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THE EFFECTIVENESS OF PSYCHOPHARMACOLOGICAL INTERVENTIONS FOR SCHIZOPHRENIA

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Abstract

Antipsychotic polypharmacy continues to be common and is likely on the rise for the treatment of schizophrenia in actual clinical environments. Existing research indicates that antipsychotic polypharmacy may provide some therapeutic advantages. For instance, combining clozapine with another antipsychotic can lead to improved symptom management. Additionally, using aripiprazole with other medications might help reverse metabolic side-effects. However, it is important to interpret the results in the literature cautiously because to the limited number of high-quality research and the possibility of significant adverse effects. Furthermore, despite the limited amount of data currently available, two smaller-scale clinical studies provide first indications that transitioning from antipsychotic polypharmacy to monotherapy may be a realistic and sensible therapeutic choice. Multiple research have investigated methods to modify the prescription practices of doctors regarding the use of multiple antipsychotic medications. These findings indicate that educational programs alone may have little impact, but more assertive measures such as directly informing doctors via letters or phone calls may be more successful in lowering the use of multiple antipsychotic medications. Antipsychotic polypharmacy may be effective for some challenging clinical circumstances, but it should be used sparingly and might potentially be avoided in a significant number of patients. The lack of evidence highlights the need for more research on both the benefits and drawbacks of antipsychotic polypharmacy, as well as the effectiveness of interventions in existing polypharmacy treatment plans.

Keywords: Additional therapy, supplementary therapy, medication for treating psychosis, combination therapy, mental disorder.

1. Introduction

The consensus among various schizophrenia treatment guidelines is to primarily use a single antipsychotic medication. The use of multiple antipsychotics is only advised as a last resort, according to several reputable sources (Addington et al.2005; Argo et al.2008; Buchanan et al.2010; Falkai et al.2005; National Collaborating Centre for Mental Health, 2010). As an example, the NICE guideline advises against starting antipsychotic combos, unless it is necessary for brief durations during drug changes (National Collaborating Centre for Mental Health, 2010; Argo et al., 2008). In addition, the Guidelines of the World Federation of Societies of Biological Psychiatry stress the use of a single antipsychotic drug for treatment, unless the patient is resistant to treatment. In such circumstances, combining clozapine with either risperidone or sulpiride may be the most effective treatment alternatives (Falkai et al., 2005).

Despite the recommendations, the use of multiple antipsychotic medications is common in real-world clinical settings. The prevalence rates of this practice vary widely, ranging from 4% to 70%, depending on the specific setting and the characteristics of the patient population. Several studies, including those by 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), and Xiang et al. (2007), have reported on this issue. Moreover, there seems to be a growing trend in the use of antipsychotic polypharmacy in some nations. In their study, Gilmer et al. (2007) examined the data of 15,962 Medicaid beneficiaries with schizophrenia in San Diego County. They discovered that the percentage of patients taking second-generation antipsychotic polypharmacy grew from 3.3% in 1999 to 13.7% in 2004.

In a nationwide cohort study conducted in Denmark, researchers observed a similar trend. The study included 13,600 newly diagnosed patients with schizophrenia between 1996 and 2005. The percentage of patients receiving treatment with multiple antipsychotic medications, excluding cases where medications were gradually switched, increased from 16.7% to 37.1% over a period of 10 years (Nielsen et al., 2010). However, a study that examined patient records over a 12-year period in Austria found a significant decline in the use of combination therapy (Edlinger et al., 2005).

This article provides a concise summary of the pros and cons of antipsychotic polypharmacy. Furthermore, this text explores the rationales for doctors' use of antipsychotic polypharmacy. Lastly, we outline potentially effective methods for decreasing the use of several antipsychotic medications. Since there is no agreed-upon definition for terms like 'polypharmacy', 'combination treatment', or 'adjunctive treatment', we have categorized polypharmacy in the following manner for the purpose of this review: 'antipsychotic polypharmacy' refers to the simultaneous use of multiple antipsychotic drugs, while 'psychotropic polypharmacy' refers to the combination of an antipsychotic drug with a different class of psychotropic drugs. This publication specifically examines the practice of using several antipsychotic medications, known as antipsychotic polypharmacy.

2. Benefits of using several antipsychotic medications

2.1. Polypharmacy with Clozapine

Although antipsychotic polypharmacy is often used to treat schizophrenia, there is a lack of controlled evidence. Clozapine has the highest number of combination studies among antipsychotics. After many case reports and case series, the first randomized clinical study (RCT) with a placebo control was conducted by Shiloh et al. (1997). They found a positive impact of combining clozapine and sulpiride in individuals who did not react to clozapine alone. The most often researched combination is the administration of clozapine with risperidone. Several minor, publicly available experiments conducted in the previous century were subsequently followed by double-blind randomized controlled trials (RCTs), which yielded inconclusive results.

Freudenreich et al. (2007) and Josiassen et al. (2005) discovered benefits when combining risperidone with clozapine compared to a placebo control group in double-blind randomized controlled trials (with sample sizes of 40 and 24, respectively). However, these favorable outcomes were not supported by another randomized controlled trial (with a sample size of 30) conducted by Anil Yagcioglu et al. (2005) and Akdede et al. (2006). In a study conducted by Honer et al. (2006), the effectiveness of combining clozapine with risperidone was compared to using clozapine with a placebo. The study included 68 patients with schizophrenia who had previously not responded to clozapine treatment alone. The study lasted for 8 weeks and followed a double-blind randomized controlled trial design. There was no statistically significant difference between the groups in terms of symptomatic improvement. Out of the 34 patients who received extra risperidone, six (17.6%) reacted to the therapy, whereas out of the 34 patients who received a placebo, nine (26.5%) responded to the treatment. The average discrepancy in the alteration of the Positive and Negative Syndrome Scale (PANSS) overall score across the groups was just 0.1 [95% confidence interval (CI) −7.3 to 7.0].

A systematic review conducted by Cochrane determined that although several clinical studies have shown the effectiveness of combining clozapine with another antipsychotic medicine, it was inconclusive as to whether any specific combination approach was superior to the others (Cipriani et al., 2009). However, the variation in outcomes might be attributed to distinct research methodologies, particularly in terms of the length of the studies. In a more recent study, Correll et al. (2009) performed a meta-analysis on 19 trials including 1229 patients. The study included 28 cases where only one medication was used and 19 cases where several medications were used simultaneously. The aim was to assess the therapeutic benefits and side effects of using multiple antipsychotic medications vs using just one medication in the treatment of schizophrenia.

Clozapine was the most often used antipsychotic, with 11 trials including 542 individuals. The study indicated that using several antipsychotic medications was more effective than using a single medication in reducing the risk of cessation for any reason (RR 0.65, 95% CI 0.54–0.78,

p<0.00001). Nevertheless, because to the limited number of studies and significant variation in research design, together with insufficient data on adverse events and dose information, it is crucial to interpret this conclusion with great care. The lack of adverse event data is particularly concerning, given the essential need for long-term antipsychotic therapy in schizophrenia (Uchida et al.2011).

Several hypothetical pharmacological factors have been proposed to explain the beneficial clinical outcomes resulting from the combination of clozapine with other antipsychotic medications. For instance, the limited inhibition of dopamine D2 receptors by clozapine might be enhanced by combining it with an antipsychotic medication, particularly if the additional medication is a potent and selective D2 blocker like the benzamides. The superior effectiveness may also be attributed to the fact that the combination of two antipsychotics results in a greater total dosage of chlorpromazine equivalents (Procyshyn et al. 2010; Suzuki et al. 2004). Ultimately, the improved effectiveness may stem from pharmacokinetic interactions that result in elevated plasma concentrations of the specific antipsychotic medications.

2.2. Non-clozapine Polypharmacy

Aripiprazole has a distinct way of working that allows it to counteract the metabolic adverse effects that might occur as a result of continuous antipsychotic medication (Chang et al. 2008, Chen et al. 2010, Fleischhacker et al. 2010, Henderson et al. 2009, Kane et al. 2009, Shim et al. 2007, and Yasui-Furukori et al. 2010). An example of a study conducted was a 16-week trial that was double-blind, randomized, and placebo-controlled. It also included a 12-week extension phase where the effects of using aripiprazole (at doses of 5-15 mg per day) as an adjunctive treatment were examined. The study focused on out-patients with schizophrenia who were already taking clozapine and had gained at least 2.5 kg in weight. This study was conducted by Fleischhacker et al. in 2010. There was a notable disparity in the amount of weight lost between those who took additional aripiprazole and those who took a placebo. The concurrent administration of aripiprazole also led to considerably larger decreases in overall and low-density lipoprotein (LDL) cholesterol levels. The findings of this study showed that the combination of aripiprazole and clozapine led to significant improvements in weight, body mass index (BMI), and fasting cholesterol levels in individuals on clozapine treatment.

3. Drawbacks of antipsychotic polypharmacy

Antipsychotic polypharmacy has been linked to excessively high total antipsychotic dosages, which can increase the risk of dose-related adverse events such as extrapyramidal motor side-effects and cognitive impairment. A survey conducted in Canada between 2005 and 2006 examined the prescription patterns of 435 out-patients with various diagnoses. The survey found that patients who were receiving multiple antipsychotic medications (antipsychotic polypharmacy) had a significantly higher ratio of prescribed daily dose to defined daily dose (a standardized measure of drug utilization approved by the World Health Organization) compared

to patients receiving only one antipsychotic medication (antipsychotic monotherapy) (1.94±0.12 vs. 0.94±0.04, $p<0.005$; Procyshyn et al.2010).

Centorrino et al. (2004) conducted a retrospective case-control study with 140 mental in-patients with mixed disorders. The study found similar results to previous research about the effectiveness of multiple vs single antipsychotic therapy. The study found that the median initial doses of antipsychotic medication were almost the same for both the polypharmacy and monotherapy groups upon admission (200 mg/d vs. 201 mg/d chlorpromazine equivalents). However, the median total final antipsychotic dose at discharge was 78% higher for patients receiving antipsychotic polypharmacy compared to those receiving monotherapy (475 mg/d vs. 267 mg/d chlorpromazine equivalents). These data emphasize that the use of several antipsychotic medications leads to an overall increase in the total dosage of antipsychotics. Hence, according to theoretical considerations, the use of numerous antipsychotic medications is anticipated to result in a proportional rise in the occurrence of antipsychotic side effects (Jeste et al. 1995; Lemmens et al. 1999; Sakurai et al. 2012).

Furthermore, the extensive body of research regarding substrates, inducers, and inhibitors in the cytochrome P450 system unequivocally demonstrates that the concurrent administration of many medicines may result in significant drug interactions. CYP3A4 and CYP2D6 have a role in the metabolism of commonly used antipsychotic medications (Urichuk et al., 2008). Drug interactions may lead to unforeseen elevations in drug levels in the body's outer regions, potentially causing a higher occurrence and/or intensity of adverse reactions. Likewise, these medication interactions might lead to reductions in drug levels, potentially resulting in inadequate therapy.

Furthermore, considering the expenses associated with medicine, the use of many antipsychotic medications, particularly second-generation antipsychotics (SGAs), raises significant concerns about cost-effectiveness. Stahl & Grady (2006) analyzed the expenses associated with prescription antipsychotic medications for 4795 out-patients who were given several antipsychotic meds, using data obtained from California Medicaid fee-for-service pharmacy claims. The cost of polypharmacy is up to three times higher per patient compared to monotherapy. The average amount spent per patient over a 75-day period for those who got monotherapy was $2382, whereas for those who received antipsychotic polypharmacy, it reached as high as $7536. The high expenses related to antipsychotic polypharmacy have been verified by studies from various clinical settings (Baandrup et al. 2011; Zhu et al. 2008). This seems to be a continuous pattern regardless of the geographical location.

4. **Summary**

Due to the scarcity of information about the effectiveness of antipsychotic polypharmacy, it is not feasible to make conclusive judgments about this treatment approach. The combination of clozapine with another antipsychotic may provide efficacy benefits, and the addition of aripiprazole can help reverse metabolic side-effects. This may be particularly useful in

challenging clinical scenarios. However, there have been persistent reports of side-effects and higher treatment expense linked with antipsychotic polypharmacy. Furthermore, many clinical studies have shown that in most instances, polypharmacy may be transitioned to monotherapy, although the existing evidence remains rather restricted.

Moreover, the use of several antipsychotic medications might be decreased by modifying doctors' prescription practices via suitable interventions. Thus, we cautiously infer that the use of several antipsychotic medications may be effective for certain individuals who are challenging to treat. Nevertheless, it should be the exception rather than the norm, and prudent monitoring of safety and tolerability is crucial. It is important to routinely reassess the need for continuing patients on this therapy regimen. Due to the vast coverage of themes and the diverse quality of accessible papers, we have done a comprehensive evaluation. Given the nature of this review, it is possible that the publications referenced may have a certain selection bias from the authors. However, we have made efforts to maintain a balanced approach. Due to the lack of sufficient evidence, it is necessary to do more investigations on this subject that is of great therapeutic importance.

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