UTI in childhood. Finally, several further infectious agents of interest could not be identified by self report (see above) and thus could not be considered for the analysis.

In conclusion, atopic and inflammatory diseases make up an important group of potential risk factors for ND and CMD. They contribute independently of further major risk factors such as childhood adversities, traumatic experiences and familial aggregation. While the amount of evidence is enormous and continuously growing, the interpretational framework is compromised by the fact, that - similarly to research on smoking and cancer - direct experimental proofs are not feasible. Meanwhile, prevention in this field might already be going on unnoticed due to classical tools such as vaccinations and appropriate treatment of infectious diseases in childhood[98].

COMMENTS

Background

There are numerous results in the literature documenting the associations between inflammatory diseases of any kind (including infectious and atopic diseases) and neurodevelopmental disorders (ND)/common mental disorders (CMD). They complement other groups of risk factors (psychosocial stressors, traumatic experiences, pre-/perinatal risk factors, hormonal processes, substances, cerebral injury).

Research frontiers

In contrast to detailed knowledge about bivariate associations and particular issues, a systemic understanding is missing: How do these associations aggregate to more general mechanisms, how do they interact and compete? A better systemic understanding of the links between inflammatory diseases and ND/CMD might help us to understand even unresolved issues such as the sex ratios or the heterogeneous age at onset in these disorders.

Innovations and breakthroughs

This is the first study to apply a comprehensive epidemiological perspective on the associations of inflammatory diseases with major groups of ND and CMD while adjusting for other groups of risk factors. It confirms that inflammatory diseases make up an important group of risk factors of ND and CMD. However, the pathways are heterogeneous and sex-specific.

Applications

Inflammatory diseases are indicators of upregulations and imbalances in immune system activity. Since the immune system activity can be modulated and infectious diseases can be prevented, new potentials for intervention and prevention become apparent.

Terminology

Th1, Th2, Th17 are T helper cells, Treg are regulatory T cells. They represent different modes of immune system activity.

Peer-review

This is a very interesting body of work as a part on renewed interest in inflammatory processes and major psychiatric diseases.

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ORIGINAL ARTICLE

Observational Study

Health-care needs of remitted patients with bipolar disorder: A comparison with schizophrenia

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Abstract

AIM

To investigate health-care needs and their correlates among patients with remitted bipolar disorder (BD) compared to patients with remitted schizophrenia.

METHODS

Outpatients with BD (n = 150) and schizophrenia (n = 75) meeting clearly defined remission criteria were included in the study along with their relatives. Diagnostic ascertainment was carried out using the Mini International Neuropsychiatric Interview. Demographic and clinical details were recorded using structured formats. Residual symptoms were assessed using standardized scales. Health-care needs were assessed on two separate scales. The principal instrument employed to assess health-care needs was the Camberwell Assessment of Need-Research version (CAN-R). To further evaluate health-care needs we felt that an additional instrument, which was more relevant for Indian patients and treatment-settings and designed to cover those areas of needs not specifically covered by the CAN-R was required. This instrument with a structure and scoring pattern similar to the CAN-R was used for additional evaluation of needs. Patients' level of

functioning was assessed using the Global Assessment of Functioning Scale and their quality of life (QOL) using the World Health Organization Quality Of Life-BREF version in Hindi.

RESULTS

An average of 6-7 needs was reported by patients with BD as well as their relatives. Commonly reported needs were in the areas of economic and welfare needs, informational needs, social needs and the need for treatment. According to the CAN-R, both patients and relatives reported that more than 60% of the total needs were being met. However, over 90% of the needs covered by the additional evaluation were unmet according to patients and relatives. Needs in the areas of economic and welfare-benefits, information, company, daytime activities and physical health-care were largely unmet according to patients and relatives. Total, met and unmet needs were significantly higher for schizophrenia, but the most common types of needs were quite similar to BD. Relatives reported more needs than patients with certain differences in the types of needs reported. Level of patients' functioning was the principal correlate of greater total and unmet needs in both groups. Significant associations were also obtained with residual symptoms and QOL.

CONCLUSION

The presence of unmet needs in remitted patients with BD was an additional marker of the enduring psychosocial impairment characteristic of the remitted phase of BD.

Key words: Health-care needs; Bipolar disorder; Schizophrenia; Remission; Patients; Relatives

Core tip: Health-care needs, functioning and quality of life (QOL) were assessed in 150 outpatients with remitted bipolar disorder (BD) and 75 with remitted schizophrenia. A high number of needs were found in BD; economic, welfare and information needs were mostly unmet. Total, met and unmet needs were significantly higher for schizophrenia, but the pattern of needs was similar to BD. Relatives reported more needs than patients with differences in the types of needs. Patient-functioning, residual symptoms and QOL were associated with higher needs. Unmet needs in remitted patients with BD were indicative of the enduring psychosocial impairment during remission.

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INTRODUCTION

The traditional view of bipolar disorder (BD) is that of a condition characterized by good outcome and complete recovery from acute episodes of the illness. However, research over the past few decades has clearly shown that a substantial proportion of remitted patients with BD continue to display subsyndromal symptoms, neurocognitive deficits and impairments in occupational and social functioning[1-3]. The diverse nature of these disabilities in BD suggests that measures beyond mere clinical symptoms are required to truly estimate the psychosocial impact of the condition during remission. Measures such as quality of life (QOL) or level of functioning are useful, but they do not generally provide much information about how the illness-related dysfunction or lack of satisfaction with treatment can be alleviated.The concept of "health-care needs" appears to overcome this shortcoming being a measure of outcome, in which subjective perceptions of patients and caregivers are evaluated in order to determine ways of improving the outcome of the illness[4].

The National Health Service and Community Care Act[5] defines "need" as the "requirement of the individual to achieve, maintain and restore an acceptable level of social independence and QOL". A health-care need is considered to be present when because of symptoms, distress or disability, the patient's level of functioning is not optimal due to some potentially remediable or preventable cause[4]. Accumulating evidence indicates that the extent to which needs of patients is met predicts their levels of disability, QOL, and satisfaction with treatment[6,7]. Accordingly, examination of needs and their correlates not only serves as the basis for improved treatment and judicious resource allocation, but also as a comprehensive indicator of the psychosocial status of patients and their psychosocial outcome following treatment[8]. Finally, in order for patients to become partners in their own treatment, it is important to understand and prioritize their personal wants and needs[4].

Despite the obvious implications of examining health-care needs of patients, very few studies have chosen to focus exclusively on examining needs among patients with BD. This contrasts with the large amount of literature available on needs of patients with other mental illnesses, particularly schizophrenia. Accordingly, the current study aimed to assess health-care needs and their correlates among patients with BD in remission, compared to those with remitted schizophrenia. Given the paucity of literature in this area, the first objective was to document the number and types of needs found among patients with BD in remission. To provide a context for the findings in BD, comparisons were carried out with health-care needs among patients with remitted schizophrenia and the correlates of health-care needs were also examined. Schizophrenia was chosen as a comparison group because of the substantial

amount of research data on health-care needs available for this condition. Based on previous research it was hypothesized that the number and types of health-care needs in BD would be similar to schizophrenia and would be associated with patient-functioning, symptom-severity and QOL. Since some differences between patients' and caregivers' evaluation of needs has been reported earlier[9,10], health-care needs were assessed both from the perspective of patients and their relatives. The eventual findings were expected to yield a better understanding of health-care needs among patients with BD in remission.

MATERIALS AND METHODS

Approval/consent

The protocol was approved by the ethics and research committees of the institute where it was conducted. Written informed consent was sought prior to induction and other ethical safeguards were maintained during the study.

Participants

Patients along with their relatives were recruited from those attending the outpatient psychiatric services of a tertiary-care hospital in north-India. Patients aged 18-60 years,with a diagnosis of BD or schizophrenia as per DSM-Ⅳ criteria[11], determined using the Mini International Neuropsychiatric Interview (MINI)[12] were included. Patients with BD had to be in remission, which was defined cross-sectionally as a score of < 8 on the 17-item Hamilton Depression Rating Scale[13] and a score of < 6 on the Young Mania Rating Scale[14]. Further, only those patients with BD without acute episodes in the 3-mo period prior to intake were included based on information from patients, relatives and case notes. Finally, patients had to be on a stable dose of psychotropics, *i.e.*, not more than 50% hikes or reductions in dosages in these 3 mo. Patients with schizophrenia were included if they met remission criteria of Andreasen *et al*[15] on the Positive and Negative Syndrome Scale for Schizophrenia (PANSS)[16]. Similar to patients with BD, only patients with no exacerbations of positive or negative symptoms and on stable doses of psychotropics in the 3-mo period prior to intake were included. Additionally, both patient groups were matched on age, gender, residence (urban/rural) and duration of illness. Patients with comorbid psychiatric or physical illnesses, substance use disorders (except nicotine use) and organic brain syndromes were excluded. Over a period of about a year, 150 outpatients with BD and a matched group of 75 outpatients with schizophrenia who fulfilled the selection criteria were inducted along with their relatives.

Assessments

Apart from confirming diagnoses with the MINI and rating symptoms, demographic and clinical details were recorded using structured formats. The principal instrument employed to assess health-care needs was the Camberwell Assessment of Need-Research version (CAN-R)[17]. The CAN-R consists of clinical and social needs divided into 22 areas. In each of these areas there are four sections, which assess the severity of need, current help received from friends or relatives, help from social services and outpatient clinics, the adequacy of help and satisfaction with the help received on a four-point scale. Though the CAN-R is a valid and reliable instrument for assessing needs of people with severe mental illnesses, it appeared to leave out some of the needs commonly reported by Indian patients. To evaluate health-care needs felt to be more relevant for Indian patients and treatment-settings, an additional instrument which was designed to cover those areas of needs not specifically covered by the CAN-R was used. The structure and scoring pattern of this instrument was similar to the CAN-R, but it had 21 items/areas not covered by the CAN-R. This scale has been used in a multi-centric Indian study on needs of patients with severe mental illnesses[18]. Finally, the level of functioning of patients was assessed using the Global Assessment of Functioning Scale (GAF)[11] and their QOL using the World Health Organization Quality Of Life-BREF version in Hindi (WHOQOL-BREF)[19].

Statistical analysis

Data were analyzed using the Statistical Package for Social Scientists, version 15.0. Continuous variables in the two groups were compared using "*t*" tests or Mann-Whitney tests, and ordinal and nominal variables using χ^2 tests. To examine the association between health-care needs and clinical and demographic correlates, Pearson's Product Moment Correlation coefficients (for normally distributed continuous data) and Spearman's Rank Correlation coefficients (for ordinal data with non-normal distributions) were estimated. Significance was set at 5%; *P* values were also adjusted for the multiple correlations carried out by using the Bonferroni correction. Separate stepwise multiple regression analyses with total and unmet needs on the CAN-R as dependent variables were carried out using patients' and relatives' reports to determine the correlates of health-care needs.

RESULTS

Profile of participants (Table 1)

Patients with BD were more likely to be married and in paid employment compared to those with schizophrenia. Relatives of patients with BD were more likely to be women and more likely to be their spouses, whereas parents outnumbered spouses in the schizophrenia group. All patients were on treatment. Clinical profiles of both groups were comparable.

Needs assessment on the CAN-R: Patients' reports (Table 2)

Though the total number of needs was relatively high

Table 1 Profile of the patients and their relatives

	Patients		Relatives		
	Bipolar disorder (*n* = 150)	Schizophrenia (*n* = 75)	Bipolar disorder (*n* = 150)	Schizophrenia (*n* = 75)	
Age (yr) mean (SD)	36.1 (10.1)	33.4 (9.9)	42.3 (12.8)	43.7 (11.7)	
Gender *n* (%)					Relatives' gender χ^2 = 6.74; P < 0.01
Male	101 (67)	42 (56)	64	46 (61)[a]	
Female	49	33	86 (57)	29	
Marital status *n* (%)					Marital status of patients χ^2 = 7.15; P < 0.01
Not married	43	35	12	5	
Married	107 (71)	40 (53)[a]	138 (92)	70 (93)	
Years of schooling mean (SD)	11.4 (4.9)	11.5 (4.4)	11.1 (5.9)	11.6 (6.24)	
Occupation *n* (%)					Occupation of patients χ^2 = 21.87; P < 0.001
Paid employment	103 (69)	27	72	44 (59)	
Others	47	48 (64)[b]	78 (52)	31	
Family type *n* (%)					
Nuclear	69	35			
Non-nuclear	81 (54)	40 (53)			
Residence *n* (%)					
Urban	86 (57)	39 (52)			
Rural	64	36			
Relationship with the patient *n* (%)					χ^2 = 11.69; P < 0.01
Spouse			68 (45%)	17 (23)[a]	
Parents			48 (32%)	30 (40)	
Sibs			16 (11%)	14 (19)	
Others			18 (12%)	14 (19)	
Age of onset (in years) mean (SD)	26.7 (9.5)	26.1 (12.7)			
Duration of illness (mo) mean (SD)	110.3 (78.9)	93.7 (65.9)			
Duration of treatment (mo) mean (SD)	99.1 (69.5)	100 (94.3)			
Number of hospitalizations in the past mean (SD)	0.7 (1.0)	0.5 (0.9)			
PANSS positive score mean (SD)	-	10.6 (5.6)			
PANSS negative score mean (SD)	-	12.3 (7.2)			
PANSS general psychopathology score mean (SD)	-	27.4 (12.6)			
YMRS score mean (SD)	2.0 (3.1)	-			
HDRS score mean (SD)	1.0 (2.1)	-			
GAF score mean (SD)	70.07 (17.79)	66.63 (15.63)			
WHOQOL-BREF scores mean (SD)	93.87 (15.17)	88.77 (17.85)			

[a]P < 0.01; [b]P < 0.001: Comparisons between BD and schizophrenia on marital status and occupation of patients, relatives' gender and relationship with patient. PANSS: Positive and Negative Syndrome Scale for Schizophrenia; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale; GAF: Global Assessment of Functioning; WHOQOL-BREF: World Health Organization Quality of Life Bref version; BD: Bipolar disorder.

among both patient groups, more than 60% of the total needs were perceived as being met. The mean number of total, met and unmet needs reported by patients was significantly higher for schizophrenia than BD. However, the pattern of individual needs was largely similar with the eight most common domains of needs in both groups being: Help with providing welfare-benefits, information about the condition and its treatment, help with household skills, help for allaying psychological distress, the need for company and social life, help regarding physical-health problems, help with daytime activities, help with self-care, and help for coping with psychotic symptoms. Among these domains, needs were perceived to be unmet in the areas of welfare-benefits, company, and information (mainly for schizophrenia) by a greater proportion of the patients. Patients with schizophrenia reported significantly greater needs in some additional domains including help with psychotic symptoms, the need for company, telephones and transport, and financial needs.

Needs assessment on the CAN-R: Relatives' reports (Table 3)

The overall pattern of needs and the eight most common needs reported by relatives was similar to that of patients. Like patients about 60% of the total needs were perceived to be met by relatives. Additionally, the mean number of total needs and met and unmet needs were significantly higher for those with schizophrenia than those with BD. Certain significant differences were, however, noted between patients and relatives. For the BD group, the mean number of total needs (t = 1.97; P < 0.05) and unmet needs (t = 2.01; P < 0.05) was significantly higher according to the relatives. Similar to patients' reports, the need for help with psychotic symptoms and for transport were greater among those with schizophrenia, but unlike patients, relatives reported significantly greater total needs in the domains of accommodation and help with the household skills. Finally, while in the BD group, the need for welfare benefits and company (among the eight most common needs) were perceived as being largely unmet, in the schizophrenia group unmet needs were greater in two additional areas of help with daytime activities and information about the condition and its treatment, where the proportion of relatives reporting unmet needs was significantly greater than those reporting information needs to be met (χ^2 = 13.79; P < 0.01).

Help received and satisfaction with help: Patients' and relatives' reports

Patients' and relatives' reports about the help received from formal (health-care services) and informal sources (family), and their satisfaction with this help revealed certain common trends across both patient groups. Firstly, both patients and relatives reported that they had hardly received any help from either formal or informal sources and were largely dissatisfied with the help received in three of the eight areas where needs

Table 2 Health-care needs on the Camberwell Assessment of Need-Research version - as reported by patients

	Bipolar disorder *n* = 150			Schizophrenia *n* = 75			*t* values
Total needs - mean (SD)		6.03 (2.87)			7.45 (2.80)		3.54[d]
Met needs - mean (SD)		3.92 (2.21)			4.58 (2.32)		2.07[a]
Unmet needs - mean (SD)		2.1 (1.70)			2.87 (1.88)		3.01[b]
Domains	Total needs *n* (%)	Met needs *n* (%)	Unmet needs *n* (%)	Total needs *n* (%)	Met needs *n* (%)	Unmet needs *n* (%)	χ^2 values
Accommodation	11 (7)	11 (7)	0 (0)	9 (12)	7 (9)	2 (3)	1.34
Food	16 (11)	16 (11)	0 (0)	12 (16)	10 (13)	2 (3)	1.3
Household skills	92 (61)	86 (57)	6 (4)	55 (73)	52 (69)	3 (4)	3.17
Self care	28 (19)	25 (17)	3 (2)	18 (24)	15 (20)	3 (4)	0.87
Daytime activities	65 (43)	44 (29)	21 (14)	41 (55)	21 (28)	20 (27)	2.57
Physical health	68 (45)	47 (31)	21 (14)	32 (43)	27 (36)	5 (7)	0.14
Psychotic symptoms	44 (29)	38 (25)	6 (4)	67 (89)	60 (80)	7 (9)	72.01[d]
Information about condition and treatment	106 (71)	61 (41)	45 (30)	60 (80)	24 (32)	36 (48)	2.25
Psychological distress	87 (58)	73 (49)	14 (9)	40 (53)	32 (43)	8 (11)	0.44
Safety to self	14 (9)	14 (9)	0 (0)	5 (7)	4 (5)	1 (1)	0.46
Safety to others	21 (14)	16 (11)	5 (3)	8 (11)	5 (7)	3 (4)	0.49
Alcohol	8 (5)	8 (5)	0 (0)	0 (0)	0 (0)	0 (0)	2.73
Drugs	13 (9)	8 (5)	5 (3)	4 (5)	1 (1)	3 (4)	0.39
Company	74 (47)	36 (24)	38 (25)	50 (67)	24 (32)	26 (35)	6.07[a]
Intimate relationships	17 (11)	7 (5)	10 (7)	10 (13)	3 (4)	7 (9.3)	0.04
Sexual expression	14 (9)	9 (6)	5 (3)	3 (4)	0 (0)	3 (4)	1.34
Child care	21 (14)	18 (12)	3 (2)	10 (13)	6 (8)	4 (5)	0.019
Basic education	9 (6)	7 (5)	2 (1)	7 (9)	6 (8)	1 (1)	0.84
Telephone	33 (22)	28 (19)	5 (3)	27 (36)	23 (31)	4 (5)	5.01[a]
Transport	19 (13)	14 (9)	5 (3)	18 (24)	12 (16)	6 (8)	4.67[a]
Money	30 (20)	22 (15)	8 (5)	30 (40)	12 (16)	8 (11)	10.22[a]
Welfare benefits	114 (76)	1 (1)	113 (75)	63 (84)	0 (0)	63 (84)	1.91

[a]$P < 0.05$; [b]$P < 0.01$; [d]$P < 0.001$: Comparisons between BD and schizophrenia on total, met and unmet needs and different types of needs. BD: Bipolar disorder.

were commonly expressed including welfare-benefits (93%-98%), information about the condition and its treatment (59%-73%), and the need for company and social life (45%-56%). In the areas of help regarding physical-health problems and with daytime activities, some help was received from friends and family; still, about a-third to half of the respondents were dissatisfied with help received. In the areas of help with the household skills and for allaying psychological distress, majority of the respondents (73%-100%) reported receiving help from informal sources, and were satisfied with the help received. In the area of psychotic symptoms, a majority of the patients with schizophrenia and their relatives (85%-90%) acknowledged receiving help from health-care services and were satisfied with the help received; though respondents in the bipolar group did not receive much help from formal sources, the majority were still satisfied by the help received in this area (83%-90%).

Additional evaluation of health-care needs of patients (Table 4)

Results of the additional evaluation of needs showed that a larger proportion of the needs (over 90%) reported by patients or their relatives were unmet in contrast to the CAN-R evaluation. Similar to the CAN-R evaluation, total, met and unmet needs were significantly greater among those with schizophrenia. Common areas of needs included those for free treatment, reimbursement of medical expenses, financial help, help with work or job reservations, travel concessions, and the need for psychoeducation. Patients expressed the need for travel concessions, disability certificates which would enable them to avail welfare-benefits, and the need for self-help groups, while relatives reported needs in the areas of rehabilitation and help with the stress of caregiving. Not unsurprisingly, the majority of the respondents (79%-100%) reported that they had received little help in these areas. Unlike the CAN-R evaluation, there were no differences between the patients' and relatives' reports.

Correlates of health-care needs (Table 5)

Univariate associations between health-care needs and demographic, clinical and psychosocial variables revealed that the GAF and the WHOQOL-BREF scores demonstrated significant inverse associations with total needs based on relatives' reports, and unmet needs based on reports of both patients and their relatives. Table 5 also includes the results of separate stepwise multiple regression analyses with total needs and unmet needs being the dependent variables in each analysis. The GAF scores, PANSS positive scores, and scores on the psychological-health domain of the WHOQOL-BREF explained about 25% variance in the total needs scores (GAF scores - 18%; PANSS positive scores - 5%;

Table 3 Health-care needs of patients on the Camberwell Assessment of Need-Research version - as reported by their relatives

	Bipolar disorder n = 150			Schizophrenia n = 75			t values
Total needs		6.72 (3.19)			8.36 (2.91)		3.37[f]
Met needs		4.15 (2.34)			4.99 (2.18)		2.57[a]
Unmet needs		2.57 (2.31)			3.37 (2.58)		2.37[a]
Domains	Total needs	Met needs	Unmet needs	Total needs	Met needs	Unmet needs	χ^2 values
Accommodation	12 (8)	11 (7)	1 (1)	15 (20)	13 (17)	3 (4)	6.82[b]
Food	32 (21)	30 (20)	2 (1)	23 (31)	20 (27)	3 (4)	2.35
Household skills	103 (69)	90 (60)	13 (9)	63 (84)	56 (75)	7 (9)	6.07[a]
Self-care	36 (24)	31 (21)	5 (3)	25 (33)	19 (25)	6 (8)	2.20
Daytime activities	77 (51)	51 (34)	26 (17)	43 (57)	21 (28)	22 (29)	0.72
Physical health	79 (53)	62 (41)	17 (11)	39 (52)	31 (41)	8 (11)	0.01
Psychotic symptoms	47 (31)	37 (25)	10 (7)	69 (92)	59 (79)	10 (13)	73.68[f]
Information about condition and treatment	106 (71)	62 (41)	44 (29)	60 (80)	17 (23)	43 (57)	2.25[1]
Psychological distress	87 (58)	70 (47)	17 (11)	49 (65)	39 (52)	10 (13)	1.12
Safety to self	8 (5)	8 (5)	0 (0)	6 (8)	5 (7)	1 (1)	0.61
Safety to others	31 (21)	19 (13)	12 (8)	14 (19)	9 (12)	5 (7)	0.12
Alcohol	11 (7)	8 (5)	3 (2)	2 (3)	2 (3)	0 (0)	1.23
Drugs	18 (12)	5 (3)	13 (9)	4 (5)	2 (3)	2 (3)	1.82
Company	83 (55)	37 (25)	46 (31)	45 (60)	18 (24)	27 (36)	0.44
Intimate relationships	25 (17)	10 (7)	15 (10)	12 (16)	3 (4)	9 (6)	0.02
Sexual expression	13 (9)	5 (3)	8 (5)	2 (3)	0 (0)	2 (3)	2.01
Child care	25 (17)	20 (13)	5 (3)	12 (16)	8 (11)	4 (5)	0.02
Basic education	8 (5)	5 (3)	3 (2)	7 (9)	6 (8)	1 (1)	1.28
Telephone	34 (23)	28 (19)	6 (4)	25 (33)	21 (28)	4 (5)	2.94
Transport	26 (17)	13 (9)	13 (9)	24 (32)	14 (19)	10 (13)	6.22[a]
Money	31 (21)	20 (13)	11 (7)	24 (32)	10 (13)	14 (19)	3.47
Welfare benefits	117 (78)	1 (1)	116 (77)	66 (88)	1 (1)	65 (87)	3.29

[a]$P < 0.05$; [b]$P < 0.01$; [f]$P < 0.001$: Comparisons between BD and schizophrenia on total, met and unmet needs and different types of needs. [1]Between A significantly greater proportion of relatives than patients with schizophrenia reported that needs in the area of information about the condition and its treatment were unmet ($\chi^2 = 13.79$; $P < 0.01$). BD: Bipolar disorder.

WHOQOL-BREF psychological-health domain scores - 2%) according to relatives' reports. The same variables explained about 28% to 35% of the variance in unmet needs scores according to patients' or relatives' reports, with 22% to 29% of the variance being explained by the GAF scores alone.

DISCUSSION

There could be two possible reasons for carrying out assessments of health-care needs in any group of patients[4,7,8]. Firstly, the needs elicited serve as a comprehensive index of the psychosocial outcome of the disorder. Secondly, such assessments provide a picture of needs from the perspective of patients and their relatives, indicating areas that could be targeted to improve the outcome of the disorder. The results of this study provide information particularly for remitted patients with BD on these two aspects.

Health-care needs among patients with BD according to patients

The average number of total needs reported by the patients themselves on the CAN-R was about six, which fell within the range of 4 to 10 needs reported by patients with severe mental illnesses on the CAN-R[18,20-22]. Though comparison with other studies was difficult because of differences in patient-samples, methodology and assessment instruments, the mean number of total needs among patients with BD of the present study was quite similar to previous reports of patients with either BD[23-25], or severe mental illnesses including BD[9,18,22,26-28]. Combining the findings of the CAN-R and the scale for additional evaluation of needs suggested that needs were most frequently expressed in three or four broad clusters. The commonest of these were economic and welfare needs including needs for welfare-benefits, free treatment, financial help, travel concessions or disability benefits and help with obtaining jobs.The second group consisted of the need for information about the condition and its treatment, and for psychoeducational programmes for meeting this need. The third group consisted of social needs such as the need for help with household skills and help with psychological distress, the need for company and help with daytime activities, and the need for self-help facilities to cater to these social needs. Finally, physical health needs and the need for treatment of psychotic symptoms were also commonly expressed. The pattern of needs reported by patients of the current study was broadly similar to the ones reported by other studies of BD, which have found that needs are most frequently expressed in social, treatment, informational, and economic or welfare domains[9,23-25].

On the CAN-R a majority of the patients and relatives reported their needs to have been met. Nevertheless, needs in the areas of economic and welfare-benefits, information, company, daytime activities and physical

Table 4 Additional areas of needs: Patients' and relatives' reports[1]

	Bipolar disorder-mean (SD) (n = 150)	Schizophrenia-mean (SD) (n = 75)		t values		
Needs of patients reported by patients						
Total needs	2.39 (1.87)	3.08 (2.08)		2.52[a]		
Met needs	0.23 (0.61)	0.27 (0.64)		0.38		
Unmet needs	2.15 (1.73)	2.81 (1.9)		2.6[a]		
Needs of patients reported by relatives						
Total needs	2.67 (2.26)	3.33 (2.13)		2.13[a]		
Met needs	0.19 (0.49)	0.48 (1.37)		2.29[a]		
Unmet needs	2.47 (2.09)	2.85 (1.82)		1.34		
		Patients			Relatives	
Seven common areas of additional needs-bipolar disorder (n = 150)	Total needs	Met needs	Unmet needs	Total needs	Met needs	Unmet needs
Free treatment	69	4	65	4	65	70
Medical reimbursement	56	3	53	3	53	67
Job reservations/occupational help	42	1	41	1	41	44
Financial help	35	4	31	4	31	44
Psychoeducation	30	10	20	10	20	29
Travel concessions	20	2	18	2	18	24
Patient groups, clubs, societies	17	0	17	0	17	22
Seven common areas of additional needs - schizophrenia (n = 75)						
Medical reimbursement	53	0	53	50	1	49
Free treatment	44	0	44	48	1	47
Job reservations/occupational help	35	1	34	32	4	28
Financial help	28	1	27	30	1	29
Psychoeducation	19	6	13	15	7	8
Travel concessions	12	0	12	15	2	13
Certification needs	11	1	10	11	4	7

[a]P < 0.05: Comparisons between BD and schizophrenia on total, met and unmet needs and different types of needs. [1]This additional evaluation was carried out using an instrument designed to cover those areas of needs not specifically covered by the CAN-R; it had 21 areas with a format similar to the CAN-R; only results pertaining to the seven most common needs are depicted. CAN-R: Camberwell Assessment of Need-Research version; BD: Bipolar disorder.

health-care needs were largely perceived as being unmet, and participants were mostly dissatisfied with the help received from the health-care services. In other areas patients received help from friends and family; therefore, these needs were reported as being met, and patients were satisfied with the help received. The additional evaluation also confirmed that economic, welfare and information needs were the ones most likely to remain unmet. The proportion of met *vs* unmet needs and the types of unmet needs in this study were very similar to several Indian studies, which have assessed health-care needs among patients with severe mental illnesses including schizophrenia and BD[18,22,25,29-31]. The pattern of primacy of economic and welfare needs in Indian studies is also quite unlike the pattern of needs reported in Western studies, where a greater amount of help and benefits are usually received from health-care services; therefore, social needs are more often unmet than economic, welfare or treatment needs[7,24,32-35]. These differences clearly reflect the inadequate support that patients receive from formal health-care services in India, which forces them to turn to their family and friends to fulfil their needs[18,22,26]. They also emphasize the fact that socio-cultural factors such as the pre-eminence of the family in providing care, and the limited reach of the local health-care services probably have a greater bearing on the pattern of needs, particularly unmet ones, than other factors such as the type of psychiatric disorder[20,36,37].

Comparison of health-care needs between patients with BD and schizophrenia

That the type of psychiatric disorder has minimal influence on expressed needs was endorsed by other results of this study, which indicated that there were very few differences between patients with BD or schizophrenia in most aspects of health-care needs assessed. Nevertheless, the total number of needs, the number of met and unmet needs, and needs in the domains of company, financial help, transport and telephones were all significantly higher for schizophrenia. This was a consistent finding on the CAN-R as well as the additional evaluation of needs and across reports of both patients and their relatives. This was probably because patients with schizophrenia had greater levels of residual psychopathology even in their remitted stage than patients with BD. The fact that patients with schizophrenia reported greater needs in the area of psychotic symptoms, and that the severity of positive psychotic symptoms was associated with the extent of total and unmet needs provided further support for the notion that residual positive symptoms contributed to the greater number of needs in schizophrenia[30]. However, apart from these differences, the pattern of

Table 5 Correlates of health-care needs[1,2]

Univariate associations	CAN-R scores as per patients' reports (n = 225)			CAN-R scores as per caregivers' reports (n = 225)		
	Met needs	Unmet needs	Total needs	Met needs	Unmet needs	Total needs
Duration of illness	-0.237					
GAF scores		-0.422			-0.553	-0.443
WHOQOL total scores		-0.294			-0.367	-0.306
WHOQOL general		-0.288			-0.276	-0.306
WHOQOL physical health					-0.300	
WHOQOL psychological		-0.267			-0.287	-0.295
WHOQOL social relationship		-0.287			-0.304	-0.249
WHOQOL environment					-0.337	-0.242
Multiple regression analyses						
	Unmet needs - patients' reports			Unmet needs - relatives' reports		
	R square	Adjusted R square		R square	Adjusted R square	
GAF	0.203	0.199		0.291	0.288	
GAF, PANSS positive	0.270	0.264		0.340	0.334	
GAF, PANSS positive, Psychological Health domain of WHOQOL- BREF	0.293	0.283		0.361	0.353	
				Total needs - relatives' reports		
GAF				0.182	0.178	
GAF, PANSS positive				0.236	0.229	
GAF, PANSS positive, Psychological Health domain of WHOQOL- BREF				0.258	0.248	

[1]Pearson's Product Moment Correlation coefficients or Spearman's Rank Correlation coefficients; [2]Only those significant associations that persisted after adjusting for multiple correlations using Bonferroni correction are depicted. Bonferroni value = 0.05/60 = 0.00083. CAN-R: Camberwell Assessment of Need-Research version; GAF: Global Assessment of Functioning; WHOQOL-BREF: World Health Organization Quality of Life Bref version; PANSS: Positive and Negative Syndrome Scale for Schizophrenia; BD: Bipolar disorder.

needs including the seven or eight areas where needs were commonly expressed, either on the CAN-R or on the additional evaluation were largely similar between the two groups. Other comparisons of health-care needs between schizophrenia and BD have generally reported a similar profile in both disorders[18,25,27,28], though one study found that patients with affective disorders had higher levels of unmet needs in certain areas[9].

Health-care needs: Patients vs relatives

Relatives' reports of needs on the CAN-R, including the most common needs, the overall pattern of needs, the proportion of needs met, and the differences between schizophrenia and BD were mostly similar to that of patients. However, for the BD group the number of total needs and unmet needs was significantly higher according to the relatives. Finally, there some differences between patients' and relatives' reports in individual domains of the CAN-R and the type of unmet needs, with relatives usually placing more emphasis on social and informational needs than the patients themselves. This was in line with most of the previous research on the subject, which has indicated that relatives generally report greater number of needs, and/or their perceptions regarding areas of need differ from those of patients[9,36,38,39]. Differing views of needs among patients and relatives could be a consequence of the additional component of caregiver-burden that relatives have to face, since certain studies have found that a higher level of caregiver-burden is usually associated with higher levels of expressed needs and differences in the types of needs reported by relatives[9,40].

Correlates of health-care needs

The level of patient-functioning emerged as the single most important correlate of health-care needs, particularly unmet needs among both patient groups. This was similar to earlier reports of a positive association between greater number of needs and higher levels of dysfunction[7,18,21,29,33]. Moreover, the associations between needs and functioning, between needs and residual symptoms and between needs and QOL also underlined the fact the extent and pattern of needs was a useful index of the overall psychosocial status of remitted patients with BD or schizophrenia[6,7,33,34,41,42].

Limitations

The findings of this study need to be viewed in the context of its methodological limitations. Principal among these was that it was a hospital-based study of remitted patients from a single centre; this hinders the generalization of its results to other patient populations with differing clinical profiles. Moreover, though the CAN-R has been used among Indian patients it is yet to be properly validated in Indian settings, particularly among patients with BD. The fact that the additional evaluation carried out using a self-designed instrument yielded somewhat different findings suggests that the CAN-R might need some modifications before being used among Indian patients.

Conclusions

These methodological lacunae notwithstanding, several findings of this study may be of relatively novel significance. Firstly, patients with BD even when they were in remission had wide ranging health-care needs, many of which were unmet. Impaired functioning, residual symptoms and QOL emerged as the principal mediators of total and unmet needs. Thus, the presence of unmet health-care needs is an additional marker of the enduring psychosocial impairment characteristic of remitted BD. Accordingly, treatment of BD should place greater emphasis on addressing the unmet needs of patients with BD even after patients achieve remission. Secondly, relatives expressed a somewhat different pattern of needs than patients, which indicates that their input is vital for comprehensive assessment and management of needs in BD. Lastly, despite some differences the overall pattern in which economic and welfare needs superseded treatment and social needs was very similar across BD and schizophrenia. This suggests that socio-cultural and health-service related factors have a relatively greater impact on the pattern of needs than diagnostic categories. Though examination of health-care needs in BD remains a priority area for further research, it is equally important for future studies to incorporate the socio-cultural context while examining health-care needs of remitted BD, since this appears to be the appropriate way to improve the treatment and outcome of BD.

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COMMENTS

Background

Elicitation of health-care needs in any group of patients serves as a comprehensive index of the psychosocial outcome of the disorder. Such assessments also provide a picture of needs from the perspective of patients and their relatives indicating areas that could be targeted to improve the outcome of the disorder. Despite the obvious implications of examining health-care needs of patients, very few studies have chosen to focus exclusively on examining needs among patients with bipolar disorder (BD), particularly during phases of remission. This contrasts with the large amount of literature available on needs of patients with schizophrenia.

Research frontiers

The type of health-care needs is heavily dependent on the socio-cultural setting and the nature and quality of the local health-care services. However, very few studies from developing countries have undertaken comprehensive assessments of health-care needs among patients with mental illnesses. This information is necessary for judicious allocation of resources for treatment of mental illnesses in these countries.

Innovations and breakthroughs

Given the paucity of research in the area, this study attempted to assess health-care needs and their correlates in BD during remission, compared to remitted schizophrenia. The relatively novel findings of this study were: (1) patients with BD even when they were in remission had wide ranging health-care needs, many of which were unmet; (2) impaired functioning, residual symptoms and quality of life (QOL) emerged as the principal mediators of total and unmet needs; (3) relatives reported more needs than patients and a somewhat different pattern of needs than patients; and (4) despite some differences the overall pattern in which economic and welfare needs superseded treatment and social needs was very similar across BD and schizophrenia indicating that socio-cultural and health-service related factors have a relatively greater impact on the pattern of needs than diagnostic categories.

Applications

The implications of these findings for the treatment of BD are that: (1) the presence of unmet health-care needs is an additional marker of the enduring psychosocial impairment characteristic of remitted BD; accordingly, treatment of BD should place greater emphasis on addressing the unmet needs of patients with BD even after patients achieve remission; (2) the input provided by relatives is vital for comprehensive assessment and management of needs in BD; and (3) it is important for future studies to incorporate the socio-cultural context while examining health-care needs in order to improve the treatment and outcome of BD.

Terminology

Health-care needs: The National Health Service and Community Care Act, 1990 defines "need" as the "requirement of the individual to achieve, maintain and restore an acceptable level of social independence and QOL". A health-care need is considered to be present when because of symptoms, distress or disability the subject's level of functioning falls below the optimum, and this is due to some potentially remediable or preventable cause.

Peer-review

The manuscript is relatively well-written and easy to follow.

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ORIGINAL ARTICLE

Randomized Clinical Trial

Influence of different second generation antipsychotics on the QTc interval: A pragmatic study

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Abstract

AIM

To investigate whether differential influence on the QTc interval exists among four second generation antipsychotics (SGAs) in psychosis.

METHODS

Data were drawn from a pragmatic, randomized head-to-head trial of the SGAs risperidone, olanzapine, quetiapine, and ziprasidone in acute admissions patients with psychosis, and with follow-up visits at discharge or maximally 6-9 wk, 3, 6, 12 and 24 mo. Electrocardiograms were recorded on all visits. To mimic clinical shared decision-making, the patients were randomized not to a single drug, but to a sequence

of the SGAs under investigation. The first drug in the sequence defined the randomization group, but the patient and/or clinician could choose an SGA later in the sequence if prior negative experiences with the first one(s) in the sequence had occurred. The study focuses on the time of, and actual use of the SGAs under investigation, that is until treatment discontinuation or change, in order to capture the direct medication effects on the QTc interval. Secondary intention-to-treat (ITT) analyses were also performed.

RESULTS

A total of 173 patients, with even distribution among the treatment groups, underwent ECG assessments. About 70% were males and 43% had never used antipsychotic drugs before the study. The mean antipsychotic doses in milligrams per day with standard deviations (SD) were 3.4 (1.2) for risperidone, 13.9 (4.6) for olanzapine, 325.9 (185.8) for quetiapine, and 97.2 (42.8) for ziprasidone treated groups. The time until discontinuation of the antipsychotic drug used did not differ in a statistically significant way among the groups (Log-Rank test: P = 0.171). The maximum QTc interval recorded during follow-up was 462 ms. Based on linear mixed effects analyses, the QTc interval change per day with standard error was -0.0030 (0.0280) for risperidone; -0.0099 (0.0108) for olanzapine; -0.0027 (0.0170) for quetiapine, and -0.0081 (0.0229) for ziprasidone. There were no statistically significant differences among the groups in this regard. LME analyses based on ITT groups (the randomization groups), revealed almost identical slopes with -0.0063 (0.0160) for risperidone, -0.0130 (0.0126) for olanzapine, -0.0034 (0.0168) for quetiapine, and -0.0045 (0.0225) for ziprasidone.

CONCLUSION

None of the SGAs under investigation led to statistically significant QTc prolongation. No statistically significant differences among the SGAs were found.

Key words: Psychosis; QTc prolongation; Antipsychotics; Clinical trial; Pragmatic design

Core tip: Antipsychotic drugs have a bad reputation of prolonging the QTc interval, and thereby possibly leading to fatal incidents of Torsade de pointes arrhythmias and sudden cardiac death. Differential propensities for QTc prolongation among second generation antipsychotics (SGAs) have been claimed, but lack substantial support from pragmatic studies. None of the SGAs was statistically significantly prolonging the QTc interval in the present pragmatic study, and no statistically significant differences among the drug groups were found for this outcome. Even in a situation with a substantial proportion with QTc prolongation at admittance any of the SGAs under investigation seemed to be safe choices in the present study.

Olsen RE, Kroken RA, Bjørhovde S, Aanesen K, Jørgensen HA, Løberg EM, Johnsen E. Influence of different second generation antipsychotics on the QTc interval: A pragmatic study. *World J Psychiatr* 2016; 6(4): 442-448 Available from: URL: http://www.wjgnet.com/2220-3206/full/v6/i4/442.htm DOI: http://dx.doi.org/10.5498/wjp.v6.i4.442

INTRODUCTION

Sudden cardiac death (SCD) is a rare, but dramatic event in patients with schizophrenia, with a standardized mortality rate of 4.5 compared to in the general population[1]. Antipsychotic drugs have been implicated as conveying a risk for SCD because of their potential for prolonging the heart rate corrected QT (QTc) interval of the electrocardiogram (ECG) which may lead to polymorphic ventricular tachycardia [Torsade de pointes (TdP)], ventricular fibrillation and heart arrest[2,3]. Some agents have even been temporarily or permanently withdrawn from the market[4,5]. Indeed different propensities for inducing QT interval prolongation have been reported for various antipsychotic drugs, with ziprasidone among the worst offenders[2,6]. Several methodological issues have been raised however, with regards to how well differences, derived mainly from phase III randomized controlled trials (RCTs), might translate into usual clinical practice[2,7]. Potential limitations include the numerous exclusion criteria, with a risk of selection bias, and the short durations of most RCTs of antipsychotic efficacy. To combat some of the limitations, the pragmatic trial of effectiveness design has been launched in an attempt to deliver more relevant data for clinical decision makers. Effectiveness studies are characterized by heterogeneous samples and study settings more representative of usual clinical practice[8].

Pragmatic studies investigating the different propensities of QTc prolongation of second generation antipsychotics (SGAs) in real-life settings are rare, but we have previously reported QTc interval findings from a pragmatic RCT of SGAs in acutely admitted patients with psychosis and followed for 24 mo[9]. Only the intention-to-treat (ITT)/overall change of the QTc intervals during the full 24-mo follow-up were analysed in this study, regardless of the many drug changes that occurred during the study. Furthermore, we have recently published cross-sectional data on the proportion with prolonged QTc intervals at admittance and at the end of the acute treatment phase approximately 4 wk later[10]. About a quarter of the sample had borderline prolonged or prolonged QTc intervals at admittance, with a reduction of this proportion at follow-up. The substantial proportion with prolonged QTc intervals could theoretically be at particular risk if the "wrong" antipsychotic drug were initiated, and we want to compare risperidone, olanzapine, quetiapine, and ziprasidone head-to-head in a consecutive sample in the

period from initiation in the acute phase of psychosis, up until discontinuation, in order to determine which drug, if any, could be considered the safest in this regard.

Accordingly, the primary aim was to investigate whether differential influence on the QTc interval existed among the SGAs under investigation. We hypothesized that ziprasidone would increase the QTc interval during follow-up, and that the QTc interval change in those receiving ziprasidone would be different from that in the other drug groups.

MATERIALS AND METHODS

Study design

The Bergen Psychosis Project (BPP) compared the effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone with a 2-year follow-up[9]. The study was approved by the Regional Committee for Medical Research Ethics (RCMRE) and the Norwegian Social Science Data Services, and was sponsored independently of the pharmaceutical industry. The study investigates the first allocated antipsychotic drugs until treatment discontinuation or change to another antipsychotic drug, to isolate the effect of the drugs on the QTc interval.

Patients

The RCMRE allowed eligible patients to be included before informed consent was provided. This enabled a clinically representative sample. Adults acutely admitted for psychosis were consecutively recruited when antipsychotic drugs in the oral formulation were indicated. A symptom threshold for inclusion was set at $\geqslant$ 4 on at least one of the following items of the Positive and Negative Syndrome Scale (PANSS)[11]: Delusions, Hallucinatory behavior, Grandiosity, Suspiciousness/persecution, or Unusual thought content. Diagnostic valuations were conducted by the clinical staff (psychiatrists or specialists in clinical psychology) according to the ICD-10 (http://apps.who.int/classifications/icd10/browse/2010/en). Exclusion criteria were: Antipsychotic drugs in the oral formulation not indicated, manic psychosis because of concerns of reduced cooperativeness with assessments, other behavioral or mental reasons causing inability to cooperate, language barrier towards spoken Norwegian, electroconvulsive therapy indicated, or established clozapine treatment. Drug-induced psychosis was not an exclusion criterium when antipsychotic drug therapy was deemed indicated by the attending clinician.

Treatments

Eligible patients were offered the first SGA in a random order of the investigational agents. The result of the randomization was known both to the clinical staff and the patient. The SGA that was first on the list defined the randomization group. The treating physician and/or the patient could select the next drug in the sequence if the first could not be used. Reasons for unselecting the first drug included contraindications, or negative experiences with previous use of the drug. In theory, contraindications or previous negative experiences could also include QTc-interval pathologies but this was not the case for any of the patients screened for eligibility. The same procedure was repeated if the next drug could not be used. Doses, concomitant use of other medicines, or antipsychotic drug changes were determined by the attending physician or psychiatrist. Combinations of antipsychotic drugs were not allowed except in some sporadic instances.

Importantly, the present study does not focus on the randomization groups but on the actual chosen SGA from the sequence. We have previously reported that there were no statistically significant differences among the randomization groups regarding the percentage choosing a different SGA from the first one on the list[9].

Clinical assessments

Assessments were conducted at baseline, at discharge or at 6-9 wk from baseline if still admitted, and at 3, 6, 12, and 24 mo from baseline. Other than the PANSS interview, the assessments included the Calgary Depression Scale for Schizophrenia[12], the Clinical Drug and Alcohol Use Scales[13], the Clinical Global Impression-Severity of Illness scale[14], and the Global Assessment of Functioning-Split Version, Functions scale[15]. Blood was collected between 8 am and 10 am for analysis of serum levels of the antipsychotic drugs.

Until discharge, or at 6-9 wk at the latest the study procedures were part of the hospital's routine quality project for patients with psychosis, and the procedures were part of the patients' medical record. At this point, the patients were asked for informed consent to be contacted and included in the follow-up project.

At follow-up visits 3, 6, 12, and 24 mo after baseline, measures of psychopathology, blood sampling, and ECG recordings were repeated, and all medications were recorded.

QTc assessments

The QTc interval estimation was done automatically by a Philips Pagewriter Trim II cardiograph at admission and discharge/at 6-9 wk when the patient was still in hospital. At later visits after discharge, a Schiller AT-101 cardiograph was used. Bazett's formula was used for correction. The ECG recording at baseline was done before the first administration of the study SGAs.

Statistical analysis

The baseline data of were analyzed using IBM SPSS software, version 23.0, and by means of exact χ^2 tests (categorical data) and one-way ANOVAs (continuous data). These tests were also applied for baseline comparisons between those lost to follow-up before retesting and those with repeated tests.

Power analyses were run in R (http://www.r-project.org) by means of linear mixed effects (LME) models. The baseline QTc interval and standard deviations were based on the results of the model used in the present

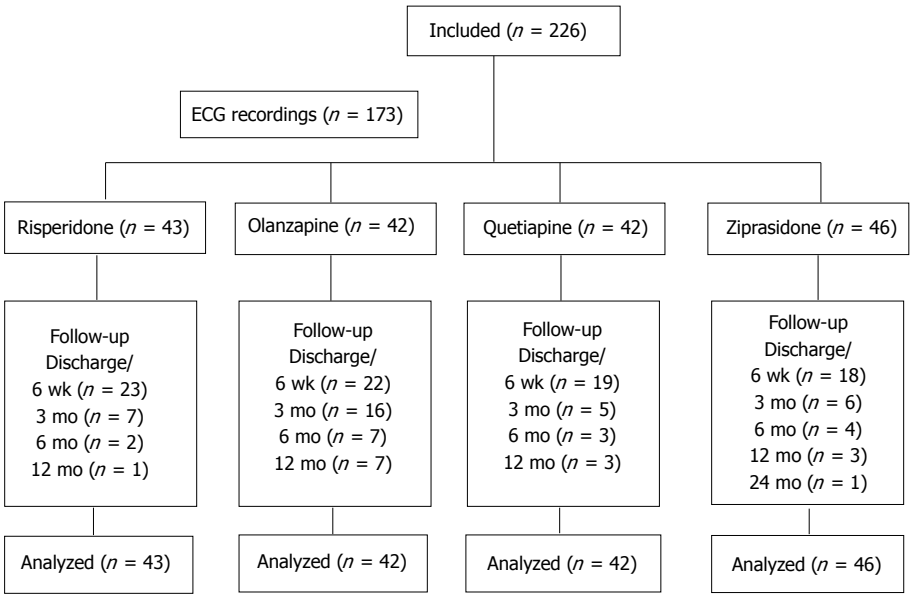

Figure 1 Flow of participants (*n*) through the study. ECG: Electrocardiogram.

study, and slope differences between the groups deemed to be of clinical significance were used in the model. The drop-out rate was set to 3% per month, and 10000 simulations were run. Based on the power analysis the study should have 96% power to detect 2.5% QTc interval differences between the drug groups with 30 subjects in each group.

Changes in the QTc intervals were analysed in R by means of LME models (http://www.r-project.org)[16]. Fixed effects, *i.e.*, systematic differences between the drugs, gave different linear slopes in the four treatment groups, technically a group-by-time interaction with a potential for baseline group differences. The sensitivity analyses based on the ITT groups had no baseline group differences as this was based on the randomization groups. The model calculated overall QTc interval change per day during follow-up that could be visually represented by the slope of a linear curve with time plotted against the QTc interval. The model utilized all available data and handled different numbers of visits by individual patients, as well as differences in time between visits. The LME has demonstrated superior statistical power in studies where missing data cannot be ignored[17], as is the case in the present study. Benjamini-Hochberg adjustments were applied for multiple comparisons. An α-level = 0.05, two-sided, was used as a threshold for statistical significance. The statistical review of the study was performed by a biomedical statistician.

RESULTS

A total of 226 patients were included in the study, and 173 patients underwent ECG assessments. The study enrolment and follow-up is presented in Figure 1.

Information about baseline demographics and clinical descriptives are given in Table 1. There were no statistically significant differences between those with and without ECG assessments, respectively, for any baseline characteristic except for the distribution of alcohol use (exact χ^2 test: P = 0.002), with a larger proportion with alcohol dependency among those without ECG recordings compared to those with ECG recordings (21.2% *vs* 7.0%). There were no statistically significant differences among the SGAs for any of the descriptives except for a higher PANSS positive subscale score in the olanzapine group compared to the risperidone group (one-way ANOVA: P = 0.025; mean difference 2.7 points; 95%CI: 0.2-5.1), and compared to the ziprasidone group (one-way ANOVA: P = 0.045; mean difference 2.5 points; 95%CI: 0.4-4.9). There were no statistically significant differences for any baseline characteristic between those with only a baseline test and those with repeated tests.

The mean antipsychotic doses in milligrams per day with standard deviations (SD) were 3.4 (1.2) for risperidone, 13.9 (4.6) for olanzapine, 325.9 (185.8) for quetiapine, and 97.2 (42.8) for ziprasidone treated groups. The mean serum levels in nanomoles per liter with SD and dose reference ranges were 73.3 (54.6) (30.0-120.0) for risperidone, 108.2 (70.9) (30.0-200.0) for olanzapine, 414.2 (548.2) (100.0-800.0) for quetiapine, and 131.0 (101.0) (30.0-200.0) for ziprasidone. The time until discontinuation of the SGAs did not differ in a statistically significant way among the groups (Log-Rank test: P = 0.171).

There were no statistically significant differences among the groups for the concomitant use of another antipsychotic drug, antidepressant, mood stabilizer, benzodiazepine, or anticholinergic drug at any visit except for a higher proportion of concomitant benzodiazepine use in the quetiapine group at the 12-mo visit (exact χ^2 test: P = 0.026)

The maximum QTc interval recorded at any follow-

Table 1 Baseline demographics and clinical characteristics *n* (%)

Characteristics	Risperidone (*n* = 43)	Olanzapine (*n* = 42)	Quetiapine (*n* = 42)	Ziprasidone (*n* = 46)	All patients (*n* = 173)
Gender					
Male	34 (79.1)	28 (66.7)	29 (69.0)	29 (63.0)	120 (69.4)
Antipsychotic naïve	17 (40.5)	15 (35.7)	21 (50.0)	20 (44.4)	73 (42.7)
Alcohol last 6 mo					
None/no misuse	10 (23.3)	7 (16.7)	7 (16.7)	10 (21.7)	34 19.7)
Dependency	2 (4.7)	4 (9.5)	6 (14.3)	0 (0.0)	12 (6.9)
Drugs last 6 mo					
None	26 (60.5)	31 (73.8)	30 (71.4)	32 (69.6)	119 (68.8)
Misuse	10 (23.3)	6 (14.3)	7 (16.7)	7 (15.2)	30 (17.3)
Diagnosis[1]	*n* (39)	*n* (42)	*n* (41)	*n* (44)	*n* (166)
Schz and rel.	22 (56.4)	25 (59.5)	25 (61.0)	22 (50.0)	94 (56.6)
Acute	4 (10.3)	4 (9.5)	2 (4.9)	4 (9.1)	14 (8.4)
Drug-induced	6 (15.4)	6 (14.3)	5 (12.2)	5 (11.4)	22 (13.3)
Affective	4 10.3)	4 (9.5)	6 (14.6)	5 (11.4)	19 (11.4)
Rest	3 (7.7)	3 (7.1)	3 (7.3)	8 (18.2)	17 (10.2)
Age mean (SD)	34.5 (15.6)	32.3 (11.2)	37.2 (14.8)	32.4 (13.5)	34.1 (13.9)
QTc admittance mean (SD)	422.1 (39.7)	420.9 (33.5)	421.1 (25.1)	420.4 (22.0)	421.1 (30.4)
PANSS total mean (SD)	73.4 (14.0)	76.0 (14.3)	73.6 (14.0)	70.8 (12.4)	73.4 (13.7)
PANSS positive mean (SD)	18.6 (4.9)	21.3 (4.6)	20.0 (3.6)	18.8 (3.9)	19.7 (7.5)
PANSS negative mean (SD)	20.8 (8.1)	18.3 (7.3)	19.2 (7.1)	18.4 (7.4)	19.2 (7.5)
PANSS general mean (SD)	34.0 (6.5)	36.4 (6.6)	34.4 (7.6)	33.6 (6.3)	34.6 (6.8)
CDSS mean (SD)	6.8 (4.9)	6.3 (4.9)	6.4 (4.9)	7.8 (6.4)	6.9 (5.3)
GAF-F mean (SD)	30.8 (5.9)	30.1 (6.0)	30.6 (7.2)	32.2 (5.0)	30.9 (6.0)
CGI mean (SD)	5.2 (0.6)	5.3 (0.7)	5.1 (0.7)	5.0 (0.6)	5.2 (0.6)

[1]Patients with missing diagnoses are not included in the list. *n*: Number of patients with ECG at baseline and or ECG at discharge; SD: Standard deviation; Antipsychotic naïve: No life-time exposure to antipsychotic drugs before index admission; First admission: Index admission was the first admission to a mental hospital; Misuse: Misuse or Dependence according to Drake *et al*[13]; Schz and rel.: Schizophrenia and related disorders: Schizophrenia, schizo-affective disorder, acute polymorphic psychotic disorder with symptoms of schizophrenia, acute schizophrenia-like psychotic disorder, delusional disorder; Acute: Acute psychosis other than those categorized under Schz and rel.; Affective: Affective psychosis; Rest: Miscellaneous psychotic disorders; All diagnoses are according to ICD-10; PANSS: The Positive and Negative Syndrome Scale; CDSS: The Calgary Depression Scale for Schizophrenia; GAF-F: The Global Assessment of Functioning, split version, Functions scale; CGI: The Clinical Global Impression, severity of illness scale.

up visit was 462 milliseconds (ms). None of the drug groups had statistically significant changes of the QTc interval (LME: $P \geqslant 0.36$ for all). The QTc interval change per day with standard error was -0.0030 (0.0280) for risperidone; -0.0099 (0.0108) for olanzapine; -0.0027 (0.0170) for quetiapine, and -0.0081 (0.0229) for ziprasidone (Figure 2).

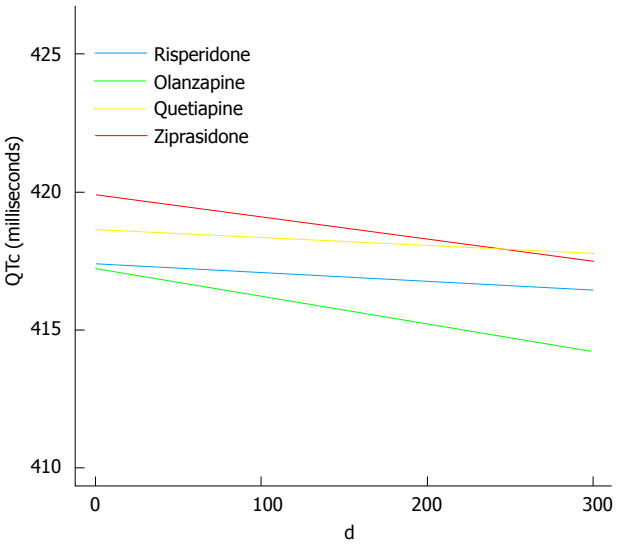

Figure 2 Change of QTc intervals. The curves were generated based on the drug-specific linear mixed effects slopes for risperidone, olanzapine, quetiapine, and ziprasidone, respectively. The curves are confined to the first 300 d because the bulk of data was obtained before this point in time.

There were no statistically significant differences among the groups for change of the QTc interval (LME: $P \geqslant 0.72$ for all). As a sensitivity analysis, we also performed LME analyses based on the ITT groups (the randomization groups), revealing almost identical slopes with -0.0063 (0.0160) for risperidone, -0.0130 (0.0126) for olanzapine, -0.0034 (0.0168) for quetiapine, and -0.0045 (0.0225) for ziprasidone.

Serum potassium, sodium, and calcium were measured at baseline and at first follow-up. There were no statistically significant differences among the drug groups for any of these electrolytes. Serum prolactin was measured at all points of follow-up. The prolactin level was higher in the risperidone group compared to the quetiapine group at baseline (one way ANOVA: $P = 0.015$; mean difference 350.3; 95%CI of the mean 46.7-654.0), and significantly higher in the risperidone group compared to all the other groups at first follow-up (one way ANOVA: $P = 0.004$). These differences did not persist at later visits.

DISCUSSION

SGAs are among the groups of drugs that have a bad reputation for prolonging the QTc interval, and thereby possibly leading to fatal incidents of TdP and SCD. This issue has received a lot of attention in previous studies, and differential propensities for QTc interval prolongation have been found among antipsychotic drugs[2]. The implications for usual clinical practice are unresolved, however, as the experimental designs of the majority of the studies may limit the generalizability of their findings[8]. The present study was conducted as close to clinical practice as possible by virtue of its pragmatic design. It aimed to investigate whether or not four first-line SGAs used in the acute treatment of psychosis

increased the QTc interval - and if so - is there a basis for a ranking between these drugs, regarding the risk of such a prolongation?

The main results of the study were that none of the SGAs prolonged the QTc intervals in a statistically significant way, and that no statistically significant QTC interval differences among the SGAs were found. These findings do not support some of the previous literature, including the comprehensive meta-analysis of 15 different antipsychotics by Leucht and collaborators[6], where ziprasidone was among the top three antipsychotics with regards to QTc prolongation. A recent review also finds that ziprasidone prolongs the QTc interval, but with heterogeneous results in different studies[18]. Theoretically, short term treatment with antipsychotics may not give sufficient plasma levels to influence the heart cells but we find this unlikely as both mean doses and serum levels for the SGAs under investigation were in the therapeutic range. However, pharmacokinetic estimations are beyond the scope of the present study. Indeed, we have previously demonstrated that the distinct side-effect profiles derived from phase Ⅲ RCTs are dampened in pragmatic studies[19].

Moving beyond the mean scores one might suspect the existence of a subgroup of patients with pathologically prolonged QTc intervals, but not numerous enough to alter the mean scores substantially. All the more there is reason to believe this group could be clinically very important. During follow-up, however, none of the participants had critically prolonged QTc intervals as the maximum QTc interval recorded was 462 ms. In a previous study we reported that approximately 25% of the patients had prolonged QTc intervals, or borderline prolongations, at the time of admittance to hospital[10]. Most likely, this prolongation was due to other causes than the use of SGAs including agitation, because many of the patients had never used antipsychotic drugs before, or those who had used SGAs had, in many instances, discontinued their antipsychotics some time before hospital admission. Taken together, the present study seems to indicate that, even in a situation with a substantial proportion of patients with QTc prolongation at admittance, any of the SGAs under investigation are safe choices.

Some limitations to the study need consideration. For one, attrition was substantial during follow-up. Two hundred and twenty-six patients participated in the study, but only 173 patients underwent ECG assessments because of feasibility issues in the acute phase. There were no statistically significant differences in baseline characteristics between those with and without ECG assessments except a small difference in alcohol consumption patterns. Therefore, selection bias seems unlikely. Furthermore, no baseline characteristics showed statistically significant differences between those with only baseline tests and those with repeated tests. Finally we chose LME statistics for the longitudinal data analyses to handle drop-outs and missing data.

Even though the BPP was a randomized study, the randomization was not to a single SGA but to a sequence of all of the four SGAs under investigation to mimic the clinical process of choosing a drug for a patient as closely as possible. The first drug in the sequence defined the randomization group, but about 20% chose a different SGA than the one first on the list in the sequence, although this proportion did not differ in a statistically significant way among the groups, as accounted for in a previous publication[9]. In the present study, we focused not on the randomization groups, but on the drugs actually used as we wanted to investigate the direct drug effects on the ECG. However, this also violates the effects of randomization and could introduce bias. However, the 173 patients divided themselves by chance into fairly even large groups for the four SGAs, and the only statistically significant baseline difference among the drug groups was a higher PANSS positive subscale score in the olanzapine group. Also no statistically significant differences in times to discontinuation were found. Finally, the sensitivity analyses based on ITT groups gave almost identical results. Significant bias therefore seems unlikely.

ECG assessments were carried out using two automatic measuring devices which both used Bazett's formula for heart rate correction of the QT intervals. As this formula has a tendency to overcorrect QT intervals at higher heart rates, Frederica's formula is now the preferred one. Both the stress associated with acute admissions as well as psychotropic medications themselves could increase the heart rate in patients with mental illness. Nielsen and collaborators[2] described incident differences in measurements by 12 ms when the heartrate was > 70/min (Bazett's 475 ms *vs* Frederica's 463 ms), and increases to 24 ms (508 *vs* 484) when the heartrate was > 80/min. Accordingly, the use of Bazett's formula in our study may have led to higher QTc measures compared to if Frederica's formula had been used. Ideally, all the recordings should have been carried out with the same equipment, but for practical reasons this was not possible. We have no reason to suspect that this should introduce bias, and believe the use of the same correction formula is the most important factor for comparable recordings.

The use of concomitant medication was equally distributed among the groups. However, it cannot be ruled out with certainty that the effects of other drugs may have influenced the slopes of the QTc recordings. The direction of any such influence would be hard to predict. There were more men than women in the study, which may have led to somewhat lower mean QTc total intervals as women have longer QTc intervals than men. This should not have introduced bias to the group comparisons as gender was evenly distributed among the drug groups. The risperidone group had higher serum prolactin levels at baseline and the first follow-up, but not thereafter. Any influence on the QTc interval from the prolactin level could only be speculative.

Despite the above mentioned limitations we conclude that our findings do not support that any of the

SGAs under investigation leads to QTc prolongation. No statistically significant differences among the SGAs were found, and all the drugs on which the study is based may be considered to be safe alternatives in this regard.

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COMMENTS

Background

The ability of antipsychotic drugs to prolong the QT interval of the electrocardiogram (ECG) has been associated with increased risk of sudden cardiac death in patients using these drugs.

Research frontiers

Although differential propensities among various antipsychotics for QT prolongation have been found, the generalizability to, and hence the clinical relevance of these findings in, the population have been questioned.

Innovations and breakthroughs

The majority of clinical antipsychotic drug trials typically include highly selected patient samples where concomitant illicit drug use, other mental or physical comorbidities, or the need for other psychotropics are exclusion criteria. Furthermore, the follow-up is often of short duration. The main advantages of the present study include the consecutive recruitment of acutely admitted patients with psychosis; the diagnostically and symptomatically heterogeneous sample, and the long follow-up. These factors should make the results more applicable for pharmacological decision making in clinical departments.

Applications

Based on the present study, all the second-generation antipsychotics under investigation seem to be safe choices in acutely admitted patients with psychosis.

Terminology

The QT interval: The ECG measure of the duration of ventricular de- and repolarization of the heart.

Peer-review

In this paper, the authors investigated investigate whether differential influence on the QTc interval exists among four second generation antipsychotics (SGAs) in 173 patients. They concluded that none of the SGAs under investigation led to QTc prolongation and no differences among the SGAs were found. This study is straightforward and generally well described.

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SYSTEMATIC REVIEWS

Cognitive-behavioural therapy for obsessive-compulsive disorder co-occurring with psychosis: Systematic review of evidence

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Abstract

AIM

To review available evidence on the use of cognitive behavioural therapy (CBT) for treating obsessive compulsive disorder co-occurring with psychosis.

METHODS

In this paper we present a detailed and comprehensive review of the current literature focusing on CBT treatment of obsessive compulsive disorder (OCD) co-occurring with schizophrenia or schizoaffective disorder. We identified relevant literature published between 2001 and May 2016 through MEDLINE/PubMed search using as search string ("obsessive compulsive disorders" or "obsessive compulsive symptoms") and ("schizophrenia" or "schizoaffective disorder" or "psychosis") and ("cognitive behavioural therapy"). Other citations of interest were further identified from references reported in the accessed articles. The search was limited to studies written in English and carried out in adult patients. A total of 9 studies, 8 case reports and 1 case series, were found.

RESULTS

The reviewed evidence indicates that CBT is: (1) safe, *i.e.*, does not worsen psychotic symptoms; (2) well accepted, with a discontinuation rate quite similar to that reported for patients with OCD without psychosis comorbidity; (3) effective, with a symptom reduction quite similar to that reported for patients with OCD without psychosis and for SRIs treatment of OCD co-occurring with psychosis; and (4) effective in patients with OCD induced by second-generation antipsychotic as well as in patients with OCD not induced by second-generation antipsychotic. Alcohol/substance use disorder comorbidity and OCD onset preceding that of SCH/SA was predictors of poor outcome. These results are derived only by additional studies with adequate sample size.

CONCLUSION
Our results support the use of CBT for OCD in patients with psychosis.

Key words: Obsessive compulsive disorder; Obsessive compulsive symptoms; Schizophrenia; Schizoaffective disorder; Cognitive behavioural therapy; Second-generation antipsychotic; Clozapine

Core tip: Ten percent of patients with schizophrenia fulfill criteria for obsessive compulsive disorder (OCD) and in 1/3 of cases OCD onset is related to second-generation antipsychotic (SGA) treatment. Reviewed evidence indicates that cognitive-behavioral therapy for OCD in patients with psychosis is: (1) safe (does not worsen psychotic symptoms); (2) well accepted (discontinuation rate similar to that reported for patients with OCD without psychosis); (3) effective (symptom reduction similar to that reported for patients with OCD without psychosis); and (4) effective in patients with OCD induced by SGA as well as in patients with OCD not induced by SGA. These conclusions are preliminary.

Tundo A, Necci R. Cognitive-behavioural therapy for obsessive-compulsive disorder co-occurring with psychosis: Systematic review of evidence. *World J Psychiatr* 2016; 6(4): 449-455 Available from: URL: http://www.wjgnet.com/2220-3206/full/v6/i4/449.htm DOI: http://dx.doi.org/10.5498/wjp.v6.i4.449

INTRODUCTION

The association of schizophrenia (SCH) or schizoaffective disorder (SA) with obsessive compulsive disorder (OCD) or symptoms (OCS) is quite common. In a meta-analysis of 36 studies, including a total of 3.308 patients with SCH, the pooled prevalence rate reported for OCD was 12% and for OCS of 30%[1]. This prevalence rate is higher than that of OCD in general population (2%-3%)[2] and of SCH in patients with primary OCD (1.7%)[3]. Up to 20% of patients with OCS/OCD co-occurring with psychosis report the onset or aggravation of obsessive compulsive symptoms after beginning treatment with a second-generation antipsychotic (SGA), mainly with serotonergic antagonist antipsychotics as clozapine and, at less extend, with olanzapine[4-9]. Some authors suggested that in these cases OCS might be considered an adverse event of SGA and introduced the term "antipsychotic-induced OCS" or "secondary OCS" (s-OCS)[5,10]. Nevertheless, because sometimes OCS occur or worsen also under no treatment or treatment with first-generation antipsychotics which are not primarily 5HT2-R-antagonistic[11], an interaction between genetic/biological predispositions, psychosocial factors and treatments could better explain the phenomenon[12].

The presence of OCS in patients with schizophrenia is associated with depressive symptoms, high suicide risk, cognitive impairment, poor social functioning, poor perceived quality of life, and poor prognosis[13-18]. The relationship between OCS and positive and negative symptoms is unclear[19]. Although etiological hypotheses have been put forward to explain the high OCS/OCD co-occurrence in patients with schizophrenia, the causes of this comorbidity remain unclear. As reported by Schirmbeck *et al*[20]: (1) epidemiological data do not confirm the hypothesis of a random association between the two syndromes; (2) clinical data do not confirm the hypothesis that OCS/OCD protects against psychotic disintegration[21,22]; and (3) to date, results of neurobiological studies attempting to validate the hypothesis of a separate subtype of psychosis, a so-called "schizo-obsessive disorder"[23,24] comprising typical positive, negative and cognitive symptoms of SCH and OCS are inconsistent.

Despite the increasing awareness that OCS/OCD co-occurring with SCH-SA are common and disabling, research on treatment strategies for these complex and treatment-resistant patients is scanty. The American Psychiatric Association practice guidelines[25] suggest to stabilize first psychotics symptoms using an antipsychotic drug and subsequently to treat OCS by the augmentation with a serotonin reuptake inhibitor (SRI), *e.g.,* citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, and clomipramine. Evidence on the efficacy and safety of this augmentation strategy is limited and controversial, and is based to our knowledge on 16 studies (132 patients), most of which are single or multiple case reports. Several studies demonstrated the beneficial effect of antipsychotic-SRI combination, while some studies showed poor response, a risk of psychosis worsening and sometimes aggressiveness (for a review see[26]). Furthermore, the antipsychotic-SRI combination produces some clinically significant pharmacokinetic drug interactions: (1) some SRIs (such as fluvoxamine, fluoxetine, paroxetine and venlafaxine) may increase the plasma concentration of particular antipsychotics (such as clozapine, olanzapine, risperidone) by inhibition of hepatic cytochrome P450 isoenzymes (*e.g.,* 1A2, 2D6) and consequently may increase the risk of adverse events; and (2) the anticholinergic properties of clomipramine limit its use in elderly patients and in those treated with low-potency typical antipsychotics or anticholinergic agents. Some authors suggested to treat OCS co-occurring with psychosis by augmenting antipsychotics with a mood stabilizer, but evidence supporting this strategy is limited to 11 patients treated with lamotrigine[27]. As regards s-OCS, several options were proposed: Waiting for spontaneous resolution, gradually reducing the antipsychotic dosage, switching to another antipsychotic, combining an antiserotoninergic SGA with either a dopaminergic SGA (amisulpiride or aripiprazole) or a mood stabilizer, and augmenting SGA with a SRI[25,26]. So far, very limited evidence supports each of these options, that are generally grounded on theoretical

considerations and/or on the findings of single case reports or case series. Furthermore, the use of SRIs in patients with psychosis is not always safe, as previously discussed, and the dose reduction of clozapine or the switch from clozapine to another SGA could induce an exacerbation of psychotic symptoms.

Hence, an alternative to pharmacological approaches to primary and secondary OCS/OCD co-occurring with SCH/SA is needed.

Of the other existing treatment options for non-comorbid OCD, cognitive-behavioral therapy incorporating exposure and ritual prevention (CBT) is the psychological therapy most supported by research evidence[25].

The aim of this study is to review available evidence on the use of CBT with or without ritual prevention for treating OCD co-occurring with SCH/SA.

MATERIALS AND METHODS

In this paper we present a detailed and comprehensive review of the current literature focusing on CBT treatment of OCD co-occurring with SCH/SA. We identified relevant literature published between 2001 and May 2016 through MEDLINE/PubMed search using as search string ("obsessive compulsive disorders" or "obsessive compulsive symptoms") and ("schizophrenia" or "schizoaffective disorder" or "psychosis") and ("cognitive behavioural therapy"). The title and the abstract of the retrieved articles were reviewed by the two authors independently and non-pertinent papers were excluded. Of 182 papers screened, only papers including original articles which directly addressed CBT treatment for OCD co-occurring with psychosis were retained for review and inclusion in this study. Other citations of interest were further identified from references reported in the accessed articles. The search was limited to studies written in English and carried out in adult patients. A total of 9 studies, 8 case reports and 1 case series, including overall 31 patients, were found.

RESULTS

Effectiveness of CBT for OCD comorbid with psychosis

No randomized, controlled trials investigated the efficacy of CBT for OCD in patients with psychosis. However, several important suggestions can be derived from the identified case reports and case series. Table 1 shows the demographic and clinical characteristics and the response to CBT of the 10 patients included in the 8 case reports; characteristics and treatment response of the 21 patients included in the case series are reported separately[28-35]. Briefly, 8 patients were male, the mean age was 28 years (range 19-50), and the mean duration of OCD before starting CBT was 7 years (range 1-15). In 1 patient CBT did not include ERP strategies, and in 6 patients psychological treatment was supplemented with pharmacological treatment (SSRIs). One patient, despite an initial reduction of OCS after starting CBT, dropped out. Of the other 9 patients, 5 showed a full remission and 4 a clinical relevant decrease of OCS severity. Some studies reported follow-up assessments, lasting from 6 mo to 3 years, suggesting a long-term stabilization of the improvement. Although case reports suggest a potential benefit of CBT for OCD co-occurring in psychosis, caution is needed in interpreting these results because of the small number of cases and the heterogeneity of the treatment as regards CBT duration (from "few" to 45 h) and concomitant use of SSRIs.

More homogeneous and clinically useful information can be derived from the case series reported by Tundo *et al*[36] in a naturalistic study including 21 consecutive patients (age 18-65 years) meeting DSM-IV[37] criteria for OCD of at least moderate severity [Yale-Brown Obsessive Compulsive Scale[38,39] (Y-BOCS) total score $\geqslant$ 16] and either for SCH or SA of up to moderate psychotic severity (Positive and Negative Symptoms[40] total score < 95). Treatment included antipsychotics, in association with mood stabilizers in SA patients (50% of cases), for SCH or SA and CBT for OCD. Patients were treated in a tertiary care setting, in which treatment guidelines were personalized taking into account each patient's insight into illness, treatment adherence, Axis I comorbidity and alcohol/substance use disorder. ERP strategies were supplemented with cognitive techniques and other ad hoc interventions, when necessary. Psychotherapy was scheduled flexibly: The mean number of CBT sessions was 34 (range 23-41) in patients with SA and 31 (range 8-40) in patients with SCH. During the study, 5 patients with SCH discontinued the therapy: One refused it after the first session, 1 was hospitalized because of the worsening of psychosis and 3 said that CBT was ineffective. Patients who dropped out from the study had their last observation carried forward for statistical analysis, thus 21 patients were analyzed.

The results showed a significant OCS reduction over 12 mo (Y-BOCS total score 30.8 ± 6.7 at baseline, 22.3 ± 8.3 after 12 mo of treatment), as well as improvements in severity of illness, as measured by Clinical Global Impression-Severity[41] (CGI-S) (5.5 ± 1.6 at baseline, 4.5 ± 1.0 after 12 mo of treatment), and functional improvement, as measured by the Global Assessment of Functioning[42] (GAF) (49.2 ± 10.1 at baseline, 55.9 ± 12.3 after 12 mo of treatment). At the end of the trial, 52% patients were rated as much or very much improved, 33% as responders and 19% as remitters. The 1-year change from baseline in the YBOCS score was 8.1 (95%CI: 5.4-10.8), only slightly lower than that observed in pre-to-post treatment comparisons of ERP (mean 11.4; range 10.5-12.2), and CBT studies (mean 10.6; range 8.5-12.8) in primary OCD[43]. Furthermore, insight into illness significantly increased.

Effectiveness of CBT for OCD induced by SGA

MacCabe *et al*[28] first described the case of a men with OCS emerging one year after starting clozapine and responding to 4 mo of CBT (Y-BOCS total score decreased from 12 to 4). The result was maintained at

Table 1 Case reports of cognitive-behavioural therapy for obsessive-compulsive disorder co-occurring with psychosis

Ref.	Demographic characteristics	OCD duration	Treatments	CBT duration	OCD response	Follow up
Ganesan *et al*[30]	Male, 33 yr	12 yr	CBT/ERP + SSRI	NA	Remitted	8 wk
	Male, 31 yr	11 yr	CBT/ERP + SSRI	NA	Improved	8 wk
	Female, 25 yr	1 yr	CBT/ERP + SSRI	NA	Improved	8 wk
MacCabe *et al*[28]	Male, 50 yr	5 yr	CBT/ERP	4 mo	Remitted	11 mo
Ekers *et al*[31]	Male, 31 yr	15 yr	CBT/ERP	20 h	Remitted	6 mo
Peasley-Miklus *et al*[29]	Male, 22 yr	12 yr	CBT/ERP	6 mo	Responded	36 mo
Rufer *et al*[32]	Female	NA	CBT/ ERP + SSRI	45 h	Improved	15 mo
Kobori *et al*[33]	Male, 26 yr	6 yr	CBT + SSRI	19 h	Remitted	24 mo
Rodriguez *et al*[34]	Male, 19 yr	< 2 yr	CBT/ERP + SSRI	Few hours	Dropped out	
Hagen *et al*[35]	Male, > 20 yr	several years	CBT/ERP	9 h	Remitted	6 mo

OCD: Obsessive compulsive disorder; CBT: Cognitive behavioural therapy; ERP: Exposure and responser prevention; SSRI: Selective serotoninergic reuptake inhibitor; NA: Not available.

follow-up, 11 mo later.

Recently, Tundo *et al*[44] reanalyzed their case series to compare the adherence to and the effectiveness of CBT in patients with SCH/SA and comorbid primary OCD (p-OCD) to those with secondary OCD (s-OCD). As suggested by Schirmbeck *et al*[45], they used the order of three events (first psychotic manifestation, start of SGA treatment and subsequent onset of OCD) to define s-OCD. The authors reported an OCD induction in 7 out 21 patients, related to olanzapine in 4 patients and to clozapine in 3 patients. Neither of these drugs nor their dosages were changed during the study.

During the trial the improvement of OCS did not differ significantly between s-OCD and p-OCD (Y-BOCS total score at baseline 28.0 ± 2.3 and 32.1 ± 1.6, respectively; after 12 mo of treatment 24.0 ± 2.1 and 24.5 ± 1.5, respectively), while global functioning, as measured by GAF, improved more rapidly in patients with p-OCD. At 12 mo drop-out rates (s-OCD 14.3% *vs* p-OCD 28.6%) were lower and improvement (s-OCD 57.1% *vs* p-OCD 50%), response (s-OCD 42.9% *vs* p-OCD 28.6%) and remission (s-OCD 42.9% *vs* p-OCD 7.1%) rates proved to be higher in patients with s-OCD, although not significantly. The findings indicate that the adherence to CBT in patients with psychosis and s-OCD did not differ from that of patients with psychosis and p-OCD and the drop-out rate is similar to that reported in the literature for CBT in patients with OCD without psychosis comorbidity[44]. Improvement, response and remission rates in s-OCD group did not differ from those of p-OCD group and are quite similar to those reported in the literature for pharmacological treatment of OCD comorbid with schizophrenia[44].

Predictors of response

Tundo *et al*[46] identified two outcome predictors of CBT effectiveness on co-occurring OCS: The alcohol/substance use disorder comorbidity and the temporal onset of OCD compared to that of SCH/SA.

Patients with alcohol/substance use disorder were significantly less likely to improve than those without this comorbidity (0% *vs* 68%, respectively; $P = 0.012$). The rate of improvement was lower in patients in which OCD onset preceded that of SCH/SA than in patients in which OCD onset occurred after that of SCH/SA or in patients in which the onset of the two disorders was simultaneous (0%, 50%, and 83.3%, respectively; $P = 0.067$).

CBT tolerability

One reason why CBT as treatment for OCS co-occurring with schizophrenia has been scarcely investigated can be related to safety and tolerability concerns[47]. In this regard, a focus group evaluating clinician's perceptions on CBT use among patients with severe mental illness reported the fear that intervention-related arousal would result in severe exacerbation of psychotic symptoms[48].

However, the results of the studies included in this review do not support these concerns and, on the contrary, suggest that CBT not only significantly decreases OCS severity, but also ensures a stable remission of psychosis or even the improvement of psychotic symptoms.

In fact, psychotic exacerbation was reported in 2 of 31 patients reviewed. In one case the patient showed reluctance to commit to ERP so the therapist focused on different cognitive techniques[29]. In the other case CBT was discontinued because of psychotic exacerbation and subsequent hospitalization after more than 6 mo of psychotherapy[36]. The authors argued that the worsening of psychotic symptoms was related to the natural course of schizophrenia and not to the symptom intensification triggered by the involvement in ERP.

Therefore, available results, although limited by the small sample size and the lack of controlled clinical trials, provide encouraging evidence about safety and tolerability of CBT in patients with OCS/OCD co-occurring with psychosis.

DISCUSSION

In patients with schizophrenia or schizoaffective disorder the co-occurrence of OCD or OCS is quite common (12% and 30%, respectively) and it is associated with

high impairment (great burden of disease, anxiety and depressive symptoms, suicide risk, cognitive impairment, poor social and vocational functioning, and poor prognosis). In about 1 in 4 cases the onset or aggravation of OCS took place after the beginning of SGA treatment. In clinical practice the more frequent treatment of p-OCD and s-OCD is pharmacotherapy, mainly the association of antipsychotic and SRI, while data on the efficacy and the safety of pharmacotherapy are limited and controversial.

The results of the present review support the use of CBT for treating OCS/OCD in patients with SCH/SA. The available data show that this psychological treatment is: (1) safe, *i.e.,* it does not worsen psychotic symptoms; (2) well accepted, with a drop-out rate quite similar to that reported for patients with OCD without psychosis comorbidity; (3) effective, with a symptoms reduction quite similar to that reported for patients with OCD without psychosis and for SRIs treatment of OCD co-occurring with psychosis; and (4) effective in patients with s-OCD as well as in patients with p-OCD. Only subjects with lifetime alcohol/substance use disorder pose a challenge.

Our findings should be interpreted taking into account the limitations of studies included in this review: (1) they are all case-reports; (2) they include a small number of patients; (3) their methodological quality is low; and (4) they do not include a control group or control treatments and, as a consequence, it is not possible to attribute the observed effects to CBT, to the natural course of illness or to non-specific therapeutic factors. So, randomized clinical trials and observational studies with larger samples are required to confirm the safety, the tolerability and the efficacy/effectiveness of CBT for OCS/OCD in patients with psychosis. Despite these limitations, however, the available evidence provides useful information for clinicians planning OCS treatment in patients with SCH/SA and suggests that in these patients CBT might be a viable alternative to pharmacological treatment with SRI. So, in our opinion psychiatrists should not only rely on pharmacotherapy, the most common treatment in clinical practice (for a review see[49]), but also on CBT, to select the appropriate treatment for each patient according to their clinical judgment. According to our experience, pharmachotherapy should be used in patients who either refused or did not respond to CBT and, *vice versa,* CBT should be tried in patients who did not respond to medication or are at higher risk of psychotic exacerbation. In high resistant patients further potential options could be some somatic treatments (*e.g.,* electroconvulsive therapy, repetitive transcranial magnetic stimulation, deep brain stimulation)[50-52] and psychological treatments alternative to CBT (*e.g.,* psychodynamic therapy)[53]. Further clinical trials are warranted to accrue evidence on the efficacy of CBT as well as pharmacological treatment and their combination and to provide useful information to define specific guidelines for the treatment of OCS/OCD in schizophrenia.

COMMENTS

Background

More than 10% of patients with schizophrenia (SCH) have comorbid obsessive compulsive disorder (OCD) and in about 20% of cases the onset or worsening of obsessive compulsive symptoms (OCS) is related to treatment with second-generation antipsychotic (SGA), typically serotonergic antagonist antipsychotics as clozapine and olanzapine. The OCS-psychosis comorbidity is associated with high suicide risk, cognitive impairment, poor social functioning and quality of life, and poor prognosis. Management of this condition is a hard challenge for physicians and the evidence on the efficacy and safety of antipsychotic-SRI combination, the most frequent treatment in clinical practice, is limited and controversial.

Research frontiers

An alternative to pharmacological approach to OCS/OCD co-occurring with psychosis could be cognitive-behavioral therapy incorporating exposure and ritual prevention (CBT), the currently available psychological treatment for non-comorbid OCD most supported by research evidence.

Innovation and breakthroughs

The present article aims to review available evidence on the use of CBT for treating OCD co-occurring with SCH.

Applications

The review suggests that CBT for OCD co-occurring with psychosis is: (1) safe, *i.e.,* does not worsen psychotic symptoms; (2) well accepted, with a discontinuation rate quite similar to that reported for patients with OCD without psychosis comorbidity; (3) effective, with a symptom reduction quite similar to that reported for patients with OCD without psychosis and for SRIs treatment of OCD co-occurring with psychosis; and (4) effective in patients with OCD induced by SGA as well as in patients with OCD not induced by SGA.

Terminology

The study does not include terms that may not be familiar to the majority of the readers.

Peer-review

This is a comprehensive review of the literature.

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