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INTERNATIONAL ARCHIVES OF MEDICINE
SECTION: PSYCHIATRY AND MENTAL HEALTH
ISSN: 1755-7682

2015
Vol. 8 No. 264
doi: 10.3823/1863

Treating Patients with Antipsychotics: an Individualized Management

REVIEW

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Abstract

Introduction: Subjective well-being, quality of life, cognition and psychosocial performance, including employment, have become endpoints of interest and goals for patients, families, clinicians and researchers. In this line, it is important to clarify the adverse effects caused by antipsychotics in order to innovate and complement treatment of patients with an individualize approach according to the patient's needs and predispositions.

Objectives: Discuss new treatment's way for patients using antipsychotics, elucidating the pros and cons of their use.

Results: Atypical antipsychotics cause weight gain and lead to a higher risk of diabetes and other metabolic sequelae than their typical counterparts. Besides, second-generation(atypical) has also shown adverse effects like: akathisia, sedation, abnormal metabolic laboratory results, and weight gain. On the other hand, talking about the first-gentration (typical) antipsychotics, their clinical effectiveness is challenged by increased acute and chronic extrapyramidal side effects and related symptoms of dysphoria, compared to second-generation (atypical) antipsychotics. In addition, available evidence indicates that antipsychotic medications increase the risk of cerebrovascular adverse events (CVAEs) and death when used to treat elderly patients with Behavioral and Psychological Symptoms of Dementia (BPSD). Besides, some studies show that patient populations that are prescribed antipsychotic agents have a higher cardiovascular mortality rate than the general population. Considering that, we can see that each psychotic patient will need an individualized treatment according to their physical, social and psychological limitations and needs, leading us to realize the significance of this paper since it emphasizes the holistic management of this kind of patient.

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Conclusion: With the aim of known safety concerns and uncertainty over long-term risks and benefits, it is clear the need to reevaluate clinical practice standard and strengthen efforts to educate especially primary care physicians, concerning the known safety and efficacy of antipsychotic medications to give the patients a treatment that is based on their quality of life.

Keywords
Antipsychotics; Quality of life; Manegement.

Introduction

The medical practitioners are divided largely into two polar camps: the analytical and psychological vs. the organic and directive. The first group developed an ideology that rejects the use of organic treatments and directive methods as usually ineffective, symptomatic at best, and destructive of the growth potential of the patient by fostering pathological dependence (KANE *et al.*, 2010).

Antipsychotics are widely used in treating psychosis and other psychiatric conditions (PAULOSE-RAM *et al.*, 2007; CHIEN *et al.*, 2007). Their primary indication remains schizophrenia and schizophrenia-related disorders, but most antipsychotic drugs are now used on-label to treat a broad range of symptoms and disorders, including bipolar mania and depression, unipolar depression that is unresponsive to standard antidepressant treatment, Tourette's disorder and irritability associated with autistic disorder (HERT *et al.*, 2012).

However, the opinion of analytical and psychological is reinforced by the obvious ineffectiveness of most organic therapies, complicated by the addictive potential and social incapacitation often produced by antipsychotic medications (KANE *et al.*, 2010).

These medications are associated with risk of cerebrovascular adverse events (CVAEs) and death when used to treat elderly patients with dementia (MITTAL *et al.*, 2011) and can induce cardiovascular and metabolic abnormalities (obesity, hyperglycemia, dyslipidemia and the metabolic syndrome) that are associated with an increased risk of type 2 diabetes mellitus and cardiovascular disease (HERT *et al.*, 2012).

Thereby, it is important to clarify the adverse effects caused by antipsychotics in order to innovate and complement treatment of patients with unified treatments that does not follow the universal protocol and individualize treatment according to the needs and predispositions of the patient and should include components like: 1) psychoeducation/boosting motivation increasing self-knowledge and becoming a partner in therapy; 2) cognitive reappraisal (learning to think accurately about one's own thinking); 3) preventing emotional avoidance (accepting emotional experience and increasing emotional literacy); and 4) changing behavioral habits in the context of exposure treatment (SCHRAMM *et al.*, 2011; BARLOW *et al.*, 2011).

Results/Discussion

In order to make clear why it isimportant to haveother forms of treatment, like transdiagnostic approach, we will elucidate the scientificdivergencesthat involvemost common medicationsused to treatpsychiatricdisorders in order emphasize the besttreatmentto promotes patient'squality of life.

Atypical antipsychotic medications are approved for marketing and labeling by the US Food and Drug Administration (FDA) for treating schizophrenia, bipolar disorder, and depression under drug-specific circumstances (MAHER *et al.*, 2011). In this line, due to their importance, it is relevant to discuss about their approaches.

Over the last two-decades, first generation or ''typical'' agents introduced in the late 1950 s and 1960 s have largely been replaced by a second generation of ''atypical'' antipsychotics (ALEXANDER, *et al.* 2011). Apparently this change is based on the facts that It has been shown that conventional antipsychotics are equally or even more harmful compared with atypical antipsychotics (GILL *et al.*, 2005; HERRMANN *et al.*, 2004; LAYTON *et al.*, 2005; Wang, *et al.*, 2005; KALES *et al.*, 2007; KLEIJER *et al.*, 2009).

Moreover, the clinical effectiveness of first-generation antipsychotics, a measure of objective and subjective outcomes encompassing symptom-based and functional effects, is challenged by increased acute (FISCHER-BARNICOL *et al.*, 2008) and chronic (CORRELL *et al.*, 2004) extrapyramidal side effects and related symptoms of dysphoria, compared to second-generation (atypical) antipsychotics (SGAs) (KANE *et al.*, 2010). However, serious and distinct adverse effects of atypicals have emerged (ALEXANDER, *et al.* 2011).

The most commonly prescribed atypical antipsychotic medications are quetiapine, risperidone, aripiprazole, and olanzapine (ALEXANDER *et al.*, 2010). Other atypical antipsychotic medications include asenapine, clozapine, iloperidone, paliperidone, and ziprasidone (MAHER *et al.*, 2011).

Atypical antipsychotics cause weight gain and lead to a higher risk of diabetes and other metabolic sequelae than their typical counterparts (ATKINS *et al.*, 2004; MAHER *et al.*, 2011). Besides, it is important to balance thepositive and negative aspects of each drug applied for a specific disorder, since, for example, a study on anxiety in patients with bipolar disorder found that risperidone was no more effective than placebo (SHEEHAN *et al.*, 2009; MAHER *et al.*, 2011). Additionally, for major depressive disorder, adjunctive aripiprazole was frequently associated with akathisia and also linked to a statistically significant elevation in the occurrence of sedation and significant weight gain.

Overall, SPIELMANS, *et al.* 2013, found that treatment was linked to several adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine combination (OFC), and aripiprazole), abnormal metabolic laboratory results (quetiapine and OFC), and weight gain (all four drugs, especially OFC). (SPIELMANS *et al.*, 2013)

So, it is relevant to attempt to thoroughly understand the risk–benefit profiles of these adjunctive treatments for major depressive disorder taking into account the lack of benefit with regards to quality of life or functional impairment, and the abundant evidence of potential treatment-related harm (SPIELMANS *et al.*, 2013).

On the other hand, talking about the typical ones, studies concluded that commonly prescribed doses of haloperidol, olanzapine, and risperidone, but not quetiapine, were associated with a short-term increase in mortality. (MITTAL *et al.*, 2011) The findings of NASRALLAH *et al.,* 2004, suggested that the mortality in elderly patients receiving haloperidol is significantly higher than in those receiving the atypical antipsychotics risperidone or olanzapine.

Even though, the use of typical agents has declined, but continues predominantly for schizophrenia. In contrast, atypical agent use has dramatically increased, both substituting for typical agents and expanding into new indications, such as bipolar disorder and depression. (ALEXANDER, *et al.* 2011) **(Figure 1)**

Figure 1: Adverse effects of antipsychotic.

FIRST-GENERATION ANTIPSYCHOTICS

Extrapyramidal side effects + symptoms of dysphoria

SECOND-GENERATION ANTIPSYCHOTICS:

	ABNORMAL METABOLIC LABORATORY RESULTS	AKATHISIA	SEDATION	WEIGHT GAIN	SHORT TERM INCREASE IN MORTALITY	STROKE
ARIPIPRAZOLE		X	X	X		
QUETIAPINE	X		X			
OLANZAPINE/ FLUOXETINE COMBINATION	X		X		X	
RISPERIDONE			X	X	X	X (in elderly)

Cerebrovascular Risks

Behavioral and Psychological Symptoms of Dementia (BPSD) have been defined as a heterogeneous range of psychological reactions, psychiatric symptoms, and behaviors, which may be disruptive, unsafe, and impair the care of the patient in a given environment (Bharucha *et al.*, 2002; Mittal 2011). Increasingly, antipsychotic medications are being used to treat these behaviors (Alexopoulos *et al.*, 2004; Schneider *et al.*, 1990). However, there are emerging concerns about the cerebrovascular-related adverse effects of antipsychotic use (Wooltorton 2002; Mittal 2011; Wu *et al.*, 2013). Available evidence indicates that antipsychotic medications increase the risk of CVAEs and death when used to treat elderly patients with BPSD. The risk is higher when used in patients with vascular dementia and above the recommended doses for these medications. The risk of CVAEs appears to remains high for about 20 months and the risk of death is elevated in the first 30 days and possibly to 2 years (Mittal *et al.*, 2011).

Besides, according to Kleijer *et al.*, when patients use antipsychotics for more than 3 months, the increased risk returns to baseline levels. This can be explained as only those patients who tolerated their first exposure were able to receive more prescriptions. These patients apparently are less susceptible for the adverse cerebrovascular effects of antipsychotics. The study indicates to that conventional antipsychotics are more harmful than atypical antipsychotics. Potential mechanisms proposed to explain this association between antipsychotics and cerebrovascular events include thromboembolic effects, altered platelet function, cardiovascular effects (orthostatic hypotension, arrhythmias) and the atherosclerotic effects of deregulation of glucose and lipid metabolism (Kleijer *et al.*, 2009).

Judicious use of these medications with careful assessment of the risk/benefit ratio and close monitoring of the risk factors will reduce side-effects like CVAEs and death thereby prevent undue suffering to patients and their families (Mittal *et al.*, 2011).

Cardiovascular and Metabolic Risk

Mechanisms underlying antipsychotic cardiometabolic adverse effects are incompletely understood. This hampers the identification of high-risk patients, low-risk antipsychotics and preventive/ameliorative treatments. In addition, some studies show that patient populations that are prescribed antipsychotic agents have a higher cardiovascular mortality rate than the general population (Correll *et al.*, 2011). Although all antipsychotic drugs can induce cardiovascular and metabolic dysfunction (especially in drug-naive, first-episode and pediatric populations), olanzapine and clozapine are most likely to cause such adverse effects. Besides, an unfavourable risk profile for myocardial infarction (MI) is associated with various lifestyle factors and co-morbidities that are more prevalent among patients with severe mental illness (Brauer *et al.*, 2011).

These adverse effects are especially prominent in vulnerable populations, such as patients with a first episode of schizophrenia, those who have not previously taken antipsychotic agents (drug-naive), children and adolescents (Hert *et al.*, 2011; Maayan *et al.*, 2010; Correll *et al.*, 2011). Nevertheless, patients receiving antipsychotic treatment, including these especially vulnerable groups, are often insufficiently assessed for cardiovascular and metabolic risk factors (Morrato *et al.*, 2010; Morrato *et al.*, 2010; Mitchell *et al.*, 2012).

Patients with severe mental disorders are at even higher risk than the general population for obesity, for example (Fleischhacker *et al.*, 2008; Hert *et al.*, 2009). In addition to medical consequences, obesity in the mentally ill can cause treatment non adherence and decreased quality of life (Maayan *et al.*, 2010).

In general terms, antipsychotic-related weight gain and obesity result from a medication-induced or –

aggravated imbalance between energy intake (type, amount and frequency of ingested calories) and energy expenditure (type, amount and frequency of activity/exercise). Several moderators and mediators for weight gain during antipsychotic treatment that influence how much weight is gained have been reported, including patient factors (age, BMI, gender), familial factors (family history of obesity, parental BMI), illness-related factors (treatment naı¨ve, extent of symptom reduction, lack of prior antipsychotic treatment) and treatment variables (duration, dose and drug type) resulting in high inter-individual variability in weight gain (MAAYAN *et al.*, 2010; COCCURELLO *et al.*, 2010).

Despite an increasing awareness of the clinical significance of antipsychotic-induced weight gain (CORRELL *et al.*, 2009; HEART *et al.*, 2009; MAAYAN *et al.*, 2010; MAAYANS *et al.*, 2010; PARSONS *et al.*, 2009), recent data suggest that the magnitude of this side effect has been constantly underestimated by studies in chronically treated adult populations since drug-naı¨ve patients gain significantly more weight than patients exposed to antipsychotics in the past (CORRELL *et al.*, 2009). For example, drug-naı¨ve pediatric patients were at far greater risk for risperidone-induced weight gain than pediatric patients as well as adult patients with substantial prior antipsychotic exposure (CORRELL *et al.*, 2009).

Metabolic Syndrome

The major components of the metabolic syndrome are generally agreed to include central obesity, hypertension, dyslipidemia, and glucose intolerance or insulin resistance. In general, the risk of developing the metabolic syndrome is greatest with clozapine, olanzapine and chlorpromazine. However, these associations can differ substantially in naturalistic cohorts of patients (KESSING *et al.*, 2010), probably owing to confounding by indication (meaning that low-risk agents are mostly prescribed to patients at high risk of developing the metabolic syndrome) (HERT *et al.*, 2012).

Olanzapine and clozapine are associated with the highest risk of dyslipidemia, whereas risperidone and quetiapine confer an intermediate risk, and aripiprazole and ziprasidone confer a low risk of this metabolic abnormality. The dyslipidemic adverse effects of clozapine, olanzapine and quetiapine manifest as abnormal elevations in levels of serum triglycerides and as an increase in total, LDL and non-HDL cholesterol levels (SIMON *et al.*, 2009).

Another study conducted in antipsychotic-drug-naive pediatric patients showed a dose-dependent effect of olanzapine on serum lipid profiles and blood glucose levels, and a dose-dependent effect of risperidone on weight gain, as well as serum lipid pro-files (CORRELL *et al.*, 2009). Abnormalities in glucose and lipid metabolism often occur via increased abdominal adiposity; however, antipsychotic drugs associated with pronounced metabolic adverse effects can also have a direct molecular effect (HERT *et al.*, 2012).

The biological and behavioral risk factors for type 2 diabetes mellitus are well identified. The most important factors are overweight and obesity, particularly central obesity (QIN *et al.*, 2010) and physical inactivity (QIN *et al.*, 2010; HARTEMINK *et al.*, 2006; ALBERTI *et al.*, 2007). Additional behavioral risk factors include smoking and a poor-quality diet (for example, low in whole grains and fiber) (HERT *et al.*, 2011).

Unsatisfying health care

The majority of patients receiving antipsychotic treatment in psychiatric hospitals or general healthcare clinics are not monitored for metabolic risk factors, even those that are simple to measure, such as obesity and high blood pressure. (MORATTO *et al.*, 2010; MORATTO *et al.*, 2010; BARNES *et al.*, 2007; LAMBERT *et al.*, 2009; HASNAIN *et al.*, 2010; HERT *et al.*, 2012).

Even after publication of FDA warnings and recommendations from the American Diabetes As-

sociation (ADA) and the American Psychiatric Association (APA), the frequency of baseline testing for blood glucose and serum lipid levels in patients receiving second-generation antipsychotic agents have changed very little (MORATTO *et al.*, 2010; HAUPT *et al.*, 2009; HERT *et al.*, 2012).

Moreover, the publication of monitoring guidelines, showed that although guidelines slightly increased monitoring, most patients do not receive adequate testing for cardiovascular and metabolic abnormalities–a prerequisite for timely treatment of these abnormalities (MITCHELL *et al.*, 2012).Likewise, most children, who initiated treatment with a second-generation antipsychotic drug, did not receive the recommended screening for blood glucose and serum lipids (HERT *et al.*, 2012).

Poor quality medical care contributes greatly to excessive mortality in elderly people with mental disorders, second only to heart failure (WHEELER *et al.*, 2010) Another important barrier is that few patients with mental illness seek medical help, even when they have acute cardiovascular syndromes. (WHEELER *et al.*, 2010; HENNEKENS *et al.*, 2005).

Conclusion

These findings emphasize the importance of establishing and implementing a standardized monitoring system for all patients receiving antipsychotic drugs. Clearly, lifestyle-related factors that are easy to measure, such as weight, waist circumference and blood pressure, should be monitored at appropriate intervals in all patients treated with antipsychotic drugs.

Subjective well-being (NABER, *et al.*, 2005; LAMBERT, *et al.*, 2006), quality of life (YUNG, *et al.*, 1996), cognition (GREEN, *et al.*, 2008; HARVEY, *et al.*, 2006; KEEFE, *et al.*, 2010) and psychosocial performance, including employment (LEHMAN, *et al.*, 2002; EVANS, *et al.*, 2004; MCGURK, *et al.*, 2010), have become endpoints of interest and goals for patients, families, clinicians and researchers (KANE *et al.*, 2013).

Healthy diet, regular exercise and smoking cessation reduce patients' cardiovascular and metabolic risk; low-risk antipsychotic agents, adding weight-lowering medications and/or treating significant cardiovascular and metabolic abnormalities might also help.

In addition, psychiatrists, physicians, nurses and other members of the multidisciplinary care team can educate and motivate people with severe mental illness to improve their lifestyle through effective behavioral interventions, including smoking cessation, dietary measures and regular exercise. However, if lifestyle interventions do not succeed, other medications, including statins, antihypertensive therapy or antidiabetic agents, might be indicated. Moreover, pharmacologic treatments (such as metformin or topiramate) can be added to reduce antipsychotic-drug-related weight gain. New antipsychotic drugs should be developed that are weight-neutral and that do not have metabolic adverse effects, or that can even reverse pre-existing cardiovascular and metabolic abnormalities in patients with mental illness who are at an increased risk of cardiovascular and cerebrovascular morbidity and mortality (HERT *et al.*, 2012).

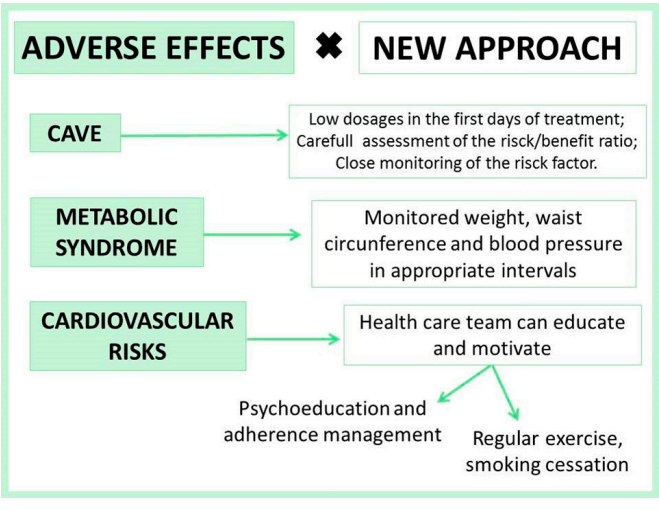
To move toward these important goals, it has become clear that the field needs to study and engage in the routine application of measurement based psychiatry, clinical and shared decision making, psychoeducation and adherence management, as well as in the integration of rational psychosocial treatment elements in the often too one-sided pharmacologic treatment planning (KANE *et al.*, 2010; DIXON *et al.*, 2009). Future studies designed to investigate the coronary side-effects of antipsychotic agents are recommended.

In light of known safety concerns and uncertainty over long-term risks and benefits, these trends may signal a need to reevaluate clinical practice patterns and strengthen efforts to educate physicians, especially primary care physicians, concerning the known safety and efficacy of antipsychotic medications. At

the same time, a new generation of clinical trials is needed to evaluate the safety and efficacy of antipsychotic medications in conditions for which they are commonly prescribed but for which the evidence base remains underdeveloped (OLFSON *et al.*, 2012).

Facing the exposed discussion we can realize that it is necessary a new approach to treatment with antipsychotics aiming to reduce side effects, and to achieve an individualized therapeutic that covers the physical, psychological, and social limitations of each patient, treating the patient as a whole and not just the disease. Side effects should be compared to the benefits and only then action should be taken. Before prescribing risperidone, one should not overlook the patient's age, especially if he or she is elderly; it is a simple assessment that can reduce mortality and improve the patient's quality of life. Assessing the social occupation of the patient before determining the doses of the drugs, taking into account the sedation promoted by them, should also be a constant concern. Non-drug treatments like the ones shown in **Figure 2** should also be stimulated.

Figure 2: New approach for reduced adverse effects of treatment with antipsychotic medication. CVAE: cerebrovascular adverse events.



Acknowledgments

We would like to thank Scientific Writing Lab, Medicine School – Federal University of Cariri – UFCA for the support.

Conflict of Interest

The authors have declared no conflicts of interest.

Role of Funding Source

None.

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