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Switching to antipsychotic monotherapy vs. staying on antipsychotic polypharmacy in schizophrenia: A systematic review and meta-analysis☆

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ABSTRACT

Background: While recent meta-analyses have reported the superiority of antipsychotic polypharmacy (APP) over antipsychotic monotherapy (APM) in schizophrenia, switching to APM can be beneficial in terms of side effects. To determine whether patients receiving APP should switch to APM or stay on APP, we conducted a systematic review and meta-analysis.

Methods: Randomized controlled trials (RCTs) examining a switch from APP to APM vs. staying on APP were systematically selected from a previous meta-analysis comparing APP with APM in patients with schizophrenia. In addition, we conducted an updated systematic literature search using MEDLINE, Embase, and Cochrane Central Register of Controlled Trials. Data on study discontinuation, relapse, psychopathology, neurocognition, extrapyramidal symptoms, and body weight/body mass index (BMI) were extracted and synthesized.

Results: A total of 6 RCTs involving 341 patients were included. All studies examined a switch from 2 antipsychotic agents to a single agent. Clozapine-treated patients were included in 3 studies. There was a significant difference in study discontinuation due to all causes in favor of staying on APP ($N = 6$, $n = 341$, $RR = 2.28$, 95% $CI = 1.50–3.46$, $P < 0.001$). There were no significant differences in relapse, any psychopathology, neurocognition, extrapyramidal symptoms, or body weight/BMI between the 2 groups. The quality of evidence was low to very low.

Conclusions: The findings suggest that clinicians should closely monitor patient condition when switching to APM after receiving 2 antipsychotics. Given the low to very low overall quality of the evidence, the findings should be considered preliminary and inconclusive.

1. Introduction

Recent meta-analyses have demonstrated the superior efficacy of antipsychotic polypharmacy (APP) over antipsychotic monotherapy (APM) in schizophrenia (Correll et al., 2009; Galling et al., 2017; Taylor et al., 2012), although the significance disappeared when limited to double-blind trials in the most recent one (Galling et al., 2017). In addition, a cohort study reported that APP was favored over APM in terms of rehospitalization (Tiihonen et al., 2019) and mortality (Katona et al., 2014), which is inconsistent with previous findings (Joukamaa et al., 2006; Waddington et al., 1998). Meanwhile, it appears that APP is associated with more frequent side effects than APM, including extrapyramidal symptoms (Carnahan et al., 2006), metabolic disturbances (Correll et al., 2007), and neurocognitive deficits (Chakos et al., 2006; Hori et al., 2006). Additionally, the complex drug regimen of APP increases the risk of nonadherence to antipsychotics (Fenton et al., 1997).

The prevalence of APP has been increasing in real-world clinical settings (Gilmer et al., 2007; McCue et al., 2003; Nielsen et al., 2010) with the rate of 19.6% (Gallego et al., 2012), which can be interpreted as

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clinical efforts to manage treatment resistance and insufficient response to antipsychotic treatment (Malandain et al., 2018). On the other hand, a study reported that antipsychotics were inadequately combined without optimizing the dose of a single agent (Tsutsumi et al., 2011). In addition, clinical guidelines for the treatment of schizophrenia generally recommend APM (Buchanan et al., 2010; Galletly et al., 2016; Hasan et al., 2013, 2012; Remington et al., 2017). With this background, clinicians may try to switch from APP to APM.

While a switch from APP to APM can improve medication adherence, side effects, and neurocognitive function, it may increase the risk of worsening symptoms. The question remains unclear whether patients with schizophrenia receiving APP should switch to APM or stay on APP. To date, there have been a number of randomized controlled trials (RCTs) comparing switching to APM with staying on APP (Borlido et al., 2016; Constantine et al., 2015; Essock et al., 2011); however, no meta-analysis has been available. To answer this clinically important question, we conducted a systematic review and meta-analysis of RCTs examining a switch from APP to APM vs. staying on APP in patients with schizophrenia.

2. Methods

2.1. Literature search and study selection

There exists a meta-analysis conducted by Ortiz-Orendain et al. (2017), including 62 RCTs with treatment arms consisting of APP along with APM in patients with schizophrenia spectrum disorders (i.e., schizophrenia, schizoaffective disorder, and schizophreniform disorder). From these 62 studies, we first selected the studies that met the following additional eligibility criteria: (1) examining switching from APP (i.e., receiving ≥2 antipsychotic agents simultaneously) to APM (i.e., receiving a single antipsychotic agent) vs. staying on APP; and (2) reporting in English.

Considering that Ortiz-Orendain et al. performed their literature search a few years ago, we conducted an updated systematic literature search (last search: May 9, 2019). MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched with the following keywords: (antipsychotic* OR neuroleptic*) AND (combin* OR add-on* OR addition* OR supplement* OR cotreatment* OR co-treatment* OR adjunctive* OR concurrent* OR concomitant* OR simultaneous* OR parallel* OR polypharmacy* OR polytherapy* OR augment*) and with limitations of randomized controlled trial, humans, publication since 2016, and English language. Two authors (K.M. and T.T.) independently conducted the literature search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2009). Studies that met the following eligibility criteria were selected: (1) RCTs; (2) including ≥70% of patients with schizophrenia spectrum disorders (i.e., schizophrenia, schizoaffective disorder, and schizophreniform disorder); and (3) examining switching from APP to APM vs. staying on APP. Any disagreements about study selection were resolved by consensus with 2 other authors (Y.T. and H.T.).

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).

2.2. Data extraction

Two authors (K.M. and T.T.) independently extracted the following clinical outcome data in both switching to APM and staying on APP groups from the selected studies: (1) number of patients who discontinued the study due to all causes, lack of efficacy, and side effects; (2) number of patients who relapsed and were hospitalized; (3) mean ± standard deviation (SD) changes from baseline to endpoint in the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) or the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) total scores, the PANSS or BPRS positive and negative subscale scores, and the Clinical Global Impression-Severity scale (CGI-S) (Guy, 1976) scores as psychopathology measures; (4) mean ± SD changes in the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2008) composite scores; (5) mean ± SD changes in the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970) total scores, the Barnes Akathisia Rating Scale (BARS) (Barnes, 1989) total or global scores, and the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) total or Item 8 scores; (6) mean ± SD changes in serum prolactin levels; and (7) mean ± SD changes in body weight/body mass index (BMI). Any disagreements about data extraction were resolved by consensus with 2 other authors (Y.T. and H.T.). If reports on the studies did not provide sufficient data, we contacted the corresponding authors in an attempt to obtain additional information; the authors of 3 studies provided additional data.

2.3. Data analysis

Meta-analyses were performed using Review Manager (RevMan) version 5.3. Outcome data were combined and compared between the switching to APM and staying on APP groups. The primary outcome was study discontinuation due to all causes. 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. Study heterogeneities were quantified using I^2 statistic with I^2s ≥ 50% indicating significant heterogeneity. All effect sizes with a $P < 0.05$ were considered significant.

As sensitivity analyses, we separately analyzed the following sets of studies to exclude the influence of study quality, study duration, switching strategy to APM, clozapine use, and antipsychotic dose reduction: (1) double-blind studies; (2) studies with a ≥2-month duration; (3) studies not abruptly discontinuing an antipsychotic agent when switching to APM; (4) studies not including patients receiving clozapine; and (5) studies including patients receiving mean chlorpromazine equivalent (CPZE) dose of <600 mg/day in either switching to APM or staying on APP group.

Publication bias was assessed using visual inspection of funnel plots for each outcome, since there were only 6 studies included in the analysis. If they do not show obvious asymmetry, it indicates a low possibility of significant publication bias.

Finally, we assessed overall quality of the evidence regarding the effects of switching to APM vs. staying on APP on each clinical outcome according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Handbook (available at http://gdt.guidelinedevelopment.org/app/handbook/handbook.html).

3. Results

3.1. Included studies

Six studies (4 from Ortiz-Orendain's meta-analysis and 2 from the additional literature search) (Borlido et al., 2016; Constantine et al., 2015; Essock et al., 2011; Hori et al., 2013; Repo-Tiihonen et al., 2012; Yoon et al., 2016) including 341 patients (n = 177 for switching to APM and n = 164 for staying on APP) met the eligibility criteria and were included in our meta-analysis (Fig. 1). The characteristics of the included studies are summarized in Table 1. All studies were published in 2000 or later and reduced the number of antipsychotics from 2 to 1. Among the studies, 2, 3, and 1 were double-blind, rater-blind, and open-label trials, and 1 and 3 had a study duration of <2 months and <6 months, respectively. Five studies gradually discontinued antipsychotics when switching from APP to APM. Three studies did not include patients receiving clozapine and 3 studies included patients receiving mean CPZE dose of >600 mg/day in either group.

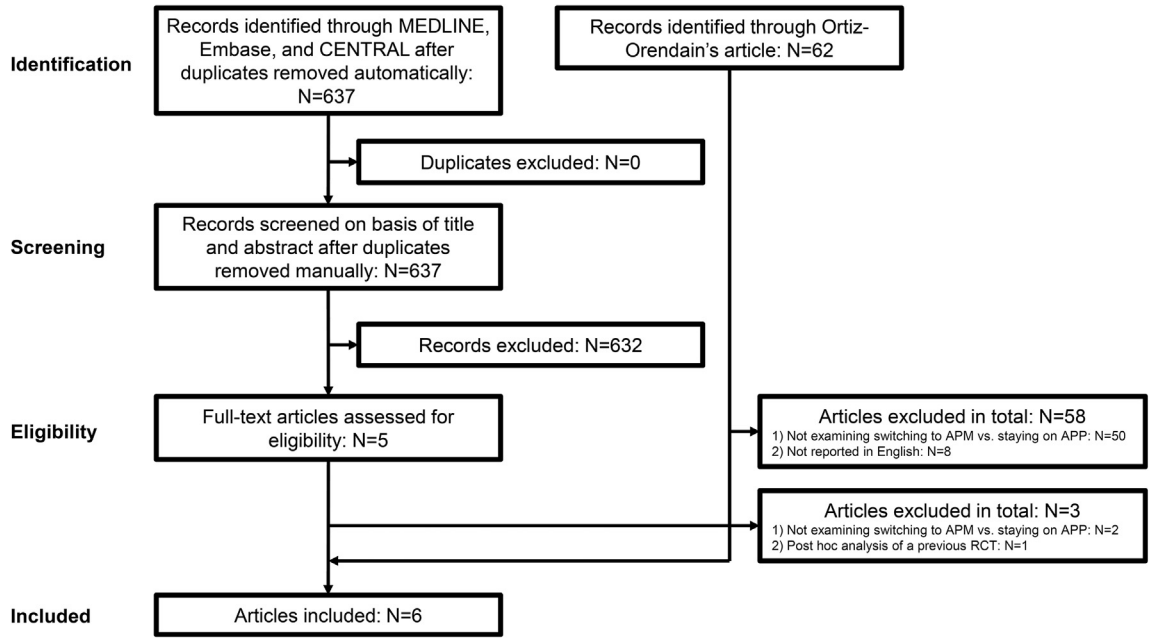


Fig. 1. PRISMA flow diagram of the literature search.

The results of risk of bias assessment are displayed in Supplementary eFig. 1. Most studies did not clearly report random sequence generation or allocation concealment. None of the studies were sponsored by pharmaceutical industry.

3.2. Study discontinuation

There was a significant difference in study discontinuation due to all causes in favor of staying on APP (N = 6, n = 341, *RR* = 2.28, 95% *CI* = 1.50–3.46, *P* = 0.0001, I^2 = 0%) (Fig. 2). No significant difference was found in study discontinuation due to lack of efficacy or side effects between the 2 groups (Fig. 2). The overall quality of the evidence was low (Supplementary eTable 1).

3.3. Relapse and efficacy

There were no significant differences in relapse or any psychopathology outcomes (the PANSS/BPRS total, positive subscale, and negative subscale scores and the CGI-S scores) between the 2 groups (Fig. 3). Only 1 study contributed to the synthesized data for hospitalization and the BACS composite scores. The overall quality of the evidence was low to very low (Supplementary eTable 1).

3.4. Side effects

There was no significant difference but a significant study heterogeneity in body weight/BMI between the 2 groups. Only 1 study contributed to the synthesized data for the SAS, BARS, or AIMS scores (Supplementary eFig. 2). No data was available for serum prolactin levels. The overall quality of the evidence was very low (Supplementary eTable 1).

3.5. Sensitivity analyses

There were no significant differences in any clinical outcomes to which ≥2 studies contributed between the switching to APM and staying on APP groups in double-blind studies (N = 2) (Supplementary eTable 2). There was a significant difference in study discontinuation due to all causes in favor of staying on APP in the following studies: studies with a ≥2-month duration (N = 5), studies not abruptly discontinuing an antipsychotic when switching to APM (N = 5), studies not including patients receiving clozapine (N = 3), and studies including patients receiving mean CPZE doses of <600 mg/day (N = 2) (Supplementary eTable 2). There was also a significant difference in study discontinuation due to lack of efficacy in favor of staying on APP in studies with a ≥2-month duration (N = 4), studies not including patients receiving clozapine (N = 3), and studies including patients receiving mean CPZE doses of <600 mg/day (N = 2) (Supplementary eTable 2).

4. Discussion

The current meta-analysis revealed that staying on APP was significantly superior to switching to APM for study discontinuation due to all causes; however, it also demonstrated no significant differences in any other clinical outcomes such as discontinuation due to lack of efficacy or side effects, relapse, psychopathology, neurocognition, extrapyramidal symptoms, and body weight/BMI between the 2 groups. The overall quality of the evidence was low or very low. The largest study included in this meta-analysis reported that the majority of patients who discontinued the study simply returned to receiving their previous APP regimens (Essock et al., 2009); thus, it may be worth trying to switch to APM if necessary since this type of strategy is commonly used in the real-world clinical settings. On the other hand, given that no significant benefits of switching to APM have been observed, clinicians should carefully determine whether to switch to APM or stay on APP based on each patient situation. It should be noted that all included RCTs evaluated switching from 2 antipsychotic agents to 1 agent; thus, our finding cannot not apply to situations where the number of antipsychotic agents is reduced in patients receiving 3 or more agents.

Some studies have shown that APP is associated with high-dose antipsychotic treatment (Procyshyn et al., 2010; Suzuki et al., 2004). However, since none of the included studies reported the doses of antipsychotics after intervention, the degree to which antipsychotic doses reduced cannot be evaluated in this meta-analysis. Also, in the switching to APM group, an increase in the dose of an antipsychotic was allowed in more than half of the studies (Borlido et al., 2016; Constantine et al., 2015; Essock et al., 2011; Hori et al., 2013). Among the 6 studies, 3 studies included patients receiving mean CPZE doses of ≥600 mg/day in either switching to APM or

Table 1
Summary of randomized controlled trials examining switching to antipsychotic monotherapy vs. staying on antipsychotic polypharmacy in patients with schizophrenia.

Study design				Inclusion criteria			Antipsychotic treatment		APP					APM				
Study name	Blinding	Study duration	Duration of switching to APM	Diagnosis	Symptoms	Antipsychotic treatment: duration	Antipsychotic type and dose, mg/day	Clozapine users	Total, N	Outpatients, N	Male, N	Mean age (SD), years	Mean illness duration (SD), years	Total, N	Outpatients, N	Male, N	Mean age (SD), year	Mean illness duration (SD), years
Borlido 2016	Double blind	12 weeks	0	SCZ, SCA	NA	≥30 days	2 APs, APP: 241 (128), APM: 329 (202)	N = 15 (8 in APM, 7 in APP)	17	12	10	48 (27–68)[a]	NA	18	14	14	47 (26–64)[a]	NA
Constantine 2015	Rater blind	12 months	Within 60 days	SCZ, SCA	Chronic and stable for >3 months	≥90 days	2 APs, APP: 1236 (555), APM: 987 (321)	N ≥ 1[b]	47[c]	47[c]	21[c]	47.0 (11.1)[c]	12.7 (8.6)[c]	43[c]	43[c]	21[c]	43.9 (9.6)[c]	10.6 (6.9)[c]
Essock 2011	Rater blind	6 months	Within 30 days	SCZ, SCA	Chronic and stable for >3 months	≥6 months	2 APs, APP: 326, APM: 388	None	62[d]	62[d]	34[d]	NA	NA	65[d]	65[d]	50[d]	NA	NA
Hori 2013	Rater blind	24 weeks	Within 12 weeks	SCZ	Chronic and stable for >3 months	≥3 months	2 APs, APP: 635 (204), APM: 618 (186)	None	18[c]	18[c]	10[c]	36.1 (10.2)[c]	23.5 (6.0)[c]	17[c]	17[c]	9[c]	36.6 (11.9)[c]	24.7 (4.8)[c]
Repo-Tiihonen 2012	Double blind	12 weeks	4 weeks	SCZ	Chronic and seriously ill (insufficient response to clozapine-olanzapine combination therapy)	≥2 months	Clozapine and olanzapine, doses were not reported.	N = 12 (all participants)	5	0	4	50 (9.6)	NA	7	0	7	44.1 (7.6)	NA
Yoon 2016	Open label	4 weeks	4 weeks	SCZ, SCA, SCF	Chronic and stable for >2 months, with hyperprolactinemia	>1 month	Aripiprazole and another AP, APM: 610 (256), APP: 586 (268)	None	14[c]	NA	2[c]	35.0 (7.3)[c]	8.9 (6.6)[c]	18[c]	NA	4[c]	34.7 (8.0)[c]	8.4 (7.4)[c]

Abbreviations: AP, antipsychotic; APM, antipsychotic monotherapy; APP, antipsychotic polypharmacy; SCZ, schizophrenia; SCA, schizoaffective disorder; SCF, schizophreniform disorder; SD, standard deviation; NA, not assessed.
[a] Median (range).
[b] The exact number was not reported.
[c] Number included in final analysis.
[d] Number at baseline.

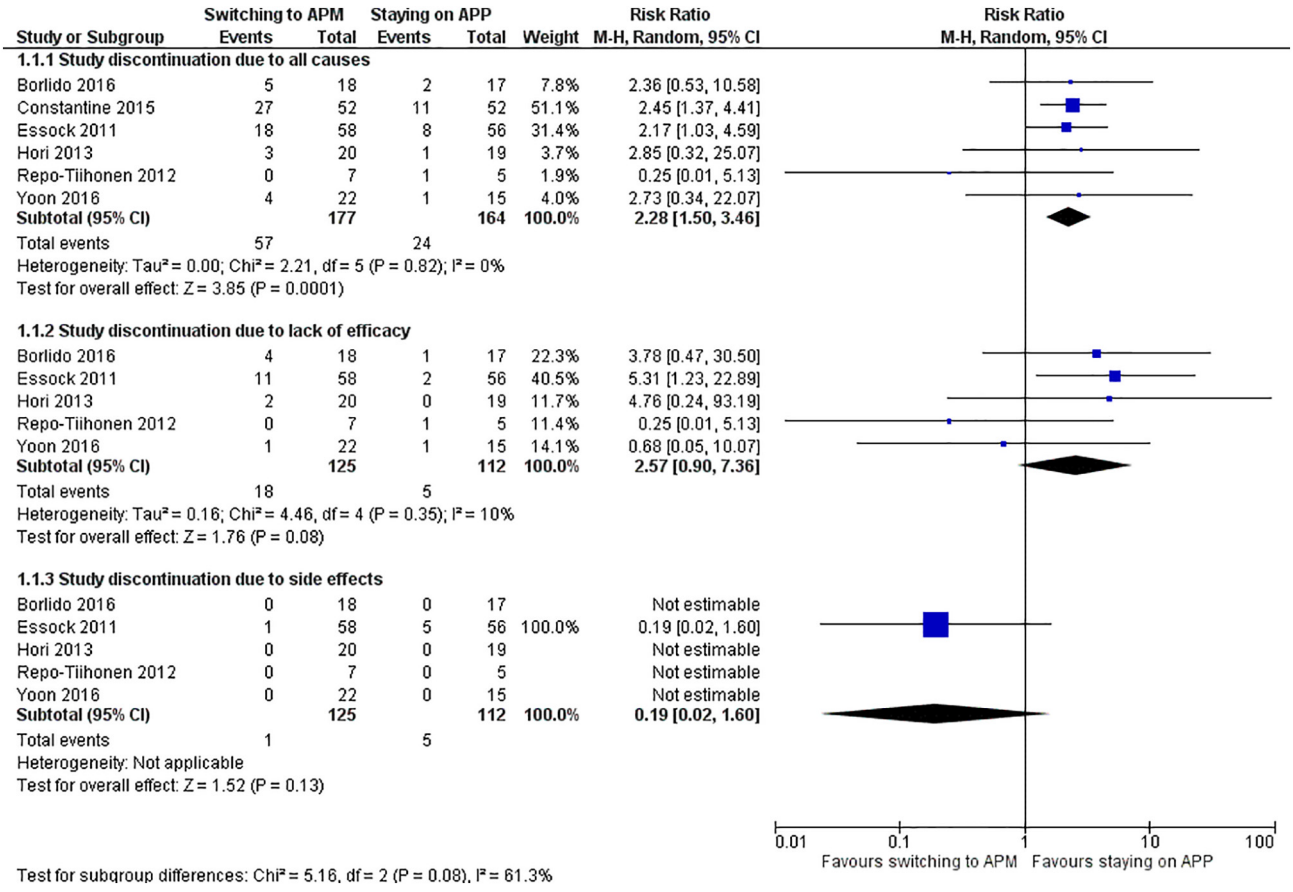


Fig. 2. Study discontinuation. Abbreviations: APM, antipsychotic monotherapy; APP, antipsychotic polypharmacy; CI, confidence interval.

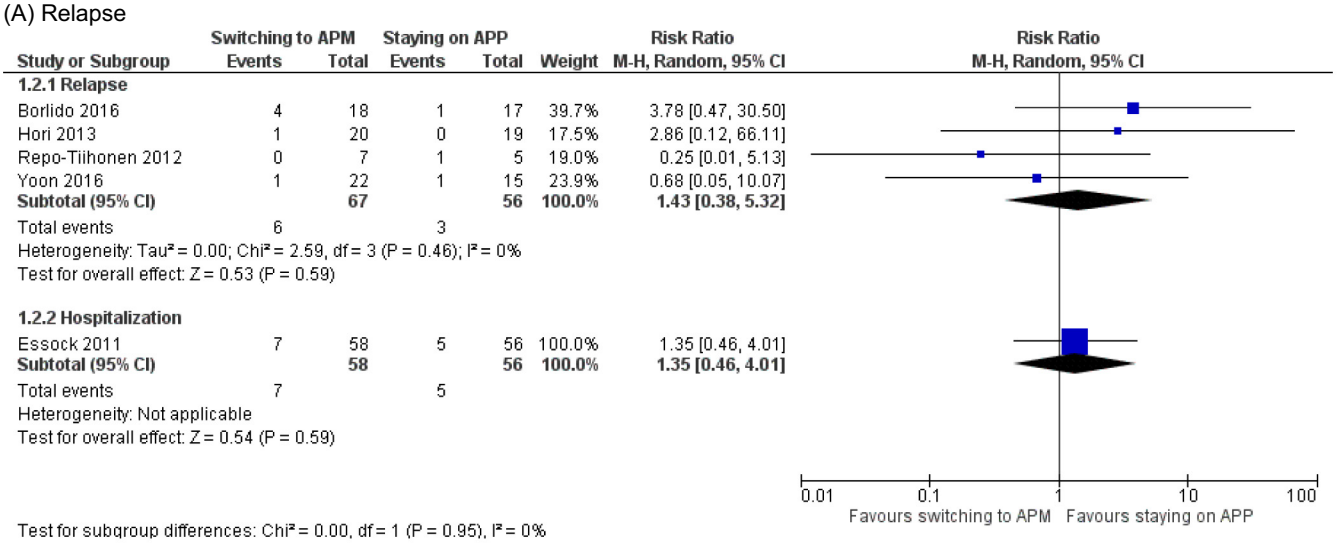
staying on APP group (Constantine et al., 2015; Hori et al., 2013; Yoon et al., 2016). After excluding these studies, the superiority of staying on APP for study discontinuation due to all causes remained unchanged and study discontinuation due to lack of efficacy became statistically significant, which suggests that switching to APM is associated with a risk of study discontinuation regardless of the baseline total dose of the 2 antipsychotics.

When switching antipsychotics, gradual discontinuation of the current antipsychotic is generally recommended (Buckley, 2007; Cerovecki et al., 2013; Correll, 2010; Lambert, 2007; Newcomer et al., 2013), although a recent meta-analysis has reported no significant differences in any clinical outcomes between immediate and gradual discontinuation (Takeuchi et al., 2017). This strategy can be applied when switching from APP to APM. Given that the majority of RCTs included in this meta-analysis employed a gradual switch to APM with the duration ranging from 4 to 12 weeks, more gradual switching from APP to APM may be desirable to minimize the risk of study discontinuation.

It is important to consider which types of antipsychotics are combined in each study. To date, several studies have examined adding another antipsychotic to clozapine in patients with treatment-resistant schizophrenia and indicated a modest benefit from adjunctive antipsychotic treatment (Bartoli et al., 2019; Taylor et al., 2012; Tiihonen et al., 2019). However, research examining the effect of switching from clozapine-another antipsychotic combination to clozapine or another antipsychotic monotherapy is scarce. In this meta-analysis, 2 studies reported antipsychotic combinations that included clozapine at least for some patients (Borlido et al., 2016; Constantine et al., 2015) and 1 study administered clozapine to all patients (Repo-Tiihonen et al., 2012). Repo-Tiihonen et al. targeted patients receiving clozapine-olanzapine therapy and attempted to discontinue the olanzapine that had been previously added to clozapine. Contrary to the findings of this meta-analysis, they found no significant difference in study discontinuation between the 2 groups (Repo-Tiihonen et al., 2012); however, the sensitivity analysis confirmed that there remained a significant difference in study discontinuation due to all causes in favor of staying on APP in the studies that did not include patients receiving clozapine. More evidence is required to establish the effects of switching from APP to APM, especially focusing on clozapine. Another issue that should be examined is switching from non-clozapine APP to clozapine monotherapy. A recent analysis indicated that clozapine monotherapy is associated with better outcomes than non-clozapine APP (Velligan et al., 2015).

The results of the current meta-analysis should be interpreted with caution for several reasons. First, additional data, especially for continuous variables, were not obtained, although we contacted the authors of all included studies. Second, only 2 of the 6 studies were conducted in a double-blind design, which may have affected the results. Third, in most studies patients were in the chronic phase of schizophrenia, which indicates that the results may not apply to patients in the early stages of schizophrenia. Fourth, the number of included studies was small, which could lead to type 2 error. Fifth, the definition of APP (e.g., the lowest dose of combined antipsychotic) was not clearly defined in most studies. Only Essock et al. stated that patients receiving <100 mg/day of quetiapine were excluded (Essock et al., 2011). Lastly, the duration of all studies was ≤1 year, which may have underestimated the risk of study discontinuation because after limiting studies to those with a ≥2 month duration, staying on APP was found to be superior to switching to APM in terms of study discontinuation due to lack of efficacy. In addition, the second largest and only study with a 1-year duration, reported that patients frequently experienced symptom exacerbation during the second 6 months after switching from APP to APM (Constantine et al., 2015). Taken together, double-blind RCTs

(A) Relapse



(B) Efficacy

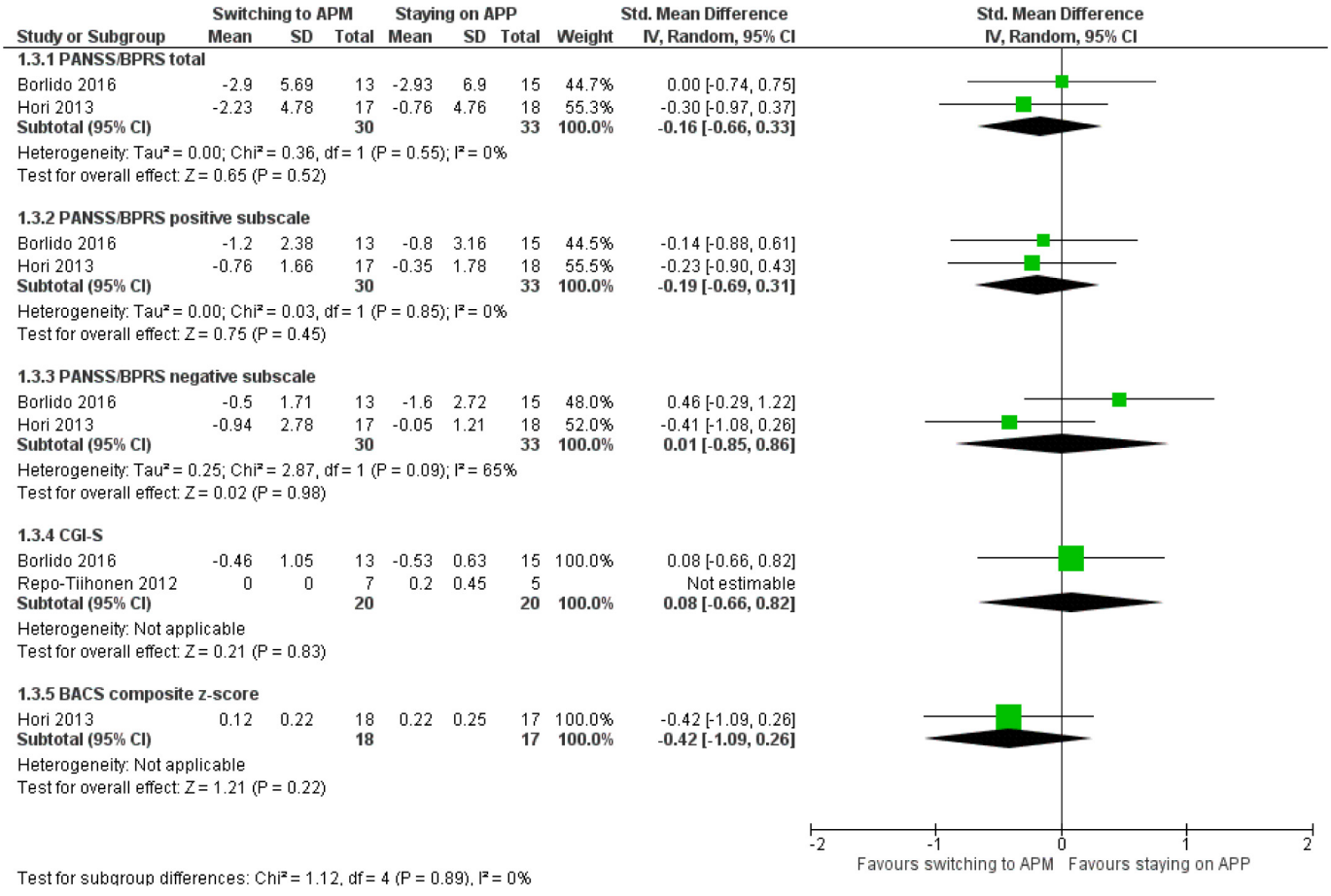


Fig. 3. Relapse and efficacy. Abbreviations: APM, antipsychotic monotherapy; APP, antipsychotic polypharmacy; CI, confidence interval; PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale; SMD, standardized mean difference; CGI-S, Clinical Global Impression-Severity scale; BACS, Brief Assessment of Cognition in Schizophrenia.

with a longer duration examining various combinations of antipsychotics are warranted to confirm these findings.

In conclusion, the current meta-analysis of 6 RCTs comparing switching to APM with staying on APP demonstrated a significant difference in study discontinuation due to all causes in favor of staying on APP, but there were no significant differences in relapse, efficacy, or side effects. Given that the overall quality of the evidence was low to very low, more evidence on this clinically important issue is needed urgently.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.030.

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None.

Contributors

Drs. Matsui, Tokumasu, Takekita, and Takeuchi designed the study. Drs. Matsui and Tokumasu conducted the systematic literature search, data extraction, and meta-analyses. Drs. Matsui, Tokumasu, Takekita, and Takeuchi prepared the first draft of the manuscript. All authors provided significant contributions to the manuscript and have approved the final manuscript.

Declaration of Competing Interest

Dr. Matsui has received speaker's honoraria from Eisai, Meiji Seika Pharma, Mochida, MSD, Otsuka, and Yoshitomiyakuhin, and a research grant from Eisai.

Dr. Tokumasu has no competing interests to disclose.

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