Critical review of antipsychotic polypharmacy in the treatment of schizophrenia

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Abstract

Antipsychotic polypharmacy remains prevalent; it has probably increased for the treatment of schizophrenia in real-world clinical settings. The current evidence suggests some clinical benefits of antipsychotic polypharmacy, such as better symptom control with clozapine plus another antipsychotic, and a reversal of metabolic side-effects with a concomitant use of aripiprazole. On the other hand, the interpretation of findings in the literature should be made conservatively in light of the paucity of good studies and potentially serious side-effects. Also, although the available data are still limited, two smaller-scale clinical trials provide preliminary evidence that converting antipsychotic polypharmacy to monotherapy could be a valid and reasonable treatment option. Several studies have explored strategies to change physicians’ antipsychotic polypharmacy prescribing behaviours. These have revealed that, while the impact of purely educational interventions may be limited, more aggressive procedures such as directly notifying physicians by letters or phone calls can be more effective in reducing antipsychotic polypharmacy. In conclusion, antipsychotic polypharmacy can work for some clinically difficult conditions; however, it should be the exception rather than the rule and may be avoidable in many patients. More importantly, the paucity of the data clearly emphasizes the need for further investigations on not only advantages and disadvantages of antipsychotic polypharmacy, but also regarding effective interventions in already prescribed polypharmacy regimens.

Received 30 December 2011; Reviewed 30 January 2012; Revised 17 February 2012; Accepted 22 March 2012; First published online 2 May 2012

Key words: Add-on treatment, adjunctive treatment, antipsychotic, combination, polypharmacy, schizophrenia.

Introduction

Basically all available schizophrenia treatment guidelines recommend antipsychotic monotherapy and suggest the use of two or more antipsychotics only as a last resort (Addington et al. 2005; Argo et al. 2008; Buchanan et al. 2010; Falkai et al. 2005; National Collaborating Centre for Mental Health, 2010; Royal Australian and New Zealand College of Psychiatrists, 2005). For example, the NICE guideline states not to initiate antipsychotic combinations, except for short periods when changing medications (National Collaborating Centre for Mental Health, 2010). Similarly, the Texas Medication Algorithm Project recommends antipsychotic monotherapy for the first three stages (stage 1, a second-generation antipsychotic (SGA); stage 2, a SGA not tried in stage 1 or 2 first-generation antipsychotic (FGA); stage 3, clozapine) and only proposes the use of antipsychotic polypharmacy at stage 4 (clozapine plus SGA, FGA or electroconvulsive therapy) and thereafter (Argo et al. 2008). Moreover, the World Federation of Societies of Biological Psychiatry Guidelines emphasize antipsychotic monotherapy except for treatment-resistant cases for which the combination of clozapine with risperidone or sulpiride may reflect the best treatment options (Falkai et al. 2005). Such recommendations in favour of antipsychotic monotherapy are unequivocal irrespective of geographical regions; in fact, the Japanese guidelines also advocate the use of a single antipsychotic drug for the treatment of schizophrenia (Japanese Society of Psychiatry and Neurology, 2008).
Despite all of these recommendations, antipsychotic polypharmacy is common in real-world clinical settings with prevalence rates varying widely (4–70%), depending on the setting and the patient population (Ito et al. 2005; Koen et al. 2008; Paton et al. 2003; Procyshyn et al. 2010; Santone et al. 2011; Stahl & Grady, 2006; Tsutsumi et al. 2011; Xiang et al. 2007). Furthermore, the use of antipsychotic polypharmacy seems to be increasing in some countries. Gilmer et al. (2007) analysed the data from Medicaid beneficiaries with schizophrenia ($n=15\,962$) in San Diego County and found the proportion of patients receiving second-generation antipsychotic polypharmacy to have increased from 3.3% in 1999 to 13.7% in 2004. This trend was also observed in a nationwide cohort study of all newly diagnosed patients with schizophrenia in Denmark ($n=13\,600$) between 1996 and 2005; the percentage of patients treated with antipsychotic polypharmacy except for cross-tapering situations increased from 16.7 to 37.1% over a 10-yr period (Nielsen et al. 2010). On the other hand, a longitudinal chart review of a 12-yr observation period found a considerable decrease of combination treatments in Austria (Edlinger et al. 2005).

In the present review, advantages and disadvantages of antipsychotic polypharmacy are summarized. In addition, the reasons why physicians utilize antipsychotic polypharmacy are discussed. Finally, we describe potentially successful interventions for reducing antipsychotic polypharmacy.

As there is no clear consensus on the definition of ‘polypharmacy’, ‘combination treatment’ or ‘adjunctive treatment’, we have classified polypharmacy as follows: ‘antipsychotic polypharmacy’ (i.e. a concurrent use of more than one antipsychotic drug) and ‘psychotropic polypharmacy’ (i.e. the combination of an agent from a different class of psychotropic drugs with an antipsychotic) for the purpose of this review. In this manuscript, we focus on antipsychotic polypharmacy.

**Potential advantages of antipsychotic polypharmacy**

**Polypharmacy with clozapine**

Even though antipsychotic polypharmacy is frequently employed for the treatment of schizophrenia, controlled data are limited. Clozapine is the antipsychotic for which by far the most combination studies exist. Following a number of case reports and case series, the first placebo controlled, randomized clinical trial (RCT) was performed by Shiloh et al. (1997), who reported a favourable effect of a clozapine/sulpiride combination in patients who had not responded to clozapine monotherapy. The most frequent combination studied is clozapine and risperidone. A number of small, open trials published in the last century were followed by double blind RCTs, which were inconclusive. While Freudenreich et al. (2007) and Josiassen et al. (2005) found advantages when adding risperidone to clozapine over a placebo control group in double blind RCTs ($n=40$ and $n=24$, respectively), these positive results could not be confirmed by another RCT ($n=30$) by Anil Yagcioglu et al. (2005) and Akdede et al. (2006). In the largest sample evaluated so far, Honer et al. (2006) compared the efficacy of clozapine combined with risperidone to clozapine plus placebo in 68 patients with schizophrenia who had previously failed to respond to clozapine monotherapy in an 8 wk double blind RCT. No significant difference between groups was found for symptomatic benefit: six of 34 (17.6%) patients receiving additional risperidone and nine of 34 (26.5%) patients receiving add-on placebo responded to treatment. The mean difference in the change of the Positive and Negative Syndrome Scale (PANSS) total score between groups amounted to only 0.1 [95% confidence interval (CI) –7.3 to 7.0].

Zink et al. (2009) added either ziprasidone ($n=12$) or risperidone ($n=12$) to clozapine in an RCT of treatment-resistant schizophrenia patients and found improvements on both combinations. These findings are difficult to interpret given the lack of a monotherapy control group.

A Cochrane review concluded that, although several clinical trials have demonstrated efficacy of clozapine plus another antipsychotic drug, it was not possible to show whether any particular combination strategy was superior to the others (Cipriani et al. 2009). However, the discrepancy between results may be attributable to different study designs, especially regarding study duration. Paton et al. (2007) meta-analysed the data from four RCTs (166 patients); the two studies with a duration of $\geq 10$ wk favoured antipsychotic polypharmacy with clozapine in terms of ‘response’ defined as a $\geq 20\%$ reduction in the PANSS or Brief Psychiatric Rating Scale [response rates: 42% vs. 9%; relative risk (RR) 4.41, 95% CI 1.38–14.07, $p=0.01$], whereas the two studies of $<10$ wk’ duration did not (26% vs. 27%; RR 0.59, 95% CI 0.27–1.30). More recently, Correll et al. (2009) conducted a meta-analysis of 19 studies (1229 patients), including 28 monotherapy and 19 co-treatment arms, and compared therapeutic and adverse effects between antipsychotic polypharmacy and monotherapy in schizophrenia. The antipsychotic used the most was clozapine (11 studies, 542 patients). Antipsychotic
polypharmacy was found to be superior to monotherapy with regard to all-cause discontinuation (RR 0.65, 95% CI 0.54–0.78, \( p < 0.00001 \)). However, in light of the small number of trials included and the considerable inhomogeneity concerning study methodology, as well as a lack of sufficient adverse event data and dosage information, this finding needs to be interpreted with much caution. Especially, the unavailability of adverse event data is of concern considering the necessity of long-term antipsychotic treatment for schizophrenia (Uchida et al. 2011). Furthermore, a majority of the data come from one specific region (China), which limits the generalizability of the data. Moreover, this is a mix of trials in which patients were started on combination treatments and studies in which the second drug was added later. In view of these limitations, the authors modestly concluded that antipsychotic polypharmacy may be superior to monotherapy in certain clinical situations although the database was subject to possible publication bias and too heterogeneous to justify clinical recommendations. Finally, in a large, prospective, long-term observational study of schizophrenia treatment (the Schizophrenia Outpatient Health Outcomes Study sponsored by Eli Lilly), treatment with more than one antipsychotic drug was associated with a lower likelihood of recovery at month 36 compared to olanzapine [odds ratio (OR) 0.564, 95% CI 0.363–0.876, \( p = 0.0108 \); Novick et al. 2009], although details on the combination of antipsychotic drugs were not reported (Haro et al. 2003). Moreover, antipsychotic polypharmacy was not directly compared to monotherapy with any other antipsychotic.

Thus, although the findings are not always consistent, clozapine augmented with another antipsychotic drug may be beneficial for symptom control.

A number of pharmacological considerations, although speculative, have been put forward to explain some of the positive clinical effects of combining clozapine with other antipsychotics. For example, clozapine’s low dopamine D2 blockade could be augmented by adding an antipsychotic, especially in the case of strong and specific D2 blockers such as the benzamides. Superior efficacy may also be explained by the fact that combining two antipsychotics leads to a higher overall dose of chlorpromazine equivalents (Procyshyn et al. 2010; Suzuki et al. 2004). Finally, enhanced efficacy could be the result of pharmacokinetic interactions leading to higher plasma levels of the respective antipsychotic drugs.

**Non-clozapine polypharmacy**

Due to its unique mechanism of action, aripiprazole may reverse metabolic side-effects caused by ongoing antipsychotic treatment. As shown in Table 1,

<table>
<thead>
<tr>
<th>Author (yr)</th>
<th>n</th>
<th>Duration</th>
<th>Baseline AP</th>
<th>Add-on AP</th>
<th>Prolactin level</th>
<th>Metabolic parameters</th>
<th>EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shim et al. (2007)</td>
<td>56</td>
<td>8 wk</td>
<td>HPD</td>
<td>APZ</td>
<td>Decreased</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Chang et al. (2008)</td>
<td>62</td>
<td>8 wk</td>
<td>CLZ</td>
<td>APZ</td>
<td>Decreased</td>
<td>TG↓</td>
<td>n.s.</td>
</tr>
<tr>
<td>Henderson et al. (2009)</td>
<td>16</td>
<td>10 wk</td>
<td>OLZ</td>
<td>APZ</td>
<td>n.a.</td>
<td>BW↓, TG↓, VLDL↓</td>
<td>n.s.</td>
</tr>
<tr>
<td>Kane et al. (2009)</td>
<td>323</td>
<td>16 wk</td>
<td>RIS</td>
<td>APZ</td>
<td>RIS group: decreased</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Fleischhacker et al. (2010)</td>
<td>207</td>
<td>16 wk</td>
<td>QTP, CLZ</td>
<td>APZ</td>
<td>n.a.</td>
<td>BW↓, TC↓, LDL↓</td>
<td>n.s.</td>
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<tr>
<td>Chen et al. (2010)</td>
<td>24</td>
<td>8 wk</td>
<td>RIS ASP SLP</td>
<td>APZ</td>
<td>RIS group: decreased</td>
<td>n.a.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Yasui-Furukori et al. (2010)</td>
<td>16</td>
<td>8–16 wk</td>
<td>RIS</td>
<td>APZ</td>
<td>Decreased</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

AP, Antipsychotic; EPS, extrapyramidal side-effects; HPD, haloperidol; APZ, aripiprazole; PLB, placebo; CLZ, clozapine; OLZ, olanzapine; RIS, risperidone; QTP, quetiapine; ASP, amisulpride; SLP, sulpiride; TG, triglyceride; BW, body weight; VLDL, very low density lipoprotein; TC, total cholesterol; LDL, low density lipoprotein; n.a., not available; n.s., not significant.
prolonged patient hospitalization; therefore, avoiding polypharmacy was 23%; low-potency antipsychotic drugs such as quetiapine and chlorpromazine were strongly associated with long-term antipsychotic polypharmacy.

In conclusion, the available research suggests that there appear to be some clinical benefits of antipsychotic polypharmacy in clinically difficult conditions. However, these findings need to be interpreted with much caution in light of the paucity of controlled data and the potential of side-effects, as described below.

Potential disadvantages of antipsychotic polypharmacy

First, antipsychotic polypharmacy has been reported to be associated with excessively high total antipsychotic dosages (Procysyn et al. 2010; Suzuki et al. 2004), which in turn are expected to increase the risk of dose-related adverse events, including extrapyramidal motor side-effects as well as cognitive impairment (Jeste et al. 1995; Lemmens et al. 1999; Sakurai et al. 2012). A prescription survey that included 435 outpatients with mixed diagnoses in Canada between 2005 and 2006 found that the prescribed daily dose: defined daily dose (the international unit of drug utilization that has been approved by WHO) ratio for patients who were receiving antipsychotic monotherapy (1.94 ± 0.12 vs. 0.94 ± 0.04, p < 0.005; Procysyn et al. 2010). Similar findings were also observed in a retrospective case-control study of multiple vs. single antipsychotic treatment in 140 psychiatric in-patients with mixed diagnoses (Centorrino et al. 2004). They revealed that, while the median initial doses were nearly identical at admission for both the polypharmacy and monotherapy groups (200 mg/d vs. 201 mg/d chlorpromazine equivalents), the median total final antipsychotic dose at discharge was 78% higher for those receiving antipsychotic polypharmacy vs. monotherapy (475 mg/d vs. 267 mg/d chlorpromazine equivalents). These findings underscore that antipsychotic polypharmacy results in increases of total doses of antipsychotics. Therefore, in theory, the use of multiple antipsychotic drugs is expected to lead to a dose-dependent increase of antipsychotic side-effects (Jeste et al. 1995; Lemmens et al. 1999; Sakurai et al. 2012).

Second, the accumulated evidence on substrates, inducers and inhibitors in the cytochrome P450 system
clearly indicates that the use of two or more drugs can lead to relevant drug interactions. For example, CYP3A4 and CYP2D6 are involved in the metabolism of frequently used antipsychotic drugs (Urichuk et al. 2008). Drug interactions can result in unexpected increases in peripheral drug concentrations, which could result in a greater incidence and/or severity of side-effects. Similarly, such drug interactions can also result in decreases of drug concentrations, with insufficient treatment as a possible consequence.

Third, in light of medication cost, antipsychotic polypharmacy, especially with SGAs, is of serious concern in terms of cost-effectiveness. Stahl & Grady (2006) examined the cost of prescribed antipsychotic drugs for 4795 out-patients who received antipsychotic polypharmacy, using the data from California Medicaid fee-for-service pharmacy claims. Polypharmacy cost up to three times more per patient than monotherapy; the mean amount paid per patient for a 75-d period for patients who had received monotherapy was $2382 and that for patients who had received antipsychotic polypharmacy was as high as $7536. High cost associated with antipsychotic polypharmacy has also been confirmed by reports from other clinical settings (Baandrup et al. 2011; Zhu et al. 2008); this seems a consistent trend irrespective of geographic region.

Fourth, antipsychotic polypharmacy may be associated with an increased risk of death, although findings are inconsistent. For example, a 10-yr prospective study that included a cohort of 88 in-patients with schizophrenia in Ireland demonstrated that 39 of the 88 patients died; the maximum number of antipsychotics given concurrently for each individual predicted reduced survival (RR 2.46, 95% CI 1.10–5.47, \( p = 0.03 \); Waddington et al. 1998). A population-based study of a cohort of 7217 Finns demonstrated similar findings (Joukamaa et al. 2006). During a 17-yr follow-up, 39 of 99 people with schizophrenia died; after adjustment for age, gender, somatic diseases and other potential risk factors for premature death, the increased RR of natural death was 2.50 (95% CI 1.46–4.30) per one antipsychotic agent added to the regimen. Antipsychotic polypharmacy is often associated with greater amounts of total antipsychotic dose (Procyshyn et al. 2010; Suzuki et al. 2004). An association between a greater degree of exposure to antipsychotic drugs and a higher risk for sudden cardiac death has been reported for both typical and atypical antipsychotic drugs (Ray et al. 2009). Combined, these findings suggest that excessive antipsychotic dosing due to polypharmacy could result in the increased risk of cardiac sudden death, which may explain the observed association between antipsychotic polypharmacy and increased death rates. On the other hand, a large population-based, nested case-control study has not confirmed the increased risk of death in patients treated with antipsychotic polypharmacy (Baandrup et al. 2010b). From a population of 27 633 patients with schizophrenia or non-affective psychoses in Denmark, 193 who died of natural causes within a 2-yr period and 1937 age- and gender-matched controls were identified. Risk of natural death did not increase with the number of concurrently used antipsychotic drugs in comparison to antipsychotic monotherapy (no antipsychotics: OR 1.48, 95% CI 0.89–2.46; 2 antipsychotics: OR 0.91, 95% CI 0.61–1.36; \( \geq 3 \) antipsychotics: OR 1.16, 95% CI 0.68–2.00). Hence, although the possibility for increased mortality due to antipsychotic polypharmacy is still inconclusive, physicians need to be aware of this potentially serious risk.

Finally, complicated regimens of antipsychotic polypharmacy may discourage patients from taking pills as prescribed. Although a relationship between adherence and polypharmacy has not been investigated in schizophrenia, previous reports in other chronic illnesses such as diabetes and hypertension have demonstrated that the use of multiple medications often lowers patients’ adherence to medications, resulting in poorer outcomes (Benner et al. 2009; van Bruggen et al. 2009). Benner et al. (2009) evaluated the association between prescription burden and medication adherence in 5759 patients who were started on antihypertensive and lipid-lowering therapy in the US. Among patients treated with none, one and two medications in the year prior to starting therapy, 41, 35 and 30% respectively of patients were adherent. Furthermore, among patients with \( \geq 10 \) medications, only 20% were adherent. This relationship also seems true for patients with diabetes; an inverse relationship was observed between the number of drugs and patients’ medication adherence in 1283 patients in the Netherlands (van Bruggen et al. 2009). If this relationship also holds true for schizophrenia, the negative impact of using multiple antipsychotics on adherence behaviour would be obvious.

In summary, antipsychotic polypharmacy can cause a variety of problems in terms of safety, acceptability, cost and outcomes. Although some findings are inconsistent, physicians should take note of these potential adverse effects when considering polypharmacy.
Why do physicians prescribe polypharmacy?

Surveys have identified a variety of reasons for the use of antipsychotic polypharmacy (Correll et al. 2011; Ito et al. 2005; Sernyak & Rosenheck, 2004). Sernyak & Rosenheck (2004) interviewed the treating psychiatrists of 66 patients with schizophrenia who received multiple antipsychotic drugs at two Veterans Administration medical centers in the US. The most common reason for the use of antipsychotic polypharmacy was reducing positive symptoms (61%), followed by reducing negative symptoms (20%), decreasing total amount of medication (9%) and reducing extrapyramidal symptoms (5%). In addition, psychiatric symptoms were thought to have been refractory to adequate duration and dosage of antipsychotic monotherapy in 65% of patients. Interestingly, although antipsychotic polypharmacy was intended to be transitional during a process of antipsychotic switch in 39% of patients, the switch had been successfully completed in only 46% of these patients after 6–12 months. On the other hand, not only psychiatrists but also nurses may be involved in the decision-making process. Ito et al. (2005) examined the factors associated with antipsychotic polypharmacy and excessive dosing in 96 patients with schizophrenia in 19 acute psychiatric units in Japan and elucidated nurses’ requests and psychiatrists’ characteristics and perceptions of prescribing practice and algorithms. Logistic regression analysis revealed that the use of multiple antipsychotic drugs and excessive dosing were influenced by the psychiatrists’ scepticism towards the use of algorithms (‘I doubt the validity and evidence of an algorithm’) and nurses’ requests for more drugs (‘I would like to ask a psychiatrist to increase the current dosage or add another drug’). A survey of prescriber attitudes towards antipsychotic polypharmacy by Correll et al. (2011) provided additional information on the rationale and concerns around this practice. Forty-four psychiatrists who participated in this survey reported using antipsychotic polypharmacy in 17.0% of antipsychotic-treated patients. They rated when they felt prescribing multiple antipsychotic drugs was justified (0 = none to 10 = extreme), and how concerned they were (0 = none to 10 = extreme) on a 10-point scale. The reason given the largest degree of justification was cross-titration (9.2 ± 1.4, mean ± s.d.), followed by a failed clozapine trial (8.2 ± 2.2), randomized, controlled clinical trial evidence (8.0 ± 2.0), and clozapine intolerance (7.7 ± 2.6). Prescribers felt moderately (5.0 ± 1.9) concerned about antipsychotic polypharmacy, mostly due to chronic side-effects (7.6 ± 2.0), lack of evidence (7.1 ± 2.2), non-adherence risk (6.7 ± 2.3), mortality risk (6.7 ± 3.2), increased cost (4.9 ± 2.5) and higher total antipsychotic dose (4.2 ± 2.9).

Thus, these surveys indicate that psychiatrists claim to utilize antipsychotic polypharmacy as a last resort, mainly to try to manage difficult to treat patients with schizophrenia. Indeed, the use of antipsychotic polypharmacy has been reported to be associated with difficult clinical situations, including severe psychopathology, residual psychotic symptoms, poor insight into illness and involuntary admission (Table 2; Biancosino et al. 2005; Chakos et al. 2006; Grech & Taylor 2012; Morrato et al. 2007; Santone et al. 2011; Sim et al. 2004; Xiang et al. 2007).

Table 2. Characteristics associated with antipsychotic polypharmacy

<table>
<thead>
<tr>
<th>Demographics and employment status</th>
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<tbody>
<tr>
<td>Male</td>
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<tr>
<td>Young</td>
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<tr>
<td>Single</td>
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<tr>
<td>Unemployment</td>
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<tr>
<td>Symptomatology</td>
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<tr>
<td>Severe psychopathology</td>
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<td>Residual psychotic symptoms</td>
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<td>Poor cognitive function</td>
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<td>Poor insight into illness</td>
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<tr>
<td>Presence of psychiatric co-morbidity</td>
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<tr>
<td>Treatment settings and conditions</td>
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<tr>
<td>Psychiatric hospital</td>
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<tr>
<td>In-patients</td>
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<tr>
<td>Involuntary admission</td>
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<tr>
<td>More frequent admissions</td>
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<tr>
<td>Use of depot</td>
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Biancosino et al. (2005), Chakos et al. (2006), Grech & Taylor (2012), Morrato et al. (2007), Santone et al. (2011), Sim et al. (2004), Xiang et al. (2007).
been tried for a median of 84 d. These findings raise the concern that psychiatrists may start polypharmacy without exploring the entire dose range of more than one different antipsychotic.

**Switching from polypharmacy to monotherapy – clinical trials**

While the evidence on how antipsychotic polypharmacy is utilized in clinical practice has accumulated, data on how to deal with patients with schizophrenia who are being treated with multiple antipsychotic medications are still scarce. Suzuki *et al.* (2004) conducted a pragmatic open-label trial to convert antipsychotic polypharmacy to monotherapy in 47 patients with chronic schizophrenia in a cross-tapered fashion. Twenty-four patients (54.5%) remained stable, 10 patients (22.7%) improved and 10 (22.7%) worsened. Overall, social functioning, evaluated by the Global Assessment of Functioning and the Clinical Global Impresssion, remained unchanged. The 10 deteriorated patients improved again shortly after the reintroduction of their original treatment regimens. Essock *et al.* (2011) have reported a 6-month RCT, within which 127 out-patients with schizophrenia who were receiving two antipsychotics were either switched to monotherapy by discontinuing one antipsychotic or stayed on polypharmacy. Time to all-cause treatment discontinuation was shorter in the monotherapy group. Furthermore, treatment discontinuation was significantly more frequent in the monotherapy group than in the polypharmacy group (31.0% vs. 14.3%). However, looking at it from a different angle, two-thirds of the patients assigned to the monotherapy group were successfully switched to monotherapy. In addition, no significant difference was observed between the two groups with regard to psychiatric symptom change or incidence of hospitalization. Furthermore, BMI decreased significantly in the monotherapy group, compared to the polypharmacy group.

Although the data are still limited, in light of the feasibility of switching patients from polypharmacy to monotherapy, as well as potential benefits associated with the switch, the next challenge will be in predicting who should be maintained on polypharmacy and who can be switched to monotherapy.

Although further investigations are clearly warranted, the current available evidence suggests that converting antipsychotic polypharmacy to monotherapy could be a useful and reasonable treatment option in schizophrenia. Moreover, even though there is a certain risk of clinical worsening following a switch to monotherapy, clinicians always have the option to reinstate polypharmacy.

**Interventions to modify physicians’ prescribing habits regarding polypharmacy**

Interventions to change physicians’ prescribing habits constitute another strategy to reduce antipsychotic polypharmacy. Factors involved in prescribing patterns are complex. Availability and dissemination of treatment guidelines and recommendations have not always produced the desired change in physicians’ prescribing behaviours (Chen *et al.* 2000; Leslie & Rosenheck, 2004; Paton *et al.* 2008; Sernyak *et al.* 2003). Baandrup *et al.* (2010a) found that multifaceted educational interventions failed to decrease antipsychotic co-prescribing in schizophrenia in Denmark. The intervention was aimed at psychiatric healthcare providers and consisted of 1 d of didactic lectures, six 3-h educational outreach visits and an electronic automatic reminder during drug prescribing. However, no significant difference in the prevalence of antipsychotic polypharmacy was observed between the intervention and control groups. In the UK, an audit of antipsychotic prescriptions followed by feedback of benchmarked data and delivery of bespoke change interventions did not reduce the prevalence of high-dose therapy and antipsychotic polypharmacy (baseline 43%; re-audit 39%) either (Paton *et al.* 2008). On the other hand, Thompson *et al.* (2008) demonstrated a decrease in antipsychotic polypharmacy prescribing with a somewhat more aggressive intervention in the UK. In this controlled study with a 5-month follow-up, the intervention included a 30-min structured personal visit to consultant psychiatrists, dissemination of a workbook for doctors and nurses and reminder stickers on charts for patients who were receiving multiple antipsychotic drugs. Ward pharmacists applied removable reminder stickers to medication charts when patients were given polypharmacy and the stickers remained as long as two or more antipsychotic drugs were used. At the 5-month follow-up, the prevalence of antipsychotic polypharmacy had modestly decreased in the intervention group (from 47.8 to 40.4%). In an earlier study, Laska *et al.* (1980) had demonstrated that educating clinicians to reduce the use of multiple antipsychotics in the treatment of schizophrenia had only a modest impact in a state psychiatric centre in the US. Subsequently, a computerized drug review system was implemented, which notified clinicians of medication orders deviating from clinical guidelines,
which resulted in a drastic 10-fold decrease in the rate of antipsychotic polypharmacy prescribing. Hazra et al. also examined the impact of active prescription monitoring and direct feedback from pharmacists on antipsychotic polypharmacy in a psychiatric hospital in Canada (Hazra et al. 2011). As a result, a three-fold decrease in the prevalence rates of polypharmacy was observed after 2 yr and co-prescriptions of three antipsychotics were effectively eliminated. These findings suggest that active monitoring of prescribing patterns, in conjunction with targeted educational interventions, can have a significant impact on prescribing practices.

In summary, while educational interventions that are passive have only accounted for small effects, a more active form of intervention such as directly notifying physicians by letters or phone calls can decrease the use of antipsychotic polypharmacy, even if it may be perceived as fostering a ‘big-brother’-like atmosphere (Laska et al. 1980).

Conclusions

Because of the limited evidence on antipsychotic polypharmacy, especially with regard to its potential efficacy, it is not possible to draw firm and definitive conclusions on this mode of therapy. Efficacy advantages of clozapine plus another antipsychotic and a reversal of metabolic side-effects with the concomitant use of aripiprazole may apply in clinically difficult situations. On the other hand, side-effects associated with antipsychotic polypharmacy as well as increased treatment cost have consistently been reported. Moreover, clinical trials have shown that polypharmacy could be converted to monotherapy in a majority of cases although the available data are still limited. Furthermore, antipsychotic polypharmacy can be reduced through changes in physicians’ prescribing habits with appropriate interventions. We therefore tentatively conclude that antipsychotic polypharmacy may work for some difficult to treat patients. However, it should be the exception rather than the rule and judicious safety/tolerability monitoring is essential.

The necessity of maintaining patients on such a treatment regimen needs to be regularly re-evaluated. Since the topics that are covered in this review are extensive and the quality of the available reports is very variable, we have conducted a synthetic review. Due to the nature of such a review, the articles cited may reflect a certain selection bias of the authors, although we have strived for balance. Given the paucity of available data, further studies on this clinically highly relevant issue are warranted.

Acknowledgement

The authors thank Dr Takefumi Suzuki for his insightful comments.

Statement of Interest

Dr Fleischhacker has received research grants from Alkermes, Janssen Cilag, Eli Lilly, BMS/Otsuka and Pfizer. He has received honoraria for educational programmes from Janssen, Pfizer and AstraZeneca, speaking fees from AstraZeneca, Pfizer, Janssen Cilag, Roche, Lundbeck, BMS/Otsuka and advisory board honoraria from BMS/Otsuka, Wyeth, Janssen Cilag Neurosearch, Amgen, Lundbeck, Endo, United Biosoce, Targacept, MedAvante and AstraZeneca. Dr Uchida has received grants from Pfizer, speaker’s honoraria from Otsuka Pharmaceutical, Eli Lilly, Novartis Pharma, Shionogi, and Janssen Pharma within the past 2 yr.

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