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Gradual vs. wait-and-gradual discontinuation in antipsychotic switching: A meta-analysis

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ABSTRACT

To address whether wait discontinuation (i.e., introducing the new antipsychotic while maintaining the first for a period before initiating its discontinuation) is superior to non-wait discontinuation (i.e., initiating the first antipsychotic's discontinuation when introducing the new antipsychotic) in antipsychotic switching, we conducted a meta-analysis of randomized controlled trials comparing gradual vs. wait-and-gradual antipsychotic discontinuation in patients with schizophrenia. The meta-analysis of 5 studies (n = 410) demonstrated no significant differences in any clinical outcomes, including study discontinuation, psychopathology, extrapyramidal symptoms, and treatment-emergent adverse events, between the two groups. These findings indicate either strategy can be used in clinical practice.

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1. Introduction

Despite how common antipsychotic switching occurs in clinical practice during the treatment of schizophrenia (Agid et al., 2011), how to switch antipsychotics still remains an open question. We have recently conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) examining immediate vs. gradual antipsychotic discontinuation in antipsychotic switching in patients with schizophrenia, where no significant differences were found in any clinical outcomes between the 2 strategies (Takeuchi et al., In press). Further to this question, there are variations in how to discontinue the current antipsychotic when switching to a new agent. One involves introducing the new antipsychotic while maintaining the first for a period before initiating its discontinuation (i.e., wait discontinuation) (Cerovecki et al., 2013; Correll, 2006; Weiden et al., 1997), which is recommended as a safe approach by experts (Kane et al., 2003). Compared to non-wait discontinuation (i.e., initiating the first antipsychotic's discontinuation when introducing the new antipsychotic), wait discontinuation can be superior for prevention of symptom exacerbation as it allows maintenance of the first antipsychotic at the same dose until the new antipsychotic has been introduced; on the other hand, wait discontinuation can be associated with decreased tolerability, especially during the period of antipsychotic overlap. However, whether a wait strategy is superior to a non-wait approach remains unclear. To address this question, we conducted a meta-analysis of RCTs to compare efficacy and tolerability between gradual and wait-and-gradual antipsychotic discontinuation in antipsychotic switching in patients with schizophrenia.

2. Methods

The detailed methods of the systematic literature search are described elsewhere (Takeuchi et al., In press). In the systematic literature search, we identified 5 RCTs examining gradual vs. wait-and-gradual antipsychotic discontinuation in antipsychotic switching in patients with schizophrenia. Two authors (H.T. and S.T.) independently extracted the following clinical outcome data in both gradual and wait-and-gradual antipsychotic discontinuation groups from the 5 studies: (1) number of patients who discontinued the study due to all causes, inefficacy, and intolerability; (2) mean ± standard deviation (SD) changes from baseline to endpoint in the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) or Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) total, PANSS positive subscale, PANSS negative subscale, and Clinical Global Impression - Severity scale (CGI-S) (Guy, 1976) scores as psychopathology measures, and the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970) total,

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Barnes Akathisia Rating Scale (BARS) (Barnes, 1989) total or global, and Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) total or Item 8 scores as extrapyramidal symptom (EPS) measures; and (3) number of patients who experienced treatment-emergent adverse events (TEAEs) that were reported in ≥2 out of the 5 studies. If reports on the studies did not provide sufficient data, we contacted the corresponding authors and/or funding pharmaceutical company, accessed the ClinicalTrails.gov website, and/or applied to data-sharing organizations to which pharmaceutical companies sometimes belong in an attempt to obtain additional information. Any disagreements about data extraction were resolved by consensus. Risk of bias for each included study was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions (available at http://handbook.cochrane.org).

Meta-analyses were performed using Review Manager (RevMan) version 5.3. Outcome data were combined and compared between gradual and wait-and-gradual antipsychotic discontinuation groups. For dichotomous and continuous outcomes, pooled estimates of risk ratios (RRs) and standardized mean differences (SMDs) were calculated with 2-sided 95% confidence intervals (CIs) using a random-effects model, respectively. As reported (Takeuchi et al., In press), because we were able to obtain from Pfizer the individual data on all 3 studies included in a pooled analysis (Weiden et al., 2003), we treated this pooled analytic study as 3 separate studies (i.e., Weiden et al., 2003). As a result, a total of 7 comparisons of gradual and wait-and-gradual antipsychotic discontinuation were yielded.

As sensitivity analyses, we separately analyzed the following 3 sets of studies: (1) switching to ziprasidone (N = 2); (2) switching to aripiprazole (N = 2); and (3) adopting an immediate introduction strategy of the new antipsychotic (N = 4). All effect sizes with a $P < 0.05$ were considered significant. Study heterogeneities were quantified using I^2 statistic with I^2s ≥ 50% indicating significant heterogeneity.

3. Results

The 5 studies (Ganguli et al., 2008; Pae et al., 2009; Stip et al., 2010; Takeuchi et al., 2008; Weiden et al., 2003) involved 410 patients (n = 208 and n = 202 for the gradual and wait-and-gradual antipsychotic discontinuation, respectively). The characteristics of these studies are summarized in Table 1. Three studies were performed with raters blinded and the remaining 2 were open-label studies. In most studies, risperidone, olanzapine, or typical antipsychotics were prescribed as the current antipsychotic prior to randomization, while risperidone (N = 1), ziprasidone (N = 2), or aripiprazole (N = 2) were introduced as the new antipsychotic. The current antipsychotic's discontinuation was initiated after a period that ranged from 3 days to 4 weeks, with the actual discontinuation occurring over a period ranging from 4 days to 6 weeks, while the new antipsychotic was initiated at a full dose in 4 studies (i.e., immediate introduction). The results of risk of bias assessment are displayed in Supplemental Fig. 1. Four out of 5 studies were funded by pharmaceutical companies.

There was no significant difference in the number of patients who discontinued the study due to all causes, inefficacy, or intolerability between the gradual and wait-and-gradual antipsychotic discontinuation groups (Fig. 1). In terms of psychopathology, no significant difference was found in the PANSS/BPRS total, PANSS positive subscale, PANSS negative subscale, or CGI-S scores between the 2 groups (Fig. 2). Regarding EPS, there was no significant difference in the scores on the

Table 1
Randomized controlled trials examining gradual vs. wait-and-gradual antipsychotic discontinuation in antipsychotic switching in patients with schizophrenia.

Study	Blinding	Duration	N	Switching strategy			
				Current antipsychotics		New antipsychotics	
				Type (frequency) and mean dose[a]	Discontinuation strategy	Type and mean dose	Introduction strategy
Ganguli et al., 2008	Rater-blind	6 weeks	40	OLZ (100%) 15.5 mg/day	GD (reduce by 50% at day 0 and 100% at week 1)	RIS 4.9 mg/day	GI (introduce 2 mg/day at day 0, increase to 4 mg/day at day 3, and titrate the dose after week 1)
			42	OLZ (100%) 16.4 mg/day	WGD (reduce by 50% at week 1 and 100% at week 2)	RIS 4.4 mg/day	
Pae et al., 2009	Rater-blind	12 weeks	29	RIS (52%), OLZ (36%), other AAPs (12%)	GD (reduce by 50% by week 2 and 100% by week 4)	APZ 10–30 mg/day (mean dose not reported)	II (introduce 10 mg/day at day 0 and then titrate between 10 and 30 mg/day)
			27	RIS (46%), OLZ (46%), AMI (8%)	WGD (reduce at week 2 and 100% by week 6)		
Stip et al., 2010	Open-label	6 weeks	18	HPD (67%), other TAPs (33%)	GD (reduce by 50% at day 0 and 100% at week 1)	ZIP 86.1 mg/day	II (introduce 80 mg/day at day 0 and titrate between 80 and 160 mg/day after day 2)
			18	HPD (67%), other TAPs (33%)	WGD (reduce by 50% at day 3 and 100% at week 1)	ZIP 87.6 mg/day	
Takeuchi et al., 2008	Open-label	14 weeks	27	AAPs (78%), TAPs (22%)	GD (reduce by 25% at day 0, 50% at week 2, 75% at week 4, and 100% at week 6)	APZ 18.4 mg/day	II (introduce 12 mg/day at day 0 and titrate between 12 and 30 mg/day after week 2)
			26	AAPs (92%), TAPs (8%)	WGD (reduce by 25% at week 4, 50% at week 6, 75% at week 8, and 100% at week 10)	APZ 18.6 mg/day	
Weiden et al., 2003	Rater-blind	6 weeks	39	TAPs (100%)	GD (reduce by 50% at day 0 and 100% at week 1)	ZIP 91.9 mg/day	II (introduce 80 mg/day at day 0 and titrate between 40 and 160 mg/day after day 2)
			34	TAPs (100%)	WGD (reduce by 50% at day 4 and 100% by week 1)	ZIP 91.4 mg/day	
Weiden et al., 2003			36	OLZ (100%)	GD (reduce by 50% at day 0 and 100% at week 1)	ZIP 91.1 mg/day	
			34	OLZ (100%)	WGD (reduce by 50% at day 4 and 100% by week 1)	ZIP 90.2 mg/day	
Weiden et al., 2003			20	RIS (100%)	GD (reduce by 50% at day 0 and 100% at week 1)	ZIP 92.7 mg/day	
			21	RIS (100%)	WGD (reduce by 50% at day 4 and 100% by week 1)	ZIP 86.9 mg/day	

Abbreviation: AAPs, atypical antipsychotics; AMI, amisulpride; APZ, aripiprazole; GD, gradual discontinuation; GI, gradual introduction; HPD, haloperidol; II, immediate introduction; OLZ, olanzapine; RIS, risperidone; TAPs, typical antipsychotics; WGD, wait-and-gradual discontinuation; ZIP, ziprasidone

[a] If reported.

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