Efficacy of mirtazapine as adjunct therapy to antipsychotics in the treatment of chronic schizophrenia

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Aim: The aim of this article was to review the literature and evaluate the evidence that is available on the effectiveness of mirtazapine as adjunct therapy to antipsychotics for chronic schizophrenia. **Case Study:** SC, a 44 year old male with a previous psychiatric history of chronic paranoid schizophrenia, voluntarily presented to an acute mental health service with insomnia, delusional ideations, and negative symptoms. He was subsequently diagnosed with relapse of his schizophrenia and prescribed olanzapine. He responded poorly and slowly, which then prompted the addition of mirtazapine as an augmenting agent to the regimen. His insomnia resolved shortly after and significant improvement of his negative symptoms was observed. **Methods:** A literature search was conducted using the ScienceDirect and Pubmed databases. The search terms mirtazapine AND chronic schizophrenia; mirtazapine AND antipsychotics AND chronic schizophrenia AND efficacy were used. **Results:** Four randomised controlled trials and one open-label trial were identified. Two of the randomised trials demonstrated substantial reduction in the total scores of the Positive and Negative Syndrome Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS) when mirtazapine was combined with the antipsychotics, risperidone and clozapine, respectively. The remaining studies showed that mirtazapine in combination with risperidone yields greater improvement in neurocognition. There were no studies identified that directly investigated the efficacy of a combined olanzapine and mirtazapine treatment strategy. **Conclusion:** Current level II evidence suggests that mirtazapine may be beneficial as an adjunct agent in patients with chronic schizophrenia. However, this evidence is limited to a select number of primary therapies and the mechanism and long term effects are currently unclear.

Case Report

SC, a 44-year-old Caucasian male with a background of chronic paranoid schizophrenia, was brought in by his sister to an Acute Mental Health Service with a 12 month history of insomnia which he believed was a consequence of the depot (Risperidone Consta) he was given a year ago. He averaged two to three hours of sleep most nights and had delusional beliefs about needing two to three blood transfusions to remove the "chemicals from the depot" from his blood stream. He also appeared to have somatic delusions as he believed that the contents of the depot were slowly being leached out through his sweat and feet as "aqua ammonia".

SC had previously worked as a banana farmer, but was currently unemployed and lived alone. Collateral history from his sister further revealed that SC was socially withdrawn from his family and friends, lacked motivation to resume his job as a banana farmer or any other employment and failed to look after his personal hygiene. He had no other significant past medical history. His only treatment for schizophrenia prior to admission had been with olanzapine 10mg, however, his compliance with this medication had been poor, according to his sister.

On assessment, SC looked unkempt with long, dry, frizzy hair and a long, scraggly beard. He had a lean build and was dressed in worn-out jeans and a faded, dirty t-shirt. He had downcast eyes but was passively cooperative. His speech was slow with low volume and he needed to be prompted repeatedly. He said he always had a frustrated mood

due to his lack of sleep and rated it "0/10". His affect was stable and blunted. He had delusional beliefs regarding his health and persecution but no perceptual changes. Both his insight and judgment were poor and he was assessed to have a moderate risk for suicide/self-harm.

SC was diagnosed with a relapse of his chronic paranoid schizophrenia. He was continued on olanzapine, with an increased dose, which saw a reduction in his delusional thought processes and an improvement in his insight and judgment. However, he continued to suffer from insomnia and his avolition, reduced socialisation, and diminished emotional responsiveness remained unchanged. Mirtazapine was added to the regimen and improvement in all these domains was seen within one to two weeks.

Introduction

Schizophrenia is characterised by psychotic symptomatology being present for longer than a one-month period, with some symptoms persisting for at least six months. [1] It is a multi-domain disorder that typically consists of a combination of positive symptoms such as delusions, hallucinations, disorganised speech, or grossly disorganised or catatonic behaviour, negative symptoms such as affective flattening, alogia, or avolition, and cognitive symptoms such as deficits in working memory, attention, or executive functions. These symptoms are further associated with social/occupational dysfunction and are not accounted for by another disorder. [1] Whilst DSM-5 does not specifically classify schizophrenia into acute or chronic forms, it indicates that the course of schizophrenia varies, with some patients showing exacerbations and remissions, whilst others remain chronically ill with symptoms lasting greater than 1 year. [1] The pharmacological management of schizophrenia primarily addresses the positive symptoms of the disorder as they are responsive to all approved antipsychotics, however, negative symptoms only respond modestly at best to these antipsychotics. [2] This is of particular concern in patients with chronic schizophrenia as this form of the illness is usually characterised by an increasing prominence of negative symptoms throughout its course, leading to poor functional outcomes and quality of life for these patients. [2] Literature suggests that certain antidepressants may have a beneficial impact on negative symptoms. [2] In the above case, SC was first given olanzapine however responded only partially which in turn prompted the addition of mirtazapine. This makes us question whether the use of mirtazapine as add-on therapy to antipsychotics is efficacious in the treatment of chronic schizophrenia.

Objective

The objective of this article was to evaluate the evidence that is available on the effectiveness of mirtazapine as adjunct therapy to antipsychotics for chronic schizophrenia.

Data Collection

To address the objective identified above, a literature search of the ScienceDirect and Pubmed databases was done with limits set to include articles that were written between the year 2000 and the present time. References from retrieved articles were also reviewed for relevance and inclusion in the review. The search terms were mirtazapine AND chronic schizophrenia; mirtazapine AND antipsychotics AND chronic schizophrenia AND efficacy. The search identified five studies: four randomised, double-blind, placebo-controlled trials (Level II Evidence) and one open-label trial (Level III-3 Evidence). Of these studies, none specifically investigated the combination therapy of olanzapine and mirtazapine (that which is relevant to the patient described in the case report). They did, however, investigate the efficacy of mirtazapine with other related second-generation antipsychotics.

Discussion

Pharmacology of mirtazapine

According to the dopamine hypothesis, schizophrenia is attributed to an excess of dopamine in the striatum and a deficiency of dopamine in the frontal cortex. [3] The excess dopamine is responsible for the positive symptoms of the condition whilst the negative symptoms are thought to be a result of the frontal dopaminergic deficiency. [3]

Mirtazapine selectively antagonises post-synaptic 5-HT_2 (subtypes 2A and 2C) and 5-HT_3 receptors, which may contribute to its anxiolytic properties as well as enhance dopaminergic neurotransmission. [4] Specifically, combined mirtazapine and antipsychotic therapy results in concurrent blockade of 5-HT_2A and D_2 receptors. This is thought to selectively stimulate dopaminergic activity in the mesocortical pathway or frontal cortex without increasing its activity in the mesolimbic and nigrostriatal areas of the brain, thereby improving the negative and cognitive symptoms of the disorder. [3]

Mirtazapine may also indirectly increase dopamine output in the medial prefrontal cortex. [3] One preclinical study suggested that noradrenaline reuptake transporters clear extracellular dopamine into noradrenergic nerve terminals. [3] As mirtazapine increases noradrenaline levels, greater competition between dopamine and noradrenaline for the same reuptake transporter may exist, which can subsequently cause elevation in dopamine levels. [3]

Another primary mechanism of action is antagonism of central presynaptic α_2-adrenergic inhibitory autoreceptors, leading to increased release of noradrenaline. [4] It also blocks α_2-heteroreceptors in serotonergic nerve terminals, resulting in enhanced 5-HT_{1A}-mediated serotonin neurotransmission. [4] Increased central noradrenergic and serotonergic activity helps alleviate symptoms of inattention, impaired concentration, and anxiety. [4]

Whilst no drug has received Therapeutic Goods Administration approval for the treatment of negative symptoms of schizophrenia, [3] the continually improving understanding of mirtazapine's mechanisms of action has prompted several clinical trials to investigate its role, as well as the role of other antidepressants, in the management of this disorder.

Effects of mirtazapine on the negative symptoms of chronic schizophrenia

One study was identified that evaluated the efficacy of mirtazapine as add-on therapy to risperidone in patients with chronic schizophrenia and prominent negative symptoms. It was an eight week, randomised, double-blind, placebo-controlled trial involving a sample of 40 in-patients who met the DSM-5 criteria for schizophrenia with 20 participants assigned to risperidone 6mg/day + mirtazapine 30mg/day and 20 participants assigned to risperidone 6mg/day + placebo. [5] All participants were acutely psychotic on a background of chronic schizophrenia. Patients were assessed at baseline and at the end of the study using the Positive and Negative Syndrome Scale (PANSS) as the primary outcome measure. [5]

The study found that the mirtazapine group had a greater mean improvement in the negative symptoms ($p<0.001$) and PANSS total scores over the eight-week period. [5] Furthermore, clinical response (characterised by a 50% or more reduction in the PANSS total score) was seen in 68.18% of patients receiving mirtazapine compared to 31.81% of those assigned to placebo. The difference was significant ($p=0.03$). [5] This study showed the superior efficacy of mirtazapine in comparison to placebo in the augmentation of risperidone treatment in chronic schizophrenia. Given that no significant adverse effects were observed with the administered dose of mirtazapine, [5] the study further suggests its use as a potential combination treatment strategy particularly when negative symptoms prevail. Whilst no issues were observed in this study period, mirtazapine is notoriously known for its propensity to cause weight gain. [6] Its use as add-on therapy must therefore be judiciously tailored given the higher prevalence of metabolic syndrome in patients with chronic mental illnesses such as schizophrenia. [6]

A similar eight week, randomised, double-blind, placebo-controlled trial tested the role of mirtazapine in augmenting clozapine therapy for patients with chronic schizophrenia. [7] Its methodology and criteria for inclusion were similar to that of the aforementioned study. The study involved 48 in-patients, half of whom were assigned to mirtazapine 30mg/day and the other half administered placebo. [7] Each patient was on a stable dose of clozapine monotherapy for at least one month prior to the study. Their doses ranged from 150-650mg daily and did not change throughout the study. [7] The primary efficacy measure was the Scale for the Assessment of Negative Symptoms (SANS) total scores. The study saw a substantial reduction in scores for the mirtazapine group compared to the placebo group with particular improvements on the SANS subscales avolition/apathy and anhedonia/asociality. [7] Mirtazapine also showed greater superiority over placebo in the Brief Psychiatric Rate Scale (BPRS) total score at the end of the trial. [7]

The evidence from both studies indicates that the combination of antipsychotics and mirtazapine may be more effective for the treatment of negative symptoms in chronic schizophrenia than antipsychotics alone. However, both studies had limitations, namely the small sample sizes and the short treatment period, given the long-term nature of the illness. Furthermore, whether these findings can be generalised to all second-generation antipsychotics such as olanzapine is also worthwhile questioning.

Effects of mirtazapine on neurocognition

The efficacy of adjunctive mirtazapine in chronic schizophrenia does not appear to be limited to improving the negative symptoms of the illness. The literature suggests that add-on mirtazapine may also have desirable effects on neurocognition. [8, 9] An eight week, double-blind clinical trial was conducted whereby 21 patients with chronic schizophrenia, stabilised on risperidone, were randomly assigned to adjunctive treatment with either mirtazapine or a placebo. Cognitive performance was measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). [8] Unlike the placebo group, the mirtazapine group saw statistically significant improvements in the RBANS total scores, and also in the subscales for immediate and delayed memory. [8] Like all other studies discussed so far, the short treatment period was a major limitation.

This shortcoming was addressed in another study with a similar methodology and criteria for inclusion. It was a six week double-blind, randomised trial with a six week open label extension phase, designed to explore the effects of prolonged mirtazapine treatment. [10, 11] During the extension phase, the twelve week mirtazapine exposure group (i.e. those who received mirtazapine from the beginning) and the

six week mirtazapine exposure group (i.e. those who received placebo initially and were then shifted to mirtazapine at the extension phase) both showed improvement in the areas of visual-spatial functions, verbal/visual memory, executive functions, verbal fluency, and general mental and psychomotor speed. [10, 11] However, the twelve week mirtazapine exposure group was found to convey neurocognitive superiority over the six week mirtazapine exposure group, [10, 11] suggesting that additional benefits may be yielded with prolonged treatment.

Conclusion

Chronic schizophrenia is a complex illness that is characterised by a combination of positive, negative and cognitive symptoms. [1] Whilst antipsychotics are the recommended first-line treatment, the prolonged nature of the illness often results in residual negative symptoms and sustained neurocognitive deficits that tend to have a poor response to antipsychotics. [2] Current level II evidence suggests that the use of adjunct mirtazapine to antipsychotics may augment the treatment of chronic schizophrenia by alleviating the negative symptoms of the disorder. However, this evidence is limited to a select number of primary therapies and the long-term effects are currently unclear. Given that no studies were identified that specifically addressed the efficacy of a combined treatment strategy of olanzapine and mirtazapine, it is difficult to determine the appropriateness of the management approach taken for SC's illness.

Before the use of mirtazapine as an adjuvant to antipsychotics in chronic schizophrenia can be recommended for clinical practice, it is important to conduct large-scale, placebo-controlled studies that are lengthy in duration, so that the full efficacy and potential side effects of mirtazapine can be properly explored. Its tendency for weight gain/exacerbation of metabolic syndrome, especially in combination with atypical antipsychotics which share a similar risk profile, is of particular concern. [6] It may also be worthwhile to determine whether mirtazapine is synergistic with most or only selective antipsychotics.

Nonetheless, SC's considerable improvement upon administration of mirtazapine provides the grounds for questioning what treatment approach is best for a patient with chronic schizophrenia.

Acknowledgements

None.

Consent declaration

Informed consent was obtained from the patient for publication of this case report.

Conflict of interest

None declared.

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