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Effect of discontinuation *v.* maintenance of antipsychotic medication on relapse rates in patients with remitted/stable first-episode psychosis: a meta-analysis

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Abstract

Background. Discontinuation of antipsychotics predisposes patients with remitted/stable first-episode psychosis (FEP) to a higher risk of relapse, but it remains unclear how long discontinuation increases the relapse rate in these patients compared with maintenance.

Methods. This meta-analysis of randomized controlled trials (RCTs) compared relapse rates in FEP patients between antipsychotic treatment discontinuation and maintenance groups at 1, 2, 3, 6, 9, 12 (primary), and 18–24 months. The risk ratio (RR) and numbers needed to treat/harm (NNT/NNH) were calculated using a random-effects model.

Results. Ten RCTs were identified ($n = 776$; mean study duration, 18.6 ± 6.0 months). The antipsychotics were discontinued abruptly in four RCTs (which reported data only at 12 months) and after tapering off gradually over several months (mean length, 3 months) in six RCTs. Compared with the discontinuation group, the maintenance group experienced significantly fewer relapses at all time points except 1 month [RR (NNT): 2 months, 0.49 (13); 3 months, 0.46 (9); 6 months, 0.55 (6); 9 months, 0.48 (3); 12 months, 0.47 (3); and 18–24 months, 0.57 (4)]. The maintenance group was associated with higher discontinuation due to adverse events (RR, 2.61; NNH, not significant).

Conclusions. Maintaining antipsychotic treatment prevented relapse for up to 24 months in FEP patients. Discontinuation of antipsychotics for ⩾2 months significantly increased the risk of relapse. However, 45.7% of patients who discontinued antipsychotics for 12 months (39.4% after 18–24 months) did not experience a relapse.

Introduction

Schizophrenia is a common chronic mental disorder, with a worldwide prevalence of 0.27–0.83% (Messias *et al.*, 2007; van Os and Kapur, 2009), and a major contributor to the global burden of diseases (Whiteford *et al.*, 2013). Its onset is normally first observed during early adulthood (Sham *et al.*, 1994), and patients with schizophrenia tend to show repeated relapses (Emsley *et al.*, 2013), which, particularly in the early stages of the disease, can aggravate the disease course and affect the prognosis. Frequent relapses contribute to the development of resistance to antipsychotics and to chronic psychotic symptoms (Byerly *et al.*, 2007; Emsley *et al.*, 2013). It is therefore important that psychiatrists manage patients in the early stages of psychotic disorders, such as at first-episode psychosis (FEP) (Robinson *et al.*, 2005).

A meta-analysis of randomized controlled trials (RCTs) that included only patients with FEP showed that the maintenance of antipsychotic treatment was superior to discontinuation for preventing relapses over 7–12 months, with a large effect size [risk ratio (RR) 0.47; 95% confidence interval (95% CI) 0.38–0.58; number needed to treat (NNT) = 3] (Leucht *et al.*, 2012). Therefore, the discontinuation of antipsychotics is not recommended for patients with FEP. Guidelines issued by the UK National Institute for Health and Care Excellence (NICE) explicitly warn of the risk of relapse associated with the discontinuation of antipsychotic treatment within the first 2 years of diagnosis, recommending that the withdrawal of antipsychotics should be undertaken gradually and should invariably be accompanied by close monitoring for signs and symptoms of relapse for a period of at least 2 years (NICE, 2014). Recently, we identified two further RCTs, not included in the earlier meta-analysis (Leucht *et al.*, 2012), that compared maintenance and discontinuation of antipsychotic treatment in patients with FEP (Wunderink *et al.*, 2007; Gaebel *et al.*, 2011). To obtain more robust

evidence on whether maintenance of antipsychotic treatment was superior to discontinuation for preventing relapses in patients with remitted/stable FEP, we conducted an updated systematic review and meta-analysis that incorporated these RCTs.

The previous meta-analysis showed there was a greater risk of relapse after 7–12 months from discontinuing antipsychotics in patients with remitted/stable FEP (Leucht *et al.*, 2012); however, it remains unclear how the length of discontinuation of antipsychotics treatment affects relapse rates in this patient group. Conceivably, discontinuation of antipsychotic treatment for only a few months might increase the risk of relapse in these patients. For this reason, our meta-analysis considered relapse rates at 1, 2, 3, 6, 9, 12, and 18–24 month(s) from the discontinuation of antipsychotics in patients with remitted/stable FEP.

Murray and colleagues suggested that psychiatrists should be cautious about the long-term prophylactic use of antipsychotics for patients with schizophrenia, identifying several risks (Murray *et al.*, 2016). First, the long-term use of antipsychotics may result in adverse effects on physical health, such as tardive dyskinesia and cardiometabolic risk. Second, it can result in dopamine D2/D3 receptor upregulation and resultant supersensitivity. Third, the long-term use of high-dose first-generation antipsychotics (FGAs) carries a risk of reducing cortical volume and increasing ventricular volume; however, the risk may be less with low-dose and second-generation antipsychotics (SGAs). The adverse effects appear to be reversible on discontinuing the antipsychotics. Thus, the maintenance of antipsychotic treatment may have negative as well as positive impacts on the biological, psychological, and social prognosis for FEP patients. In this study, therefore, we performed additional meta-analyses comparing the maintenance and discontinuation of antipsychotic treatment in term of efficacy (the improvement of psychopathology), effectiveness (quality of life), and safety (discontinuation rate and the incidence of individual adverse events after treatment discontinuation) for patients with remitted/stable FEP.

We also performed moderator analyses, including a subgroup and a meta-regression analysis, to explore the influence of individual study characteristics on the primary outcome (relapse rate at 12 months); these study characteristics included antipsychotics class, antipsychotic dose at baseline, diagnosis, duration of illness, sponsorship, total number of patients, study duration, and how the antipsychotics were discontinued in the discontinuation group. In addition, we examined the associations between meta-analysis results for relapse rates at 1, 2, 3, 6, 9, and 12 months and the length of time between starting to taper off antipsychotic treatment until full discontinuation.

Methods

Search strategy and inclusion criteria

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher *et al.*, 2009); the PRISMA checklist is presented in online Supplementary Appendix 1. The study was registered with PROSPERO (CRD42017077679, https://www.crd.york.ac.uk/prospero/).

To identify relevant RCTs, three authors (Taro Kishi, Yuki Matsuda, and Yuki Matsui) independently searched Scopus, MEDLINE, Cochrane Library, and PsycINFO databases for studies published prior to 6 January 2018, using the following search strategy: 'schizophrenia OR psychosis' AND 'randomized' AND 'first-episode' AND 'discontinuation OR withdrawal OR intermittent.' No language restriction was applied to the literature search. The same three authors independently assessed the retrieved reports against the inclusion and exclusion criteria and selected those that were eligible. In addition, the reference lists of the included articles and review articles were manually searched for additional relevant published and unpublished research, including conference abstracts. We also searched the clinical trial registries ClinicalTrials.gov (http://clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform (http://www.who.int/ictrp/search/en/) to ensure the set of RCTs was comprehensive and to minimize the influence of publication bias.

Data synthesis and outcome measures

We defined the primary outcome as the relapse rate at 12 months after the discontinuation of antipsychotic treatment in patients with remitted/stable FEP (online Supplementary Table S1) and the secondary outcomes as the relapse rates at 1, 2, 3, 6, 9, and 18–24 months.

Other outcomes included Positive and Negative Syndrome Scale (PANSS) positive, negative and general subscale scores (Kay *et al.*, 1987), quality of life scores assessed by the Lancashire Quality of Life Profile (LQLP) (Oliver *et al.*, 1997) and the World Health Organization Quality of Life Instruments-BREF (http://www.who.int/en/), and extrapyramidal symptoms scores, assessed by the Simpson–Angus Scale (SAS) (Simpson and Angus, 1970) and the Liverpool University Neuroleptic Side-Effect Rating Scale [(LUNSERS) (Day *et al.*, 1995)]. We also recorded discontinuation rates due to all causes, discontinuation due to adverse events, discontinuation because of withdrawal of consent, discontinuation due to loss to follow-up, and the use of anticholinergic drugs/incidence of tremor.

Data extraction

Three authors (Taro Kishi, Yuki Matsuda, and Yuki Matsui) independently extracted data from the included studies. The analysis was based on intention-to-treat or modified intention-to-treat principles; when data required for the meta-analysis were missing, the original study investigators were contacted to obtain the unpublished data. For studies in which Kaplan–Meier survival curves were reported, the relapse rate was measured from the curves with use of a ruler. The study by Gaebel and colleagues reported completer analysis data with respect to the PANSS subscale, LQLP, and SAS scores (Gaebel *et al.*, 2011); we, therefore, included those data in the meta-analysis to increase the sample size as much as possible.

Meta-analysis methods

The meta-analyses were conducted using Review Manager version 5.3 for Windows (Cochrane Collaboration, http://tech.cochrane.org/Revman). A random-effects model (which is more conservative than a fixed effect model and produces wider CIs) was selected for this meta-analysis because of potential heterogeneity across the studies (DerSimonian and Laird, 1986; Higgins and Green, 2011). Dichotomous outcomes were presented as RRs with 95% CIs. When an intergroup difference with respect to treatment efficacy or adverse events based on the RR was statistically significant, the NNT or number needed to harm (NNH) was

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calculated as the reciprocal of the risk difference. For continuous data, the standardized mean difference was calculated from the Hedges' g effect sizes. The heterogeneity of the included studies was assessed using the I^2 statistic, with $I^2 \geqslant 50\%$ considered indicative of considerable heterogeneity (Higgins *et al.*, 2003); this did not show considerable heterogeneity with respect to the primary outcome.

The meta-analyses included studies that involved different medications and treatment arms. We, therefore, conducted the following subgroup analyses to identify factors that may have influenced the primary outcome. (1) Antipsychotics class: SGAs alone *v.* SGAs and FGAs *v.* FGAs alone. (2) Placebo-controlled studies *v.* non-placebo-controlled studies. (3) Schizophrenia-only studies *v.* studies with various psychotic disorders, such as schizoaffective and brief psychotic disorders (a full list is provided in Table 1). (4) Industry-sponsored studies *v.* Non-industry-sponsored studies. (5) Studies with abrupt discontinuation of antipsychotics *v.* studies where the antipsychotics were discontinued after gradually tapering the dose over several months (details are provided in Table 1). (6) Studies that included only patients remitted at baseline *v.* other studies. (7) The study of Wunderink and colleagues, in which 46.2% of the patients did not discontinue antipsychotics (Wunderink *et al.*, 2007), *v.* other studies. (8) Studies with known psychological intervention *v.* other studies. Any subgroup that included only one study was excluded from the discussion.

The primary outcome could also have been influenced by other sources of bias. A meta-regression analysis was therefore performed to evaluate the association between meta-analysis results for the primary outcome and certain modulators, including the total number of patients, study duration, publication year, percentage of male patients, age, duration of illness, and antipsychotic dose at baseline. This used Comprehensive Meta-Analysis software version 2 (Biostat Inc., Englewood, NJ, USA).

We performed a further meta-regression analysis to examine whether the effect sizes in terms of relapse rates at 1, 2, 3, 6, 9, and 12 months were associated with the length of time from starting to taper off the antipsychotic treatment until complete discontinuation, using the mean length of time in each study. This analysis excluded the studies where the discontinuation of antipsychotics was abrupt; meta-regression analysis cannot handle zero values.

In addition, the methodological quality of the included articles was assessed according to the Cochrane Risk of Bias criteria (Cochrane Collaboration, http://www.cochrane.org/).

Results

Study characteristics

The initial literature search retrieved 1452 articles; of these, 1041 were eliminated because of duplication. Of the remaining articles, 390 were eliminated based on a review of the abstract and/or title. The full text of the remaining 21 articles was reviewed, resulting in the elimination of 13 articles: five reported the same study, seven were review articles, and one study included subjects other than FEP patients. Thus, eight reports of RCTs were included in the analysis (Kane *et al.*, 1982; Crow *et al.*, 1986; McCreadie *et al.*, 1989; Gaebel *et al.*, 2002, 2011; Wunderink *et al.*, 2007; Chen *et al.*, 2010; Boonstra *et al.*, 2011) (online Supplementary Fig. S1). Two additional RCTs (Hogarty and Goldberg, 1973; Rifkin *et al.*, 1979) were identified following a manual search through the reference lists of the review articles (online Supplementary Fig. S1) (Leucht *et al.*, 2012; De Hert *et al.*, 2015; Alvarez-Jimenez *et al.*, 2016). No further studies were found in the clinical trial registers. Finally, 10 RCTs that compared the maintenance and discontinuation of antipsychotics were included in this study; these included a total of 776 patients, with mean study duration of 18.6 ± 5.97 months (Table 1). All were published in English.

Five of the RCTs included only patients with remitted FEP, whereas the other five included only patients with schizophrenia. All the patients were adult outpatients (mean age, 23.1 years); 48.6% were men. One RCT used only quetiapine (Chen *et al.*, 2010), whereas five others used only FGAs. Antipsychotic treatment was discontinued abruptly in four of the RCTs (Hogarty and Goldberg, 1973; Rifkin *et al.*, 1979; Kane *et al.*, 1982; McCreadie *et al.*, 1989); these reported data only for 12 months. In the other six RCTs, the antipsychotics were discontinued in a tapered fashion (Table 1), with the mean length of time from the start of tapering to complete discontinuation being 12.1 weeks (Table 1). Thus, a subset of patients of the discontinuation group had not fully discontinued antipsychotic treatment within several months. However, all patients in the discontinuation groups completely discontinued their antipsychotic medication before the study completed, with the exception of the study by Wunderink and colleagues, in which 46.2% of the patients in the discontinuation group did not fully discontinue antipsychotics within the study period (Wunderink *et al.*, 2007). Detailed methodological quality analyses of the RCTs based on the Cochrane Risk of Bias criteria are presented in online Supplementary Fig. S2. Six RCTs were double-blind, placebo-controlled trials. Four were industry-sponsored studies.

Results of the meta-analyses

Relapse rate at 12 months (the primary outcome)

In the analysis of the pooled data from all 10 RCTs ($n = 739$), the relapse rate at 12 months (the primary outcome) was significantly lower in the maintenance group compared with the discontinuation group (RR 0.47; 95% CI 0.35–0.62; $p < 0.00001$; $I^2 = 31\%$; NNT = 3) (Fig. 1 and online Supplementary Fig. S3). We detected significant publication bias for the primary outcome (Egger's test p value = 0.0318; a funnel plot is presented in online Supplementary Fig. S4).

Subgroup analyses

We did not detect any subgroup differences with respect to the primary outcome between the groups in any of the subgroup analyses (online Supplementary Table S2).

Meta-regression analysis

The meta-regression analysis did not reveal any association between the effect size (maintenance group *v.* discontinuation group) with respect to the relapse rate at 12 months and any of the potential confounding variables (online Supplementary Table S3). In addition, the meta-regression analysis did not show any significant associations between the effect sizes for the relapse rates at 1, 2, 3, 6, 9, and 12 months and the length of time from starting to taper off the antipsychotic treatment until complete discontinuation (online Supplementary Table S4).

Relapse rates at 1, 3, 6, 9, and 18–24 months

Lower relapse rates were observed in the maintenance group compared with the discontinuation group at 2 months (RR 0.49; 95%

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Table 1. Characteristics of the randomized controlled trials included in the meta-analysis

(1) study name (country), (2) sponsorship	(1) study design, (2) AP at BL (AP class, dose at BL, HAL eq, mg/d)	Patients (diagnosis, total *n*, status)	Age (mean, y)/ male/duration of illness (m)	Psychosocial interventions	MT group (mean dose, mg/d)	DI group	Relapse rate at the endpoint
(1) Boonstra *et al.* (2011) (Netherlands), (2) industry	(1) 2 y-ORCT, (2) FGA + SGA (3.1)	>1 y stable and remitted FEP (DSM-IV:SZ, SA, SF, 20, OP)	29.3/85%/31.3	PT, PE, CM	Continuation of AP (NR)	Gradual tapering of AP (over 6–12 wk)	MT (45%) > DI (91%)
(1) Chen *et al.* (2010) (Hong Kong), (2) industry	(1) 1 y-DBRPCT, (2) FGA + SGA (2.54)	⩾1 y AP treatment and remitted FEP (DSM-IV:SZ, SA, SF, BPD, PNOS, 178, OP)	24.2/45%/27.6	Guideline-based CM for the first 3 y of illness	QUE (400) by cross-tapering (over 4–6 wk)	PLA by cross-tapering (over 4–6 wk, mean 35 d)	MT (41%) > DI (79%)
(1) Crow *et al.* (1986) (UK), (2) NR	(1) 2 y-DBRPCT, (2) FGA (NR)	FEP that was not unequivocally affective (NR:SZ, 120, OP)	26.1/61.7%/NR	Community-based PT	Flup-IM (40 mg/m), CHL (200), HAL (3), PIM (4), TRI (5)	First m: continuation of AP, second m: half-dose AP + half PLA, thereafter PLA	MT (46%) > DI (62%)
(1) Gaebel *et al.* (2002) (Germany), (2) non-industry	(1) 2 y-RBRCT, (2) NR (NR)	⩾4 wk AP treatment and ⩾3 m stable FEP (ICD-9:SZ, SA, 115, OP)	31/52%/21.6	NR	Continuation of AP (⩾100 CHL eq.)	Prodrome-based intervention: gradual tapering of AP (50%/every 2 wk, thus 42 days), however, reintroduced as soon as prodromal symptoms. DI again after restabilization. Crisis intervention: gradual tapering of AP (50%/every 2 wk), however, reintroduced as soon as crisis. DI again after restabilization	MT (28%) = Prodrome-based intervention (36%), MT (28%) = Crisis intervention (55%)
(1) Gaebel *et al.* (2011) (Germany), (2) non-industry	(1) 2 y-ORCT, (2) FGA (HAL) + SGA (RIS) (3.12)	1 y AP treatment and stable FEP (ICD-10: SZ, 44, OP)	33.1/56.8%/NR	PE (8 wk) or CBT (1 y) during the first year of the study	Continuation of RIS (⩽6) or HAL (⩽6)	Gradual tapering of AP (over 3 m, mean 160 d), dose reduction: 1 mg/every 1–2 wk	MT (0%) > DI (19%)
(1) Hogarty and Goldberg (1973) (USA), (2) non-industry	(1) 2 y-DBRPCT, (2) NR (NR)	2 m stable FEP (DSM-II:SZ, SA 75, OP)	NR/NR/NR	CM and rehabilitation	CHL (cross-tapering for 2 m)	PLA (duration of taper: 0 d)	MT (27.8%) > DI (61.5%)[a]
(1) Kane *et al.* (1982) (USA), (2) non-industry	(1) 1 y-DBRPCT, (2) NR (NR)	⩾4 w stable remitted FEP (RDC:SZ, 28, OP)	21.9/50.0/NR	PT and rehabilitation	FLU (5 to 20) or FLU-D (12.5–50 mg/biweekly)	PLA (duration of taper: 0 d)	MT (0%) > DI (41.2%)
(1) McCreadie *et al.* (1989) (UK), (2) industry	(1) 1 y-DBRPCT, (2) FGA (NR)	1 y no relapse FEP (RDC:SZ, 49, OP)	NR/NR/NR	NR	Flup-IM (NR), PIM (NR)	PLA (duration of taper: 0 d)	MT (0%) > DI (57%)
(1) Rifkin *et al.* (1979) (USA), (2) non-industry	(1) 1 y-DBRPCT, (2) NR (NR)	Remitted FEP [hospital diagnosis + research criteria (Kraepelinian):SZ, 16, OP]	NR/NR/NR	PT (biweekly) during the first six m of the study	FLU (5 to 20) or FLU-D (0.5–2 ml/biweekly)	PLA (duration of taper: 0 d)	MT (8.3%) > DI (57.5%)[a]

(*Continued*)

Table 1. (*Continued.*)

(1) study name (country), (2) sponsorship	(1) study design, (2) AP at BL (AP class, dose at BL, HAL eq, mg/d)	Patients (diagnosis, total *n*, status)	Age (mean, y)/ male/duration of illness (m)	Psychosocial interventions	MT group (mean dose, mg/d)	DI group	Relapse rate at the endpoint
(1) Wunderink *et al.* (2007) (Netherlands), (2) Industry	(1) 18 m-RBRCT, (2) FGA + SGA (2.6)	6 m remitted FEP (DSM-IV:SZ, SA, SF, BPD, DD, PNOS, 131, OP)	26.4/69.5%/8.9	NR	Continuation of AP (2.87) according to APA guidelines, including preferential use of low-dose SGA	Gradual tapering of AP, guided by symptom severity and patient preferences (mean 4.6 m). If early warning signs of relapse emerged, clinicians were to restart/increase the dosage of antipsychotics. 53.8% patients discontinued AP medication	MT (21%) > DI (43%)

AP, antipsychotic; APA, American Psychiatric Association; BL, baseline; BPD, brief psychotic disorder; CBT, cognitive behavioral therapy; CHL, chlorpromazine; CM, case management; d, day; DBRPCT, double-blind, randomized, placebo clinical trial; DD, delusional disorder; DI, discontinuation; DSM, Diagnostic and Statistical Manual of Mental Disorders; eq, equivalent; FEP, first episode psychosis; FGA, first generation antipsychotic; FLU(-D), fluphenazine(-decanoate); Flup-IM, flupentixol intramuscular injection; HAL, haloperidol; ICD, International Classification of Diseases; m, month; MT, maintenance; *n*, number of patients; NR, not report; OP, outpatient; ORCT, open-label, randomized, controlled trial; PE, psychological education; PIM, pimozide; PLA, placebo; PNOS, psychosis not otherwise specified; PT, psychosocial treatment; QUE, quetiapine; RBRCT, rater-blind, randomized, controlled trial; RDC, Research Diagnostic Criteria; RIS, risperidone; SA, schizoaffective disorder; SF, schizophreniform disorder; SGA, second generation antipsychotic; SZ, schizophrenia; TRI, trifluoperazine; UK, United Kingdom; USA, United States of America; wk, week; y, year.
*This is the result at 12 months. The data derived from Leucht *et al.* (2012) study.

CI 0.29–0.85; NNT = 13), 3 months (RR 0.46; 95% CI 0.30–0.70; NNT = 9), 6 months (RR 0.55; 95% CI 0.42–0.72; NNT = 6), 9 months (RR 0.48; 95% CI 0.32–0.70; NNT = 3), and 18–24 months (RR 0.57; 95% CI 0.41–0.80; NNT = 4), but not at 1 month (Fig. 1, online Supplementary Figs S5–S10).

Other outcomes

There were no significant differences between the maintenance and discontinuation groups in the PANSS positive, negative and general subscale scores, quality of life scores, or extrapyramidal symptoms scores. Similarly, there were no differences in the rates of discontinuation due to all causes, discontinuation because of withdrawal of consent, or discontinuation due to loss to follow-up, or in the use of anticholinergic drugs/incidence of tremor. However, the maintenance group was associated with more frequent discontinuation due to adverse events compared with the discontinuation group (RR 2.61; 95% CI 1.12–6.07; NNH = not significant) (online Supplementary Figs S11–S20).

Discussion

This updated systematic review and meta-analysis of RCTs compared relapse rates at 1, 2, 3, 6, 9, 12, and 18–24 month(s) between remitted/stable FEP patients whose antipsychotic treatment was maintained with those whose treatment was discontinued. The risk of relapse was confirmed to be very high after 9, 12, and 18–24 months of antipsychotic discontinuation, with large effect sizes (NNT = 3–4). Thus, we consider that the maintenance of antipsychotic treatment is beneficial for preventing relapse for 18–24 months in remitted/stable FEP patients. Importantly, our meta-analyses showed that the discontinuation of antipsychotics was associated with a significant risk of relapse in a period as short as 2 months, with a medium effect size (NNT = 13). The meta-analysis of the relapse rate at 2 months included only RCTs in which discontinuation of the treatment was tapered; given that the mean length of time from starting to taper off antipsychotic treatment to complete discontinuation was 12.1 weeks, this meant a subset of patients of the discontinuation group had not fully discontinued antipsychotic treatment at 2 months. Thus, gradually tapering antipsychotic treatment with the aim of complete discontinuation within several months may also increase the risk of relapse. We, therefore, recommend that reducing the antipsychotic dose for a remitted/stable FEP patient should be accompanied by close monitoring by the clinician for signs and symptoms of relapse within 2 months after starting the reduction.

We compared outcomes related to efficacy, effectiveness, and safety between the maintenance and discontinuation groups. There were no significant differences between the groups in the improvement of psychopathology, quality of life scores, discontinuation due to all causes, discontinuation because of withdrawal of consent, discontinuation due to loss to follow-up, or extrapyramidal symptoms scores, but the maintenance group was associated with more frequent discontinuation due to adverse events than the discontinuation group. However, the numbers of RCTs and patients included in most of these meta-analyses were small. Furthermore, because the relevant data were not available, the meta-analyses did not include cognitive function, social function, employment status, or individual adverse events that are considered to be important outcomes for evaluating long-term treatment benefits for patients with schizophrenia (Owen *et al.*, 2016). A few of the included RCTs reported no significant differences in social functioning scores, mortality rates, and

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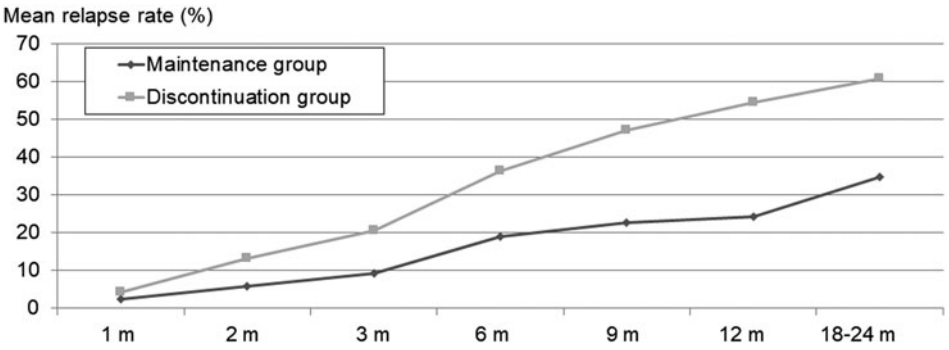

	1 m	2 m	3 m	6 m	9 m	12 m	18-24 m
N (*n*)	6 (605)	6 (605)	6 (605)	6 (605)	6 (605)	10 (739)	4 (383)
RR	0.55	0.49	0.46	0.55	0.48	0.47	0.57
95% CI	0.21–1.41	0.29–0.85	0.30–0.70	0.42–0.72	0.32–0.70	0.35–0.62	0.41–0.80
p	0.21	0.01	0.0002	<0.00001	0.0002	<0.00001	0.001
I^2	0%	0%	0%	0%	44%	31%	43%
NNT	na	13	9	6	3	3	4

Fig. 1. Relapse rates. 95% CI, 95% confidence interval; m, month(s); *N*, number of studies; *n*, number of patients; na, not applicable; NNT, number needed to treat; RR, risk ratio.

employment rates between the maintenance and discontinuation groups (Wunderink *et al.*, 2007; Chen *et al.*, 2010; Gaebel *et al.*, 2011). Taking all these findings together, the maintenance of antipsychotic treatment was beneficial for preventing relapses for at least 18–24 months, but it increased the risk of discontinuation due to adverse events. It remains unclear whether the maintenance of treatment had significant beneficial effects on cognitive function, social function, employment rate, and mortality rate, factors that are associated with the prognosis of the disease.

The discontinuation group showed no increased risk of relapse at 1 month. However, all the studies included in the meta-analysis for 1 month involved the tapered discontinuation of antipsychotics. Because a subset of the patients in the discontinuation group of the studies continued to receive antipsychotics at 1 month, this may have influenced the finding of no significant risk with discontinuation. We cannot, therefore, infer that 1 month of discontinuation is not associated with a risk of relapse.

We also examined whether there was a difference between abrupt and tapered discontinuation in the impact on the primary outcome (the relapse rate at 12 months) and found no significant difference (online Supplementary Table S2). Furthermore, our meta-regression analysis did not show any significant associations between the effect sizes for relapse rates at 1, 2, 3, 6, 9, and 12 months and the length of time from starting to taper of antipsychotic treatment to complete discontinuation (online Supplementary Table S4).

Notably, our meta-analysis showed that, although maintenance group showed lower relapse rates than the discontinuation group at 2, 3, 6, 9, 12, and 18–24 months, 45.7% of the patients whose antipsychotics were discontinued for 12 months (39.4% after 18–24 months) did not experience a relapse (Fig. 1). Wunderink *et al.* conducted a naturalistic extension study (Wunderink *et al.*, 2013) that followed for a further 5 years after the completion of the original 18 months RCT (Wunderink *et al.*, 2007). The extension study ($n = 103$) showed an inferior recovery rate and functional remission in the maintenance group compared with the discontinuation group, although there were no significant differences in relapse rate and symptom remission between the groups. However, the study had several biases, including not retaining the original randomized treatment allocation and not controlling for additional treatment (Goff *et al.*, 2017); this made their results hard to interpret, and a large-scale high-quality research design replication study is needed. Nevertheless, as our meta-analysis demonstrated, there are patients with remitted/stable FEP who do not suffer a relapse when their antipsychotic treatment is discontinued, although there are currently no clinical measures or biomarkers for prospectively identifying this subpopulation (Goff *et al.*, 2017). Further research is needed to determine predictive biomarkers to help with shared decision-making and a personalized medicine approach (Goff *et al.*, 2017).

There are several differences between first-episode and multiple-episode patients with respect to their response to antipsychotics and the incidence of antipsychotics-induced adverse events (Robinson *et al.*, 2005; Hasan *et al.*, 2012). For example, during the treatment of FEP, a low dose of antipsychotics has been shown to be as effective as a standard dose (Merlo *et al.*, 2002; Oosthuizen *et al.*, 2004). Conversely, compared with chronically ill patients, patients with FEP exhibit an increased risk of adverse events following antipsychotic treatment, including neurological, metabolic, and endocrine adverse events (Merlo *et al.*, 2002; Oosthuizen *et al.*, 2004; Robinson *et al.*, 2005; Hasan *et al.*, 2012). In addition, patients with FEP were shown to exhibit a higher frequency of relapse during the initial 5-year period after the first recovery, with a cumulative first relapse rate of 81.9% (Robinson *et al.*, 1999). Therefore, as several treatment guidelines for schizophrenia recommend, antipsychotics associated with a lower risk of adverse events should be selected for the treatment of FEP (Buchanan *et al.*, 2010; Hasan *et al.*, 2012; NICE, 2014). The findings also imply that the use of the lowest effective antipsychotic dose is critical for improved treatment outcomes.

Egger's test identified a publication bias, but the meta-regression and subgroup analyses revealed no associations

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between the effect sizes with respect to relapse rates and the various modulators considered (online Supplementary Tables S2–S4). Although the present meta-analysis included studies additional to those included in previous studies (Leucht *et al.*, 2012; De Hert *et al.*, 2015; Alvarez-Jimenez *et al.*, 2016), the number of studies and patients included remained small. The observed publication bias was therefore likely to be due to the small sample size. However, because of the publication bias, future studies with larger sample sizes are needed to improve the generalization of these findings. A limitation of this study was the study duration of the included RCTs were 1–2 years, so it remains unclear whether maintaining antipsychotic treatment for more than 2 years reduces the risk of relapse in patients with remitted/stable FEP. Another limitation was that the meta-analyses included studies that used various definitions of relapse (online Supplementary Table S1); these differences may have had an impact on the meta-analysis results.

In conclusion, our results suggested that maintaining antipsychotic treatment was beneficial for preventing relapses for at least 2 years in remitted/stable FEP patients, although it remains unclear whether this would be the case for longer than 2 years because the study duration of the included RCTs were 1–2 years. Notably, the discontinuation of antipsychotics for ⩾2 months significantly increased the risk of relapse. However, some patients with remitted/stable FEP did not suffer a relapse after discontinuation of their antipsychotic treatment, although there are currently no clinical measures or biomarkers for prospectively identifying this subpopulation. Further research is needed to establish these predictive biomarkers to help with shared decision-making and a personalized medicine approach. In addition, it should be noted that antipsychotics were frequently discontinued because of adverse events, suggesting that the maintenance of antipsychotic treatment is associated with a greater risk of adverse events than is discontinuation.

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Author contributions. Dr Kishi had full access to all the data in the study and takes responsibility for the integrity of the data along with the accuracy of the data analysis. Dr Kishi was involved in the study concept and design. Drs Kishi and Ikuta performed the statistical analysis. Drs Kishi, Ikuta, Matsuda, Matsui, and Inada performed acquisition and interpretation of the data. All the authors wrote the manuscript. Drs Iwata and Mishima supervised the review.

Conflict of interest. None.

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