"First do no harm." A systematic review of the prevalence and management of antipsychotic adverse effects

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Abstract

Aims: We aim to identify the prevalence and management strategies of nine clinically important categories of antipsychotic adverse effects, namely: extrapyramidal symptoms; sedation; weight gain; type II diabetes; hyperprolactinaemia; metabolic syndrome, dyslipidaemia; sexual dysfunction; and cardiovascular effects.
Background: Antipsychotic drugs are widely prescribed for schizophrenia and other mental disorders. The adverse effects of antipsychotics are common, with a potential negative impact on adherence and engagement. Despite this, the scientific study of the prevalence or management of adverse antipsychotic effects is a neglected area.
Method: A systematic review was undertaken using pre-defined search criteria and three databases, with hand searching of citations and references. Inclusion was agreed on by two independent researchers after review of abstracts or full text. Quality analysis of included studies was conducted using pre-agreed criteria.
Results: In total, 53 studies met inclusion criteria, revealing the following: (1) antipsychotic polypharmacy was associated with increased frequency of adverse effects, and (2) a longer duration of treatment is associated with greater severity (e.g. higher BMI); (3) clozapine was more strongly associated with metabolic disturbance than other antipsychotics in three studies and olanzapine was associated with the most weight gain in three studies; (4) hyperprolactinaemia was more common in women than men, but 50% men noted sexual dysfunction versus 25–50% in women; (5) despite clinical guideline recommendations there is a low rate of baseline testing for lipids and glucose; and (6) seven studies described adverse effect management strategies, but only two examined their efficacy – one found a significant reduction in weight with non-pharmacological group therapy and the other found a significant reduction in dyslipidaemia with statins.
Conclusions: Antipsychotic adverse effects are diverse and frequently experienced, but are not often systematically assessed. There is a need for further scientific study concerning the management of these side effects.

Keywords
Antipsychotics, adverse effects, prevalence, management

Introduction

Antipsychotic medications are the cornerstone treatment for schizophrenia, and are widely used in other mental disorders (Taylor et al., 2008). Use of these medications is often part of a long-term maintenance treatment programme, so the deleterious physical, psychological and indeed social impact of any adverse effects is particularly important. Antipsychotic adverse effects are commonly encountered by both the patient and prescriber (Leucht et al., 2009a, 2012), and are diverse ranging from neurological or extrapyramidal symptoms (EPS) to adverse metabolic effects including weight gain and hyperprolactinaemia, as well as cardiac effects such as QTc prolongation.

Studies (Fleischhacker et al., 1994; Lambert et al., 2004; McCann et al., 2009) have examined the effect of antipsychotic adverse side effects on adherence with antipsychotic medication. Lambert et al. (2004) reported that the majority of patients with schizophrenia rated sexual dysfunction, EPS and psychic effects as more distressing than sedation or vegetative adverse effects, and concluded that previous negative experiences due to adverse effects significantly influenced non-adherence with present and future therapy. This association between adverse effects and non-adherence was also demonstrated in two other studies (Fleischhacker et al., 1994; McCann et al., 2009).

Despite this, and the fact that antipsychotics have been available since 1952, there appears to be a relative dearth of specific data on the prevalence of adverse effects, and particularly on their management. We therefore aimed to

- Systematically review studies regarding the prevalence of nine categories of clinically important adverse antipsychotic effects, namely EPS, sedation, sexual dysfunction, hyperprolactinaemia, metabolic syndrome, weight gain, type 2 diabetes, dyslipidaemia and cardiovascular effects;

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- Systematically assess the quality of the published studies which met our a priori inclusion criteria; and
- Systematically search for data on the management of these nine pre-specified categories of clinically important antipsychotic effects.

Methodology

Search strategy and study eligibility

An electronic search of the following databases was carried out: Embase, PsychINFO and Ovid MEDLINE(R). The subject headings used included:

(a) **Management.mp**, or Medication Therapy Management, Disease Management, Management or **Prevalence.mp**, or Prevalence and

(b) **Antipsychotic.mp** or Atypical Antipsychotic Agent, Neuroleptic Agent, and

(c) **Antipsychotic side effects.mp** or Adverse Drug Reaction or **Extrapyramidal symptoms.mp** or Extrapyramidal Symptom, **Tardive Dyskinesia.mp** or tardive dyskinesia, **Akathisia.mp** or akathisia, **Parkinsonism.mp** or parkinsonian like symptoms, **Sedation.mp** or Conscious Sedation, Sedation, **sexual function.mp** or Sexual Dysfunction, Sexual function, **Metabolic Disorder.mp** or metabolic disorder, **diabetes mellitus.mp** or diabetes mellitus, **Dyslipidaemia.mp** or Dyslipidaemia, Hyperlipidaemia, **Prolactin.mp** or prolactin, **Hypertension.mp** or hypertension, **Weight gain.mp** or Weight gain, **Cardiac side effects.mp** or heart, side effect, adverse drug reaction, cardiotoxicity, **long QT prolongation.mp** or long QT syndrome,

(d) **Case Control Studies.mp.** or Case-Control Study, **Cohort Studies.mp.** or Cohort Analysis

The results of the search were screened for suitability. These studies were further screened for eligibility based on the inclusion criteria:

a. Full-text literature published in English.
b. Case-control, cohort studies, or cross-sectional studies.

Randomised controlled trials (RCTs) are primarily able to determine whether a given treatment has efficacy or adverse effects, but tend to be too small or short to establish the frequency and severity of adverse effects (AEs). Observational studies allow a more detailed and long-term assessment of AEs, and the strengths of observational studies are supported by a review by Concato et al. (2000), who concluded that the findings of well-planned observational studies do not systematically overestimate the magnitude of treatment effects compared with RCTs on the same topic. However, different definitions and end-point measurements are often used in observational studies, and observational studies are subject to various forms of bias. Thus, a quality analysis of observational studies was carried out on all articles included in this review. For the purpose of our study we have chosen to omit RCTs from our review, due to the relative short-term nature of most such studies. RCTs also did not fulfil the aims of our study, which was to review studies whose primary objective was to address the prevalence or management of antipsychotic AEs. We excluded RCTs of the management of AEs as these have been systematically evaluated in the Cochrane Library and other systematic reviews. Our aim in this article was to better understand the frequency and management of AEs in the real world of clinical practice which RCTs are not usually designed to answer.

With regards to future research, the findings of observational studies on the prevalence and management of antipsychotic AEs would provide a basis for clinical trials assessing particular interventions for antipsychotic AEs.

Data extraction

The shortlisted studies were then analysed and the following data were extracted:

a) Prevalence of AEs and associations
b) Incidence of AEs and associations
c) Management strategies for AEs

Quality of studies

The studies included in this systematic review were assessed for quality. A score was given for study design: 4, prospective cohort studies/follow-up studies; 3, retrospective cohort studies; 2, case control studies and 1, cross-sectional survey. The studies were also assessed using the following criteria: explicit aims, size of the population investigated, presence of a control group for comparison (for management strategies), validity and reliability of methods, response and drop-out rates specified, use of standardised validated outcome measures and well-summarised conclusions with acknowledgement of limitations and suggestions for further research.

Each of these criteria was allocated 1 point and the total score for each article was calculated. The six studies which had the highest quality scores were extracted and analysed in greater detail, in order to identify recurrent findings, and emerging themes.

We analysed studies of children and adolescents (under 18 years) separately from adults, as it has been suggested (Lewis, 1998; Whitaker and Rao, 1992) that children may be more sensitive to antipsychotic medications than adults.

Definitions of adverse effect categories

For the purpose of this study we have provided the following working definitions to aid the interpretation of results:

EPS: Extrapyramidal side effects are defined using the Simpson–Angus Rating Scale. We have also included the following under EPS: tardive dyskinesia, parkinsonism, akathisia, catatonia. Tardive dyskinesia is assessed with the Abnormal Involuntary Movement (AIMS) Scale, Schooler–Kane criteria or Glazer–Morgenstern Criteria. For akathisia this should be evaluated with the Barnes Akathisia Rating Scale (BARS), catatonia using the Bush–Francis catatonia scale. A patient was classified as having parkinsonism if he had a mean sum score of all items of SAS greater than 0.3, adhering to the convention of Simpson and Angus (1970) as employed by Leung

et al. (2003) or diagnosed using the motor examination section of the Unified Parkinson's Disease Rating Scale as employed by Van Harten et al. (2006).

Sedation: there is no standard definition of sedation. Criteria for sedation were not described in any of our included studies. Jerrell et al. (2008) employed sedation/somnolence using ICD-9 codes: 780.09, 780.54 in their report of sedation in children.

Weight gain/obesity: obesity is defined by WHO definitions. A body mass index (BMI) ≥25 kg/m^2 is defined as being overweight, a BMI ≥30 kg/m^2 as obese. Abdominal obesity defined as waist circumference >102 cm in men or >88 cm in women.

Type II diabetes: defined by the WHO as having diabetes symptoms (i.e. polyuria, polydipsia and unexplained weight loss) plus

- a random venous plasma glucose concentration ≥11.1 mmol/L, or
- a fasting plasma glucose concentration ≥7.0 mmol/L (whole blood ≥6.1 mmol/L), or
- 2 h plasma glucose concentration ≥11.1 mmol/L 2 h after 75 g anhydrous glucose in an oral glucose tolerance test (OGTT), or
- treatment with insulin/anti-diabetic drugs.

Hyperprolactinaemia: prolactin levels >500 mIU/L in men and >700 mIU/L in women. Significant hyperprolactinaemia is defined as having prolactin levels >1000 mIU/L.

Metabolic syndrome: Metabolic syndrome for both adults and children is defined by either the International Diabetes Federation (IDF) criteria for metabolic syndrome in adults and children or National Cholesterol Education Programme (NCEP) criteria for metabolic syndrome.

Dyslipidaemia: At least one of the following:

- Total Cholesterol >200 mg/dL
- HDL Cholesterol <40 mg/dL in men or <50 mg/dL in women
- Apolipoprotein B >120 mg/dL
- Triglycerides ≥150 mg/dL
- Treatment for a known lipid disorder.

Sexual dysfunction: Including but not limited to the following sexual side effects: increased or diminished sexual desire, erectile, ejaculatory, or orgasmic dysfunction, and vaginal dryness, or reproductive side effects (menorrhagia, etc).

Cardiovascular effects: This includes:

- QT segment prolongation – defined as a QT interval longer than 450 ms for men and 470 ms for women after correction with Bazzett's formula ($QT_c = QT/\sqrt{RR}$ interval)
- Hypertension defined as blood pressure (systolic/diastolic) ≥130/85
- Cardiovascular disease including, but not exclusive to coronary heart disease, cerebrovascular events, cardiovascular events (codes for myocardial infarction, ischemic/pulmonary heart disease, arrhythmias, and cardiomyopathy), cerebrovascular events (codes for cerebrovascular disease, cerebrovascular accident, cerebrovascular haemorrhage, and peripheral vascular disease), and orthostatic hypotension/syncope.

Results

Data extraction

Data was extracted from the following databases: Ovid MEDLINE(R) 1946 to May Week 4 2013, PsycINFO 1806 to May Week 4 2013, Embase 1974 to 2013 June 03.

A total of 395 articles were initially identified by the initial search strategy and a further 11 via hand search of citations and references from the initial search, resulting in a total of 406 papers. Nine articles were excluded because they were not written in English, and 321 were deemed not suitable due to the studies not addressing the aims of our review, i.e. they did not address the prevalence and management of antipsychotic effects as their primary aim (many were review papers of individual antipsychotic agents or the management of psychosis). This resulted in 76 papers for analysis based on full text, and from these two authors (SL and/or MT) independently determined that 53 studies satisfied the inclusion criteria. Our inclusion criteria consisted of English language full-text papers and original research studies, namely cohort studies, case-controlled and cross-sectional studies. The 23 papers excluded were either duplicates; no original data presented; or conference abstracts with full text not available.

The final 53 papers were further separated into the a priori categories: 1) EPS, 2) sedation, 3) sexual dysfunction, 4) hyperprolactinaemia, 5) weight gain, 6) type 2 diabetes, 7) dyslipidaemia, and 8) cardiovascular effects.

Prevalence of antipsychotic adverse effects in children

Four studies were included, but Jerrell et al. (2008), Jerrell and McIntyre (2008) and McIntyre and Jerrell (2008) are based on the same community cohort of child or adolescent patients and controls, whereas Patel et al. (2007) involved a cohort of hospital inpatients.

EPS. Two studies, Jerrell et al. (2008) and Jerrell and McIntyre (2008), using the same cohort of patients found a rate of 1.3% in the cohort before treatment compared with 1.2% in the control group. The post-treatment rate was 4.5%, with longer treatment exposure being associated with a higher risk of developing adverse neurological events.

Sedation. Jerrell et al. (2008) also noted pre-existing rates of sedation to be 8% compared with 7% in the control group. The post-treatment rate of sedation was 18%. Risk of sedation was higher for ziprasidone, quetiapine and those on multiple antipsychotics.

Weight gain. McIntyre and Jerrell (2008) found a higher prevalence of obesity or weight gain in the treated cohort (odds ratio: 2.13) with pre-treatment rates of 6% and a newly developed incidence of 14%. The risk was higher for girls, adolescents aged 13 and over, and those on multiple antipsychotics. Jerrell et al. (2008) observed similar trends, with overall rates of 20% in the treated cohort compared with 9% in the general population. Patel et al. (2007) determined that 53% of 95 inpatient children were overweight; however, the authors have suggested that the

Table 1. Summary of main findings in children.

Adverse effect	Number of studies	Major findings & positive associations	Negative association
Extrapyramidal symptoms (EPS)	2 Jerrell et al., 2008; Jerrell and McIntyre, 2008	Prevalence rates = 2–10%. Longer exposure associated with higher incidence.	Nil
Sedation	2 Jerrell et al., 2008; Jerrell and McIntyre, 2008	Greater sedation with ziprasidone, quetiapine and multiple antipsychotics. Longer exposure associated with higher risk of neurological events.	Nil
Weight gain	3 Jerrell and McIntyre, 2008; McIntyre and Jerrell, 2008; Patel et al., 2007	Inpatients had higher prevalence (up to 53%). Girls; adolescents; and those on multiple antipsychotics had greater weight gain.	Nil
Type 2 diabetes	2 Jerrell and McIntyre, 2008; McIntyre and Jerrell, 2008	Prevalence rates ranged from 2.1% to 5.2%. Girls and those on multiple antipsychotics had higher rate of developing type 2 diabetes.	Nil
Dyslipidaemia	3 Jerrell and McIntyre, 2008; McIntyre and Jerrell, 2008; Patel et al., 2007	Girls, adolescents above 13 and those taking multiple antipsychotics. Inpatient care associated with higher prevalence.	Nil
Cardiovascular disease (CVD)	2 Jerrell and McIntyre, 2008; McIntyre and Jerrell, 2008	FGA antipsychotics, those on multiple antipsychotics associated with a higher CVD risk. Hypertension rate higher for adolescents above 13.	Odds of developing hypertension unrelated to type of antipsychotics.

high prevalence of obesity may be due to geographical and ethnic differences. The absence of a non-psychiatric comparison group was also problematic.

Type 2 diabetes mellitus. Two studies (Jerrell et al., 2008; McIntyre and Jerrell, 2008) found a pre-existing rate of type 2 diabetes mellitus of 2%, with an incidence of 3% after antipsychotic treatment. The overall rate was 5% compared with 2% in the control group. Girls and those on multiple antipsychotics had a higher risk of developing type 2 diabetes.

Dyslipidaemia. McIntyre and Jerrell (2008) and Jerrell et al. (2008) also noted a 1.2% prevalence of dyslipidaemia with a 3% incidence. The risk was higher for girls, adolescents above 13 and those taking multiple antipsychotics. Patel et al. (2007) documented rates of 51% and 48% for elevated triglycerides (TG) levels and low HDL levels in hospital inpatients.

Cardiovascular effects. McIntyre and Jerrell (2008) observed that the risk of developing cardiovascular disease was higher for first-generation or conventional antipsychotics. The same study also noted that the risk of developing hypertension was higher for those aged 13 or over but unrelated to specific antipsychotics. Jerrell et al. (2008) found that those on multiple antipsychotics or on haloperidol were more likely to develop cardiovascular disease.

We did not find any data on hyperprolactinaemia or sexual dysfunction in children. Table 1 summarises the main findings in children.

Prevalence in adults

EPS. Six studies (Byne et al., 1998; Chong et al., 2003; Kobylecki et al., 2009; Leung et al., 2003; Van Harten et al., 2006; Woods et al., 2010) were included. Leung et al. (2003) found 26% prevalence for parkinsonism, 32% for catatonia and 1.3% akathisia from 225 psychiatric inpatients. Woods et al. (2010) found no association between EPS rate and class or specific antipsychotic, or anticholinergic treatment, while Chong et al. (2003) found no correlation between the prevalence of akathisia and gender.

For tardive dyskinesia, prevalence varied depending on length of exposure and ethnicity. Byne et al. (1998) reported a prevalence of 60% in chronic institutionalised elderly people with schizophrenia; Woods et al. found a baseline prevalence of 31.5% in their cohort of 619 patients. Leung et al. found a much lower 7% prevalence in a cohort of Chinese patients. Van Harten et al. (2006) reported an annual incidence of 10% for tardive dyskinesia, and that the severity of tardive dyskinesia was associated with age and akathisia but not parkinsonism. Other associations included an association with the CYP2D6 genotype and tardive dyskinesia.

Sedation. While no specific figures were provided, Brooks et al. (2011) reported that patients on second-generation antipsychotics (SGA) polytherapy were more likely to be sedated (number needed to harm (NNH)=8) compared with monotherapy.

Sexual dysfunction. SGA polytherapy was also associated with higher prevalence of sexual dysfunction (NNH=8). Three papers (Bobes et al., 2003; Fujii et al., 2010; Khawaja, 2005) reported prevalences of 49–59% for males and 25–49% for females. High rates of low libido or sexual interest (37%), erectile dysfunction and ejaculatory problems were reported in men, with amenorrhea (39%) and low sexual interest (26%) being common in women. Khawaja (2005) noted a prevalence of 48% erectile and 45% ejaculatory dysfunction in men. Sexual dysfunction was frequent with haloperidol (38%) and olanzapine (35%), and appeared to be dose related for haloperidol, risperidone and olanzapine. Fujii et al. (2010) did not find an association with class of medication.

Hyperprolactinaemia. Bushe et al. (2008) documented an overall prevalence of 33% (women 47%; men 28%) associated with all antipsychotics except clozapine, with highest prevalence rates being found in amisulpride (89%). A separate study by Bushe and Shaw (2007) which scored highly on our quality

analysis scale (13/14) found increased prolactin in 38% of patients (52% women; 26% men), with significantly elevated levels (>1000 mIU/L) found in 21%, and 74% of abnormal females with levels of >1000 mIU/L. Doknic et al. (2011) found significantly elevated prolactin levels (>2000 mU/L) in 3 of 14 female patients, but spinal bone mass density was not significantly different.

Metabolic syndrome. The prevalence of antipsychotic-related metabolic syndrome has been reported to vary from 23% to 50% (Bai et al., 2009, 2011; Falissard et al., 2011; Gautam and Meena, 2011; Hägg et al., 2006; Krane-Gartiser et al., 2011; Mackin et al., 2007b; Pallava et al., 2012; Schorr et al., 2009). Clozapine was linked with a high rate in four papers (Bai et al., 2009; Hägg et al., 2006; Krane-Gartiser et al., 2011; Schorr et al., 2009). Two studies (Gautam and Meena, 2011; Mackin et al., 2007) noted olanzapine had the most potential to cause metabolic syndrome, followed by clozapine and risperidone. The study by Gautam and Meena (2011), which was one of the highest quality, also went on to document an incidence of 11.6% at 4 months of antipsychotic medication use. Associations between metabolic syndrome and antipsychotics were found with increasing age, marital status, education level, executive jobs, ICD-10 diagnosis of schizophrenia, antipsychotic polypharmacy, duration of treatment, and a family history of diabetes and hypertension. Falissard et al. (2011) found prevalence rates of 34% for both first-generation antipsychotics (FGAs) and SGAs.

Weight gain/obesity. The prevalence of weight gain or obesity ranged from 6% to 55% in eight studies (Ahmer et al., 2008; Curtis et al., 2011; Hägg et al., 2006; Jerrell et al., 2010; Reist et al., 2007; Tsan et al., 2012; Khazaal et al., 2006; Homel et al., 2002). All the studies found weight gain or obesity to be related to olanzapine use. Three studies (Ahmer et al., 2008; Gautam and Meena, 2011; Iqbal et al., 2011) found that olanzapine caused the most weight gain. Chagnon et al. (2007) also found that genetic factors (i.e. common allele of PMCH rs7973796) may be associated with a greater BMI in olanzapine-treated patients.

Type 2 diabetes mellitus. Prevalence ranged from 2% to 28% (Banta et al., 2009; Falissard et al., 2011; Fernandez et al., 2004; Jerrell et al., 2010; Le Noury et al., 2008; MacFarlane et al., 2004; Mukherjee et al., 1996; Okumura et al., 2010; Philippe et al., 2005; Reist et al., 2007; Taylor et al., 2005; Tsan et al., 2012). Okumura et al. (2010) found that the risk of being on FGA antipsychotics doubled among patients with diabetes. Philippe et al. (2005) reported that morbidity rates were higher in women than men (3.4% vs. 1.6%), and it was only women who had a significantly raised standard morbidity ratio. Taylor et al. (2005) noted a diagnosis of type 2 diabetes was associated with increasing age. MacFarlane et al. (2004) found a cross-sectional prevalence of 8.6% (women 13%, men 8%). Mukherjee et al. (1996) found no significant difference in prevalence between gender, while Falissard et al. (2011) reported a higher prevalence in those taking FGA compared with SGA (31% vs. 28%). Fernandez et al. (2004) reported that long-term low-dose clozapine did not increase the risk for developing diabetes mellitus. One of the highest scoring studies based on our quality analysis scale, a 9-year prospective cohort study of 3470 patients by Philippe et al. (2005), documented the rise of the prevalence of diabetes over time, from a prevalence of 2.2% at inclusion to 5%, with the prevalence of diabetes in the schizophrenia cohort reported to be higher than that of the general population at all time-points.

Dyslipidaemia. Hanssens et al. (2007) adopted the SCORE criteria for diagnosing dyslipidaemia. Antipsychotic treatment was associated with dyslipidaemia rates between 15–53% (Hägg et al., 2006; Hanssens et al., 2007; Jerrell et al., 2010; Mackin et al., 2007a; Saari et al., 2004; Tsan et al., 2012). Mackin et al. (2007a) found prevalence rates of 53% and 31% for elevated triglycerides and cholesterol, respectively, in their study of monitoring practices. In a large-scale retrospective cohort study by Saari et al. (2004) of 5654 unselected Northern Finland 1966 birth cohort, the risk of dyslipidaemia in individuals treated with antipsychotic medications was further shown by regression analysis to be 2.8 for hypercholesterolaemia, 2.3 for hypertriglyceridaemia and 1.6 for high LDL cholesterol.

Cardiovascular effects. Four studies (Hägg et al., 2006; Jerrell et al., 2010; Kelly et al., 2010; Tsan et al., 2012) found rates of 16–49% for hypertension, while three studies (Jerrell et al., 2010; Mackin and Young, 2005; Muzyk et al., 2012) documented a prevalence range of 3–52% for QTc prolongation or arrhythmias. Jerrell et al. (2010) reported rates for elevated blood pressure that were higher for patients on ziprasidone. Kelly et al. (2010) revealed cardiovascular mortality in patients aged below 55 to be 1%, whereas patients over 55 had a cardiovascular mortality of 8.5% with clozapine and 3.6% with risperidone at 5 years. Mackin and Young (2005) observed a trend towards an age-related lower QTc interval with antipsychotic polypharmacy.

Interestingly, Jerrell and McIntyre (2007) noted no link between antipsychotic use and cerebrovascular problems. They did report rates of 19.7% for hypertension, with the risk of cardiomyopathy being significantly lower for aripiprazole but significantly higher for those on ziprasidone compared with first-generation or conventional antipsychotics.

Comparing FGA and SGA side effect profile

The data is somewhat limited as many of the included articles do not separate their findings by antipsychotic category. However, Brooks et al. (2011) reported a higher prevalence of dry mouth, tremor, sedation, sexual dysfunction, constipation in patients on SGA polytherapy compared with those on monotherapy.

Clozapine is the only licensed antipsychotic for treatment-resistant schizophrenia (SIGN guideline 131, 2013), and its superior efficacy has been shown in numerous studies, although this is balanced by a serious adverse effect profile (Farooq and Taylor, 2011). In our review the prevalence of AEs for clozapine is mentioned in eight articles (Bai et al., 2009, 2011; Bushe et al., 2008; Fernandez et al., 2004; Gautam and Meena, 2011; Hägg et al., 2006; Kelly et al., 2010; Schorr et al., 2009). The prevalence of metabolic syndrome in patients taking clozapine was reported to be 28–48% in four reviews (Bai et al., 2009, 2011; Gautam and Meena, 2011; Hägg et al., 2006), while Schorr et al. (2009) concluded that patients who had metabolic syndrome were more likely to be on clozapine and polytherapy. There are negative associations as well. Fernandez et al. (2004) found an 18% prevalence of type 2

diabetes in their cohort of geriatric patients on long-term clozapine, but concluded that this prevalence rate did not differ significantly from the general population. With regards to cardiovascular disease, Kelly et al. (2010) found that cardiovascular mortality did not differ significantly in participants started on clozapine (n=1084) compared with those initiated on risperidone (n=602) over 8–10 years follow-up, and Bushe et al. (2008) found no association between hyperprolactinaemia and clozapine.

Management

Seven original studies (Attux et al., 2011; Hanssens et al., 2007; Haupt et al., 2009; Mackin et al., 2007a,b; Morrato et al., 2008; Tsan et al., 2012) addressed the management of adverse antipsychotic side effects. Three papers (Haupt et al., 2009; Mackin et al., 2007a; Morrato et al., 2008) also reported varying degrees of baseline monitoring for glucose and lipids, ranging from 0% to 10.5% for lipids and between 17% and 50% for baseline glucose monitoring. Baseline testing increased modestly with SGA initiation and where there was pre-existing diabetes or dyslipidaemia (Morrato et al., 2008).

With regards to managing antipsychotic AEs, five papers reported on pharmacological and non-pharmacological interventions:

1. Hanssens et al. (2007) found that statin therapy was associated with a significant decrease in triglycerides and total cholesterol.
2. In their study of veterans with schizophrenia, Tsan et al. (2012) noted that most veterans were receiving cardiovascular care (67–76%), hepatic and renal function assays (79–84%) and psychiatry consults (66–82%). This was related to a high baseline prevalence of hypertension (43%) and diabetes mellitus (23%).
3. Attux et al. (2011), one of the highest scoring studies based on quality analysis, examined the effectiveness of a non-pharmacological intervention called the Wellness Programme which involved a combination of physical exercise, diet planning and group therapy targeted at mental wellness over 12 weeks. Significant weight loss (mean weight difference: 0.41) and significant BMI reduction (0.13) was achieved. They also found that there was a significant increase in proportion of patients undertaking physical activity after the intervention (71%).
4. Mackin et al. (2007a) reported that although prevalence rates were 53% for hypertriglyceridaemia and 31% for hypercholesterolaemia; only 7% were receiving lipid-lowering therapy. BMI and waist circumference had significantly increased at follow-up. They also reported that monitoring was poor, with no measures of adiposity, and over a half not having blood glucose or lipid monitoring during follow-up.
5. A separate study by Mackin et al. (2007b) noted that only 31% of high-risk patients were receiving prophylactic lipid-lowering therapy, and that 60% of patients were not receiving antihypertensive medications compared with 77% of controls.

Table 2 summarises the findings in adults.

Discussion

Prevalence of antipsychotic adverse effects

We have found that adverse antipsychotic effects are common and diverse. Antipsychotic polypharmacy was associated with increasing range of AEs (Gautam and Meena, 2011; Jerrell et al., 2008; Mackin et al., 2007a; McIntyre and Jerrell, 2008), and a longer duration of treatment was also associated with more severe long-term side effects such as diabetes and metabolic syndrome (Curtis et al., 2011; Taylor et al., 2005). There did not appear to be any major difference in the patterns and severity of antipsychotic AEs experienced by children and adults, but the data are limited and there are no direct comparisons.

The most frequently reported or observed antipsychotic side effects identified were sexual dysfunction, metabolic problems and weight gain. We found that up to 59% of male patients reported sexual dysfunction. Two studies (Falissard et al., 2011; Okumura et al., 2010) reported a higher rate of AEs with older FGA, whereas clozapine was more strongly associated (Bai et al., 2011; Hägg et al., 2006; Schorr et al., 2009) with metabolic syndrome than other antipsychotics, and olanzapine was associated with the largest weight gain in three studies (Ahmer et al., 2008; Gautam and Meena, 2011; Iqbal et al., 2011). The association between olanzapine and the most weight gain, and clozapine with metabolic syndrome, is consistent with the findings of a head-to-head meta-analysis by Rummel-Kluge et al. (2010), where olanzapine and clozapine showed the most elevation of weight, cholesterol and glucose. Rummel-Kluge also commented that olanzapine caused the most cholesterol elevation, and this was reflected in our review. These findings are also replicated by Leucht et al. (2013), who that noted olanzapine, followed by zotepine and clozapine were associated with highest weight gain. More longitudinal studies of adequate duration are required to assess the distribution and pattern of antipsychotic-related weight gain.

Leucht et al. (2009b) found a lower prevalence of sedation in SGAs compared with low-potency FGAs with the exception of clozapine and risperidone, and this finding is replicated again in Leucht et al. (2013), where clozapine was noted to be associated with the highest prevalence of sedation. Three studies meeting our inclusion criteria described the highest prevalence of sedation among children occurring with ziprasidone, quetiapine and antipsychotic polypharmacy (Brooks et al., 2011; Jerrell et al., 2008; McIntyre and Jerrell, 2008). Our findings of the prevalence of EPS and dyskinesia are also reflect meta-analytic results from Leucht et al. (2012), where 2% of patients developed dyskinesia and 24% of patients were receiving antiparkinsonian medication for AEs.

Aripiprazole and ziprasidone have been linked with a low prevalence of weight gain and dyslipidaemia (Khanna et al., 2013; Barak et al., 2011) but a meta-analysis of RCTs by Leucht et al. (2013) found that their adverse effect profiles for EPS and sedation were not significantly different to first-generation or conventional antipsychotics. We found that aripiprazole may have a lower risk of associated cardiomyopathy while ziprasidone use was linked to a significantly increased risk of developing hypertension, cardiomyopathy and sedation (Jerrell and McIntyre, 2007). This increased association of ziprasidone with sedation was also noted by Leucht et al. (2013), where an odds ratio of 3.8 was reported. With regards to cardiovascular effects, Leucht et al. (2013) also found that aripiprazole had a lower rate of QTc prolongation compared with ziprasidone. This is in keeping with our findings as mentioned above.

Table 2. Summary of main findings in adults.

Adverse effect	Number of studies	Main findings & positive associations	Negative associations
Extrapyramidal symptoms (EPS)	6 Byne et al., 1998; Chong et al., 2003; Kobylecki et al., 2009; Leung et al., 2003; Van Harten et al., 2006; Woods et al., 2010	Prevalence reported 1–6% for akathisia; 7–60% for tardive dyskinesia (TD); 26% for parkinsonism; and 32% for catatonia. Prevalence increases with age, but not correlated with gender, antipsychotic regime or anticholinergic treatment. The severity of TD was associated with age and akathisia but not parkinsonism.	No association between prevalence and type of antipsychotic or anticholinergic treatment. No correlation between prevalence of akathisia and gender.
Sedation	1 Brooks et al., 2011	SGA polytherapy associated with increased odds of sedation (NNH=8).	Nil
Sexual dysfunction	3 Bobes et al.,2003; Fujii et al., 2010; Khawaja, 2005	Prevalence ranged from 29–49% for women and 45–59% for men. SGA polytherapy associated with higher prevalence of sexual dysfunction (NNH=8). Frequency was elevated & dose related with haloperidol, risperidone and olanzapine.	No association with monotherapy groups.
High prolactin	3 Bushe and Shaw, 2007; Bushe et al., 2008; Doknic et al., 2011	Prevalence rates were 47–52% for women and 26–38% for men, overall prevalence of 33% reported in one study. Amisulpride associated with the highest prevalence (89%) in one study.	No association found with clozapine. Bone mass density differences were lower at spine but did not reach a significant level.
Metabolic syndrome	9 Bai et al., 2009, 2011; Falissard et al., 2011; Gautam and Meena, 2011; Hägg et al., 2006; Krane-Gartiser et al., 2011; Mackin et al. 2007a; Philippe et al., 2005; Tsan et al., 2012	Associations were found with age, marital status, education level, executive jobs, diagnosis of schizophrenia, duration of illness and family history of diabetes and hypertension. Prevalence rates ranged between 23–50%. Clozapine was associated with higher prevalence in four studies and olanzapine with higher incidence compared with other antipsychotics in two studies. No association with gender.	No association with gender. No interventions shown to significantly alter the chance of developing or reversing metabolic syndrome yet.
Weight gain/ obesity	8 Khazaal et al., 2006; Ahmer et al., 2008; Curtis et al., 2011; Hägg et al., 2006; Homel et al., 2002; Jerrell et al., 2010; Reist et al., 2007; Tsan et al., 2012	Prevalence ranged from 6–55% (average 30%) with olanzapine being associated with the most weight gain. Duration and genetic factors may be associated with antipsychotics related high BMI.	Nil.
Type 2 Diabetes	12 Banta et al., 2009; Falissard et al., 2011; Fernandez et al., 2004; Jerrell et al., 2010; Le Noury et al., 2008; MacFarlane et al., 2004; Mackin et al., 2007a; Mukherjee et al., 1996; Okomura et al., 2010; Reist et al., 2007; Taylor et al., 2005; Tsan et al., 2012	Prevalence of diabetes ranged between 2–28% and diagnosis was significantly associated with age or treatment with the overall drug.	Gender has no association with diabetes.
Dyslipidaemia	6 Hägg et al., 2006; Hanssens et al., 2007; Jerrell et al., 2010; Mackin et al., 2007b; Saari et al., 2004; Tsan et al., 2012	All studies showed an association between antipsychotic use and dyslipidaemia. Prevalence ranged from 15–53% (average 32%).	Nil.
Cardiovascular effects	7 Hägg et al., 2006; Jerrell et al., 2010; Jerrell and McIntyre, 2007; Kelly et al., 2010; Mackin and Young, 2005; Muzyk et al., 2012; Tsan et al., 2012	4 studies found prevalence of hypertension 16–49%, and prevalence of QTc prolongation/ arrhythmias to be 3–12%. QTc prolongation was associated with age, however not with antipsychotic polypharmacy. Ziprasidone was associated with a higher prevalence of elevated BP/hypertension in one study.	No link between antipsychotic usage and cerebrovascular conditions. The odds of developing cardiomyopathy were significantly lower for aripiprazole relative to conventional antipsychotics.

For the majority of the adverse effect categories we found no clear differences in prevalence by gender, but two categories demonstrated gender-specific patterns. Women more often experienced hyperprolactinaemia, including prolactin levels over 2000 mIU, and sexual dysfunction including low libido has been linked to high prolactin levels, so it is interesting that the reported prevalence of sexual dysfunction was higher in men (45–59%) than women (29–49%). It is possible that non-medication related factors may lead to sexual dysfunction. The papers reporting sexual dysfunction also did not use standardisation or age-related healthy controls, which may adversely affect the findings.

Regarding the effect of pharmacogenetics on antipsychotic side effects, two of our studies (Chagnon et al., 2007; Kobylecki et al., 2009) demonstrated the interesting interaction between gene variants and the prevalence of antipsychotic side effects, namely tardive dyskinesia and obesity. With regards to tardive dyskinesia and EPS, Zhang and Malhotra (2011) in their review found these two side effects to be associated with the poor metaboliser genotype of the enzyme CYP2D6. In our review, EPS or tardive dyskinesia were found to be more frequent with patients with cytochrome P450 enzyme CYP2D6 poor metaboliser genotype (Kobylecki et al., 2009). For weight gain/obesity, Lencz and Malhotra (2009) report an association between weight gain and the promoter region polymorphism, -759 T/C (rs3813929), in the HTR2C gene (on the X chromosome). In our review however, Chagnon et al. (2007) – a high-quality study according to our scale – concluded that the common allele of PMCH rs797379 may be associated with higher BMI in olanzapine-treated schizophrenic patients.

The management of antipsychotic side effects

From the seven studies included here, the majority reported baseline measures for testing and follow-up instead of direct management of AEs. Five of the seven studies which addressed baseline testing and follow-up monitoring revealed disappointing levels as low as 0% compliance with monitoring, despite guideline recommendations. All the papers addressing baseline testing only identified baseline testing for lipids and glucose, while the most common and potentially most distressing adverse effect, namely sexual dysfunction, was not examined with potentially significant implications on patient adherence. While both pharmacological (Hanssens et al., 2007) and non-pharmacological interventions (Attux et al., 2011) are shown to be effective in symptomatic control of antipsychotic AEs, Mackin et al. (2007a) found that only 7% of patients were receiving lipid-lowering therapy, while Tsan et al. (2012) noted high rates (67–76%) of general cardiovascular care in a group of veterans with schizophrenia. Mackin et al. (2007b) reported that only 31% of high-risk patients on antipsychotics were on prophylactic lipid-lowering therapy. These findings show that while geographic variations and local guidelines may affect management strategies for AEs, the prevention and management of AEs should be given more emphasis. Further practical details on managing the AEs of antipsychotics are best found in recent guidelines such as SIGN 131 (2013) or *Maudsley* (Taylor et al., 2012).

Limitations and recommendations

We did not attempt to perform a meta-analysis, as differing study designs of studies included in this systematic review mean that not all data are amenable to meta-analysis. We only reviewed papers that were published in English. Quality analysis of the papers was carried out and the six papers that scored highest are summarised in the supplementary data, but many studies were limited by a lack of healthy age and gender-matched control populations and small sample sizes. We therefore recommend the following be considered in the future:

- Prospective observational studies of adverse antipsychotic side effects with long-term follow-up (over 2 years). We suggest these studies include quality of life assessments attempting to specifically examine the impact of antipsychotic side effects on the daily lives of patients. This will hopefully guide practical management strategies.
- RCTs assessing the effectiveness of management strategies for antipsychotic side effects. This would provide a stronger basis for national and international guidelines.
- Long-term clinical trials on first-episode psychosis samples, with baseline monitoring and assessment of side effects at a fixed endpoints throughout treatment (e.g. 2 years or more) to enable accurate monitoring of AEs over time.

Conclusions

It is remarkable that despite the frequent use – both on-licence and 'off-label' – of antipsychotics, the scientific study of their AEs has been neglected. The most commonly occurring antipsychotic AEs, in just over half of those receiving antipsychotics according to this review, are sexual dysfunction and weight gain, with significant implications for medication adherence. Antipsychotic polypharmacy – a common clinical practice (Barnes and Paton, 2011) – appears to exacerbate the AE burden. Kendall (2011) has already noted the false dawn of therapeutic optimism that arose with the introduction of second-generation or 'atypical' antipsychotics, and our findings confirm that the AE profiles of the newer antipsychotics are as worrying as the older equivalents for the patient's long-term physical health. The rates of documented baseline monitoring are also disappointing, and the evidence base for management strategies needs strengthening. The concerns regarding the premature mortality of those with serious mental disorder (Ajetunmobi et al., 2013; Royal College of Psychiatrists, 2012) coupled with the documented under-recognition and under-treatment of the physical health of this population (Laursen et al., 2013; Mackin et al., 2007a, 2007b; Smith et al., 2013) reinforce the need to prioritise this area of study. It is also hoped that this review will provide clinicians with an overview of adverse antipsychotic side effects across all systems, and to encourage clinicians to adhere to/improve monitoring guidelines, for example by using a validated antipsychotic side effect scales such as the Glasgow Antipsychotic Side-effect Scale (Waddell and Taylor, 2008).

Declaration of Conflicting Interests

Funding

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