

A REVIEW OF THE ADVERSE SIDE EFFECTS ASSOCIATED WITH ANTIPSYCHOTICS AS RELATED TO THEIR EFFICACY

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SUMMARY

Since the introduction of antipsychotic medication for the treatment of psychosis, a wide range of different types of antipsychotic drugs have been developed while their side effects have become evident. The side effects of both the typical and atypical generation of antipsychotics have important consequences for the quality of life of recipients, stigma experienced and also the level of care of patients. It is well acknowledged that the side effects of antipsychotics reduce compliance with the medication.

In this review the data for an association between typical and atypical antipsychotics and the main side effects that are well-supported in the literature was explored: weight gain and associated metabolic effects; extrapyramidal symptoms and tardive dyskinesia; prolactin elevation and associated sexual effects; QTc elongation; and a group of miscellaneous side effects. It has been demonstrated that the production of adverse effects following the use of antipsychotic medication differs widely both between atypical and typical drugs but also within these subgroups.

Considering the wide range of antipsychotics available amongst both groups and the differing effects they have on patients in terms of side effects, there is reason to believe that a more personalised approach to antipsychotic treatment should be considered. Additionally, screening for risk factors, screening for the appearance of side effects, as well as good communication with patients about the side effects and other options available are important tasks for clinicians in order to optimise concordance with medication.

Key words: antipsychotic drugs – atypical – extrapyramidal - metabolic effects – prolactin - side effects - tardive dyskinesia – typical - weight gain - QTc

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INTRODUCTION

Antipsychotics are a class of drugs used in the treatment of psychiatric disorders, most notably schizophrenia, but also in disorders such as bipolar disorder, delusional disorder and increasingly for certain non-psychotic disorders. Since the introduction of antipsychotic medication for the treatment of psychosis, a wide range of different types of drugs have been developed under this genre. The first generation of antipsychotic medication is known as the ‘typical antipsychotics’ and these were first discovered in the 1950s. Soon following their clinical use it was recognized that they caused extrapyramidal symptoms (EPS) in patients including parkinsonism, tardive dyskinesia, akathisia and dystonia (Steck 1954). The severe side effects created a need for a new generation of these medications that would be more tolerable to the patient. Subsequently, a second generation of antipsychotics were developed known as the ‘atypical antipsychotics’, the first of which was clozapine which was clinically introduced in the 1970s. While some success has been observed with a reduction in EPS, a new list of concerning side effects have been associated with both generations of the drugs – namely weight gain and associated metabolic effects; prolactin elevation; associated sexual

side effects; and QTc prolongation. Further, when the atypical anti-psychotic group was introduced it had been hoped that compliance to antipsychotics would be improved, but a 2008 review found that the data has not supported the original expectation that there would be increased compliance and better clinical results (Voruganti 2008).

The side effects of antipsychotic medication warrant discussion due to the negative impact they can have on a patient's quality of life, compliance in taking the antipsychotics (and thereby also relapse) and the stigma experienced by the patient. In the literature, the vast majority of studies on antipsychotics explore variations in efficacy between the drugs. It has been generally thought that the newer generation of antipsychotics are more effective than the typical. Although the question of whether this is the case has sparked some debate (Nandra 2012). Horacek et al. 2006 concluded that there was no difference (Horacek 2006) while others have found that atypicals were only somewhat more efficacious (Leucht 2003). Other reviews however have shown clozapine, risperidone, amisulpride and olanzapine to have higher efficacy than typical. This is particularly true of clozapine (Horacek 2006, Tuunainen 2000). While considerations of efficacy are obviously very important for drug administration, more studies

need to be conducted exploring differences in side effects caused by these drugs. The effectiveness of any medication may be markedly impaired if its side effect profile affects its acceptability to patients.

This review explores the evidence for widely reported subcategories of side effects of both typical and atypical antipsychotics. Guidance from the National Institute for Clinical Excellence (NICE) issued in 2009 and revised in 2014 suggested that three of the main side effects discussed in this review, namely EPS, metabolic problems and sexual dysfunctions were the ones found to be the most troubling by patients. The benefits of atypical medication over typicals may not be as strong as traditionally predicted in light of side effects such as metabolic disorders and QTc prolongation. Rather, considering the large amount of variation in adverse effects related to different drugs, research should endeavour to develop personalised treatment suited to the individual. Arguably, rather than focusing on a first-line treatment with atypicals each drug should be considered for its suitability to the patient's overall health, priorities and lifestyle. Certain side effects are likely to be variably problematic for patients of different ages, gender and demographics. Additionally, it is important for clinicians to be aware of the side effects of the antipsychotic that they choose to prescribe and follow-up the patient assessing the development of these adverse effects. Beyond this, it is important that the patient is aware that there is a range of antipsychotic medications available and that while side effects may be unavoidable, there are options. This is important as once established the negative effect of the drugs can be difficult or in some cases not possible to reverse. However, where possible other symptomatic medication can be provided for the side effects.

WEIGHT GAIN AND ASSOCIATED METABOLIC EFFECTS

Weight gain and other metabolic side effects of antipsychotic medication have come to light in more recent years, in particular as a consequence of atypical antipsychotic drug use. Antipsychotics are now well-established as weight-gain inducing agents. All antipsychotics have been associated with weight gain but different medications cause it to very different extents and it is not observed in all patients, although it is an important side effect to those who are affected due to downstream effects on the patient's self-image, morbidity and mortality. The mechanism is yet to be determined but proposed mechanisms include leptin desensitisation, 5HT_{2c} antagonism, H₁ antagonism and hyperprolactinaemia.

In 2005 Lieberman et al. published the large randomized double-blind CATIE study involving 1493 patients (Lieberman 2005). This study looked at the difference in effectiveness of the typical antipsychotic perphenazine and atypical drugs taken for up to 18 months in a double-blind study. The atypical drugs were

olanzapine, quetiapine, risperidone, and ziprasidone (ziprasidone was included following its approval by the FDA during the study's second phase). The lowest rate of discontinuation was seen for olanzapine, but this was also the drug that showed the largest discontinuation due to weight gain or metabolic effects (9 percent as opposed to 1-4 percent with the other drugs, $P < 0.001$). Olanzapine averaged 0.9 kg of weight gain per month as well as increased levels of glucose, triglycerides and cholesterol. It is worth noting that many patients on Olanzapine in CATIE were being prescribed 30mg daily, above the licensed dose. Arguably, a strength of the study lies in the fact that they did not exclude patients who had stable co-morbid psychiatric conditions or substance-use disorders, and thus the study was more reflective of patients as seen in real life. In 2008, Saddicha et al. studied the Effect of olanzapine, risperidone, and haloperidol treatment on weight and body mass index in first-episode schizophrenia patients in a group of Indian patients in a randomized, double-blind, controlled, prospective study (Saddicha 2008).

They measured weight, waist circumference, waist-hip ratio, and BMI, and the patients were randomly assigned to receive haloperidol, olanzapine, or risperidone and compared with a matched healthy control group. It was found that, in 66 patients there was a prevalence of overweight in 22.7% and obesity in 31.8%. Hence the prevalence of obesity was over 30 times as high as that of the matched healthy control group ($p < 0.001$). Patients in the olanzapine group had the greatest weight gain at 5.1 kg, followed by risperidone at 4.1 kg and haloperidol at 2.8 kg. Thus obesity was very commonly linked with antipsychotic medication in the Indian (south asian) population.

In 2009 Parsons et al. pooled 10 short-term and 11 long-term follow-up (over 6 months), randomised controlled trials to create a database that was analysed (Parsons 2009). They found that weight gain was substantially different among different antipsychotics with subjects on the atypical ziprasidone experiencing the least weight gain (a 7% increase relative to baseline), in contrast with two other atypicals, olanzapine and risperidone. The weight gain effects of the typical haloperidol were comparable to those of ziprasidone. Although sponsored by Pfizer, this study found results which accorded with those of the CATIE study. The data suggests both variation between and within the atypical and typical groups of antipsychotics with regard to the extent with which they cause weight gain, with ziprasidone appearing as a good choice of antipsychotic to reduce weight-gain risk. Ziprasidone is not presently available in the UK.

Antipsychotics are also known to have other metabolic effects. The use of atypical antipsychotics has shown greater association with diabetes than typical antipsychotics. Baker et al. (2009) used the FDA AERS database to analyse the data for an association between atypical antipsychotic drugs and diabetes, and between the typical haloperidol and diabetes. Their results

demonstrated a weak association of haloperidol, aripiprazole and ziprasidone with diabetes mellitus, hyperglycemia, increased blood glucose, diabetic ketoacidosis, and non-insulin-dependent diabetes mellitus. It is worth noting that Aripiprazole is a partial agonist of D2 which is credited with having a low propensity to cause weight gain. The atypicals olanzapine, risperidone, clozapine and quetiapine showed a stronger association with diabetes-related adverse events (DRAEs). Sernyak et al. 2002 found that age-controlled patients receiving atypical antipsychotics were 9% more likely to have diabetes than those on typical antipsychotics (Sernyak 2002). Further evidence for the trend of atypicals such as olanzapine posing a greater risk for diabetes can be seen in a study in 2008 by Saddicha et al. (2008). This is particularly important as it was carried out in a south Asian (Indian) population, which is known to have a high propensity to developing diabetes. They conducted a randomized double-blind controlled study comparing glucose measurements of first-episode schizophrenia sufferers and healthy controls prior to and subsequent to receiving either the atypicals olanzapine or risperidone or the typical haloperidol. Treatment with an antipsychotic medication was associated with a significant rise in fasting glucose.

Interestingly, this study also showed a tendency toward glycemic abnormality in patients with schizophrenia. The authors compared the blood glucose levels of the 99 treatment-naive patients with schizophrenia to the 51 healthy control subjects after overnight fast and 2 hours subsequent to a 75-g oral glucose tolerance test (OGTT). While no significant difference was found following the overnight fast between the groups, the patients with schizophrenia did show a significantly greater increase in blood glucose following OGTT than did the controls. These findings indicate that patients with schizophrenia are already susceptible to those metabolic abnormalities which are often described as the metabolic syndrome.

This link between Schizophrenia and a tendency to diabetes has not, however, gone unchallenged. Perez-Iglesias et al. have argued that fasting glycaemia and insulin concentrations at baseline did not support schizophrenia to be associated with an underlying abnormality in glucose metabolism (Perez-Iglesias 2009).

Further supporting evidence for metabolic effects of antipsychotics are shown by Wu et al's study in 2008. They compared body mass index (BMI), waist-to-hip ratio, insulin, and insulin resistance index (IRI) in 128 subjects with schizophrenia (Wu 2008). The subjects were randomly allocated to take the atypicals clozapine, olanzapine, risperidone or sulpiride for 8 weeks and the results were compared with those at baseline. No significant difference between the groups was seen at baseline but repeat measurements demonstrated significant increases in IRI, C-peptide and insulin at the end of the 8 weeks on antipsychotics. Fasting glucose measurements remained the same. Across the groups 70% of patients treated with clozapine showed increased IRI

levels, compared to 62%, 31% and 35% for olanzapine-, risperidone- and sulpiride-treated patients respectively.

These studies demonstrate the differing risk of diabetes for different antipsychotics, suggesting a need for metabolic monitoring of patients taking antipsychotics. The very least that should be offered to patients after receiving antipsychotic medication is that they be weighed and have their body mass index (BMI) and waist circumference calculated at regular intervals, and more frequently during the early stages of treatment. Similarly, prior to being prescribed a diabetogenic drug such as olanzapine a patient should be assessed for other risk factors of diabetes including a family history.

A further metabolic effect of antipsychotics is that on lipids and cholesterol. First generation antipsychotics, particularly low potency phenothiazines, cause increases in triglycerides and LDL cholesterol and decreases in HDL cholesterol (Rummel-Kluge 2010). Haloperidol has a minimal effect on lipid profiles (16). Atypical antipsychotics tend to raise cholesterol and in particular triglycerides, and raised triglyceride levels are associated with obesity and diabetes. Olanzapine has the greatest propensity to increased cholesterol and lipids, quetiapine has a moderate propensity, and risperidone has a moderate to minimal propensity, while aripiprazole and ziprasidone have minimal adverse effects on blood lipids (Rummel-Kluge 2010, Sasaki 1985). Clozapine doubles triglyceride levels and increases cholesterol levels by 10% after treatment for five years (Henderson 2000).

Interestingly, some studies have tended to downplay or challenge the evidence that metabolic side effects of atypical antipsychotics are greater than those of typicals. Perez-Iglesias et al. found that there were no significant differences between haloperidol, olanzapine and risperidone concerning metabolic adverse effects after the first year of treatment (Perez-Iglesias 2009).

Importantly, the findings of Perez-Iglesias suggest that alongside considering the potential metabolic effect of antipsychotic medication, one must consider the effect of lifestyle changes. It is possible that lifestyle may change as a result of the patient receiving a diagnosis of a psychiatric illness. Being diagnosed with a psychiatric illness is likely to be a very difficult time in a patient's life, and may potentially result in comfort-eating or serve as a distraction to exercise or other similar activities that the patient may have previously engaged in. Such effects need to be accounted for when assessing metabolic effects of antipsychotics.

EXTRAPYRAMIDAL SYMPTOMS (EPS) AND TARDIVE DYSKINESIA (TD)

It was shortly after the development of the first typical antipsychotics that extrapyramidal side effects (EPS) were recognized to be a side effect of these drugs. These include parkinsonism, acute dystonia, akathisia, and Tardive Diskinaesia. These motor side effects are

less frequently encountered now than a few decades ago, most likely because of the introduction and more first-line use of the atypical generation of antipsychotics. Schooler et al. 2005 conducted a study comparing the development of EPS in first-episode psychosis patients (N=555) following use of the typical haloperidol and the atypical risperidone (Schooler 2005). They found that there were significantly more EPS and adjunctive medication use among the subjects receiving haloperidol compared to the risperidone group (but increased prolactin elevation and weight gain with risperidone). Further evidence is from 7 randomised control trials assessing EPS as a consequence of haloperidol use. They showed haloperidol resulted in increased rates/severity of parkinsonism and akathisia when compared to one or more atypical anti-psychotics (assessed by a standard rating scale) (Schooler 2005, Crespo-Facorro 2006, Crespo-Facorro 2011, Emsley 1999, Gaebel 2007, Green 2006, Kahn 2008, Lieberman 2003, Moller 2008, Sanger 1999). It would be a valid criticism that some of these studies used high doses of haloperidol in demonstrating EPS, however two of these studies used doses \leq 4 mg, i.e. a low dose. Leucht et al. 2009 published a meta-analysis of randomised control trials which similarly showed that atypical anti-psychotics produced fewer EPS than haloperidol, including at low dose levels (Leucht 2009). These findings are particularly interesting considering that most studies declare greater anticholinergic use and dropouts among patients receiving haloperidol compared to atypicals; which would be expected to reduce the appearance of EPS difference. Four of the studies included in the meta-analysis lasted long enough (more than a year) to be able to assess development of TD. It should be noted that the information from the Leucht study is acceptable even if, rather than using direct reporting of parkinsonian like symptoms some of the included studies used use of anti-cholinergics as a surrogate marker of EPS, since the use of anti-cholinergics correlates reasonably well with the incidence of EPS. The study by Schooler et al. 2005 found that the typical haloperidol led to increased rates of TD compared to the atypical risperidone, and Green et al. 2006 found the same result when comparing haloperidol to olanzapine (Schooler 2005, Green 2006). An increased risk of TD with haloperidol is further supported in a meta-analysis of 11 long-term studies by Correll et al. (2004). Glenthøj et al. 2007 found the same atypicals advantage when comparing risperidone and zuclopenthixol induced EPS (Glenthøj 2007).

The CATIE study found no significant differences between the two generations of antipsychotics in the development of EPS as assessed by rating-scale measures of severity. The typical perphenazine was found to be similarly efficacious to the atypicals quetiapine, risperidone and ziprasidone and not to cause more adverse effects (as supported by a meta-analysis by Leucht et al. 2009), but was associated with more discontinuation due to extrapyramidal effects. However,

dosing was unusually high for perphenazine which may reflect the intolerability of the EPS for those receiving perphenazine (Lieberman 2005). Disparity from normal doses was also seen for patients on risperidone, quetiapine and ziprasidone who were given unusually low doses (Lieberman 2005). Finally, one cannot be certain that the discontinuation observed was not due to other factors than just the effects of the antipsychotics. In 2008, Miller et al. (2008) performed an analysis of the CATIE data and found that the incidence rates for dystonia, parkinsonism, akathisia, and tardive dyskinesia as determined by continuous rating scale measures showed no statistically significant differences between any SGA and perphenazine, or between any pair of SGAs.

While there are studies that support the frequently-held opinion that typical antipsychotics cause more movement disorders than atypicals, studies such as the CATIE study suggest that the difference between typicals and atypicals may not be as notable as previously thought. EPS can be very disabling for the patient and contributes significantly to stigma due to the visibility of these symptoms and well-established association with antipsychotic medication. Nor are these symptoms often reversible, tardive dyskinesia for instance frequently remains even if the subject discontinues their use of antipsychotics. Due to the severe impact of EPS on a patient serious consideration should be taken prior to prescribing high-risk drugs such as haloperidol. However, there is medication such as anticholinergics that can be taken, to reduce the effects of these side effects – although often with limited success. It is worth noting that even for an EPS sparing medication such as aripiprazole case reports of acute dystonia have emerged (Oommen 2006).

PROLACTIN ELEVATION AND ASSOCIATED SEXUAL SIDE EFFECTS

Both atypical and typical antipsychotic drugs work by blocking D2 receptors and thereby reducing the increased dopamine transmission which occurs as a feature of psychosis. An undesired consequence of a lack of selectivity of antipsychotics is that they also block D2 receptors on lactotrophs and as such cause elevated release of prolactin. Indeed, increased levels of prolactin and subsequent hyperprolactinaemia is a frequent side effect of antipsychotic medication which may result in galactorrhoea, gynaecomastia, menstrual irregularities, sexual dysfunction and demineralisation of bone (osteoporosis). The link between dopamine and prolactin is supported by the findings that baseline mean serum levels of prolactin are lower in drug-naive patients with schizophrenia than in healthy controls, and some studies such as Rao et al. 1993 have even demonstrated lower baseline levels of prolactin in female drug-naive patients with schizophrenia when compared to healthy female controls (Rao 1993, Rao 1994, Meltzer

1974, Keks 1987). Antipsychotics have been shown to increase prolactin levels in both healthy controls and in patients with schizophrenia within a time-frame of minutes after administering a dose of typical antipsychotics. Meltzer et al. 1979 measured serum prolactin levels prior and subsequent to administration of the typical antipsychotic phenothiazine to 27 newly admitted patients with schizophrenia (Meltzer 1979). Within 72 hours the serum prolactin levels showed a mean 3.2-fold and 3.8-fold increase in men and women respectively. This increase in baseline levels was reflected in all subjects and remained over a three-month period, suggesting that tolerance to this side effect did not increase over time. This effect on prolactin has been shown to be dose-related, emphasizing the well-recognised need to maintain psychotic patients on the lowest effective dose of medication to reduce adverse events (Keks 1987, Green 1988, Agius 2012, Agius 2011). Smith et al. 2002 studied HPG axis function in 67 diagnosed schizophrenics who had been diagnosed and stabilised for no less than 2 years on typical antipsychotic drugs (Smith 2002). They found a significant correlation between dose of drug and plasma prolactin levels for the total group ($P < 0.001$).

Unlike the typical antipsychotics, some members of the atypical group of antipsychotics have shown more promising results with regard to prolactin levels. Across their full range of doses quetiapine (Small 1997, Arvanitis 1997) and clozapine (Meltzer 1979) showed only moderate increase in prolactin levels above the normal range at standard doses. While olanzapine is often considered to be a prolactin sparing drug, this is not the case at higher doses (Crawford 1997, Tollefson 1999). Furthermore there is evidence that two of the atypicals, risperidone and amisulpride do result in increased prolactin levels in serum in a sizeable proportion of patients (Peuskens 1995, Grunder 1999, Kim 2012). Kleinberg et al. pooled the data from two large randomised double-blind, controlled clinical trials comparing the effects of a series of doses of risperidone taken daily (1, 2, 4, 6, 8, 10, 12 and 16mg), haloperidol (10 and 20mg) and placebo. They found that both risperidone, an atypical antipsychotic, and haloperidol, a typical antipsychotic, showed a correlation between dose and plasma prolactin levels in both sexes (Kleinberg 1999). Notably, this effect may reduce after long-term treatment with some antipsychotics. Olanzapine and haloperidol treatments have been shown to not significantly affect serum prolactin levels over the long term. However, after 1 year, elevated prolactin levels were shown to persist in most patients treated with risperidone in the same study (Perez-Iglesias 2012).

Evidence from first-episode patients is important when considering hyperprolactinaemia as a side effect of antipsychotics. Riecher-Rossler et al. 2013 found that 39% of antipsychotic-naïve patients in their study showed hyperprolactinaemia not explained by any other reason. They suggest that raised prolactin levels may be present in patients with schizophrenic psychoses inde-

pendent of antipsychotic medication, and may rather be triggered by a factor such as stress. Stress itself may also trigger the outbreak of psychosis (Riecher-Rossler 2013). Furthermore, Kim et al. 2012 found that self-reported endocrine-related side effects were not associated with prolactin elevation during amisulpride treatment (Kim 2012).

Data supports the notion that elevated levels of prolactin are a consequence of long-term exposure to antipsychotics, particularly in higher doses (Turrone 2002, Graham 2011, Stubbs 2009). Especially susceptible are those treated with certain typical antipsychotics and particular atypical antipsychotics such as risperidone, paliperidone and amisulpride. While the downstream effects of hyperprolactinaemia are not common, they are among the main adverse effects quoted by patients as a reason for non-compliance (Stubbs 2009, Zadrozna-Sliwka 2007, Maggi 2013, Novick 2009). Subsequent to the first episode of psychosis a patient is often prescribed antipsychotic medication at least long term and not unusually as a life-long treatment. After such a lengthy period on the medication the patient is likely to be particularly vulnerable to effects such as osteoporosis and associated fractures due to the negative impact of prolactin on bone mineral density, especially if the medication was started prior to maximum bone mineralisation (Zadrozna-Sliwka 2007, Maggi 2013). The sexual side effects of hyperprolactinaemia such as reduced libido are likely to contribute further to non-compliance among younger patients. Therefore, this is something that should therefore be discussed and considered by the clinician and the patient when choosing between treatment options (Novick 2009, Malik 2011). However, it is important to bear in mind that libido can be affected by a range of other factors as well and there is some suggestion that the effect of reduced libido may be due to the disease itself (NICE 2006). Additionally, the consequences of raised prolactin levels are likely to be a particular problem to women who want to conceive and as such NICE also recommends that women with bipolar disorders who are trying for a baby are made aware of the reduced probability of conception due to elevated prolactin when prescribed antipsychotics.

QTc PROLONGATION

Antipsychotic drugs are associated with ECG alterations and are thought to be linked to ventricular arrhythmia and sudden cardiac death. In particular through a blocking action on cardiac potassium channels they extend the cardiac QTc interval, a risk factor for torsade de pointes (TdP), a potentially fatal condition (Glassman 2001). There is substantial evidence suggesting a role for both atypical and typical anti-psychotics in causing QTc prolongation. Since the link was first made for the typical antipsychotic thioridazine (Wright 2001), the evidence has been growing supporting their association with QTc prolongation (Reilly 2002, Zimbroff 1997) and sudden cardiac death

(Reilly 2002, Reilly 2000). In 2002, Reilly et al. conducted a case-control study of in-patients who died suddenly in five psychiatric departments (Reilly 2002). Controls were matched for age, sex and psychiatric disorder. In 69 case-control clusters they found that sudden unaccounted for death was significantly associated with being on typical thioridazine medication (adjusted odds ratio=5.3, 95% CI 1.7-16.2, P=0.004). Two years previously Reilly et al. 2000 reported that droperidol and thioridazine caused QTc prolongation in a dose-dependent way. They analysed the electrocardiograms of 101 healthy controls and 495 psychiatric patients and found that thioridazine and droperidol (odds ratio 5.4 (95% CI 2.0-13.7) and odds ratio 6.7 (95% CI 1.8-24.8) respectively) were reliable predictors of QTc prolongation as was the dose at which the antipsychotic medication was given; high dose 5.3 (1.2–24.4); very high dose 8.2 (1.5–43.6) (Reilly 2000).

Similar results have been found for the atypical group of antipsychotics. In 1997, Zimbhoff et al. found that ECGs revealed that three sertindole-taking groups had a significantly greater increase in QT and QTc intervals than the placebo group. Mean QT/QTc changes for the sertindole 12-, 20-, and 24-mg groups and placebo were 7/11 msec, 17/19 msec, and 19/21 msec, and -5/-4 msec, respectively (Zimbhoff 1997). Other studies have supported these results. Daniel et al. 1998 found that in a randomised trial comparing sertindole to haloperidol, none of the subjects receiving haloperidol had QTc intervals over 500msec ($p < 0.05$), in contrast with 8% of the subjects receiving sertindole (Daniel 1998). The atypical ziprasidone has similarly been shown to increase the QTc interval however when comparing ziprasidone to sertindole, it can be seen that the incidence of a QTc greater than or equal to 500 msec is greater with sertindole. Studies have shown the incidence of QTc elongation to be 50 or 100 times greater in subjects receiving sertindole compared to ziprasidone (FPDA 2000).

The same magnitude of effect has not been seen for other atypical antipsychotics such as risperidone and clozapine. At normal therapeutic doses, risperidone has been observed to cause minor elongation of QTc Wright 2001, Reilly 2002, Zimbhoff 1997), but has not been shown to cause TdP. Kang et al. 2000 studied the cardiovascular effects of sixty-one patients treated with clozapine. While clozapine was shown to increase the QTc interval in a dose-dependent manner, it was found that a pathological effect was rare. In the one patient without an underlying ECG abnormality that experienced QTc prolongation (>500msec), the QTc normalised despite increasing doses of clozapine. One patient with an underlying ECG abnormality also showed an elongation to > 500 msec (Kang 2000).

Due to the potentially devastating effects of QTc prolongation ECG monitoring is important for patients prescribed antipsychotics, in particular high dose antipsychotics and in patients who are being treated with a mixture of different antipsychotics. However, there are a few potential difficulties in that psychiatrists

may have limited knowledge in how to interpret an ECG and also ECG machines are not as easily accessible in all clinical areas as in general medicine (Yerrabolu 2000). The data has shown that QTc elongation is more of a risk with certain antipsychotics than others, and this is something that clinicians need to consider in prescribing patterns, especially in patients with other risk factors for QTc elongation and arrhythmia such as ischemic heart disease and stress.

Mention should be made of further cardiovascular problems associated with the atypical antipsychotic clozapine. Tachycardia may occur in clozapine therapy, and may be related to myocarditis. Clozapine has been associated, mainly in data from Australia and New Zealand, with myocarditis and cardiomyopathy (Kilian 1999, Ronaldson 2011). Myocarditis usually occurs within eight weeks of starting clozapine, while cardiomyopathy occurs later. Hence patients should be monitored closely for signs of heart failure associated with these conditions especially in the first few months of starting treatment. Signs of myocarditis include tachycardia, fever, flu-like symptoms, fatigue, dyspnoea, chest pain, ST depression on ECG, eosinophilia and enlarged heart on radiography. Cardiomyopathy will present with signs of heart failure (Kilian 1999, Ronaldson 2011). Furthermore, Clozapine has been linked with a risk of pulmonary thromboembolism, as have some other antipsychotic drugs (Hagg 2000).

A cardiovascular side effect of antipsychotics is their effects on blood pressure.

Postural hypotension occurs with antipsychotics which are antagonistic at postsynaptic adrenergic alpha1 receptors. Such drugs are clozapine, olanzapine, quetiapine and risperidone (Taylor 2009, Taylor 1995). Quetiapine is particularly well known in this respect (McManus 1999). In contrast, some antipsychotics, such as clozapine, olanzapine and risperidone can induce hypertension because they are antagonists at pre-synaptic alpha2 adrenergic receptors, causing noradrenaline release and hence increased vagal activity and vasoconstriction (Abi-Dargham 2005, Gupta 1994).

OTHER MISCELLANEOUS SIDE EFFECTS OF ANTIPSYCHOTICS

A number of other side effects of antipsychotics exist.

Most antipsychotics are known to lower the seizure threshold in patients with epilepsy, and in patients on clozapine it is known that seizures can occur for the first time (Pacia 1994). This effect can also occur with other antipsychotics (Pisani 2002, Hedges 2003, Zhang 2012). Almost all antipsychotics have been associated with hyponatraemia (de Leon 1994), and this in itself can reduce the seizure threshold. The hyponatraemia may be caused by water intoxication (de Leon 1994), drug-induced syndrome of inappropriate antidiuretic hormone (Siegler 1995), and severe hyperlipidaemia or hyperglycaemia (Siegel 1998).

Table 1. Issues related to side effects of antipsychotic medication

- Adverse events of antipsychotics reduce patients' quality of life, compliance with taking the antipsychotics (and thereby also relapse) and the stigma experienced.
- Important side effects include weight gain and associated metabolic effects; extrapyramidal symptoms and tardive dyskinesia; prolactin elevation and sexual effects; QTc elongation.
- The appearance of adverse events differ greatly between antipsychotic drugs.
- In choosing antipsychotic medication, efficacy must be balanced by tolerability of the medication.
- A personalised approach to treatment taking into account the subjective impact of certain side effects on a patient's life could potentially benefit the patient.
- Communication between patients and doctors about the adverse events and screening for side effects are important.

Another rare but potentially fatal side effect of all anti-psychotics is neuroleptic malignant syndrome. This is a syndrome of sympathetic hyperactivity as a result of dopaminergic antagonism. Psychological stress and genetic predisposition are involved in its development. Symptoms include fever, diaphoresis, rigidity, confusion, fluctuating consciousness, fluctuating blood pressure, tachycardia, leucocytosis and altered liver function tests. A raised plasma creatinine kinase is an important marker (Guze 1985).

Constipation is a common but a little discussed side effect of antipsychotics. Antipsychotic agents differ in their liability to induce constipation, but clozapine is a common cause. Constipation can be severe and can lead to serious consequences such as paralytic ileus, bowel occlusion and death (De Hert 2011) Ischemic colitis may also result (Shah 2013).

Sedation is a well known side effect of many antipsychotics, indeed they are often referred to as major tranquillisers. Quetiapine is one good example of an antipsychotic which is well known to cause sedation (McManus 1999, Datto 2009).

There are also some other side effects which relate specifically to clozapine. It is well known that Clozapine can cause neutropenia and occasionally agranulocytosis (Schulte 2006). This requires that patients be regularly monitored for this condition initially, for 8 weeks every week, then subsequently every 2 weeks for the next 8 weeks, then monthly while the patient is under treatment. Hypersalivation (Fritze 1995), fever (Kohen 2009), nausea, nocturnal enuresis (Warner 1994), may also occur. Less common reported side effects of clozapine include colitis, delirium, eosinophilia, heat Stroke, hepatic Failure, pancreatitis, pericardial effusion, pneumonia, thrombocytopenia, and single case reports of vasculitis and ocular pigmentation (Taylor 2009).

Finally, chlorpromazine causes photosensitivity, and the NICE for schizophrenia have recently drawn attention to this fact (NICE 2014).

DISCUSSION

This review has demonstrated that despite the development of a new generation of drugs, side effects are still a significant issue for both the typical and

atypical antipsychotics. The broad range of side effects of antipsychotics, both of the typical and atypical generation, have important consequences for the quality of life of recipients and also for their level of care. It is well acknowledged that the side effects of antipsychotics reduce compliance with the medication. In this review it has been demonstrated that the production of adverse effects following the use of antipsychotic medication differs widely both between atypical and typical drugs but also within these subgroups. Considering the wide range of antipsychotics available among both generations and the differing effects they have on patients in terms of side effects, a more personalised approach to antipsychotic treatment needs to be considered. Such an approach has recently been advocated by NICE. For instance, medication should be titrated by the psychiatrist in conjunction with the patient to the lowest efficacious dose to try to reduce the side effects experienced to a minimum. The side effects experienced should also be targeted for the individual patient, e.g. anticholinergic medication such as procyclidine for EPS, or weight management programs for the obese and overweight patients. Such improvements in lifestyle as weight management programs are also advocated by NICE, but it would be useful to have data on how effective such programs are in fact in reducing such side effects as weight gain once they have been established.

Furthermore, with so many wide ranging side effects of antipsychotics, psychiatrists need to maintain a very effective watch on their patients and intervene as necessary. Patients should be made aware from the outset of starting antipsychotic medication that should they experience side effects that there are measures that can be taken to address this, as they may suffer in silence as it were thinking that the side effect is a necessary evil, or they may not think to attribute the effect to the medication and as such neglect to mention it to their psychiatrist. Psychiatry requires the same diagnostic and therapeutic acumen as the general physician.

Many studies in the field have focused on the different levels of efficacy of antipsychotic medication, with arguably not enough consideration provided for the important role of side effects in patient satisfaction with

their medication. The prevalence of side effects with antipsychotics are common and can be severe and disabling, adding to the stigma and poor self-image already experienced by many psychiatric patients. Ideally future research will further explore both typical and atypical antipsychotic side effects and the patient opinion of the drugs that they are taking, and to combine this work with studies of efficacy in reducing psychotic symptoms. Conflict may arise between efficacy data and data on side effects which can only be resolved by explaining the different options to the patients. The use of atypical medication as first-line treatment should be carefully considered and each drug should arguably be considered on its own merit as suited to the patient. However, on balance, it appears that the typicals often have more severe side effects such as EPS and this often does lead to atypicals sensibly being used as first-line for first-episode psychosis, at least in the short-term.

NEW CONSIDERATIONS

New atypical Antipsychotics are being introduced. Asenapine is a new atypical antipsychotic which has been introduced in the UK as a treatment for Mania, but it is also used in the USA for treatment of Schizophrenia. An attraction for using this medication is that it is suggested to improve cognitive defects in Schizophrenia, however, unlike other atypicals, extrapyramidal side effects are said to be more common in Asenapine than in Olanzapine (Buchanan 2012). On the other hand, the same study suggested that weight gain was consistently lower with asenapine (Buchanan 2012). Lurasidone is also said to improve cognition and depressive symptoms (Samalin 2011), but equally it does also appear to cause extrapyramidal side effects. Thus Samalin et al. (2011) report that 'it seems to have a significant although moderate link with the occurrence of akathisia, extrapyramidal symptoms, and hyperprolactinemia at the start of treatment.' On the other hand, they also report that 'Lurasidone differs from the other second-generation antipsychotics by having a good tolerability profile, in particular for cardiometabolic tolerability' (Samalin 2011).

Hence there arises an important consideration, which is that side effects of antipsychotic medication do vary from medication to medication, and that therefore when choosing a medication, the balance of side effects in different medications within individual patients needs to be considered when considering the choice of medication for any individual.

Lucht et al. (2013) have conducted a multiple-treatments meta-analysis of 15 antipsychotic medications in schizophrenia. They found that Antipsychotics differed substantially in side-effects. The drugs studied included clozapine, amisulpride, olanzapine, risperidone, paliperidone, zotepine, haloperidol, quetiapine, aripiprazole, sertindole, ziprasidone, chlorpromazine, asenapine, lurasidone and iloperidone .

All these medications were assessed in terms of the main side effects we have discussed. The outcomes were that odds ratios compared with placebo for extrapyramidal side-effects ranged from 0.30 (clozapine, the best medication in this respect) to 4.76 (haloperidol, the worst medication in this respect) (Lucht 2013). For sedation the odds ratios compared with placebo were 1.42 (amisulpride, the best medication in this respect) to 8.82 (clozapine the worst medication in this respect) (Lucht 2013). While they reported that standardised mean differences compared with placebo for weight gain varied from -0.09 for the best drug (haloperidol) to -0.74 for the worst drug (olanzapine) (Lucht 2013). Standardised mean differences compared with placebo for prolactin increase ranged from 0.22 (aripiprazole, the best medication in this respect) to -1.30 (paliperidone, the worst medication in this respect) (Lucht 2013). Finally standardised mean differences compared with placebo for QTc prolongation ranged from 0.10 (lurasidone, the best medication in this respect) to -0.90 (sertindole, the worst medication in this respect) (Lucht 2013). Clearly, from these figures, all the medications studied could , to varying degrees , have each of the studied side effects in different degrees.

Side effects in relation to efficacy

Clearly, when choosing antipsychotics for a particular patient, the efficacy of the medication needs to be taken into consideration.

The Cutlass study has shown that Clozapine is more efficacious than other antipsychotics (Davies 2008). Hence, given its side effect profile, it is reserved for resistant schizophrenia. However, more controversially, it has suggested that first and second generation antipsychotic medications were similar in efficacy (Jones 2006). It is possible that biases within the study design, may have contributed to this result (Agius 2010). This has also been suggested by the CATIE study previously discussed, even though Olanzapine, which was often prescribed in CATIE in a dose of 30 mg, which is higher than it is licenced for, appears the more efficacious medication, when discontinuation rates were used as a measure of efficacy (Lieberman 2005). The discontinuation rates between Perphenazine and Olanzapine were quite similar, suggesting that there was little difference between the two medications in efficacy (Lieberman 2005). Meanwhile, it has been pointed out that the doses used of Quetiapine and Ziprasidone were particularly low, which might account for their lower efficacy in the study (Lieberman 2005). Metanalyses tell a different story. Davies had early on shown that , leaving aside Clozapine, which is to be considered the most efficacious, reserved for resistant schizophrenia antipsychotic medications could be divided into two groups; those which were more efficacious, such as Olanzapine, Amisulpride, and Risperidone, and those which were less efficacious, such as Quetiapine (Davis 2003), and later Lucht et al's further Metanalyses

included Aripiprazole (Lucht 2009). They showed that ‘Clozapine was superior to zotepine and, in doses >400 mg/day, to risperidone’ (Lucht 2009). ‘Olanzapine proved superior to aripiprazole, quetiapine, risperidone, and ziprasidone. Risperidone was more efficacious than quetiapine and ziprasidone,’ (Lucht 2009) thus showing that all atypical antipsychotics are not the same in efficacy.

Returning to the 2013 study by Lucht et al., it is clear that not all the medications studied were similar in efficacy. It was reported that ‘All drugs were significantly more effective than placebo’ (Lucht 2013). The results suggested that clozapine was the most efficacious, while a more efficacious group of medications included amisulpride, olanzapine, risperidone, paliperidone, and zotepine, while a rather less efficacious group included haloperidol, quetiapine, aripiprazole, sertindole, ziprasidone, chlorpromazine, asenapine, lurasidone and iloperidone (Lucht 2013).

This brief survey of efficacy data demonstrates that, when choosing antipsychotic medication for a particular patient, efficacy needs to be balanced against side effects, as well as side effects being balanced against each other. To give some examples of this, the higher efficacy of clozapine needs to be balanced against its low propensity to extrapyramidal side effects and its high propensity to weight gain, while on the other hand, the low propensity of aripiprazole to hyperprolactinaemia, weight gain and extrapyramidal side effects needs to be balanced against its lower efficacy compared to Olanzapine, which in turn is more likely to cause weight gain and metabolic syndrome.

CONCLUSION

Personalised medicine is a medical model already on the increase within healthcare and is the idea that care is tailored to the individual patient, according to both their needs and desires. Side effects and efficacy of the range of medication should be considered on a case by case basis. For instance, to a younger demographic of patients, sexual dysfunction may be a relatively larger problem, as may also be weight gain. For an older demographic and in particular those with co-morbid cardiovascular problems, the QTc prolongation may be a bigger issue to consider when choosing an antipsychotic. Additionally, it is likely that the same drug will have different effects on different patients, and genetics and environmental factors are likely to play a role. It is possible that in the future genetic testing may become useful in aiding the choice of antipsychotic medication. It is vital that doctors are conscious of these issues that differ between both drugs and patients. Additionally, there needs to be more awareness regarding side effects among the patients receiving them – doctors should be asking questions to detect them and ensure that patients are aware of them. Patients are often prescribed medication with little or no knowledge of alternative drugs available and as such accept side

effects as a consequence. It is fortunate that in the field there is a multitude of antipsychotic drugs available – the most should be made of this to recognise the limitations and advantages of each drug for a particular patient. In this way, care and long-term success of treatment can be optimised.

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