

WPA SECTION REPORT**Side effects of atypical antipsychotics: a brief overview**ALP ÜÇÖK^{1,2}, WOLFGANG GAEBEL^{1,3}¹WPA Section on Schizophrenia²Department of Psychiatry, Istanbul University Medical Faculty, Millet Street, Capa 34390, Istanbul, Turkey³Department of Psychiatry and Psychotherapy, Heinrich-Heine-University Düsseldorf, Bergische Landstraße 2, D-40629 Düsseldorf, Germany

This paper reviews the available evidence concerning the side effects of atypical antipsychotics, including weight gain, type II diabetes mellitus, hyperlipidemia, QTc interval prolongation, myocarditis, sexual side effects, extrapyramidal side effects and cataract. Some recommendations about how to prevent and manage these side effects are also provided. It is concluded that atypical antipsychotics do not represent a homogeneous class, and that differences in side effects should be taken into account by clinicians when choosing an antipsychotic for an individual patient.

Key words: Schizophrenia, atypical antipsychotics, side effects, treatment guidelines, individual treatment

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Patients with schizophrenia suffer from increased rates of multiple medical problems, due to their lifestyle (high smoking prevalence, high-fat diet), inherent neglect of personal care, and barriers to treatment of physical illness (1). A further important contributor to adverse health outcomes is the side effect profile of antipsychotic medications. Since the introduction of the second generation or atypical antipsychotics (AAP), these agents have been widely prescribed for the management of patients with schizophrenia, bipolar disorders, other psychotic disorders or conditions with severe behavioral disturbance. The increasing use of AAP is in part due to their lower propensity to induce extrapyramidal symptoms and tardive dyskinesia compared to typical antipsychotics.

Now, more than 15 years after the first atypical antipsychotic entered the market, psychiatrists have gradually come to realize that while extrapyramidal symptoms and tardive dyskinesia occur less frequently with atypical agents, these medications may present a different set of adverse effects. The quality of available evidence for the association of specific antipsychotics with particular side effects varies considerably. In this article, we review the recent findings concerning weight gain, diabetes mellitus (DM), hyperlipidemia, QTc interval prolongation, myocarditis, sexual side effects, extrapyramidal side effects and cataract in patients receiving AAP.

WEIGHT GAIN

Forty to sixty-two percent of people with schizophrenia are overweight or obese. Obesity increases these patients' risk for cardiovascular morbidity and mortality. In addition, excessive weight and obesity can have important effects on an individual's adjustment in the community, adherence to prescribed medication, ability to participate in rehabilitation efforts, and self-image (2).

Treatment with first- and second-generation antipsychotics can contribute to weight gain (3-5). A meta-analysis

by Allison and Casey (4) provided an estimate of the mean weight gain in patients receiving standard doses of antipsychotics over a 10-week period: the mean increases were 4.45 kg with clozapine, 4.15 kg with olanzapine, 2.92 kg with sertindole, 2.10 kg with risperidone, and 0.04 kg with ziprasidone. Data on quetiapine have been variable, but it seems that the weight gain liability on this drug may be similar to that of risperidone (6). Weight gain with olanzapine at the commonly used dose of 15mg/day may exceed 10 kg during the first year of treatment (7). On the other hand, weight gain seems to be dose-dependent: Rondanelli et al (8) reported no change in weight in elderly patients who received 1.4 mg/day risperidone or 4.4 mg/day olanzapine or 75 mg/day quetiapine over a 12-month period.

Marder et al (9) recommended that the patient's body mass index (BMI) should be recorded before medication initiation or change and at every visit for the first 6 months. The patient should be weighed (and the BMI recorded) at least quarterly when he stabilizes, and more often if he is overweight. BMI monitoring should be supplemented with the measurement of the patient's waist circumference. A gain of one BMI unit in a normal-weight or overweight patient should lead the clinician to consider an intervention. Intervention may include nutritional counseling (for both the patient and caregiver or food preparer), initiation of a personal exercise program, use of medications that promote weight loss, and/or a change of the antipsychotic medication to another one associated with less weight gain (10,11).

DIABETES MELLITUS

The prevalence of type-2 DM in people with schizophrenia is more than twice higher than in the general population (12). In the past decade there have been numerous case reports, retrospective studies, and epidemiological investigations suggesting that certain AAP may be associated with a greater risk of DM than others. Most of these studies indi-

cate that drugs associated with greater weight gain (e.g., clozapine, olanzapine) are associated with increased risk of DM in comparison to no treatment or a drug producing less weight gain (2,13-15). However, the studies suffer from a number of limitations (most importantly, the reliance on insensitive, unreliable, surrogate markers for diabetes).

Evidence from case reports suggests that new onset type-2 DM and diabetic ketoacidosis occur more frequently with clozapine and olanzapine treatment, with relatively fewer case reports on quetiapine and risperidone (2). In a recent study, it has been reported that 6.9% of patients receiving AAP developed new-onset type-2 DM over a one-year period, and that the risk was higher with olanzapine exposure, while quetiapine and risperidone showed no effect relative to haloperidol (16).

The underlying mechanisms of antipsychotic-induced disturbances of glucose metabolism are unknown. The studies are often confounded by concomitant weight gain and dyslipidemia, which are known diabetic risk factors. Increased abdominal obesity, especially visceral obesity, can increase insulin resistance and contribute to hyperglycemia and diabetes both in healthy subjects and patients with schizophrenia.

As diabetes occurrence is not always associated with weight gain, monitoring weight alone may be insufficient to screen for DM risk. The methods that can be used to assess the effects of medications on glucose and insulin metabolism include (ranked least to most sensitive/reliable): random glucose, glycated haemoglobin (HbA_{1c}), fasting plasma glucose, homeostasis model assessment insulin resistance (HOMA-IR), post-prandial glucose, the oral glucose tolerance test (OGTT) and the intravenous glucose tolerance test (IVGTT), and the hyperinsulinaemic-euglycaemic clamp. In a recent animal study, it has been reported that olanzapine and clozapine acutely impaired insulin sensitivity whereas ziprasidone and risperidone had no effect (17). Similarly, higher fasting insulin and insulin resistance index levels were reported in first episode patients with schizophrenia who were treated with clozapine and olanzapine compared to risperidone and sulpiride (18).

Consensus guidelines have been published which elaborate on the differences in risk between agents and provide specific monitoring recommendations (9,19,20). However, a recent study showed that the rate of screening for metabolic side effects of atypical antipsychotics is still low (21). Psychiatrists had the lowest rate of screening, particularly in non-schizophrenic patients and those who take lower doses of atypicals.

HYPERLIPIDEMIA

Serum lipid levels may be influenced by multiple factors, including genetics, diet, weight gain, and exogenous agents like alcohol and medications. It seems that there is an association between use of dibenzodiazepine-derived atypi-

cal antipsychotics (i.e., clozapine, olanzapine, quetiapine) and higher serum triglyceride levels (22). Both risperidone and ziprasidone are non-dibenzodiazepine AAP, and appear to have minimal effects on serum lipids (22,23).

In a recent study, it was found that clozapine and olanzapine, but not risperidone, were associated with increase in cholesterol and triglyceride levels at the end of an 8-week treatment in patients with first-episode schizophrenia (18). Similar changes due to olanzapine or clozapine, but not amisulpride or ziprasidone, were reported as early as in the fourth week of treatment (24). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), olanzapine was associated with greater and significant adverse effects on lipids, while ziprasidone was the only antipsychotic associated with improvement in these metabolic variables (25).

PROLONGATION OF QTc INTERVAL

Prolongation of the QTc interval of the electrocardiogram (ECG) may be associated with the development of torsade de pointes, a ventricular arrhythmia that can cause syncope and may progress to ventricular fibrillation and sudden death (26). The average QTc interval in healthy adults is approximately 400 msec. A QTc interval of 500 msec or greater is considered to be a substantial risk factor for torsade de pointes. In the CATIE study (25), there were no different effects of olanzapine, risperidone, quetiapine and ziprasidone on QTc interval.

A recent focus on the QTc interval and antipsychotics emerged during trials of two AAP, sertindole and ziprasidone. Sertindole in the amount usually administered in a clinical dose was found to increase the QTc interval by 22 msec, and the increase was dose dependent. There was evidence of increased risk of arrhythmias and unexpected deaths with this drug (26). On the other hand, Wilton et al (27) investigated mortality rates and cardiac dysrhythmias in prescription-event monitoring studies of sertindole and two other drugs (risperidone and olanzapine) for comparative purposes. No statistically significant difference was found in mortality rates. Six cases of QTc prolongation were identified in the sertindole group, giving a risk rate of 1.3%, which was similar to that reported in clinical trials with this antipsychotic, and higher than in patients treated with olanzapine and risperidone.

In initial trials, ziprasidone was found to increase the QTc interval by 6-10 ms (27). The US Food and Drug Administration (FDA) was concerned that the prolongation might be considerably higher at ziprasidone's maximal plasma concentration or when ziprasidone was administered with a drug that inhibited its metabolism. This concern led to a study that was carried out by Pfizer at the request of FDA. When each agent was administered in conjunction with a drug that inhibited its metabolism, the results for the mean increase in the QTc interval were as follows: ziprasidone 20.3 ms, risperidone 11.6 ms, olanzapine 6.8 ms, que-

tiapine 14.5 ms, thioridazine 35.6 ms, and haloperidol 4.7 ms. The intervals were not substantially affected by the inhibitor. As suggested in a recent paper (9), in the absence of increased risk factors for QTc interval prolongation or cardiac arrhythmias, ziprasidone can be prescribed without ECG monitoring. However, patients who are to be treated with this drug should receive a baseline ECG before treatment is initiated if any of the following cardiac risk factors are present: known heart disease, a personal history of syncope, a family history of sudden death at under age 40 years (especially if both parents had sudden death), or congenital long QTc syndrome. A subsequent ECG is indicated if the patient presents with symptoms associated with a prolonged QTc interval (e.g., syncope).

MYOCARDITIS

Case reports suggest that clozapine is associated with an increased risk of myocarditis (28,29). Less than one hundred cases have been reported up to now. Eighty percent of cases occurred within 6 weeks of the patient's starting clozapine, and the mortality rate approached 40%. Myocarditis should be suspected in clozapine-treated patients who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or ECG findings such as ST abnormalities and T wave inversions.

As recent evidence suggests that clozapine is associated with a low (0.015% to 0.188%) risk of potentially fatal myocarditis or cardiomyopathy (30), we do not recommend routine monitoring for myocarditis. However, we recommend that clinicians who prescribe clozapine be alert for the symptoms of myocarditis in patients who receive this medication. If myocarditis is identified, clozapine should be stopped and the patient should be urgently evaluated by a primary health care provider.

SEXUAL SIDE EFFECTS

Human sexual function is complex and is affected in many ways by schizophrenia, antipsychotic drugs, comorbid mental disorders such as depression, DM, substance use and smoking, as well as by social isolation, disturbances in interpersonal relations and partner problems. It has been reported that patients with schizophrenia are more commonly affected by sexual dysfunction than those with affective disorders, and that untreated schizophrenia patients have fewer dysfunctions compared to those on antipsychotic medication (31). Antipsychotic-induced sexual dysfunction is related to the effects of the drugs on alpha-1 and alpha-2 adrenergic, H1 histamine and dopaminergic receptors, in particular to the blockade of D2 receptors in pituitary lactotroph cells, which leads to an excess of prolactin secretion (32,33).

Prolactin elevation is less of a concern with AAP. The ex-

ception is risperidone, which results in a prolactin increase similar to that associated with first-generation antipsychotics. A meta-analysis by Kleinberg et al (34) found that prolactin levels in patients who were taking 2-16 mg/day of risperidone were similar to those in patients taking 20 mg/day of haloperidol, while those of patients taking 1-16 mg/day of risperidone were significantly higher than those of patients receiving 10 mg/day of haloperidol. Studies of other AAP have found that these agents may result in transient elevations in prolactin levels, which tend to return to the normal range within a few days (35-38).

When hyperprolactinemia occurs during treatment and is associated with menstrual or sexual dysfunction, consideration should be given to changing the patient's medication to a prolactin-sparing agent.

EXTRAPYRAMIDAL SIDE EFFECTS

Besides the subjective feeling of discomfort, extrapyramidal side effects of antipsychotics in general can add to the stigma associated with schizophrenia. Some patients can have preexisting motor abnormalities, before the initiation of any antipsychotic medications. However, the overwhelming majority of cases of extrapyramidal symptoms appear to be due in large part to exposure to antipsychotic medication.

Meta-analyses indicate that, when AAP are used at recommended doses, they are associated with significantly lower rates of extrapyramidal side effects compared with (generally high-potency) conventional antipsychotics (39). Some AAP (e.g., risperidone and olanzapine) have a dose-response relationship for extrapyramidal side effects, while with others (e.g., clozapine, quetiapine) this relationship is not apparent.

On the basis of available data, tardive dyskinesia appears to occur significantly less frequently with clozapine, risperidone, olanzapine and quetiapine than with typical antipsychotics (40). Fewer data are available for ziprasidone and aripiprazole, but early evidence suggests a low risk of tardive dyskinesia with these drugs as well.

We recommend that the patients at high risk for extrapyramidal symptoms (i.e., elderly patients and those who have experienced dystonic reactions, clinically significant parkinsonism, and/or akathisia) who are taking AAP be examined every 6 months.

CATARACT

Because patients with schizophrenia often have risk factors for lens opacities, such as DM, hypertension and poor nutrition, clinicians should inquire about visual changes and ensure that guidelines for visual monitoring are followed. Certain AAP may be associated with an increased risk of ocular lens opacities. An epidemiologic study that used the UK General Practice Research Database did not find an

overall increase in the risk for cataracts among patients treated with antipsychotics (41).

Focal triangular cataracts were found in beagle dogs that received quetiapine for 6 or 12 months. The dogs received four times the maximum human dose of the drug on a milligram-per-kilogram basis. This prompted concern despite there being no known causal link between quetiapine and lens opacities in humans (42). Cataracts were not found in other species, including monkeys. Nevertheless, quetiapine's manufacturer issued formal recommendations for ophthalmological follow-up examinations with the use of this drug. Infrequent occurrences of cataract development have been documented in people taking olanzapine but, again, without an established causative association. A similar situation is seen with ziprasidone. There were no significant differences among the patient groups in the incidence of new cataracts in the CATIE study (25).

Periodic ocular examinations of the lens are suggested for patients prescribed long-term treatment with phenothiazines or quetiapine. However, after studying 34 cases of lens opacities in 620,000 patient exposures to quetiapine in the U.S., Fraunfelder (43) concluded that cataractogenesis secondary to quetiapine is "unlikely" by World Health Organization's guidelines, and that it is unnecessary to require biannual ophthalmic examinations.

CONCLUSIONS

AAP have helped to improve the lives of many patients with schizophrenia by alleviating positive and negative symptoms and bringing some improvement in cognitive function. Accordingly, evidence-based international schizophrenia treatment guidelines recommend these drugs as first-line treatment (44). However, these medications do not represent a homogeneous class, given their differences in effect size regarding both alleviation of clinical symptoms (45) and their potential for inducing side effects such as new-onset DM, weight gain, hyperlipidemia, or sexual and cardiac dysfunction.

Clinicians have to take into account these differences when choosing an antipsychotic for an individual patient and when screening and monitoring for physical problems. It will be a task for further guideline revision to develop explicit algorithms for differential drug indications depending on the individual symptom profile and risk status concerning potential side effects. We believe that the full spectrum of marketed antipsychotics (including the typical drugs) should be kept available. "The right drug for the right patient" (46) is a claim still valid today.

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