

Review

## Use of concomitant medication in the treatment of schizophrenia

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Schizophrenia is a life-long disorder that requires continuous pharmacotherapy. About 10 to 30% of patients with schizophrenia show poor response to antipsychotic medication alone, therefore concomitant medication is often used. The rationale for the addition of concomitant medication is often unclear and based on limited evidence. The most frequently prescribed concomitant medications in the treatment of schizophrenia include anticholinergic medication, antidepressants, anxiolytics for example, benzodiazepines, lithium and anticonvulsant medication for example, valproex. Indications for adding these medications to antipsychotic treatment regimens vary from controlling specific symptoms associated with schizophrenia for example, anxiety symptoms, aggressive behavior and suicidality, to managing adverse effects for example, parkinsonian side effects caused by antipsychotic medication. Although there is a need for concomitant medication in the treatment of schizophrenia, each patient needs to be assessed individually since the use of concomitant medication can also have negative treatment implications, for example an increase in the occurrence of adverse effects and drug interactions. Due to the diversity of the disease profile of schizophrenia, no one adjunctive treatment benefits all patients, therefore the choice of specific treatment is best guided by the clinical characteristics and presentation of the individual patient. The aim of this paper is thus to present a qualitative review of the literature.

**Key words:** Schizophrenia, concomitant medication, antipsychotics, anticholinergics, antidepressants.

### INTRODUCTION

Schizophrenia is a debilitating psychiatric disorder, not only impacting on the individual, but also creating an economic burden on society (Schultz and Andreasen, 1999). It is the most disabling of psychiatric disorders (Mueser and McGurk, 2004) and one of the major contributors to the global burden of disease (Saha et al.,

2005). Both genetic and environmental factors have been implicated in the etiology of schizophrenia – rates of schizophrenia have been found to be higher among relatives of patients than in the general population, and environmental risks for example, prenatal and perinatal events and sociodemographic factors are associated

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risks for development of schizophrenia (Mueser and McGurk, 2006).

Schizophrenia has been linked to a hyperdopaminergic state resulting in the expression of positive or psychotic symptoms (Kapur et al., 2006). Antipsychotic medications mainly exert their therapeutic action through antagonism of D<sub>2</sub> dopamine receptors (Tort et al., 2006) resulting in decreased neuronal sensitivity to dopamine. The dopamine hypothesis is further based on observations that dopamine agonists (e.g. amphetamine) may exacerbate schizophrenia (Featherstone et al., 2007), and that an increased density of D<sub>2</sub> dopamine receptors may be detected in striatal brain areas of schizophrenic patients (Hirvonen et al., 2005). However, the dopamine hypothesis is not fully explanatory since some drugs have a higher affinity for other receptors than for D<sub>2</sub> dopamine receptors – many antipsychotic drugs also antagonize  $\alpha_1$ -adrenergic, muscarinic acetylcholine, and H<sub>1</sub> histamine receptors.

Antipsychotic medication differs in their affinity for D<sub>2</sub> dopamine receptors as well as affinity for other receptors in the central nervous system. Antipsychotic medication is divided into the typical or first generation antipsychotic medication and atypical or second generation antipsychotic drugs. While high potency first generation antipsychotic medication act mainly via the D<sub>2</sub> dopamine receptor (Uchida et al., 2007), atypical antipsychotic medication are more potent as 5-HT<sub>2</sub> serotonin receptor antagonists than D<sub>2</sub> dopamine receptor antagonists (Meltzer, 2004). The finding that multiple dopamine and serotonin receptors play a role in the action of antipsychotic drugs have supplanted the idea that only D<sub>2</sub> receptor antagonism is the basis for antipsychotic action of neuroleptic drugs and have resulted in other hypotheses for schizophrenia.

There is emerging evidence suggesting that symptoms of anxiety and depression in schizophrenic patients may also be associated with serotonergic dysfunction. The selective serotonin reuptake inhibitor citalopram was shown to reduce symptoms of depression/anxiety in such patients (Taiminen et al., 1997). Interestingly, evidence (González-Maeso et al., 2008) reported that there was an upregulation of serotonin 5-HT<sub>2A</sub> receptors and a downregulation of metabotropic glutamate receptors in post-mortem brain from untreated schizophrenic patients, suggesting a pattern that could predispose psychosis. It was demonstrated that the serotonin 5-HT<sub>2A</sub> receptors and metabotropic glutamate receptors exist as functional complexes in the brain cortex. Activation of the latter attenuated hallucinogen-specific signaling and behavioral responses (González-Maeso et al., 2008).

The finding that NMDA receptor hypofunction, as caused by NMDA receptor antagonists, induce a schizophrenia-like psychosis (Olney and Farber, 1995) resulted in the glutamate hypothesis for schizophrenia.

Blockade of NMDA receptors results in excessive release of glutamate and acetylcholine, with the end-result of triggering potential schizophrenia-type symptoms (Olney et al., 1999). NMDA receptor hypofunction also results in a compensatory upregulation of D<sub>2</sub> dopamine receptors (Onhuma et al., 2005), explaining the efficacy of antipsychotic medications acting via D<sub>2</sub> dopamine receptor antagonism.

Symptoms of schizophrenia are categorized as positive and negative symptoms, as well as cognitive impairment (Mueser and McGurk, 2006). Positive or psychotic symptoms include delusions, hallucinations or thought disorders, and bizarre behaviour (Merck, 1999), and negative symptoms include blunted affect, anhedonia, apathy and alogia (Mueser and McGurk, 2006).

Due to the complex pathophysiology of schizophrenia, monotherapy with antipsychotics are not always effective to control all symptoms associated with schizophrenia. Although all marketed antipsychotics have proved to be effective in the treatment of positive symptoms associated with schizophrenia, negative symptoms do not always respond adequately to these drugs. Even the newer second generation antipsychotic medication has not resolved this problem (Leucht et al., 1999; Rummel et al., 2005).

The aim of this paper is thus to present a qualitative review of the literature on concomitant use of medication in the treatment of schizophrenia.

## METHODOLOGY

In this review, the data source was a literature search conducted using the search engine PubMed, for articles related to concomitant use of drugs in schizophrenia. The following Mesh terms were used as keywords: schizophrenia PLUS anticholinergic; schizophrenia PLUS anxiolytic, schizophrenia PLUS antidepressants, schizophrenia PLUS anticonvulsants, schizophrenia PLUS lithium. The search was restricted to English language, full text articles, available for free or subscribed to by the institution. Articles were reviewed by the two authors individually, after which content was discussed for inclusion in this review.

## LITERATURE REVIEW

### Concomitant medications in schizophrenia

While the term “polypharmacy” refers to both combination therapy (combining one or more antipsychotic medications) or augmentation therapy (simultaneous use of antipsychotics and other agents), the focus of this paper is on augmentation therapy. Schizophrenia is a life-

long disorder, requiring continuous pharmacological maintenance therapy once a patient has been stabilized.

Since 10 to 30% of patients with schizophrenia show poor response to antipsychotics alone (Wolkowitz, 1993), concomitant medication is often used during the maintenance phase of schizophrenia (Siris, 1993; Williams et al., 1999). The rationale for this is however often unclear and based on limited evidence (Novick et al., 2005; Hertz and Marder, 2002).

The most frequently prescribed concomitant medication used in schizophrenia include anticholinergic medication, antidepressants, benzodiazepines, lithium and anticonvulsants (Novick et al., 2005; Parepally et al., 2002; Mueser and McGurg, 2006). Indications for concomitant medications range from controlling specific symptoms associated with schizophrenia, for example anxiety symptoms, aggressive behavior and suicidality, to managing adverse effects, for example Parkinsonian side effects (Parepally et al., 2002) caused by antipsychotic medication.

### ***Anticholinergic medication***

Studies by Scarr et al. (2007) have demonstrated a decrease in the hippocampal expression of  $M_4$  but no change in  $M_1$  muscarinic acetylcholine receptors of schizophrenic patients. Since muscarinic acetylcholine receptor expression was not increased in these patients, they concluded that anticholinergic drugs may not contribute to the antipsychotic effects per se, but rather reduce and control extrapyramidal adverse effects caused by antipsychotic drugs.

Anticholinergic medication is often prescribed during treatment with especially the older antipsychotic medication. First generation antipsychotic medication blocks all four major dopaminergic pathways. The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons. The antagonistic effects of older antipsychotic medication at dopamine receptors may however, alter this balance, and cause a relative excess of cholinergic stimulation resulting in extrapyramidal adverse effects. Anticholinergic drugs are thus co-administered to counteract the acetylcholine/dopamine imbalance caused by dopamine blockade, reducing the extrapyramidal adverse effects.

Atypical antipsychotic drugs are used less frequently in combination with anticholinergic drugs (Novick et al., 2005). The atypical antipsychotic drugs have a lower affinity for  $D_2$  dopamine receptors, resulting in a sufficiently lower incidence of extrapyramidal adverse effects when compared to typical antipsychotic drugs. Some of the newer antipsychotic drugs also exhibit anticholinergic properties of their own for example, thioridazine, clozapine

and olanzapine, and may not alter the acetylcholine / dopamine balance (Johnson et al., 2005).

Addition of concomitant medication to antipsychotic treatment, may in some cases be associated with a higher incidence of adverse effects, since it contributes to the already existing side-effect profile of antipsychotic drugs, for example anticholinergic medication has been found to impact negatively on cognitive functions, including attention and concentration (Huegel et al., 1997). Increasing the possible adverse effects that a patient might experience will impact adversely on compliance, but similarly will untreated extrapyramidal symptoms.

In conclusion, anticholinergic medication is thus primarily indicated to counteract the adverse effects caused by especially the older or typical antipsychotics. When including anticholinergic medication in an antipsychotic treatment regimen it is important to consider the positive indications (effective management of adverse effects caused by antipsychotic drugs, and increased compliance due to management of adverse effects) as well as the negative indications (increased adverse effects, and possible negative impact on compliance).

### ***Anxiolytic medication***

Anxiolytic medication, specifically benzodiazepines, is used frequently in combination with antipsychotic drugs to control specific symptoms associated with schizophrenia. Anxiety disorders and anxiety symptomatology are highly prevalent in schizophrenia (Seedat et al., 2007). Lysaker and Salyers (2007) reported that higher levels of anxiety were associated with greater hallucinations, withdrawal, depression, and feelings of hopelessness (Seedat et al., 2007) indicating the need for anxiolytic co-therapy in schizophrenia. Gaillard et al. (2006) mentions that the advantages of using benzodiazepines in combination with antipsychotics may act on positive or negative symptoms of schizophrenia and has been found particularly helpful in patients with high levels of anxiety.

Secondly, benzodiazepines are used to treat neuroleptic induced akathisia, a medication-induced movement disorder associated with neuroleptic drugs, characterized by motor restlessness accompanied by increased nervous or restless movement (DSM-IV). Neuroleptic induced akathisia is one of the most distressing adverse effects associated with the use of antipsychotics (Lima et al., 2007).

A third indication for anxiolytic medication in schizophrenia is the augmentation of the effect of antipsychotic medication through indirect action on dopamine. The stimulation of GABA by benzodiazepines

may reduce pre-synaptic release of dopamine in the mesolimbic brain region (Wolkowitz et al., 1992; Gaillard et al., 2006) thus augmenting the antipsychotic action of the antipsychotic drugs. Although beneficial, the addition of benzodiazepines to a treatment regimen is not without problem. The use of benzodiazepines is associated with sedation and cognitive impairment, behavioral disinhibition, exacerbation of psychotic symptoms, and the potential for dependence, withdrawal and abuse (Stimmel, 1996). Benzodiazepines in combination with clozapine increase the frequency of cardiovascular and respiratory accidents (Gaillard et al., 2006). Furthermore, polypharmacy with antipsychotics and benzodiazepines are associated with a substantial increase in mortality; this was not observed with concomitant use of antidepressants (Tiihonen et al., 2012).

The concomitant use of benzodiazepines with antipsychotics appears to have no clinical benefit, except for the short term sedative effects (Dold et al., 2012).

### **Antidepressants**

Although depression has been reported as a comorbid disorder frequently associated with schizophrenia (Voon and Lang, 2004), the role of antidepressant medication in the treatment of schizophrenia remains uncertain. According to Novick et al. (2005), no convincing evidence could be found to support or refute the use of antidepressants for treatment of depression in people with schizophrenia. A large percentage of patients diagnosed with schizophrenia do suffer from depressive symptoms. The suicide risk in people with schizophrenia is associated with experiencing these depressive symptoms, and antidepressant use in schizophrenia is associated with decreased suicide deaths (Tiihonen et al., 2012). Effective treatment of depressive symptoms in schizophrenia should therefore lead to improvement in health, quality of life and reduced suicide risk – as such concomitant use of antidepressants and anxiolytics were found to improve quality of life in patients living with schizophrenia (Ritsner et al., 2006).

Although Munjiza et al. (1998) indicate the need for antidepressants in the treatment of postschizophrenic depressive syndrome, there remains a lack of evidence to provide clear guidance about the use of antidepressants to treat depression in schizophrenia, since there are no indication antidepressants is beneficial in all cases (Whitehead et al., 2002). Use of antidepressants in patients with high intensity of positive symptoms may actually exacerbate psychotic symptoms (Voon and Lang, 2004)

One of the main indications for the use of antidepressant medication in the treatment of schizophrenia seems to be the management of negative

symptoms. While antipsychotic drugs are effective in the management of positive symptoms, it remains difficult to manage negative symptoms associated with schizophrenia. A combination of antipsychotic drugs and antidepressant medication may however be more effective in treating negative symptoms of schizophrenia than antipsychotic drugs alone (Rummel et al., 2005). A study by Novick et al. (2005) found a higher antidepressant use associated with higher intensity of negative symptoms while a high intensity of positive symptoms was associated with lower antidepressant use indicating the use of antidepressants for the treatment of negative symptoms.

Increasing the number of medications in a treatment regimen increases the risk of problems associated with treatment and especially an increase in potential drug interactions. A variety of drug interactions have been reported when combining antipsychotic medication with antidepressant drugs, for example quetiapine administered with fluvoxamine caused increased serum levels of quetiapine (Castberg et al., 2007). A variety of pharmacokinetic interactions, involving changes in the activity of drug-metabolizing enzymes, occur with newer antipsychotics (Spina and Leon, 2007) and elderly patients have been found to be increasingly susceptible to the serotonin syndrome when atypical antipsychotic medication (for example, trazodone, risperidone, quetiapine) were combined with certain antidepressants (for example, sertraline, phenelzine) (Kohen et al., 2007).

The use of antidepressant co-therapy in schizophrenia seems warranted when dealing with patients with a high intensity of negative symptoms or management of associated depressive symptoms, resulting in improved health and quality of life adjunctive treatment should however be guided by the clinical characteristics of the individual patient.

### **Anticonvulsant medication**

Many people with schizophrenia do not achieve a satisfactory treatment response with ordinary antipsychotic drug treatment. In these cases, various add-on medications are used with valproate being one of these (Schwartz et al, 2008). Studies by Benes and Beretta (2001) provide evidence of a defect in GABA-ergic neurotransmission, being triggered under conditions when the dopamine system is altered, for example conditions like schizophrenia.  $\gamma$ -aminobutyric acid (GABA) is synthesized from the amino acid L-glutamate by the enzyme glutamate decarboxylase through a process of decarboxylation. It has been demonstrated that the expression of glutamate decarboxylase is reduced in schizophrenic patients (Benes et al., 2007). Identification of the possible role of GABA in the

pathophysiology of schizophrenia has led to the use of drugs such as divalproex (sodium valproate and valproic acid) as adjunct with antipsychotics in the treatment of schizophrenia (Casey et al., 2003).

The main indication for the use of concomitant anticonvulsant medication in schizophrenia is the augmentation of antipsychotic action. Anticonvulsants, for example divalproex augments the effect of the antipsychotic medication on both positive and negative symptoms of schizophrenia (Casey et al., 2003) via a modulatory influence of GABA on dopamine in the cortico-striatal-thalamic pathway.

Valproate is thought to act through more than one mechanism in providing its broad pharmacological activity. It has been shown that GABA levels increase after the administration of valproate, and it may be attributed to the inhibition of GABA degradation, increased GABA synthesis, and decreased GABA turnover (Owens and Nemeroff, 2003).

In a recent Cochrane review, Schwartz et al. (2008) found that, while the addition of valproate/valproic acid may be beneficial in managing the schizophrenic patient by a quicker onset of action, decreased aggression, and a significant reduction in tardive dyskinesia, no significant effect of valproate as an adjunct to antipsychotic medication has been evident. Large trials are necessary to support or refute the use of valproate/valproic acid as concomitant to antipsychotic medication.

Further indications for anticonvulsants as concomitant to antipsychotics in schizophrenia include protection against seizures induced by high doses of antipsychotics, specifically clozapine (Lundblad et al., 2015), as well as augmentation in treatment-resistant patients – it is postulated by Onhuma et al. (2013) that the glutamatergic properties of lamotrigine may play a role in treatment resistant schizophrenia, resulting in improved response in these patients.

### **Lithium**

Lithium is often given as adjunctive therapy to schizophrenic patients who may not respond best to typical antipsychotic drugs. However, Leucht et al. (2007) concluded in a comprehensive study that the effectiveness of lithium as an adjunct to antipsychotic drugs have remained inconclusive, and the need for further, large, simple and well-designed trials are justified. According to Leucht et al. (2007) such trials should concentrate on two target groups: 1) people with no affective symptoms, to determine whether lithium has an effect on the core symptoms of schizophrenia, and 2) people with schizoaffective disorders for whom lithium is widely used in clinical practice, although there is no evidence to support this use.

### **CONCLUSIONS**

It is clear that, due to the complexity of schizophrenia and the difficulty with adequate management of the disease with antipsychotic medications alone, indications exist for the use of adjunctive medication. These indications include management of adverse effects caused by antipsychotic medication, augmenting the action of antipsychotic medication, and addressing specific symptoms of schizophrenia not adequately addressed by the antipsychotic medication alone.

Careful consideration when including concomitant medication is however necessary. The number of medications in a treatment regimen has been shown to influence patient adherence since it impacts on the complexity of the treatment regimen (George et al., 2004). If the medication scheme becomes more complex with the addition of concomitant medication, this will negatively impact on compliance, especially in schizophrenic patients where adherence to medication is already poor (Byerly et al., 2007; Volavka et al., 2007). A direct correlation between the degree of compliance in schizophrenia and the clinical outcome has been observed in studies which indicated poor pharmacological treatment compliance as one of the main problems when treating schizophrenic patients (De Hert et al., 2007).

It is still not clear which patients will respond more positively to augmentation therapy, making it difficult to adopt rational pharmacotherapy. This highlights the need for randomized, controlled clinical trials examining adjunctive use of antidepressants, anxiolytics and sedative hypnotics to target symptoms of anxiety, depression, and insomnia in patients with schizophrenia, also indicated by the CATIE study (Chakos et al., 2011).

### **Conflict of Interest**

The authors have not declared any conflict of interest.

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