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Interventions to reduce antipsychotic polypharmacy: A systematic review☆,☆☆

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ABSTRACT

Background: It still remains unclear as to how to counteract antipsychotic polypharmacy that remains controversial but common. The objective of this study was to synthesize the clinical evidence to reduce antipsychotic polypharmacy (i.e. use of multiple antipsychotics) in schizophrenia.
Methods: A literature search was performed to identify clinical trials that attempted to reduce antipsychotic polypharmacy in patients with schizophrenia by any form of systematic intervention using PubMed as well as MEDLINE, EMBASE, and PsycINFO (last search: June 2012). The search terms included "antipsychotics" and "polypharmacy". Cross-referencing was also performed.
Results: The literature search identified 17 studies. Only 3 studies (1 randomized controlled trial and 2 open-label trials) were found that systematically switched antipsychotic polypharmacy to monotherapy. In two of them, more than two thirds of the subjects successfully completed the switch (40/58, 69.0%; 34/44, and 77.3%, respectively) while less than half the subjects tolerated it in the other study (6/14 and 42.9%) although the sample size was very small. On the other hand, 14 studies that examined impacts of interventions have physicians refrain from antipsychotic polypharmacy. While a modest intervention with educational approach alone was effective in three of the five articles, a more assertive intervention that directly cautioned physicians on the use of polypharmacy was effective in 10 of 12 articles.
Conclusion: The literature search revealed the paucity of the data. Careful switching from polypharmacy to monotherapy seems feasible in a majority of patients with schizophrenia. Assertive interventions, rather than passive educational approaches alone, appear more effective in reducing antipsychotic polypharmacy.

1. Introduction

Antipsychotic polypharmacy (i.e. concurrent use of more than one antipsychotic drug) has been prevailing in real-world clinical settings with prevalence rates ranging from 4% up to 70%, depending on the treatment setting and the patient population (Paton et al., 2003; Ito et al., 2005; Stahl and Grady, 2006; Xiang et al., 2007; Koen et al., 2008; Procyshyn et al., 2010; Santone et al., 2011; Tsutsumi et al., 2011). Furthermore, the use of antipsychotic polypharmacy appears to have been increasing in some countries, including the US and Denmark (Gilmer et al., 2007; Nielsen et al., 2010) although it has been decreasing in certain countries/regions such as Japan and Hong Kong (Tsutsumi et al., 2011; Xiang et al., 2012; Yoshio, 2012). The evidence on the effectiveness of antipsychotic polypharmacy from clinical trials has been inconsistent (Cipriani et al., 2009; Correll et al., 2009), but this therapy is clearly associated with a variety of unwanted effects, including increases in adverse events (Ray et al., 2009; Uchida et al., 2009; Misawa et al., 2011), unnecessary economic burden (Stahl and Grady, 2006), and low adherence to treatment (Benner et al., 2009; Bailey and Kodack, 2011). In fact, all available clinical guidelines for schizophrenia recommend antipsychotic monotherapy and suggest the usage of antipsychotic polypharmacy as a last resort (Canadian Psychiatric Association, 2005; Royal Australian and New Zealand College of Psychiatrists, 2005; Falkai et al., 2006; Argo et al., 2008; Buchanan et al., 2010; National Collaborating Centre for Mental Health, 2010). Although the pros and cons of antipsychotic polypharmacy have frequently been discussed both from theoretical and real-world perspectives, the evidence is still scarce as to how to deal with patients who have already received such treatment. This issue is critically important in clinical practice, given the high and likely increasing prevalence rates of antipsychotic polypharmacy in patients with schizophrenia.

A systematic review of currently available publications will improve our understanding of how to counteract this common but controversial

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practice and also elucidate potentially effective strategies to deal with this therapy. The objective of this study was to synthesize the evidence on trials that attempted to reduce antipsychotic polypharmacy, defined as simultaneous use of multiple antipsychotic drugs, in a systematic fashion for patients with schizophrenia.

2. Methods

A comprehensive literature search was performed to identify studies that attempted to reduce antipsychotic polypharmacy in patients with schizophrenia as a main interest by any form of systematic interventions. The following search terms were used in this systematic literature search, using PubMed, Ovid MEDLINE(R), EMBASE and PsycINFO (last search: June 2012): (antipsychotic or antipsychotics or neuroleptic or neuroleptics) AND (polypharmacy or polytherapy or combination). Only articles written in English and Japanese were included. Cross-referencing of the identified articles was also performed. Literature search was conducted independently by two of the authors (H.T. and T.S.). Eligible interventions were critically appraised for their study design and summarized accordingly.

3. Results

A total of 17 studies were identified through the literature search and critically appraised in this review. Of the 17 studies, 3 were clinical trials that systematically switched antipsychotic polypharmacy to monotherapy and 14 were studies that examined impacts of interventions to have physicians refrain from antipsychotic polypharmacy.

3.1. Direct interventions to change regimens

The literature search identified only 3 clinical trials that systematically converted polypharmacy to monotherapy: 1 randomized controlled trial (RCT) and 2 open-label trials.

Godleski et al. (1989) conducted a 12-month open-label trial in which one of two simultaneously used antipsychotics was discontinued in 14 chronic inpatients with mixed diagnoses (12 with schizophrenia and 2 with schizoaffective disorder) (Godleski et al., 1989). This study targeted difficult-to-treat patients who had a duration of illness of more than 10 years with a current hospitalization lasting at least 1 year and had been refractory to five antipsychotic medications as well as to lithium and carbamazepine. At baseline, all patients were treated with two FGAs, and one of them was tapered by roughly 10% every 1 to 2 weeks. The choice of which antipsychotic to continue was determined considering of larger relative doses, previous efficacy, patient preference and route of administration. The results showed that the conversion to antipsychotic monotherapy was successful in 6 of 14 patients (42.9%) (chlorpromazine equivalent dose, from 2533 mg/day to 1883 mg/day) while the rest of 8 patients experienced a clinical worsening and therefore did not complete the conversion to antipsychotic monotherapy (chlorpromazine equivalent dose, from 3463 mg/day to 2494 mg/day).

Suzuki et al. (2004) conducted a pragmatic open-label trial to convert antipsychotic polypharmacy to monotherapy with a main antipsychotic drug in 47 patients with chronic schizophrenia in a cross-tapered fashion (Suzuki et al., 2004). A main antipsychotic was defined as the drug that accounted for a majority of the daily chlorpromazine equivalent dose in each subject. Of 44 patients for whom evaluation was feasible, 24 (54.5%) remained stable, 10 (22.7%) showed improvement, and 10 patients (22.7%) worsened; this means 34/44 (77.3%) successfully completed the switch to antipsychotic monotherapy. Scores in the Global Assessment of Functioning (GAF) and the Clinical Global Impression (CGI) remained unchanged. The 10 patients who experienced clinical worsening were managed by the reintroduction of their previous antipsychotics. This study had several limitations. Only first generation antipsychotics (FGAs) were studied with an exception of risperidone because of the availability at the time of the study. The assessment was confined to global impression and functioning, and the study was open-label.

Essock et al. (2011) reported a six-month RCT to compare outcomes between staying on antipsychotic polypharmacy and switching to monotherapy in 127 outpatients with schizophrenia who were receiving multiple antipsychotic drugs (Essock et al., 2011). Each participant and physician decided together which of the two antipsychotics to discontinue in the switching group. Time to all cause treatment discontinuation was shorter in the monotherapy group than the polypharmacy group. Moreover, while only 8 of the 56 patients (14.3%) in the polypharmacy prematurely withdrew from the study, 18 of the 58 patients (31.0%) who were assigned to monotherapy did so. However, from a different viewpoint, approximately two-thirds (69.0%) of the patients assigned to the monotherapy group were successfully switched to antipsychotic monotherapy. Moreover, weight control was better with monotherapy and no significant difference was observed between the two groups with respect to psychiatric symptom change or incidence of hospitalization.

3.2. Interventions to have physicians refrain from antipsychotic polypharmacy

We have found that interventions used in previous trials can be, albeit somewhat arbitrarily, sorted into the following two categories: (1) modest interventions that mainly include one-way, passive dissemination of knowledge by providing educational seminars and lectures on the demerits of antipsychotic polypharmacy and (2) assertive interventions in which physicians are encouraged to refrain from the use of polypharmacy by more active forms of communication such as face-to-face feedback, letters and phone calls.

3.2.1. RCT

The literature search identified only three RCTs that compared effectiveness between modest and assertive interventions in reducing antipsychotic polypharmacy (Table 1).

Owen et al. (2008) compared the effectiveness between an assertive multi-component strategy in which a trained nurse promoted adherence to treatment guidelines and a modest basic educational implementation strategy that represented usual care in two Veterans Affairs (VA) centers in the US (Owen et al., 2008). 291 participants with acute exacerbation of schizophrenia were enrolled and assessed at baseline and six months after the intervention. Both strategies failed to reduce rates of the patients who were prescribed antipsychotic polypharmacy of a FGA plus a second generation antipsychotic (SGA) at the endpoint (14% to 23% in the basic intervention group and 11% to 10% in the enhanced group). Thus, the enhanced strategy did not increase guideline-recommended switching to monotherapy, which underscores the challenges of changing physicians' prescribing behaviors.

Thompson et al. (2008) conducted a five-month pragmatic cluster RCT to investigate the effectiveness of an assertive multi-faceted intervention in 4 trusts with 19 adult acute psychiatric units in England (the DEBIT trial) (Thompson et al., 2008). The multi-faceted intervention comprised of an educational/cognitive behavioral workbook, an educational visit to consultants and a reminder system on medical charts. This five-month intervention resulted in a significantly lower prevalence of antipsychotic polypharmacy at the endpoint (47.8% to 40.4%), compared with guideline dissemination alone (34.8% to 41.8%) (adjusted odds ratio: 0.43, 95% confidence interval: 0.21–0.90, $p = 0.028$). However, the effect size was relatively modest, and there was a considerable between-unit variation in the rates of polypharmacy. Therefore, the authors emphasized the importance of local political and cultural issues in the prescribing process.

In a one-year controlled quasi-experimental study, Baandrup et al. (2010) evaluated the effect of an assertive multifaceted educational