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The risks and benefits of switching patients with schizophrenia or schizoaffective disorder from two to one antipsychotic medication: A randomized controlled trial

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ABSTRACT

Background: : Despite little evidence to support its use and practice guidelines discouraging the practice, antipsychotic polypharmacy is widely prevalent in schizophrenia. This randomized controlled trial studied the effects of switching patients stable on two antipsychotic medications to one antipsychotic medication.
Method: : 104 adult outpatients with schizophrenia from 7 community mental health centers clinically stable on concurrent treatment with 2 antipsychotics were randomly assigned to stay on polypharmacy or to switch to antipsychotic monotherapy. Participants were followed for 1-year with assessments of symptoms and side effects occurring every 60 days (7 total assessments). We examined differences in time trajectories in symptoms (PANSS, CGI) and side effects (EPS, metabolic, other) as a function of group assignment (switch vs. stay) and time, using intention-to-treat analysis.
Results: : Participants who switched to antipsychotic monotherapy experienced greater increases in symptoms than stay patients. These differences emerged in the second 6 months of the trial. All-cause discontinuation rates over the 1-year trial were higher in the switch-to-monotherapy group than in the stay-on-polypharmacy group (42% vs. 13%; $p < 0.01$). There were no differences in change over time in any of the side effect measures, except that stay patients experienced a greater decrease in Simpson Angus total scores than switch patients.
Conclusion: : Clinicians should be cautious in switching patients with chronic schizophrenia who are stable on 2 antipsychotics to one antipsychotic. Given the challenges in discontinuing antipsychotic polypharmacy, adequate trials of evidence-based treatments such as clozapine and long-acting injectable antipsychotics should be undertaken in inadequately responsive schizophrenia patients before moving to antipsychotic polypharmacy.

1. Introduction

The concurrent use of two or more antipsychotics in the treatment of schizophrenia is widely prevalent worldwide (Li et al., 2015; Park et al., 2014; Sun et al., 2014) and continues to increase (Gilmer et al., 2007; Mojtabai and Olfson, 2010) despite unfavorable risk/benefit data (Fleischhacker and Uchida, 2012; Gallego et al., 2012; Young et al., 2015) and notwithstanding expert guidelines recommending against the practice (Buchanan et al., 2010; National Collaborating Centre for Mental Health, 2009; Tandon et al., 2008). One explanation for the persistence of the practice is that good data on the risks and benefits of initiating antipsychotic polypharmacy are limited and their results are equivocal at best (Barnes and Paton, 2011; Correll et al., 2009; Hatta et al., 2014; Katona et al., 2014). Another is that in routine clinical settings, the decision more often confronting clinicians involves the *discontinuation* of antipsychotic polypharmacy rather than its initiation (Tani et al., 2013; Tsutsumi et al., 2011). Since switching relatively stable patients on antipsychotic monotherapy to another is associated with significant risk (Essock et al., 2006; Tandon et al., 2010), physicians are reluctant to switch patients relatively stable on two antipsychotic agents to antipsychotic monotherapy as it involves discontinuing one agent.

Clinical trial data regarding the risks and benefits of switching patients with schizophrenia from two to one antipsychotic are limited to two non-randomized studies with first-generation antipsychotics (Godleski et al., 1989; Suzuki et al., 2004 and two randomized trials conducted primarily with second-generation antipsychotic medications (Essock et al., 2011; Hori et al., 2013). While all these studies concluded that a majority of patients could be successfully switched from antipsychotic polypharmacy to monotherapy, the two randomized trials noted higher discontinuation rates in the switch group (31% vs. 14% in Essock et al. and 15% vs. 0% in Hori et al.) because of worsening symptoms.

This study aims to build on the above work and reports on the risks and benefits of switching from antipsychotic polypharmacy to monotherapy in 104 patients with schizophrenia or schizoaffective disorder over a 12-month period.

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2. Methods

2.1. Study participants

Between November 2011 and November 2012, seven sites including 6 not-for-profit community mental health providers and one psychosocial rehabilitation center recruited patients with schizophrenia or schizoaffective disorder (*DSM-IV-TR*, American Psychiatric Association, 2000) who had been receiving 2 antipsychotic medications concurrently for at least 90 days. Recruits had to have been stable on this medication regimen, as indicated by the lack of a psychiatric hospitalization or emergency room visit in the previous 90 days, and the treating physician's certification that there were no plans to change the antipsychotic regimen. Diagnosis was confirmed through review of medical records and use of the Schizophrenia Checklist (Astrachan et al., 1972). All patients were between 18 and 64 years old, enrolled in Florida's Medicaid program, and with a stable residence and/or case manager who could keep in touch with the patient during the study period. Exclusion criteria included incarceration, legal incompetence, co-occurring developmental disability, pregnancy, a general medical condition that in the opinion of the treating physician made it unsafe for the patient to participate in the study, or having had 2 or more unsuccessful trials of antipsychotic monotherapy or clozapine of sufficient durations and doses as defined by the Florida Medicaid Drug Therapy Management Program (2011) guidelines for adults within the prior 3 years.

The study protocol was approved by the University of South Florida Institutional Review Board and its implementation was overseen by a Data and Safety Monitoring Board. Additionally, each site received review and approval of the protocol either from its internal IRB or from the Western Institutional Review Board. The ability of recruits to consent to participate in the study was initially assessed by their treating physician. Potential subjects then received a thorough description of the study and had to correctly answer at least 7 of 10 questions to indicate clear understanding of the study and the consent process. Participants were paid a stipend at baseline and at each assessment.

After confirming that patients were eligible to participate in the study and obtaining informed consent, the research coordinator at each site applied a site-specific random assignment protocol. Randomization was to a switch or a stay condition. Participants were then informed of their research status and scheduled for baseline interviews. Switch participants were required to switch from the two antipsychotics they were currently receiving to one of these two within 60 days of baseline assessments. Physicians were free to choose which of the two antipsychotics to continue and at what dose, except that participants currently on treatment with an injectable antipsychotic or those receiving clozapine were required to remain on these medications. Of the 98 study participants who were randomized and completed baseline interviews (Fig. 1), 46 were receiving either clozapine or a long-acting injectable antipsychotic at baseline with an equal number randomized to the switch and stay groups. Stay participants were required to remain on the two antipsychotic medications they were currently receiving but treating clinicians had flexibility with dosing. Physicians were free to augment treatment of both switch and stay participants with psychotherapeutic medications other than antipsychotics.

The protocol required participants to remain in their assigned research status (switch or stay) for 360 days, unless a change was clearly needed in response to a participant's clinical condition. Participants who had to change their assigned status remained in the study and were followed through the 360-day period. While treatment was open-label, baseline and subsequent assessments were conducted by "independent assessors" blinded to the research status of participants.

2.2. Baseline and follow-up measures

The primary outcome measure was severity of symptoms assessed by the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). A secondary outcome measure was all-cause treatment discontinuation. Additional measures included the Clinical Global Impressions CGI-S (Guy, 1976), the Abnormal Involuntary Movement Scale (AIMS, Guy, 1976), the Simpson Angus Scale (SAS, Simpson and Angus, 1970) and the Barnes Akathisia Scale (Barnes, 1989) as well as body mass index (BMI) and blood pressure. Participants were assessed using these instruments at baseline and at 60, 120, 180, 240, 300, and 360 days for a total of 7 assessments. In addition, hemoglobin A1c and fasting lipids (Marder et al., 2004; Tandon and Halbreich, 2003) were obtained at baseline, and at 180 and 360 days following baseline measurements.

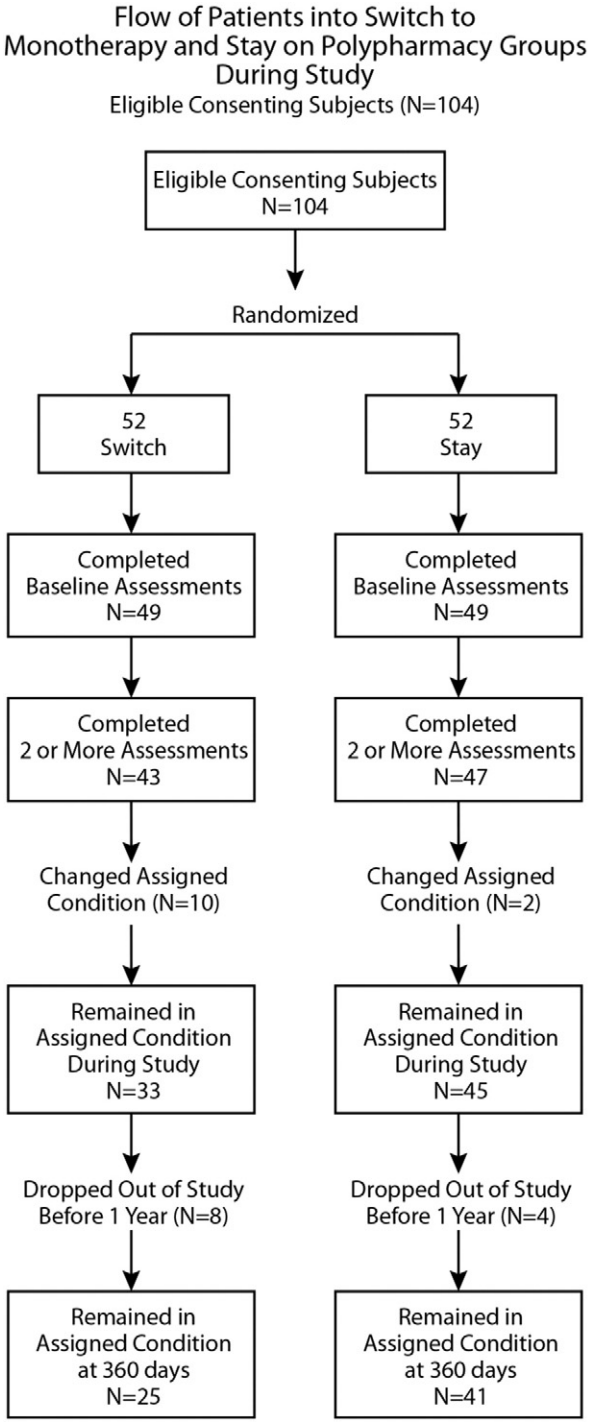

Fig. 1. Flow of patients into switch to monotherapy and stay on polypharmacy groups during study. Eligible consenting subjects (N = 104).