The risks and benefits of antipsychotics in the treatment of psychosis

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Abstract Box

Antipsychotics are important in the treatment and recovery of people with psychosis but current evidence suggests that mental health nurses are not always conversant with the risks and benefits of these drugs. This inadequate knowledge has important ramifications for the provision of safe and effective medication management. This article outlines the utility and safety considerations associated with the different groups of antipsychotic drugs currently available in order that …….

Key Points Box

The advent of antipsychotics have contributed to the revolutionalsation of mental health care but current antipsychotics are suboptimal

First generation antipsychotics are effective in treating positive symptoms but not effective in treating cognitive or negative symptoms in psychosis. Further, they induce disabling motor side effects**.**

Second generation antipsychotics are effective in trating positive symptoms and are modestly effective in treating negative and cognitive symptoms but they induce troubling metabolic side effects.

Newer antipsychotics recently introduced have the potential to treat positive symptoms without inducing troubling motor or metabolic side effects. Further**, drugs**

that target non dopamine systems currently under development offer hope of treating positive, negative and cognitive symptoms without inducing adverse side effects.

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Introduction

The central role of antipsychotics in the treatment of people with psychosis is now taken for granted by mental health professionals (Leucht *et al.* 2012) and service users also place a high importance in the use of medication to aid recovery (Piat *et al.* 2009). Irrespective of these standpoints, the effectiveness of antipsychotics is a vexed issue for a number of reasons. One reason is that antipsychotics present a considerable risk in terms of their immediate and long-term adverse effects. Evidence suggests that patients taking these drugs are three times more likely to die suddenly from cardiac arrest or stroke than the general population (Straus *et al.* 2004). Another reason relates to the widespread use of polypharmacy (Barnes and Paton 2011), which has significantly increased in recent years (Mojtabai and Olfson 2010) despite evidence of the associated risks. For these reasons, the use of antipsychotics poses important challenges. At the same time, there is ample evidence suggesting that mental health nurses have inadequate working knowledge of pharmacology and this has frequently resulted in suboptimal care to patients (Latter *et al.* 2000; Kaas *et al.* 2000; Jordan *et al.* 1999; Skingsley *et al.* 2006; Page and McKinney 2007). Not surprisingly, this has resulted in nurses lacking in confidence when discussing treatment options with service users, carers and medical colleagues (Bressington *et al.* 2012).

In response to the clear inadequacies in knowledge, the UK Nursing and Midwifery Council (NMC) have developed essential skills that nurses should demonstrate at the point of professional registration; the medication management essential skill cluster (ESC) number 36 states that: "*People can trust the newly registered graduate nurse to ensure safe and effective practice in medicines management through* ***comprehensive knowledge of medicines their actions, risks and benefits****"*. In line with this guideline, this paper seeks to discuss the different groups of antipsychotics in terms of their effects upon symptoms, their common side effects and likely safety profiles.

A little history

The French surgeon, Henri Laborit, discovered antihistamine compounds (one of which was chlorpromazine), during his search for a preoperative sedative in the 1940s. Chlorpromazine was observed to be dramatically effective in calming patients and its use spread to psychiatric clinics in the mid-1950s. The discovery that chlorpromazine dramatically reduced some psychotic symptoms stimulated the development of a range of antipsychotic drugs. These earlier drugs that are commonly referred to as conventional, classical or first generation antipsychotics (FGAs) are still in use today. Despite their effectiveness, these drugs induce very unpleasant motor side effects and this fuelled the development of the second generation antipsychotics (SGAs) which are also referred to as atypical antipsychotics. The therapeutic effects of all antipsychotics are mostly understood in terms of the dopamine hypothesis and this is summarised below.

The dopamine hypothesis

There are four known critical dopamine pathways in the brain; the mesolimbic, mesocortical, nigrostriatal and tuberoinfundibular pathways. At its most elementary exposition, the dopamine theory proposes that there is an imbalance of dopamine in the mesolimbic and mesocortical pathways. This imbalance causes abnormal neurotransmission that leads to symptom formation. Typically, in the mesolimbic pathway, there is excess dopamine causing synaptic "overload". This 'overload' in turn causes an overstimulation of the post synaptic dopamine receptors, which

manifests itself as positive symptoms such as delusions, hallucinations, thought disorder and bizarre behaviour. To prevent overstimulation and therefore symptom formation, antipsychotics work by blocking (or antagonising) post synaptic dopamine receptors.

Negative symptoms are thought to arise through dopamine dysfunction in the mesocortical pathway that may involve insufficient stimulation or more likely, the deficit of dopamine (D_1) receptors (bi-Dargham 2004). This under stimulation typically leads to the mood, negative and cognitive symptoms found in schizophrenia.

Second and third generation antipsychotics are purported to be less likely to cause EPS and more effective at treating the cognitive, affective and negative symptoms because their mechanism of action is slightly different to FGAs. SGAs block serotonin receptors in addition to dopamine receptors, this blockade of the serotonin receptors in the nigrostriatal and mesocortical pathways has the effect of keeping dopamine in balance which reduces the likelihood of SGAs causing EPS and secondary negative symptoms.

The potential benefits of antipsychotics

With respect to FGAs, their therapeutic effect is generally associated with their ability to block mesolimbic dopamine receptors; however, when they block striatal dopamine receptors of by more than 80% this significantly increases the risk of extrapyramidal side effects (EPS) such as parkinsonism, dystonia, akathisia and tardive dyskinesia. Currently, there are at least 11 different classes of antipsychotic medications available and among them are FGAs group that include phenothiazines, butyrophenones and thioxanthenes. Though effective in treating positive symptoms of psychosis, these drugs are far from being optimal treatments (Miyamoto *et al.* 2012). Between 30 and 60% of patients with acute psychotic symptoms completely fail or partially respond to these drugs and they are generally less effective against negative, mood and cognitive symptoms(Meltzer *et al.* 1998).

Other limitations of FGAs are a relative lack of efficacy in relation to social functioning, quality of life, prevention of illness progression and improvement of long-term outcomes. Therefore, the only group of patients in which FGAs are clearly

indicated are those who prefer them because they have had an excellent response to them with minimal side effects (Sharif 1998).

In response to the limited effectiveness and extensive side effects of FGAs, considerable effort has gone into developing a range of SGAs. These drugs include clozapine, olanzapine, quetiapine, risperidone and amisulpiride. The main advantage of SGAs is their reduced propensity to induce acute EPS and tardive dyskinesia. However, like FGAs, they also have their own distinct risks and benefits.

There have been numerous double-blind trials comparing the efficacy and tolerability of SGAs with FGAs for acute and maintenance therapy in schizophrenia (Miyamoto *et al.* 2003; Buckley *et al.* 2001; Leucht *et al.* 2003), the results suggest that SGAs are at least as effective as FGAs in alleviating positive symptoms of psychosis. However, there is ongoing debate as to whether SGAs are more efficacious overall than FGAs (Leucht *et al,* 2003). The conclusions from meta-analyses of eligible studies have not been entirely consistent. Geddes and colleagues reported similar efficacy when doses of haloperidol of 12 mg or less are used as a comparator to SGAs (Geddes *et al,* 2000). They further asserted that first generation antipsychotics are equally efficacious as a group but other investigators have concluded that some SGAs such as clozapine, olanzapine and risperidone are more efficacious than others, like sertindole, quetiapine and ziprasidone (Davis *et al.* 2003).

Although there is tentative evidence that SGAs are more effective than FGAs in treating negative symptoms, there is continuing debate as to whether these apparent therapeutic effects are secondary to a reduction in EPS, a reduction in psychotic symptoms or a direct effect on primary negative symptoms (Remington and Kapur 2000; Meltzer 1995). Examining the efficacy of antipsychotics on negative symptoms is fraught with problems because most clinical studies of SGAs do not distinguish between primary and secondary negative symptoms and generally involve very symptomatic patients undergoing treatment (Buchanan and Gold 1996).

Though early studies of the effect of SGAs on cognitive symptoms were inconsistent (Keefe *et al.* 1999), relatively recent controlled studies have shown that in general, SGAs may be better for cognition when compared with FGAs (Stip *et al.* 2005). Specifically, studies seem to suggest that clozapine has a protective effect on attention while olanzapine has a positive effect on memory (Meltzer 2012b; Essali *et*

al. 2009). With regard to efficacy for treatment-resistant schizophrenia, only clozapine is convincingly effective against psychotic symptoms in treatment-refractory patients (Chakos *et al.* 2001; Essali *et al.* 2009). A Cochrane review of 52 trials that compared clozapine with FGAs found clozapine to be superior to other antipsychotics on most outcome measures including symptom remission. Furthermore, patients seem more satisfied with clozapine treatment than with FGA treatment (Essali *et al.* 2009; Bressington *et al.* 2012a). It is estimated that up to 15% of patients with treatment resistant schizophrenia can experience an improvement of up to 60% within the first year of treatment with clozapine (Stahl 2008).

More recently, third generation antipsychotics (i.e. aripiprazole) with a unique mechanism of action and more favourable side effect profile are being used in practice. Generally referred to as partial agonists, these drugs have a unique receptor binding profile (Dhillon 2012). Aripiprazole partially blocks post synaptic dopamine receptors in situations of high dopamine concentrations (acute psychosis) thus, offering therapeutic benefits. Interestingly, the drug also occupies additional receptors and partially activates post synaptic dopamine receptors in situations where there is receptor under stimulation such as in the mesocortical region thereby improving negative, cognitive and mood symptom (Mailman and Murthy 2010).

Aripiprazole is effective in treating positive and negative symptoms of schizophrenia with minimal EPS or metabolic side effects. A recent systematic review of short and long terms studies found that it is associated with improvements in positive, negative, cognitive, and affective symptoms of schizophrenia (Stip and Tourjman 2010). As previously discussed, despite these potential benefits, all antipsychotics pose risks, some of which can be fatal.

Potential risks of antipsychotics.

Mental health professionals are undoubtedly responsible for sharing information about medication with service users, and monitoring the short and long term adverse effects of treatment. Clinicians also need to be mindful that the physical health state of people with severe mental illness is poor and the longer term use of antipsychotic medications can exacerbate this risk. The occurrence of side effects can cause

serious distress to patients, diminishing their quality of life, increasing carer burden and reducing adherence to medication (Keks 1996).

In terms of adverse effects, the major difference between SGAs and FGAs is the lower incidence of EPS in SGAs. However, SGAs are often more sedating (especially olanzapine, clozapine and quetiapine), and there is robust evidence for their role in early metabolic problems, including weight gain, increased risk of Type-2 diabetes and cardiovascular problems. Given the increased prevalence of cardiovascular disease in people with psychosis, it is paramount that service users are closely monitored for associated risk factors and made aware of the need to maintain a good diet and take regular exercise in order to go some way towards minimising the risks. Health promotion interventions should also be provided to early onset patients as antipsychotic related Type-2 diabetes is most likely to occur in younger adults (Saddichha *et al.* 2007).

FGAs are well known to increase serum prolactin concentration in the usual clinical dose range leading to endocrine related side effects and sexual dysfunction (Meltzer 1985). However, some SGAs (i.e. risperidone and amisulpiride) also increase prolactin serum levels and this can lead to hormonal related side effect effects such as menstrual abnormalities, galactorrhoea and sexual dysfunction. In the long term high prolactin levels can lead to reduced bone mineral density (Haddad and Wieck 2004) and a potential increased risk of some cancers (Harvey *et al.* 2008).

A relatively recent review of aripiprazole studies found that the most common adverse effects were nausea, insomnia and agitation but these effects were usually transient. This evidence suggests that aripiprazole is unlikely to be associated with clinically significant weight gain, dyslipidaemia, or increased prolactin levels. Overall, compared with placebo, aripiprazole has been reported to have a relatively low potential for inducing metabolic syndrome (Stip and Tourjman 2010).

In addition to the more common and predictable adverse effects of antipsychotics, a number of relatively rare but serious risks are also associated with antipsychotic treatment. Most antipsychotics (perhaps excluding aripiprazole) can cause ECG changes, one of the most concerning of which is prolongation of the QT_c interval. The data that relates to which antipsychotics are most likely to prolong QT is somewhat limited and therefore making risk prediction problematic. For example,

haloperidol is likely to have a high effect, whilst quetiapine and chlorpromazine exert a moderate effect (Taylor 2009). As QT_c prolongation is associated with sudden death in some individuals, ECG monitoring is vital and recommended by NICE guidelines for all patients prescribed antipsychotics.

All antipsychotics can adversely affect the blood system. Such actions include increase (leucocytosis) or decrease (leucopenia) in the number of white blood cells, which usually occurs between 6 to 8 weeks after antipsychotic initiation. Except for clozapine, this condition is transient with the majority of antipsychotic medications. A life-threatening blood adverse effect (most usually associated with clozapine) is agranulocytosis; this condition is where the granulocyte producing ability of the bone marrow is severely diminished and this has a high mortality rate of 30%. The condition can occur within the first 3 months of antipsychotic treatment. Despite the severity of this condition and its association with clozapine, recent epidemiological studies suggest that clozapine has the lowest mortality rate of any antipsychotic drug, probably due to its very large effect in reducing the risk for suicide and frequency of blood monitoring(Meltzer 2012a)

Neuroleptic malignant syndrome (NMS), like agranulocytosis, is a potentially fatal side effect of antipsychotic medication with an incidence rate of 0.02-3% and it can occur anytime during the course of antipsychotic treatment(Levenson 1985). It is typified by motor and behavioural symptoms that include muscular rigidity, dystonia, mutism and agitation. The autonomic system symptoms include hyperpyrexia, sweating, and increased pulse and blood pressure. Laboratory findings include increased white blood count, creatinine phosphokinase, liver enzymes, plasma myoglobin and myoglobinuria. The symptoms usually evolve over 72 hours, and the untreated symptoms can last for 10 to 14 days. The diagnosis is often missed during the early stages and withdrawal or agitation may be mistaken for increased psychosis. Men are affected more frequently than women and the mortality rate can reach 30% or higher when FGAs are involved. The cause of this serious condition is largely unknown. Multiple factors probably contribute to NMS, including dehydration, comorbid medical conditions and agitation (Mutsatsa 2011).

All antipsychotics reduce the seizure threshold to some degree, and therefore seizures are a potential early complication of antipsychotic treatment. Among the

first-generation antipsychotics (FGA) chlorpromazine appears to be associated with the greatest risk of seizures, whilst among the SGAs clozapine is thought to be most likely to cause convulsions (Lertxundi *et al.* 2012). The practical risk of seizures by all antipsychotics, however, is low, being 0.5 to 0.9% of all patients on antipsychotic treatment. Rapid upward titration of dosage is a risk factor, so is a history of seizures, CNS pathology and EEG abnormalities (Arana, 2000).

Though evidence is tentative, all antipsychotics are associated with an increased risk of stroke. The risk might be higher in patients receiving SGAs than those receiving FGAs (Douglas and Smeeth 2008). The elderly with dementia seem to be at an increased risk of an associated stroke than people without dementia. It follows therefore that antipsychotics should be avoided when possible in people with dementia.

Clearly, in spite of the importance of antipsychotics, areas of need remain and this has led to the recent introduction of newer drugs such as iloperidone, asenapine and lurasidone. Despite these medications being recently developed they are still classed as SGAs, this is because their mechanism of action does not involve the dopamine partial agonism seen in third generation drugs such as aripiprazole. All these newer medications are similar in terms of overall efficacy and low propensity for clinically significant weight gain or adverse changes in lipid profile. They however, differ from one another in terms of formulations, pharmacokinetics, dosing and metabolic adverse effect profiles (Bobo 2013). For example, asenapine is the first antipsychotic to be only administered sublingually, whereas iloperidone requires titration to minimize orthostatic hypotension. Asenapine and lurasidone are associated with dose-related akathisia, whereas iloperidone is not. Overall, the three newer antipsychotics seem to have a favourable metabolic side effect profile, therefore providing additional options for improved treatment in those with a propensity for developing metabolic syndromes.

The future of antipsychotic treatment

Because of the risk profile of current antipsychotics, the search for an ideal antipsychotic continues. The ideal antipsychotic should be efficacious in treating positive, negative or cognitive symptoms without compromising mental or physical well-being (Correll 2011).

Contemporary research has focused on the critical involvement of glutamate receptors as potential targets for antipsychotic action, particularly in regards to disabling negative and cognitive symptoms that are poorly controlled by current antipsychotics. This is based on the refined glutamate hypothesis that postulates that behavioural and cognitive symptoms of schizophrenia appear to be caused by a dysregulation of glutamate neurotransmission. Frustratingly, the development of novel antipsychotics that bind directly to glutamate NMDA receptors has proven challenging. Recently however, a number of potential drugs targeting the metabotropic glutamate receptor site (mGluRs) with the potential to alleviate cognitive and negative symptoms have been developed, some of which are at the clinical testing phase (Sendt *et al.* 2012). In addition, some non-glutamatergic potential antipsychotics have shown promise. These compounds are the non-hallucinogenic cannabinoid cannabidiol (Hallak *et al.* 2011) as well as the selective muscarinic (M1/M4) receptor agonist xanomeline. However, further preclinical work is required to evaluate their suitability as viable antipsychotic treatment drugs.

Conclusion

Although the advent of FGAs and SGAs has significantly contributed to the revolutionalisation of mental health car, problems because of treatment persist. FGAs induce troubling motor side effects and have little or no effect in treating negative and cognitive symptoms that are common in schizophrenia. With respect SGAs, they are modestly effective in treating cognitive and negative symptoms but they give rise to metabolic side effects. Relatively recent antipsychotics such as asenapine are purported to be better at controlling psychotic symptoms without inducing motor or metabolic side effects. There is considerable hope that drugs that target the glutamate and non glutamate system currently under development, may offer considerable hope in treating positive, cognitive and negative symptoms of psychosis without inducing troubling side effects. Overall, very troubling or potentially fatal side effects underpin current antipsychotic treatment. In this regard, it is imperative that mental health nurses should underpin their practice by a comprehensive knowledge *of antipsychotics their actions, risks and benefits as these are vitally important in maintaining safe and effective patient care.*

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