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Safety and Tolerability of Antipsychotic Polypharmacy

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Abstract

Introduction—Antipsychotic polypharmacy (APP), the concomitant use of ≥2antipsychotics, is common in clinical practice. Prior reviews have focused on the efficacy of APP, but no systematic review exists regarding the safety and tolerability of this practice.

Areas covered in this review—We conducted a systematic review of adverse effects associated with APP. Case series with ≥2 patients, chart reviews, naturalistic, data base, cohort and randomized studies that reported on the association between APP in general or specific APP combinations and global or specific adverse effect were included. We discuss methodological limitations of available studies and provide recommendations for clinicians and future research.

Expert Opinion—Across mostly small and uncontrolled studies, APP has been associated with increased global side effect burden, rates of Parkinsonian side effects, anticholinergic use, hyperprolactinemia, sexual dysfunction, hypersalivation, sedation/somnolence, cognitive impairment, and diabetes. Effects on akathisia and mortality were inconclusive. Although some combinations, particularly aripiprazole augmentation of an agent with greater side effect burden, may reduce weight gain, dyslipidemia, hyperprolactinemia and sexual dysfunction, APP should remain a last resort treatment option after monotherapy, switching and non-antipsychotic combinations have failed. More and high quality data are needed to further inform the individualized risk-benefit evaluation of APP.

Keywords

Antipsychotic; polypharmacy; adverse effects; weight gain; mortality; sedation; glucose abnormalities; EPS; anticholinergic medications; drug-drug interaction

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1. Introduction

The use of two or more antipsychotics, also called antipsychotic polypharmacy (APP), has attracted clinical, research and stakeholder interest[1, 2]. Reasons for this include: 1) APP is a fairly commonly used pharmacological practice in the treatment of psychiatric patients, especially those with psychotic disorders[3], and the percentage of schizophrenia patients receiving APP has increased during the last decade[4, 5]; 2) evidence for its efficacy and effectiveness is relatively slim or contradictory[6, 7]; and 3) concerns have been raised about the potential for increased adverse effects, problems with patient safety, and increased healthcare cost[2, 8].

The use of APP has been document since 1970s, and despite the lack of convincing efficacy data, its use continues to increase in the US and other regions[9]. Clinicians commonly resort to APP hoping to increase or speed up efficacy, treat residual symptoms, reduce the dose and the associated adverse effects of the first medication, combine complementary pharmacological side effect profiles, or as a desperate attempt after a failed clozapine and/or electroconvulsive therapy trial[10].

While previous controlled and open-label studies, as well as reviews on this topic have focused predominantly on the frequency, cost, and efficacy of APP, to date, there has not been a study that systematically summarized and evaluated the available data regarding the side effect burden associated with APP in general and associated with individual antipsychotic combinations. Therefore, we performed a systematic literature review on the topic of adverse effects in the context of APP. The aim of this study was to review the evidence for associations of APP in general and of individual combinations in particular with specific adverse effects. We further aimed to identify gaps in the literature that need to be addressed to further guide clinical practice. Based on these findings, we wished to discuss methodological issues that influence the side effect rates reported in studies of APP, synthesizing the reviewed data and making recommendations for clinical practice and future research.

2. Methods

2.1. Literature Search on APP Related Adverse Effects

An electronic PubMed and Google scholar search with no language or date restrictions was conducted with a last update on October 31st 2011, combining the following terms: “antipsychotic”, “neuroleptic”, “polypharmacy”, “combination”, “polytherapy” and “side effects”, “adverse effects”, “weight gain”, “diabetes”, “hyperlipidemia”, “hypercholesterolemia”, “dyslipidemia”, “ glucose intolerance”, “ extrapyramidal symptoms”, “dystonia”, “parkinsonism”, “akathisia”, “anticholinergic”, “tardive dyskinesia”, “hypersalivation”, “drooling”, “sedation”, “hyperprolactinemia”, “amenorrhea”, “sexual dysfunction”, “infertility”, “neuroleptic malignant syndrome”, “agranulocytosis”, “leucopenia”, “neutropenia”, “liver impairment”, “hepatitis”, “QT prolongation”, “mortality”, “seizures”, “cognition” and “cognitive impairment”. Reference lists from retrieved articles were reviewed to identify additional studies.

Included were studies that reported on the association between APP in general or specific APP combinations and global or specific adverse effect. Case series with ≥2 patients, chart reviews, naturalistic, database, cohort and randomized studies were included in this review.

2.2. Data Presentation

Given the profound methodological differences of the included studies, which preclude appropriate meaningful statistical analysis, we decided to present a qualitative description of

the relationship between specific adverse effects and APP, along with the studies supporting this relationship. Data are presented either in relationship with APP globally or, preferentially, in relationship to specific antipsychotic combinations.

3. Results

Adverse effects associated with antipsychotic polypharmacy

Antipsychotics, especially the newer, second-generation antipsychotics (SGAs) have multiple pharmacodynamic properties in addition to dopamine blockade[11]. These neurotransmitter activities are thought to be responsible for some of the beneficial effects of antipsychotics, but also for adverse effects. Below, we list the evidence for APP-associated adverse effect burden based on the clinical phenomenology, commenting on potential pharmacodynamic and pharmacokinetic origins of these adverse effects. We first review adverse effects thought to be associated with dopamine blockade, such as extrapyramidal, and prolactin related side effects. This is followed by cardiometabolic and cardiac adverse effects, as well as the remaining "other" adverse effects.

3.1. Relationship between antipsychotic polypharmacy and extrapyramidal as well as prolactin-related adverse effects

3.1.1 Parkinsonism, dystonia and akathisia: These side effects, often grouped under the name of extrapyramidal symptoms (EPS), have been, broadly speaking, linked to dopaminergic blockade. Specifically, Parkinsonism is the result of blockade of dopamine receptors in the nigro-striatal pathway. Akathisia, traditionally linked to dopamine blockade, seems to have also an extradopaminergic mechanism involving acetylcholine, γ-aminobutyric acid (GABA), norepinephrine, serotonin, and neuropeptides[12] while acute dystonia has been linked to striatal dopaminergic and cholinergic dysfunction[13].

Several authors have examined the association between APP and EPS by looking at the increased use of anticholinergic medications as a surrogate marker for clinically relevant EPS (Table 1). This finding has been described in various patient populations and settings: in 152 children and adolescents with various psychiatric diagnoses[14]; in 435 adult schizophrenia outpatients in Canada[15]; in 398 schizophrenia outpatients in Hong Kong and Beijing[16], and in 45,571 schizophrenia patients from the Veterans Administration in the US[17]. Additionally, Megna et al[18], found an increase in anticholinergic use after 6 months of treatment with SGA polytherapy. Chakos et al[19], looking at baseline data from 1,380 patients enrolled in the CATIE trial, found higher use of anticholinergic use in patients taking either a FGA or APP, and Carnahan et al[20] found an association between anticholinergic use and APP, which was mediated by antipsychotic dose. Other authors found similar results, by using data from Medicaid claims[20, 21], pharmacy claims[15, 22, 23], studying outpatients with non-affective psychosis[24], studying patients admitted in a state hospital[25, 26] and studying patients in East Asia[27] and Europe[28–32]. By contrast, in a double-blind study[33], the combination of low dose haloperidol and low dose risperidone was associated with lower scores in the Simpson-Angus Scale compared to risperidone alone in full doses. However, this APP regimen specifically attempted to avoid increased net dopamine blockage. Additionally, Kane[34], in a placebo-controlled, randomized trial, did not find any significant differences in the AIMS and Simpson-Angus scores whether aripiprazole or placebo were added for 16 weeks to 177 patients treated with risperidone and 146 patients receiving quetiapine.

Few studies looked directly at the impact of APP on akathisia (Table 1). In a 4-week, open-label trial with 12 treatment-resistant schizophrenia patients[35], adding risperidone to clozapine was associated with mild akathisia. Like for EPS, Kane[34], in a randomized clinical

trial described previously, did not find a significant difference in akathisia rates when aripiprazole or placebo was added to either risperidone or quetiapine.

3.1.2 Tardive Dyskinesia: The underlying biological cause of Tardive Dyskinesia (TD) is unknown. It is thought to result from a chronic blockade of dopamine receptors in the nigro-striatal pathway with an enduring upregulation or/and hypersensitivity of those receptors[36]. Also, it has been postulated that TD could result from dopaminergic and noradrenergic overactivity in the central nervous system with a concomitant decrease in the cholinergic and GABAergic activity[36] and/or from oxidative stress, but findings have not been conclusive[37]. Although antipsychotics, especially FGAs, have long been known to cause TD, we could not find any studies describing an association between treatment-emergent TD and APP, despite the fact that both APP and TD have been associated with long exposure to antipsychotics, high antipsychotic doses and treatment refractoriness.

3.1.3 Neuroleptic Malignant Syndrome: While the precise mechanism causing Neuroleptic Malignant Syndrome (NMS) is uncertain, dopaminergic hypofunction as a consequence of antipsychotic dopamine blockade has been implicated, although some other neurotransmitters are also likely involved[38]. As with TD, we could not find any studies that specifically described an association between NMS and APP.

3.1.4 Hyperprolactinemia and related reproductive and sexual dysfunction: Under normal circumstances, dopamine inhibits the release of prolactin from the lactotroph cells, but if this inhibition is lost (e.g., via blockade of the dopamine D2 receptors), a release of prolactin ensues, causing hyperprolactinemia and in certain cases galactorrhea. Moreover, high prolactin levels inhibit the pulsatile release of GnRH from the hypothalamus, causing a decrease in the release of FSH and LH[39] and subsequently, in susceptible individuals, leading to oligomenorrhea or amenorrhea, sexual dysfunction and infertility in women[40]. In addition, decreased libido and anorgasmia in both men and women and erectile dysfunction in men can be a consequence of elevated prolactin levels and related sex hormone dysregulation, especially in the case of syndromal hypogonadism, a state of abnormal, subphysiologic sex hormone levels.

There are several reports in the literature associating APP with hyperprolactinemia (Table 1). Montgomery[41] examined electronic medical records of 422 patients from a state hospital and found that APP was associated with hyperprolactinemia, even when antipsychotics with low impact on prolactin levels, such as quetiapine or olanzapine, were added to other antipsychotics. Similarly, Henderson[42] found higher prolactin levels in 20 patients on clozapine plus risperidone compared to 20 matched patients on clozapine alone. In a 6-weeek, double-blind study[43], significant increases in prolactin levels were found in patients on clozapine who were given risperidone vs. placebo. Additionally, in a double-blind, randomized, controlled trial with patients with limited response to clozapine[44], augmentation with sulpiride, compared to placebo, was associated with a significant increase in the serum prolactin levels. Similarly, in a randomized controlled trial with 24 schizophrenia patients on clozapine[45, 46], the addition of risperidone to clozapine was associated with an increase in prolactin levels, in contrast to the addition of ziprasidone, which was not associated with changes in baseline prolactin values.

Conversely, in several studies the addition of aripiprazole to other antipsychotics was helpful in reducing prolactin levels (Table 1). Shores[47] reviewed charts of 16 adolescents with risperidone-induced hyperprolactinemia and found a decrease in prolactin levels after the addition of aripiprazole. Mir[48] attempted an open-label switch to aripiprazole in 27 patients who had failed other antipsychotics and found that, in those who remained on APP (50%), there was a significant reduction in prolactin after 12 weeks of treatment. Similarly,

in an 8-week, open-label study[49], the addition of aripiprazole led to a decrease in prolactin levels in patients taking risperidone, sulpiride and amisulpride, although this effect was stronger for patients taking risperidone. Likewise, in an open-label study[50], a decrease in prolactin levels was found after adding aripiprazole to risperidone in 16 females with schizophrenia. In a double-blind, randomized, placebo-controlled study of 56 patients on haloperidol with hyperprolactinemia[51], a significant decrease in prolactin levels was found in patients who had aripiprazole added compared to placebo. In fact, in the aripiprazole group, 88.5% of patients normalized prolactin levels compared to only 3.6% on placebo, which occurred without any alteration in haloperidol levels. Another approach that was found to be helpful in reducing prolactin levels was the combination of antipsychotics in low doses. Lin[33], in a 6-week, double-blind study, found that patients taking low dose risperidone plus low dose haloperidol had lower prolactin levels compared to patients taking full dose risperidone.

Sexual dysfunction can partly result from antipsychotic-induced hyperprolactinemia[39], but can also arise from sedation, histaminergic or adrenergic blockade, and/or cholinergic and serotonergic blockade[52]. Moreover, it can be manifestation of primary negative symptoms or be a consequence of diabetes and other organic disorders.

Surprisingly, we only found three studies that directly examined sexual side effects in patients using APP. Mir et al[48], in a 6-month, open-label study with 27 patients, found that switching or adding aripiprazole to other antipsychotics was associated with a marked improvement in overall sexual functioning, a decrease in erectile and ejaculatory difficulties in men and a reduction in menstrual dysfunction in women. Similarly, adding aripiprazole to haloperidol led to a return of normal menstruation in 7 out of 11 females with amenorrhea or oligomenorhea, whereas this was the case in zero of 14 patients in the placebo group[51]. Conversely, Brooks[53], in a cohort study with patients from the STEP-BD study, found that SGA polytherapy (n=162) was associated with higher rates of sexual dysfunction compared to SGA monotherapy (n=1796), translating into a number-needed-to-harm (NNH) of 8.

3.2. Relationship between antipsychotic polypharmacy and cardiometabolic as well as cardiac adverse effects

3.2.1 Weight gain: The mechanisms underlying weight gain in association with antipsychotics are complex and only incompletely understood[54, 55]. Antipsychotics have been associated with increased appetite and carbohydrate craving, but receptor level causation has remained unclear. One hypothesis includes the blockade of H1 histamine receptors[56] and that this effect could be mediated through the activation of hypothalamic AMPK[57]. However, medications with very little H1 blockade, such as haloperidol, amisulpride and aripiprazole, have also been associated with significant weight gain, especially in first episode and previously unexposed patients[55]. Other receptor systems involved in antipsychotic related weight gain include dopamine, alpha-adrenergic, serotonergic, endocannabinoid and leptin receptors[55]. For example, increased levels of leptin have been associated with weight gain after treatment with antipsychotics[58] and this effect could be produced by blockade of serotonin 5HTc receptors, which might impede neural leptin[59] processing. However, leptin increase is also a result of increased fat mass, and its direct involvement in the causation of weight gain remains unclear. Moreover, a number of genetic variations in the genes associated with the neurotransmitter receptors mentioned above have been associated with weight gain[55].

APP and weight gain have been linked (Table 2). Reviewing charts of 305 inpatients, Centorrino[60] found that final weight during hospitalization was greater in subjects given multiple antipsychotics or antipsychotics with antidepressants ($p \leq 0.008$). Similarly, reviewing Medicaid claims from 4140 children and adolescents started on SGAs or two

FGAs, Jerrell[61] found that APP was associated with weight gain ($p<0.0001$). Other authors have found an association between APP and weight loss. Reinstein[62] reviewed 65 charts of patients who had gained weight on clozapine and who were given quetiapine as an augmenting agent along with a concomitant decrease of 25% of the clozapine dose and found a mean weight loss of 4.2 kg over 10 months. Karunakaran[63] reviewed the charts of 24 patients on clozapine who received add-on aripiprazole along with a concomitant decrease in the clozapine dose (mean reduction=22%) and found that 75% of the patients lost an average of 7.5 kg. Ziegenbein[64], in an open-label study, added ziprasidone to nine schizophrenia patients with limited response to clozapine and found a modest weight loss of 1.5–2 kg in two patients after 6 months of treatment, although the addition of ziprasidone allowed the reduction of clozapine by a mean of 18%. Also, in a 6-week, open-label study of 10 patients on clozapine who received aripiprazole augmentation[65], a decrease in weight ($p=0.003$) and body mass index (BMI) ($p=0.004$) was found. Fleischhacker[66] randomized 207 schizophrenia patients on clozapine to either placebo or aripiprazole, and found a significant decrease in mean weight after 16 weeks of treatment with aripiprazole vs. placebo (−2.53 vs. −0.38 kg, $p<0.001$). In a 10-week, randomized, placebo-controlled, double-blind, crossover study[67], adding aripiprazole, compared to placebo, to stable schizophrenia patients on olanzapine was associated with greater decreases in weight ($p=0.003$) and BMI ($p=0.004$) after 4 weeks of treatment.

Other studies did not confirm an association between specific APP combinations and weight changes (Table 2). Henderson[68], in an open-label study, added ziprasidone to 10 olanzapine-treated and 11 clozapine-treated patients and did not find significant changes in weight and BMI. Chang[69], in an 8-week, randomized, placebo-controlled trial of 62 treatment-resistant schizophrenia patients on clozapine, found only numeric advantages regarding weight loss for aripiprazole compared to placebo. Kane[34], in a trial described previously, did not find significant differences in weight change in patients receiving aripiprazole vs. placebo (1.3 kg vs. 1.1 kg, $p=0.7$), although numerically fewer patients in the aripiprazole combination group compared to the placebo group had ≥7% weight gain (7% vs. 13%, $p=0.45$). Honer et al[70] randomized 68 patients with schizophrenia on clozapine to adjunctive risperidone or placebo for eight weeks finding no significant differences in endpoint weight or BMI.

3.2.2 Glucose disturbance, dyslipidemia, diabetes, and metabolic syndrome:
Disturbances in glucose, lipids and other metabolic parameters have been strongly associated with SGA[71, 72]. It has been suggested that these disturbances may be related to weight gain and an increase in adipose tissue, antagonism of 5 HT2C receptors, insulin resistance, pancreatic B cell damage mediated by hyperlipidemia, and inhibition of the hepatocyte nuclear factor 1alpha, or blockade of specific muscarinic receptors[54]. However, weight-independent, dose related antipsychotic effects have also been discussed[55].

Several studies have reported on the frequency of adverse metabolic effects associated with APP (Table 2). Jerrell[61], using pharmacy claims from a Medicaid database, found that the odds for developing weight gain, type II diabetes and dyslipidemia were higher in children and adolescents receiving APP. Kessing[73], using registry data from all people treated with antipsychotics in Denmark from 1996 to 2005, found that the incidence of diabetes increased with the number of antipsychotics prescribed. Correll[74] examined the charts of 364 newly admitted inpatients and found, in bivariate analysis, a significant association of APP with metabolic syndrome. However, this association was not found in multivariate analysis when factors associated with metabolic syndrome rate were controlled for. Two recent studies also found that initially significant associations between APP and metabolic syndrome disappeared when the analyses were controlled for relevant demographic, illness or lifestyle factors[75, 76]. However, at least, in the study by Misawa et al.[75], APP was associated with pre-metabolic syndrome, defined as visceral fat obesity plus only one

additional criterion. Tirupati[77], in a cross-sectional study, recruited 221 patients with schizophrenia in a psychiatric rehabilitation setting and found higher rates of metabolic syndrome in patients on APP (range: 72.4–78.8%) compared to patients on antipsychotic monotherapy (60.3–66.6%). Citrome[78], in a case-control study of patients hospitalized for more than 60 days on treatment with antipsychotics, found a significant association between APP, clozapine, quetiapine, and treatment-emergent diabetes. In an 8-week randomized controlled trial with 68 patients with schizophrenia on clozapine[70], adding risperidone, compared to placebo, was associated with higher fasting blood glucose levels (16.2 mg/dl vs. 1.8 mg/dl, p=0.04).

Conversely, several studies described a beneficial effect of APP on metabolic status, in particular when augmenting with aripiprazole (Table 2). Karunakaran[63] reviewed charts from 24 patients on clozapine finding that the concomitant use of aripiprazole was associated with a trend-level increase in HDL (1.09 mmol/l to 1.17 mmol/l, p=0.06). Reviewing charts of 65 patients on clozapine (13 with diabetes at baseline) who received add-on quetiapine while concomitantly reducing the clozapine dose, Reinstein et al[62] found that 20% of the diabetes patients showed a normalization of blood glucose levels and HA1c after 10 months of combined treatment. Henderson et al[65], in an open-label study of 10 patients on clozapine plus aripiprazole, found a significant decrease from baseline to endpoint in total cholesterol (211±26.9 to 184.4±26.9, p=0.002) and triglycerides (274.2±228.7 to 176.1±106.0, p=0.04). Similarly, in a 10-week, double-blind, randomized, crossover, placebo-controlled study in schizophrenia patients, aripiprazole augmentation of olanzapine resulted in a significant decrease in total triglycerides (−51.7±78.2 to 47.6±52.7), VLDL-C (−3.4±7.25 to 5.1±9.3, p=0.01), and VLDL-1 and VLDL- 2 (−1.9±4.7 to 2.7±4.6, p=0.01) compared to placebo[67]. Chang et al[69] randomized 62 patients with schizophrenia with limited improvement with clozapine to adjunctive aripiprazole treatment or placebo for 8 weeks and found that aripiprazole augmentation led to significantly greater reductions in triglycerides (−31.1 mg/dL vs +24.4 mg/dL, p<.01) and non-HDL cholesterol (−13.7 mg/dL vs −3.7 mg/dL, p<0.05) compared to placebo. Lastly, in a 16-week trial of 207 patients with insufficient symptom control and weight gain >2.5 kg during clozapine treatment, addition of aripiprazole was associated with greater reduction in total and LDL cholesterol (p<0.001) than placebo[66].

Other studies did not find a relationship between APP and cardiometabolic side effects (Table 2). Taylor[79] reviewed the charts of 606 inpatients and did not find a significant difference in the prevalence of glycemic disorders between APP and monotherapy with either SGA or FGAs in those tested for Diabetes. Henderson[68], in a 6-week, open-label study, added ziprasidone to 10 olanzapine-treated and 11 clozapine-treated patients and did not find any significant changes in cholesterol levels or fasting glucose at endpoint compared to baseline. Lastly, Kane[34], in a previously described clinical trial, did not find any significant changes from baseline in fasting glucose, total cholesterol, fasting triglycerides, LDL and HDL cholesterol after 16 weeks of treatment with either aripiprazole or placebo in patients on risperidone or quetiapine.

3.2.3 Orthostasis: Orthostatic hypotension is caused by alpha-1 adrenergic blockade or anticholinergic blockade[80] and not uncommon with antipsychotic treatment. However, no reports of the relationship between APP and orthostasis were found.

3.2.4 QTc prolongation and sudden cardiac death: Heart rate-corrected Qt (QTc) prolongation has been associated with blockade of the Human ether-a-go-go-related gene (HERG) potassium channel. Substantial QT prolongation has been more commonly reported with sertindole, ziprasidone, thioridazine, and IV haloperidol[81]. QTc prolongation can occur due to drug-drug interactions, increasing blood levels of antipsychotics and is feared as a

risk factor for torsade de pointe and sudden cardiac death due to arrhythmias. In one large database study, the risk of sudden cardiac death was higher with use of either FGA or SGA, and further increased by higher doses[82]. Given the fact that mutual inhibition of antipsychotic metabolism and higher total dose are possible components of APP, it is somewhat surprising that only few studies assessed the effect of APP on QTc and none has assessed the risk of sudden cardiac death directly. In a trial described previously[45], the addition of ziprasidone to clozapine was associated with a significant increase in QTc from 387.7 to 403.2 ms, while the addition of risperidone was not associated with any changes in QTc. Ramos-Rios[83] found no association between APP and prolonged QTc in 171 patients admitted to a long-term psychiatric institution, and examining the records of 364 adults on treatment with SGA, Correll[84] also did not find any difference in QT duration or dispersion in patients on one vs. two SGA. By contrast, an association in the opposite direction was found by Mackin et al[85], who examined 103 outpatients iterated with an antipsychotic for ≥6 months finding a non-significant (p=0.08) decrease in QT interval in patients receiving APP (402.6± 24.1 ms) compared to patients on AP monotherapy (416.4±23.2 ms) (Table 2).

3.2.5 Increased mortality: Reasons for the increased mortality in schizophrenia are manifold and have been attributed to a higher incidence or cardiovascular risk factors and disease further complicated by sedentarism, poor dietary patterns, high comorbid substance use, infrequent medical follow up, and higher suicidal rates compared to normal population[54, 55, 72]. Furthermore, some authors have reported and association between an increased mortality and APP (Table 2). Waddington[86] followed 88 patients for 10 years and found that APP was associated with reduced survival. Also, Joukamaa[8] found an association between a higher number of antipsychotics at baseline and mortality after 17 years of follow up. Conversely, Baandrup[2], in a population-based, nested, case-control study, found no relationship between APP and mortality and Tiihonen[87], in a population-based cohort study, found even that long-term antipsychotics use was associated with lower mortality compared to no antipsychotic use (adjusted HR= 0.81, 95%CI: 0.77–0.84), and that APP was not more likely to produce increased mortality compared to perphenazine (adjusted HR= 1.08, 95%CI: 0.92–1.26). Notably and confirming prior findings, this study showed that clozapine was associated with significant lower risk of death by suicide, and all cause mortality compared to all other antipsychotics, whereas, at least over the medium-term follow-up in this study, no increased death from ischemic heart disease was observed.

3.3. Relationship between antipsychotic polypharmacy and other adverse effects

3.3.1. General side effects and miscellaneous: Some studies found an association between overall side effects and APP (Table 3). Centorrino[88] matched 70 patients with schizophrenia on APP to 70 patients on antipsychotic monotherapy finding that the risk of side effects was 56% higher in patients on APP. Similarly, Barbui[89], in a study of 390 clinically unstable patients with schizophrenia in four European countries, found that patients on APP complained more of side effects. Contrary to these findings, Ganesan[90] found no differences in adverse effects on the UKU side effect rating scale in a chart review of 61 patients receiving antipsychotic monotherapy versus 32 patients receiving APP. Similarly, Kane[34] in a trial described previously, did not find group differences in treatment-emergent adverse effects.

3.3.2 Sedation: Sedation is a dose related side effect primarily caused by central histamine H1 receptor blockade[91], although other receptors such as alpha 1 adrenergic and muscarinic M1 receptor have been implicated. Some studies reported on the association between APP and sedation (Table 3). In a 6-week randomized clinical trial with 30 clozapine treated patients with schizophrenia[43], the addition of risperidone was associated with significant

higher rates of sedation compared to placebo. Similarly, in bipolar disorder patients followed in the STEP-BD study, SGA cotreatment was associated with greater sedation than monotherapy (NNH=8)[53]. Conversely, Ziegenbein[92] described an improvement in daytime sedation in patients on clozapine who were given adjunctive ziprasidone, and Rocha & Hara[93] reported a decrease in sedation in three patients who received aripiprazole in addition to clozapine.

3.3.3 Ileus: Constipation and ileus can result from the use of either antipsychotics with high intrinsic anticholinergic effects or anticholinergic medications, commonly used for the treatment of EPS. Nielsen et al[94], in a study using the Danish National Patient Registry, did not find an association between APP and ileus in 26,720 patients with schizophrenia (p=0.83). Conversely, Brooks et al[53], found significantly higher rates of constipation (NNH=11) in the 10% of 1,958 SGA treated patients who were receiving APP compared to SGA monotherapy.

3.3.4 Cognitive impairment: Although cognitive deficits are already detected in treatment-naïve, first episode schizophrenia patients, antipsychotics and other psychotropic medications can lead to further cognitive impairment via antihistaminergic and anticholinergic effects as well as excessive dopamine blockade and/or addition of anticholinergic medications[95, 96]. Relatively few studies have assessed cognition in relationship to APP (Table 3). For example, Elie[97] found that APP was associated with poor cognitive performance in the BACS battery, mentioning that the effect might have been mediated by high antipsychotic doses. Similarly, Chakos et al[19] examined baseline use of antipsychotics in subjects enrolled in the CATIE trial finding that subjects on APP had lower neurocognitive composite scores. Furthermore, Hori[98] examined 67 patients with chronic schizophrenia and 92 healthy controls and found that patients on APP or high doses had lower cognitive performance. Conversely, only Kontis[99], in a cross-sectional study, found no difference in cognitive performance in patients with APP compared to patients on antipsychotic monotherapy.

3.3.5 Hypersalivation: Hypersalivation or drooling is commonly seen in patients on treatment with clozapine and other antipsychotics as part of Parkinsonian symptoms. In addition to excessive dopamine blockade, drooling has been associated with alpha 2 blockade or M4 muscarinic receptor stimulation, as seen with an active metabolite of clozapine[100]. Regarding the relationship of hypersalivation with APP, Shiloh[44], in a trial described previously, found no differences in hypersalivation between the clozapine plus sulpiride group compared to the clozapine plus placebo group. In a 4-week open-label trial[35] of 12 patients on clozapine who received add-on risperidone, increased hypersalivation was noted in almost 50% of patients. Similarly, in a chart review of 480 patients, Naber[101] found an increased incidence of hypersalivation in patients on clozapine plus FGAs compared to clozapine monotherapy. Conversely, in a report of two cases[92], adding aripiprazole along with a concomitant decrease in clozapine dose led to a decrease in hypersalivation. Moreover, in a double-blind, crossover study, adding amisulpride to clozapine reduced hypersalivation, even without clozapine dose reduction[102].

3.3.6. Leucopenia, neutropenia and agranulocytosis: Clozapine is known to cause neutropenia and agranulocytosis. While immunologic mechanisms have been postulated too, this side effect may also result from the conversion of clozapine and norclozapine into electrophilic nitrenium ions, which either bind to neutrophils causing cell death, or causing oxidative stress-induced neutrophil apoptosis[103]. The presence of antibodies against neutrophils has also been suggested as a contributor in the development of neutropenia in patients using clozapine; however, little evidence is available in this regard.

The risk of leucopenia and agranulocytosis is not exclusive of clozapine, making an additive effect conceivable. Cases have been reported with other antipsychotics[104], however routine blood testing is only required for clozapine. Nevertheless, besides isolated case reports, no larger case series or studies reporting in the association between APP and leucopenia, neutropenia or agranulocytosis were found in the literature.

3.3.7. Seizures: Antipsychotics have been known to lower the seizure threshold. Among FGAs, chlorpromazine is most commonly associated with seizures, while clozapine is most commonly associated with seizures among SGAs. Although additive effects are a potential concern, no studies on the association between seizures and APP were found.

3.3.8. Liver impairment: Elevated liver enzymes are not infrequently seen in patients treated with antipsychotics. However, in most cases these elevations are transient and do not affect treatment. The first reports came from Ebert and Shader[105], who detected increases of liver enzymes in patients being treated with chlorpromazine. More recently, abnormalities have been found in patients treated with risperidone[106], quetiapine[106], clozapine and haloperidol[107]. While these effects could be additive, we could not find any studies related to APP.

4. Conclusion

Although APP has received a lot of attention in the literature, bemoaned for the lack of a sufficient evidence base and criticized for the potential for increased acute and chronic adverse effect burden, the data base on adverse effects of APP is still relatively slim. Overall, and based on mostly uncontrolled and observational studies, there is some evidence, however, that APP carries an increased side effect burden compared to treatment with one antipsychotic. The strongest evidence exists for Parkinsonian side effects and anticholinergic use, followed by increased prolactin levels. Both these side effects can be explained by a greater total antipsychotic dose and net blockade of dopamine receptors in the APP group. In fact, lower dose combinations may not have the same increased adverse effect burden, but efficacy advantages may even be less likely[6]. On the other hand, evidence for increased akathisia was mixed, further adding to the hypothesis that akathisia may not be primarily dopamine related, which is also indicated by the fact that anticholinergic medications generally do not alleviate akathisia, while beta blockers and benzodiazepines do[108]. Moreover, APP was also associated with greater frequencies of general side effects, hypersalivation, sedation/somnolence, cognitive impairment, diabetes and, possibly, dyslipidemia, although a cohort effect of more severely physically ill patients receiving APP cannot be excluded[74]. In addition, the evidence was mixed regarding weight gain, QTc prolongation and increased mortality, and data were missing for potentially additive and relevant adverse effects, like TD, NMS, agranulocytosis, sudden cardiac death, seizures and elevated liver enzymes.

In contrast, some studies found either no difference or, with certain combinations and/or reported an improvement in side effects after addition of a second antipsychotic or when the dose of the first antipsychotic was lowered[33, 62]. In this regard, most studies reported that aripiprazole augmentation was associated with a decrease in certain side effects. Specifically, APP regimens that included aripiprazole were found to decrease sedation or hypersomnia[64, 93], hypersalivation[64], weight gain[66, 67], dyslipidemia[63, 65, 69], hyperprolactinemia[45–51], and sexual dysfunction[44, 51]. Other isolated studies reported beneficial effects for glucose with add-on quetiapine plus concurrent lowering of the clozapine dose[62], and of add-on ziprasidone[64] and low dose haloperidol in combination with low dose risperidone for reduced prolactin levels and EPS[33].

However, it is important to recognize the methodological limitations of the available data base. Most studies were chart reviews or open-label, naturalistic studies, small in sample size and lacking a control group. Despite the fact that many of these studies were observational and originated from convenience samples in clinical services, the lack of a control group may lead to erroneous conclusions because patients receiving antipsychotic polypharmacy may have a more chronic course or additional risk factors compared to patients receiving monotherapy. Conversely, the mere passage of time may reduce side effects, which may be unrelated to adjunctive antipsychotic treatment. Moreover, many studies had short follow up times and did not incorporate direct, comprehensive or detailed side effects assessments. Therefore, it is critical to design and conduct double-blind, randomized, placebo-controlled trials in order to assess more accurately the effectiveness and tolerability associated with APP. Another, related question is for how long patients who apparently responded to and tolerated APP should remain on APP. It is possible that a subset of those patients could do well after stopping the baseline antipsychotic and keeping the augmenting antipsychotic as monotherapy. It is also possible that certain side effects diminish over time or are amenable to a dose reduction of the baseline antipsychotic alone. Evidence to support the idea that APP might not be necessary or at least not be necessary long-term comes from studies by Suzuki[109] and Essock[110] who found that a sizeable subset or the majority of patients could be converted from APP to antipsychotic monotherapy. In fact, in the study by Essock et al[110], the patients converting from APP to monotherapy lost significantly more weight than those maintained on APP.

5. Expert Opinion

Results from this systematic review of adverse effects related to APP indicate that this area is understudied, but also that not all antipsychotic combinations are created equal. Clearly, antipsychotics are prescribed to decrease symptoms and suffering and, ideally, improve functioning. With this goal in mind, the use of the least side effect laden and simplest strategy is to be preferred in order to improve adherence, subjective well-being and psychological as well as physical health. Since superior efficacy of APP compared to antipsychotic monotherapy has not been clearly established[6, 7], the use of APP should generally be avoided. Our finding that APP is associated with an increased global side effect burden as well as Parkinsonian side effects, hyperprolactinemia, hypersalivation, sedation/somnolence, cognitive impairment, diabetes and, possibly, dyslipidemia, strengthens the argument to avoid APP as much as possible. However, on the other hand, the combination of two antipsychotics with at least a lowering of the initial antipsychotic may decrease certain side effects, such as glucose levels associated with clozapine or prolactin levels and EPS associated with risperidone, while maintaining sufficient dopamine blockade. Moreover, aripiprazole, likely through its partial D2 agonism has strong evidence to reduce elevated prolactin levels and related sexual dysfunction when added to another antipsychotic. Similarly, weight gain and dyslipidemia, two highly relevant adverse effects of antipsychotics that can increase cardiovascular morbidity and mortality seem to be reduced when aripiprazole is added to olanzapine and, especially to clozapine, even without lowering the doses of the higher risk antipsychotics. Particularly, the addition of aripiprazole to clozapine is attractive, since in that context a switch is generally not an option, justifying APP more. In addition, in a meta-analysis, clozapine treated patients seemed to benefit particularly from APP[6]. To date, it is still unclear via which mechanisms aripiprazole may decrease weight gain and metabolic abnormalities associate with clozapine and, possibly olanzapine. However, this effect was not seen when aripiprazole was added to risperidone or quetiapine, two SGAs that also have higher cardiometabolic burden than aripiprazole[54]. Moreover, it is unclear if this salutatory effect would also be seen with other lower risk antipsychotics when added to clozapine (or olanzapine) without lowering their dose. At least, for ziprasidone, a beneficial cardiometabolic effect when combined with clozapine

seems less likely. This is due to the fact that in a cross-over study of ziprasidone or placebo addition to clozapine or olanzapine, no improvement in body weight or metabolic parameters was observed in the ziprasidone arm[68]. Moreover, in an active-controlled trial in which either ziprasidone or risperidone were added to clozapine, patients in either arm continued to gain weight and effects were not significantly different across groups[111].

Despite the fact that many guidelines, institutions and agencies, such as The Joint Commission[112] started implementing policies discouraging the use of APP, there is actually surprisingly little evidence in favor of banning or condoning APP on a case by case basis. It is our opinion that at this point, the field lacks sufficient data to evaluate the potential risk and benefits and moderating and mediating factors of outcomes associated with APP. Thus, clearly, additional funding and comparative effectiveness studies in large and generalizable samples are needed to help evaluate a rather common clinical practice that is also associated with considerable health care costs. The predominant use of SGAs over FGAs has led to a big debate given that FGAs are substantially less expensive compared to SGA and given that many studies, including CATIE[113], could not demonstrate a significant advantage, in terms of effectiveness, of SGAs compared to FGAs. That debate is also relevant to APP. In general, if APP were substantially more effective than antipsychotic monotherapy, one could expect a decrease in health care costs via a reduction in the number and the duration of hospitalizations. However, APP has been associated with higher treatment cost as far as medication expenses is concerned[2], and no data exist that would support a decrease in inpatient or outpatient services use. Although the perception of many is that APP is expensive, not efficacious and carries a higher risk of adverse effects, our opinion is that this is, at least, not always the case and that more data are needed to determine the utility and risks of APP, both in general and in specific patient subgroups. Although some combinations, particularly those involving aripiprazole added to an agent with greater side effect burden, have the potential to reduce certain adverse effects, it is our opinion that APP is a last resort treatment option. Until more data become available that help inform this question further, we believe that APP should only be used after evidence-based treatments have been tried and failed, concretely, after a minimum of two trials of antipsychotics monotherapy in adequate dose and duration, after at least one trial with a long-acting injectable antipsychotic in patients with questionable/poor adherence, and after attempting one trial of clozapine and, at least, after considering ECT.

Article Highlights box

- APP has attracted significant clinical, research and stakeholder interest due to its common use in clinical practice, its questionable effectiveness, the possibility of increased adverse effects and the resulting high cost.
- The focus of prior review papers has been on the efficacy of APP, however no systematic review about the safety of APP had been conducted.
- APP is associated with an increased global side effect burden and a greater frequency of Parkinsonian side effects, hyperprolactinemia, hypersalivation, sedation/somnolence, cognitive impairment, diabetes and, possibly, dyslipidemia.
- Although, globally, APP is associated with higher adverse effects rates, some specific APP combinations are associated with a reduction in adverse effects. In particular, these include the addition of aripiprazole to clozapine for a reduction of weight gain and dyslipidemia, and the addition of aripiprazole to risperidone or haloperidol for a reduction of hyperprolactinemia and sexual dysfunction.

- Evidence for the findings described above comes mainly from uncontrolled studies (chart reviews, cross-sectional or case-control studies). More high quality, large-scale, randomized, controlled studies are required to determine the safety and efficacy of APP.

This box summarizes key points contained in the article

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References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

1. Stahl SM. Antipsychotic polypharmacy: squandering precious resources? J Clin Psychiatry. 2002 Feb.63:93–94. [PubMed: 11874226]
2. Baandrup L, Sorensen J, Lublin H, et al. Association of antipsychotic polypharmacy with health service cost: a register-based cost analysis. Eur J Health Econ. 2011 Mar 31.
3. Zink M, Englisch S, Meyer-Lindenberg A. Polypharmacy in schizophrenia. Curr Opin Psychiatry. 2010 Mar.23:103–111. [PubMed: 20051861]
4. Nielsen J, le Quach P, Emborg C, et al. 10-year trends in the treatment and outcomes of patients with first-episode schizophrenia. Acta Psychiatr Scand. 2010 Nov.122:356–366. [PubMed: 20528803]
5. Goodwin G, Fleischhacker W, Arango C, et al. Advantages and disadvantages of combination treatment with antipsychotics ECNP Consensus Meeting, March 2008, Nice. Eur Neuropsychopharmacol. 2009 Jul.19:520–532. [PubMed: 19411165] *A comprehensive review about the efficacy of various combinations of antipsychotics and other psychotropic medications in various psychiatric disorders
6. Correll CU, Rummel-Kluge C, Corves C, et al. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. Schizophr Bull. 2009 Mar.35:443–457. [PubMed: 18417466] * A meta-analysis focusing on the efficacy of antipsychotic polypharmacy vs. antipsychotic monotherapy.
7. Barbui C, Signoretti A, Mule S, et al. Does the addition of a second antipsychotic drug improve clozapine treatment? Schizophr Bull. 2009 Mar.35:458–468. [PubMed: 18436527]
8. Joukamaa M, Heliovaara M, Knekt P, et al. Schizophrenia, neuroleptic medication and mortality. Br J Psychiatry. 2006 Feb.188:122–127. [PubMed: 16449697]

9. Gallego JA, Bonetti J, Zhang J, et al. Prevalence and Correlates of Antipsychotic Polypharmacy: A Systematic Review and Metaregression of Global and Regional Trends from the 1970s to 2009. Schizophrenia Research. In press.
10. Correll CU, Shaikh L, Gallego JA, Nachbar J, Olshanskiy V, Kishimoto T, Kane JM. Antipsychotic Polypharmacy: A Survey Study of Prescriber Attitudes, Knowledge and Behavior. Schizophr Res. 2011 Mar 17. [Epub ahead of print] PubMed PMID 21419603.
11. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. Eur Psychiatry. 2010 Jun 25.(Suppl 2):S12–S21. [PubMed: 20620881]
12. Iqbal N, Lambert T, Masand P. Akathisia: problem of history or concern of today. CNS Spectr. 2007 Sep.12:1–13. [PubMed: 17805218]
13. Rupniak NM, Jenner P, Marsden CD. Acute dystonia induced by neuroleptic drugs. Psychopharmacology (Berl). 1986; 88:403–419. [PubMed: 2871578]
14. Hong IS, Bishop JR. Anticholinergic use in children and adolescents after initiation of antipsychotic therapy. Ann Pharmacother. 2010 Jul-Aug;44:1171–1180. [PubMed: 20587746]
15. Procyshyn RM, Honer WG, Wu TK, et al. Persistent antipsychotic polypharmacy and excessive dosing in the community psychiatric treatment setting: a review of medication profiles in 435 Canadian outpatients. J Clin Psychiatry. 2010 May.71:566–573. [PubMed: 20361903]
16. Xiang YT, Weng YZ, Leung CM, et al. Clinical and social determinants of antipsychotic polypharmacy for Chinese patients with schizophrenia. Pharmacopsychiatry. 2007 Mar.40:47–52. [PubMed: 17447172]
17. Kreyenbuhl JA, Valenstein M, McCarthy JF, et al. Long-term antipsychotic polypharmacy in the VA health system: patient characteristics and treatment patterns. Psychiatr Serv. 2007 Apr.58:489–495. [PubMed: 17412850]
18. Megna JL, Kunwar AR, Mahlotra K, et al. A study of polypharmacy with second generation antipsychotics in patients with severe and persistent mental illness. J Psychiatr Pract. 2007 Mar. 13:129–137. [PubMed: 17414692]
19. Chakos MH, Glick ID, Miller AL, et al. Baseline use of concomitant psychotropic medications to treat schizophrenia in the CATIE trial. Psychiatr Serv. 2006 Aug.57:1094–1101. [PubMed: 16870959]
20. Carnahan RM, Lund BC, Perry PJ, et al. Increased risk of extrapyramidal side-effect treatment associated with atypical antipsychotic polytherapy. Acta Psychiatr Scand. 2006 Feb.113:135–141. [PubMed: 16423165]
21. Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients 1998–2000. J Clin Psychiatry. 2004 Oct.65:1377–1388. [PubMed: 15491242]
22. Procyshyn RM, Kennedy NB, Tse G, et al. Antipsychotic polypharmacy: a survey of discharge prescriptions from a tertiary care psychiatric institution. Can J Psychiatry. 2001 May.46:334–339. [PubMed: 11387789]
23. Taylor D, Mace S, Mir S, et al. A prescription survey of the use of atypical antipsychotics for hospital inpatients in the United Kingdom. International Journal of Psychiatry in Clinical Practice. 2000; 4:41–46.
24. Florez Menendez G, Blanco Ramos M, Gomez-Reino Rodriguez I, et al. Polipharmacy in the antipsychotic prescribing in practices psychiatric out-patient clinic. Actas Esp Psiquiatr. 2004 Nov-Dec;32:333–339. [PubMed: 15529221]
25. Mason AS, Nerviano V, DeBurger RA. Patterns of antipsychotic drug use in four Southeastern state hospitals. Dis Nerv Syst. 1977 Jul.38:541–545. [PubMed: 17517]
26. Clark A, Holden N. The persistence of prescribing habits: a survey and follow-up of prescribing to chronic hospital in-patients. The British journal of psychiatry: the journal of mental science. 1987; 150:88. [PubMed: 3115352]
27. Sim K, Su A, Fujii S, et al. Antipsychotic polypharmacy in patients with schizophrenia: a multicentre comparative study in East Asia. Br J Clin Pharmacol. 2004 Aug.58:178–183. [PubMed: 15255800]

28. Kiivet RA, Llerena A, Dahl ML, et al. Patterns of drug treatment of schizophrenic patients in Estonia, Spain and Sweden. Br J Clin Pharmacol. 1995 Nov.40:467–476. [PubMed: 8703651]
29. Tognoni G. Pharmacoepidemiology of psychotropic drugs in patients with severe mental disorders in Italy. European Journal of Clinical Pharmacology. 1999; 55:685–690. [PubMed: 10638400]
30. De Hert M, Wampers M, Peuskens J. Pharmacological treatment of hospitalised schizophrenic patients in Belgium. International Journal of Psychiatry in Clinical Practice. 2006; 10:285–290.
31. De Hert M, Wampers M, van Winkel R, et al. Anticholinergic use in hospitalised schizophrenic patients in Belgium. Psychiatry research. 2007; 152:165–172. [PubMed: 17445906]
32. Hanssens L, De Hert M, Wampers M, et al. Pharmacological treatment of ambulatory schizophrenic patients in Belgium. Clin Pract Epidemol Ment Health. 2006; 2:11.
33. Lin CH, Kuo CC, Chou LS, et al. A randomized, double-blind comparison of risperidone versus low-dose risperidone plus low-dose haloperidol in treating schizophrenia. J Clin Psychopharmacol. 2010 Oct.30:518–525. [PubMed: 20814315]
34. Kane JM, Correll CU, Goff DC, et al. A multicenter, randomized, double-blind, placebo-controlled, 16-week study of adjunctive aripiprazole for schizophrenia or schizoaffective disorder inadequately treated with quetiapine or risperidone monotherapy. J Clin Psychiatry. 2009 Oct. 70:1348–1357. [PubMed: 19906340] ** An example of a well designed large-scale randomized, controlled trial, which showed no significant overall advantage of APP over monotherapy in terms of efficacy and safety.
35. Henderson DC, Goff DC. Risperidone as an adjunct to clozapine therapy in chronic schizophrenics. J Clin Psychiatry. 1996 Sep.57:395–397. [PubMed: 9746446]
36. Casey DE. Tardive dyskinesia: pathophysiology and animal models. J Clin Psychiatry. 2000; 61(Suppl 4):5–9. [PubMed: 10739324]
37. Tsai G, Goff DC, Chang RW, et al. Markers of glutamatergic neurotransmission and oxidative stress associated with tardive dyskinesia. Am J Psychiatry. 1998 Sep.155:1207–1213. [PubMed: 9734544]
38. Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry. 2007 Jun. 164:870–876. [PubMed: 17541044]
39. Wieck A, Haddad PM. Antipsychotic-induced hyperprolactinaemia in women: pathophysiology, severity and consequences. Selective literature review. Br J Psychiatry. 2003 Mar.182:199–204. [PubMed: 12611781]
40. Petty RG. Prolactin and antipsychotic medications: mechanism of action. Schizophr Res. 1999 Mar 1; 35(Suppl):S67–S73. [PubMed: 10190227]
41. Montgomery J, Winterbottom E, Jessani M, et al. Prevalence of hyperprolactinemia in schizophrenia: association with typical and atypical antipsychotic treatment. J Clin Psychiatry. 2004 Nov.65:1491–1498. [PubMed: 15554761]
42. Henderson DC, Goff DC, Connolly CE, et al. Risperidone added to clozapine: impact on serum prolactin levels. J Clin Psychiatry. 2001 Aug.62:605–608. [PubMed: 11561931]
43. Anil YAE, Kivircik ABB, Turgut TI, et al. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety. The Journal of clinical psychiatry. 2005; 66:63. [PubMed: 15669890]
44. Shiloh R, Zemishlany Z, Aizenberg D, et al. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. A double-blind, placebo-controlled study. Br J Psychiatry. 1997 Dec.171:569–573. [PubMed: 9519099]
45. Zink M, Kuwilsky A, Krumm B, et al. Efficacy and tolerability of ziprasidone versus risperidone as augmentation in patients partially responsive to clozapine: a randomised controlled clinical trial. J Psychopharmacol. 2009 May.23:305–314. [PubMed: 18562423]
46. Kuwilsky A, Krumm B, Englisch S, et al. Long-term efficacy and tolerability of clozapine combined with ziprasidone or risperidone. Pharmacopsychiatry. 2010 Aug.43:216–220. Epub 2010 Jun 29. PubMed PMID:20589598. [PubMed: 20589598]
47. Shores LE. Normalization of risperidone-induced hyperprolactinemia with the addition of aripiprazole. Psychiatry (Edgmont). 2005 Mar.2:42–45. [PubMed: 21179629]
48. Mir A, Shivakumar K, Williamson RJ, et al. Change in sexual dysfunction with aripiprazole: a switching or add-on study. J Psychopharmacol. 2008 May.22:244–253. [PubMed: 18308789]

49. Chen CK, Huang YS, Ree SC, et al. Differential add-on effects of aripiprazole in resolving hyperprolactinemia induced by risperidone in comparison to benzamide antipsychotics. Prog Neuropsychopharmacol Biol Psychiatry. 2010 Dec 1.34:1495–1499. [PubMed: 20732372]
50. Yasui-Furukori N, Furukori H, Sugawara N, et al. Dose-dependent effects of adjunctive treatment with aripiprazole on hyperprolactinemia induced by risperidone in female patients with schizophrenia. J Clin Psychopharmacol. 2010 Oct.30:596–599. [PubMed: 20814333]
51. Shim JC, Shin JG, Kelly DL, et al. Adjunctive treatment with a dopamine partial agonist, aripiprazole, for antipsychotic-induced hyperprolactinemia: a placebo-controlled trial. Am J Psychiatry. 2007 Sep.164:1404–1410. [PubMed: 17728426]
52. Malik P. Sexual dysfunction in schizophrenia. Curr Opin Psychiatry. 2007 Mar.20:138–142. [PubMed: 17278911]
53. Brooks JO 3rd, Goldberg JF, Ketter TA, et al. Safety and tolerability associated with second-generation antipsychotic polytherapy in bipolar disorder: findings from the Systematic Treatment Enhancement Program for Bipolar Disorder. J Clin Psychiatry. 2011 Feb.72:240–247. [PubMed: 20868629]
54. De Hert M, Detraux J, van Winkel R, et al. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2011 Oct.:18.
55. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. Trends Mol Med. 2011 Feb. 17:97–107. [PubMed: 21185230]
56. Matsui-Sakata A, Ohtani H, Sawada Y. Receptor occupancy-based analysis of the contributions of various receptors to antipsychotics-induced weight gain and diabetes mellitus. Drug Metab Pharmacokinet. 2005 Oct.20:368–378. [PubMed: 16272755]
57. Kim SF, Huang AS, Snowman AM, et al. From the Cover: Antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. Proc Natl Acad Sci U S A. 2007 Feb 27.104:3456–3459. [PubMed: 17360666]
58. McIntyre RS, Mancini DA, Basile VS. Mechanisms of antipsychotic-induced weight gain. J Clin Psychiatry. 2001; 62(Suppl 23):23–29. [PubMed: 11603882]
59. Sussman N. The implications of weight changes with antipsychotic treatment. J Clin Psychopharmacol. 2003 Jun.23:S21–S26. [PubMed: 12832946]
60. Centorrino F, Cincotta SL, Talamo A, et al. Hospital use of antipsychotic drugs: polytherapy. Compr Psychiatry. 2008 Jan-Feb;49:65–69. [PubMed: 18063043]
61. Jerrell JM, McIntyre RS. Adverse events in children and adolescents treated with antipsychotic medications. Hum Psychopharmacol. 2008 Jun.23:283–290. [PubMed: 18302312]
62. Reinstein MJ, Sirotovskaya LA, Jones LE, et al. Effect of clozapine-quetiapine combination therapy on weight and glycaemic control: preliminary findings. Clinical drug investigation. 1999; 18:99–104.
63. Karunakaran K, Tungaraza TE, Harborne GC. Is clozapine-aripiprazole combination a useful regime in the management of treatment-resistant schizophrenia? J Psychopharmacol. 2007 Jun. 21:453–456. [PubMed: 17050662]
64. Ziegenbein M, Kropp S, Kuenzel HE. Combination of clozapine and ziprasidone in treatment-resistant schizophrenia: an open clinical study. Clin Neuropharmacol. 2005 Sep-Oct;28:220–224. [PubMed: 16239761]
65. Henderson DC, Kunkel L, Nguyen DD, et al. An exploratory open-label trial of aripiprazole as an adjuvant to clozapine therapy in chronic schizophrenia. Acta Psychiatr Scand. 2006 Feb.113:142–147. [PubMed: 16423166]
66. Fleischhacker WW, Heikkinen ME, Olie JP, et al. Effects of adjunctive treatment with aripiprazole on body weight and clinical efficacy in schizophrenia patients treated with clozapine: a randomized, double-blind, placebo-controlled trial. Int J Neuropsychopharmacol. 2010 Sep. 13:1115–1125. [PubMed: 20459883] **Another example of a well designed and conducted randomized, controlled trial.
67. Henderson DC, Fan X, Copeland PM, et al. Aripiprazole added to overweight and obese olanzapine-treated schizophrenia patients. J Clin Psychopharmacol. 2009 Apr.29:165–169. [PubMed: 19512978]

68. Henderson DC, Fan X, Copeland PM, et al. Ziprasidone as an adjuvant for clozapine- or olanzapine-associated medical morbidity in chronic schizophrenia. Hum Psychopharmacol. 2009 Apr.24:225–232. [PubMed: 19283774]
69. Chang JS, Ahn YM, Park HJ, et al. Aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia: an 8-week, randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2008 May.69:720–731. [PubMed: 18370574]
70. Honer WG, Thornton AE, Chen EY, et al. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. N Engl J Med. 2006 Feb 2.354:472–482. [PubMed: 16452559] **This study, published in a high impact journal, showed that risperidone in addition to clozapine was not significantly more efficacious than clozapine plus placebo, in an 8-week double-blind, randomized, controlled trial.
71. Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA. 2009 Oct 28.302:1765–1773. [PubMed: 19861668]
72. De Hert M, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry. 2011; 10:52. [PubMed: 21379357]
73. Kessing LV, Thomsen AF, Mogensen UB, et al. Treatment with antipsychotics and the risk of diabetes in clinical practice. Br J Psychiatry. 2010 Oct.197:266–271. [PubMed: 20884948]
74. Correll CU, Frederickson AM, Kane JM, et al. Does antipsychotic polypharmacy increase the risk for metabolic syndrome? Schizophr Res. 2007 Jan.89:91–100. [PubMed: 17070017]
75. Misawa F, Shimizu K, Fujii Y, et al. Is antipsychotic polypharmacy associated with metabolic syndrome even after adjustment for lifestyle effects?: a cross-sectional study. BMC Psychiatry. 2011; 11:118. [PubMed: 21791046]
76. Krane-Gartiser K, Breum L, Glumrr C, et al. Prevalence of the metabolic syndrome in Danish psychiatric outpatients treated with antipsychotics. Nord J Psychiatry. 2011 Oct.65:345–352. [PubMed: 21428861]
77. Tirupati S, Chua LE. Obesity and metabolic syndrome in a psychiatric rehabilitation service. Aust N Z J Psychiatry. 2007 Jul.41:606–610. [PubMed: 17558623]
78. Citrome L, Jaffe A, Levine J, et al. Relationship between antipsychotic medication treatment and new cases of diabetes among psychiatric inpatients. Psychiatr Serv. 2004 Sep.55:1006–1013. [PubMed: 15345760]
79. Taylor D, Young C, Esop R, et al. Testing for diabetes in hospitalised patients prescribed antipsychotic drugs. Br J Psychiatry. 2004 Aug.185:152–156. [PubMed: 15286067]
80. Buckley NA, Sanders P. Cardiovascular adverse effects of antipsychotic drugs. Drug Saf. 2000 Sep.23:215–228. [PubMed: 11005704]
81. Alvarez PA, Pahissa J. QT alterations in psychopharmacology: proven candidates and suspects. Curr Drug Saf. 2010 Jan.5:97–104. [PubMed: 20210726]
82. Ray WA, Chung CP, Murray KT, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med. 2009 Jan 15.360:225–235. [PubMed: 19144938]
83. Ramos-Rios R, Arrojo-Romero M, Paz-Silva E, et al. QTc interval in a sample of long-term schizophrenia inpatients. Schizophr Res. 2010 Jan.116:35–43. [PubMed: 19892525]
84. Correll CU, Frederickson AM, Figen V, et al. The QTc interval and its dispersion in patients receiving two atypical antipsychotics. Eur Arch Psychiatry Clin Neurosci. 2009 Feb.259:23–27. [PubMed: 18574608]
85. Mackin P, Young AH. QTc interval measurement and metabolic parameters in psychiatric patients taking typical or atypical antipsychotic drugs: a preliminary study. J Clin Psychiatry. 2005 Nov. 66:1386–1391. [PubMed: 16420075]
86. Waddington JL, Youssef HA, Kinsella A. Mortality in schizophrenia. Antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. Br J Psychiatry. 1998 Oct.173:325–329. [PubMed: 9926037]
87. Tiihonen J, Lonnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet. 2009 Aug 22.374:620–627. [PubMed: 19595447]

88. Centorrino F, Goren JL, Hennen J, et al. Multiple versus single antipsychotic agents for hospitalized psychiatric patients: case-control study of risks versus benefits. Am J Psychiatry. 2004 Apr.161:700–706. [PubMed: 15056517]

89. Barbui C, Nose M, Mazzi MA, et al. Persistence with polypharmacy and excessive dosing in patients with schizophrenia treated in four European countries. Int Clin Psychopharmacol. 2006 Nov.21:355–362. [PubMed: 17012982]

90. Ganesan S, Taylor R, Rabheru K, et al. Antipsychotic polypharmacy does not increase the risk for side effects. Schizophr Res. 2008 Jan.98:323–324. [PubMed: 17950576]

91. Miller DD. Atypical antipsychotics: sleep, sedation, and efficacy. Prim Care Companion J Clin Psychiatry. 2004; 6:3–7. [PubMed: 16001094]

92. Ziegenbein M, Sieberer M, Calliess IT, et al. Combination of clozapine and aripiprazole: a promising approach in treatment-resistant schizophrenia. Aust N Z J Psychiatry. 2005 Sep.39:840–841. [PubMed: 16168043]

93. Rocha FL, Hara C. Benefits of combining aripiprazole to clozapine: three case reports. Prog Neuropsychopharmacol Biol Psychiatry. 2006 Aug 30.30:1167–1169. [PubMed: 16647796]

94. Nielsen J, Meyer JM. Risk Factors for Ileus in Patients with Schizophrenia. Schizophr Bull. 2010 Nov 26.

95. Vinogradov S, Fisher M, Warm H, et al. The cognitive cost of anticholinergic burden: decreased response to cognitive training in schizophrenia. Am J Psychiatry. 2009 Sep.166:1055–1062. [PubMed: 19570929]

96. Sweeney JA, Keilp JG, Haas GL, et al. Relationships between medication treatments and neuropsychological test performance in schizophrenia. Psychiatry Res. 1991 Jun.37:297–308. [PubMed: 1679950]

97. Elie D, Poirier M, Chianetta J, et al. Cognitive effects of antipsychotic dosage and polypharmacy: a study with the BACS in patients with schizophrenia and schizoaffective disorder. J Psychopharmacol. 2009 Jan 22.

98. Hori H, Noguchi H, Hashimoto R, et al. Antipsychotic medication and cognitive function in schizophrenia. Schizophr Res. 2006 Sep.86:138–146. [PubMed: 16793238]

99. Kontis D, Theochari E, Kleisas S, et al. Doubtful association of antipsychotic polypharmacy and high dosage with cognition in chronic schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2010 Oct 1.34:1333–1341. [PubMed: 20691745]

100. Davydov L, Botts SR. Clozapine-induced hypersalivation. Ann Pharmacother. 2000 May.34:662–665. [PubMed: 10852096]

101. Naber D, Holzbach R, Perro C, et al. Clinical management of clozapine patients in relation to efficacy and side-effects. Br J Psychiatry Suppl. 1992 May.:54–59. [PubMed: 1358128]

102. Kreinin A, Novitski D, Weizman A. Amisulpride treatment of clozapine-induced hypersalivation in schizophrenia patients: a randomized, double-blind, placebo-controlled cross-over study. Int Clin Psychopharmacol. 2006 Mar.21:99–103. [PubMed: 16421461]

103. Husain Z, Almeciga I, Delgado JC, et al. Increased FasL expression correlates with apoptotic changes in granulocytes cultured with oxidized clozapine. Toxicol Appl Pharmacol. 2006 Aug 1.214:326–334. [PubMed: 16510162]

104. Lander M, Bastiampillai T. Neutropenia associated with quetiapine, olanzapine, and aripiprazole. Aust N Z J Psychiatry. 2011 Jan.45:89. [PubMed: 21058927]

105. Ebert, MH.; Shader, RI. Hepatic effects. In: Shader, RI.; DiMasccio, A., editors. Psychotropic Drug Side Effects. Baltimore: Williams and Wilkins Co.; 1970. p. 175-197.

106. Atasoy N, Erdogan A, Yalug I, et al. A review of liver function tests during treatment with atypical antipsychotic drugs: a chart review study. Prog Neuropsychopharmacol Biol Psychiatry. 2007 Aug 15.31:1255–1260. [PubMed: 17600607]

107. Hummer M, Kurz M, Kurzthaler I, et al. Hepatotoxicity of clozapine. J Clin Psychopharmacol. 1997 Aug.17:314–317. [PubMed: 9241012]

108. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. Drug Saf. 2000 Jan.22:73–81. [PubMed: 10647977]

109. Suzuki T, Uchida H, Watanabe K, et al. A clinical case series of switching from antipsychotic polypharmacy to monotherapy with a second-generation agent on patients with chronic

schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2004 Mar.28:361–369. [PubMed: 14751434]

110. Essock SM, Schooler NR, Stroup TS, et al. Effectiveness of switching from antipsychotic polypharmacy to monotherapy. Am J Psychiatry. 2011 Jul.168:702–708. [PubMed: 21536693]
111. Kuwilsky A, Krumm B, Englisch S, et al. Long-term efficacy and tolerability of clozapine combined with ziprasidone or risperidone. Pharmacopsychiatry. 2010 Aug.43:216–220. [PubMed: 20589598]
112. Goren JL, Parks JJ, Ghinassi FA, et al. When is antipsychotic polypharmacy supported by research evidence? Implications for QI. Jt Comm J Qual Patient Saf. 2008 Oct.34:571–582. [PubMed: 18947117]
113. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005 Sep 22.353:1209–1223. [PubMed: 16172203]

Table 1

Relationship between Antipsychotic Polypharmacy and Extrapyramidal as well as Prolactin Related Adverse Effects

Increased Adverse Effects				Decreased Adverse Effects			
	Baseline Antipsychotic	**Augmenting Antipsychotic**	**Studies**		**Baseline Antipsychotic**	**Augmenting Antipsychotic**	**Studies**
EPS / Anticholinergic use	Mixed Mixed Mixed Mixed Mixed Mixed Mixed SGA Mixed Mixed Mixed Mixed Mixed Mixed SGA Mixed FGA FGA FGA Risperidone/ Quetiapine	Mixed Mixed Mixed Mixed SGA Mixed Mixed SGA Mixed Mixed Mixed Mixed Mixed Mixed Mixed Mixed FGA FGA FGA Aripiprazole	Hong ’10 Procyshyn ‘10 Kreyenbuhl ’07 Xiang ’07 Megna ‘07 De Hert ‘07 Chakos ’06 Carnahan ’06 De Hert ‘06 Hanssens ‘06 Ganguly ’04 Sim ’04 Florez Menendez ’04 Procyshyn ’01 Taylor ’00 Tognoni ‘99 Kivet ’95 Clark ’87 Mason ‘77 *No effect:* Kane ‘09	**EPS / Anticholinergic use**	Low dose risperidone	Low dose haloperidol	Lin ‘10
Akathisia	Clozapine Risperidone/ Quetiapine	Risperidone Aripiprazole	Henderson ’96 *No effect:* Kane ‘09	**Akathisia**	None	-	-
Dyskinesia /TD/NMS	None			**Dyskinesia /TD/NMS**	None		
Hyperprolactinemia	Clozapine Mixed Clozapine Clozapine Clozapine Clozapine	Risperidone Mixed Risperidone Risperidone Sulpiride Ziprasidone	Zink ‘09 Montgomery ’05 Anil ’05 Henderson ’01 Shiloh ’97 No Effect: Zink ‘09	**Hyperprolactinemia**	Haloperidol Risperidone Risperidone> Amisulpride= Sulpiride Mixed Risperidone Low dose risperidone	Aripiprazole Aripiprazole Aripiprazole Aripiprazole Aripiprazole Low dose haloperidol	Shim ‘07 Yasui-Forukori ‘10 Chen ’10 Mir ’08 Shores ‘05 Lin ‘10
Sexual Dysfunction	SGA	SGA	Brooks ‘11	**Sexual Dysfunction**	Mixed Haloperidol	Aripiprazole Aripiprazole	Mir ‘08 Shim ‘07

[a]low dose risperidone plus low dose haloperidol compared to regular dose risperidone;

EPS: extra-pyramidal symptoms; TD: tardive dyskinesia; NMS: neuroleptic malignant syndrome; FGA: first-generation antipsychotics; SGA: second-generation antipsychotics

Table 2

Relationship between Antipsychotic Polypharmacy and Cardiometabolic/Cardiac Adverse Effects

Increased Adverse Effects				Decreased Adverse Effects			
	Baseline Antipsychotic	**Augmenting Antipsychotic**	**Studies**		**Baseline Antipsychotic**	**Augmenting Antipsychotic**	**Studies**
Weight gain	Mixed Mixed Clozapine Clozapine Clozapine/ Olanzapine Risperidone/ Quetiapine	Mixed Mixed Risperidone Aripiprazole Ziprasidone Aripiprazole	Centorrino ’08 Jerrell ‘08 *No effect:* Honer ‘06 Chang ‘08 Henderson ‘09 Kane ‘09	**Body Weight**	Clozapine Olanzapine Clozapine-DR Clozapine Clozapine-DR Clozapine-DR	Aripiprazole Aripiprazole Aripiprazole Aripiprazole Ziprasidone Quetiapine	Fleischhacker ‘10 Henderson ‘09 Karunakaran ‘07 Henderson ‘06 Ziegenbein ‘05 Reinstein ‘99
Dyslipidemia	Mixed Mixed Clozapine/ Olanzapine Risperidone/ Quetiapine	Mixed Mixed Ziprasidone Aripiprazole	Tirupati ‘07 Jerrell ‘08 *No effect:* Henderson ‘09 Kane ‘09	**Dyslipidemia:** **Triglycerides** **Total Cholesterol** **LDL Cholesterol** **VLDL Cholesterol**	Clozapine Olanzapine Clozapine Clozapine Clozapine-DR	Aripiprazole Aripiprazole Aripiprazole Aripiprazole Aripiprazole	Fleischhacker ‘10 Henderson ’09 Chang ‘08 Henderson ’06 Karunakaran ‘07
Glucose elevation	Clozapine Risperidone/ Quetiapine Mixed Clozapine/ Olanzapine	Risperidone Aripiprazole Mixed Ziprasidone	Honer ’06 *No effect:* Kane ‘09 Taylor ‘04 Henderson ‘09	**Glucose**	Clozapine-DR	Quetiapine	Reinstein ‘99
Diabetes	Mixed Mixed Mixed	Mixed Mixed Mixed	Citrome ’04 Jerrell ‘08 Kessing ‘10	**Diabetes**	None	-	-
Metabolic syndrome	Mixed SGA	Mixed Mixed	Tirupati ’07 *Not independently*: Correll ’07 Krane-Gartiser ‘11 Misawa ’11 (but increased pre-MetSy)	**Metabolic syndrome**	None	-	-
Orthostasis	None			**Orhostasis**	None	-	-
Qt prolongation	Clozapine Mixed Mixed Clozapine	Ziprasidone Mixed Mixed Risperidone	Zink ‘09 *No effect:* Ramos-Rios ’10 Correll ‘09 Zink ‘09	**Qt prolongation**	Mixed	Mixed	Mackin ‘05
Mortality	Mixed FGA Mixed Mixed	Mixed FGA Mixed Mixed	Waddington ‘98 Joukamaa ‘06 *No effect:* Baandrup ‘10 Tiihonen ‘09	**Mortality**	None	-	-

Expert Opin Drug Saf. Author manuscript; available in PMC 2013 July 01.

Clozapine-DR: With concurrent "Dose Reduction" of clozapine; FGA: first-generation antipsychotics; SGA: second-generation antipsychotics

Table 3

Relationship between Antipsychotic Polypharmacy and Other Adverse Effects

Increased Adverse Effects				Decreased Adverse Effects			
	Baseline Antipsychotic	**Augmenting Antipsychotic**	**Studies**		**Baseline Antipsychotic**	**Augmenting Antipsychotic**	**Studies**
General side effects	Mixed Mixed Risperidone/ Quetiapine Mixed	Mixed Mixed Aripiprazole Mixed	Barbui ’06 Centorrino ‘04 *No effect:* Kane ‘09 Ganesan ‘08	**General side effects**	None	-	-
Sedation /somnolence	Clozapine	Risperidone	Anil Yagcioglu ’05	**Sedation/hypersomnia**	Clozapine-DR Clozapine-DR	Ziprasidone Aripiprazole	Ziegenbein ’05 Rocha & Hara ‘06
Ileus	SGA Mixed	SGA Mixed	Brooks ‘11 *No effect:* Nielsen ‘10	**Ileus**	None	-	-
Cognitive impairment	Mixed Mixed Mixed Mixed	Mixed Mixed Mixed Mixed	Elie ‘10 Chakos ’06 Hori ’06 *No effect*: Kontis ’10	**Cognitive impairment**	None	-	-
Hypersalivation	Clozapine Clozapine Clozapine	Mixed-FGA Sulpiride Risperidone	Naber ’92 Henderson ‘96 *No effect:* Shiloh ’97	**Hypersalivation**	Clozapine-DR Clozapine	Aripiprazole Amisulpiride	Ziegenbein ‘05 Kreinin ‘06
Leukopenia, neutropenia agranulocytosis	None	-	-	**Leukopenia, neutropenia agranulocytosis**	None	-	-
Seizures	None	-	-	**Seizures**	None	-	-
Elevated liver enzymes	None	-	-	**Elevated liver enzymes**	None	-	-

Clozapine-DR: With concurrent “Dose Reduction” of clozapine

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