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ARTICLE

Factors associated with successful antipsychotic dose reduction in schizophrenia: a systematic review of prospective clinical trials and meta-analysis of randomized controlled trials

This article has been corrected since Advance Online Publication and a correction is also printed in this issue

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This systematic review and meta-analysis examined predictors of successful antipsychotic dose reduction in schizophrenia. Prospective clinical trials and randomized controlled trials (RCTs) investigating antipsychotic dose reduction in schizophrenia were selected for systematic review and meta-analysis, respectively. In total, 37 trials were identified. Only 8 studies focused on second-generation antipsychotics (SGAs); no studies investigated long-acting injectable SGAs. Of 24 studies evaluating relapse or symptom changes, 20 (83.3%) met the criteria for successful dose reduction. Factors associated with successful dose reduction were study duration < 1 year, age > 40 years, duration of illness > 10 years, and post-reduction chlorpromazine equivalent (CPZE) dose > 200 mg/day. Clinical deterioration was mostly re-stabilized by increasing the dose to the baseline level ($N = 7/8$, 87.5%). A meta-analysis of 18 RCTs revealed that relapse rate was significantly higher in the reduction group than the maintenance group (risk ratio [RR] = 1.96; 95% confidence interval [CI], 1.23–3.12), whereas neurocognition was significantly improved (standardized mean difference = 0.69; 95% CI, 0.25–1.12). A subgroup analysis indicated that only a post-reduction CPZE dose ≤ 200 mg/day was associated with an increased risk of relapse (RR = 2.79; 95% CI, 1.29–6.03). Thus, when reducing antipsychotic doses, clinicians should consider the long-term risk of relapse in younger patients with a relatively short illness duration and keep the final doses higher than CPZE 200 mg/day. Further studies, particularly those involving SGAs, are warranted to determine the optimal strategies for successful antipsychotic dose reduction in schizophrenia.

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INTRODUCTION

Maintenance treatment with antipsychotics is critical to prevent negative outcomes in patients with schizophrenia [1, 2]. A meta-analysis of 65 randomized controlled trials (RCTs) provided compelling evidence that antipsychotic maintenance treatment is superior to placebo in reducing the risk of relapse in stable schizophrenia [1]. Another meta-analysis showed that total symptom scores remained almost unchanged over 1 year in patients continuing antipsychotics, whereas symptoms continuously worsened over time in those who switched to placebo [3]. However, antipsychotics are associated with various undesirable adverse effects, such as extrapyramidal symptoms (EPSs) [4], neurocognitive impairment [5–7], and sudden cardiac death [8], at least partly in a dose-dependent manner.

Accordingly, it is clinically relevant to minimize long-term antipsychotic exposure. However, the consensus as to whether, to what extent, and how to reduce antipsychotics has not been fully established [9, 10]. As a result, patients with schizophrenia may be maintained on higher doses of antipsychotics than those needed for relapse prevention. It would thus be helpful to characterize patients who are unlikely to relapse after antipsychotic dose reduction during maintenance treatment of schizophrenia. To address this clinically important issue, we conducted a systematic review of prospective clinical trials and a meta-analysis of RCTs to explore the predictors of successful antipsychotic dose reduction.

MATERIALS AND METHODS

First, we conducted qualitative analyses of prospective antipsychotic dose reduction trials, including RCTs. These trials were identified from a systematic literature review to explore factors associated with successful dose reduction based on pre-defined criteria. Second, we performed quantitative analyses (i.e., meta-analysis) of RCTs exclusively to identify factors associated with successful dose reduction using the cut-off suggested in the qualitative analyses. Then, we considered the factors replicated in both the qualitative and quantitative analyses as robust predictors of successful antipsychotic dose reduction in schizophrenia.

Literature search and study selection

Systematic literature search for prospective trials. We conducted a systematic literature search for studies examining antipsychotic dose reduction in schizophrenia on 31 March 2019, according to the Preferred Reporting Items for Systematic Reviews and Meta-

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Analyses (PRISMA) statement [11], using the MEDLINE and Embase databases with the following search terms: ((antipsychotic or neuroleptic or tranquiliz*) AND (dose or dosage) AND (reduce or reduction or low*-dose or minim* or decrease) AND schizophreni* AND adult) with limitations of human subjects and English language. We also performed cross-referencing and hand searches. We selected studies that met the following criteria: (1) original prospective clinical trials that examined antipsychotic dose reduction; (2) ≥70% of participants with a diagnosis of schizophrenia or schizoaffective disorder; and (3) ≥5 participants included in the study. We excluded studies that aimed to alter the antipsychotic formulation (e.g., oral to long-acting injectable antipsychotics [LAI-APs]) or simplify antipsychotic polypharmacy (e.g., switching 2 concurrent antipsychotics to monotherapy) because these were beyond the scope of the present study. Two authors (H.T. and S.T.) independently identified the relevant studies. Any discrepancies in study selection were resolved by consensus with the senior corresponding author (H.T.).

Selection and evaluation of RCTs. We selected RCTs comparing antipsychotic dose reduction with dose maintenance from the included studies to conduct a meta-analysis. 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). Two authors (H.T. and S.T.) independently identified the relevant studies. Any discrepancies in study selection and evaluation were resolved by consensus with the senior corresponding author (H.T.).

Data extraction

For qualitative analysis of prospective trials. We extracted the following data: (1) study information (i.e., publication year, study design, study duration, inclusion criteria, and definition of relapse); (2) patients' demographic and clinical characteristics (i.e., age, sex, treatment setting, duration of illness, and duration of treatment); (3) clinical outcomes (i.e., pre- and post-intervention symptom severity, relapse and hospitalization, treatment strategies when symptoms deteriorated and their clinical consequences, study discontinuation, and adverse effects); and (4) antipsychotic use (i.e., antipsychotic types and formulations, target doses after reduction, actual pre- and post-intervention doses of antipsychotics, and procedure, duration, and speed of reduction). The presence or absence of statistically significant differences was also extracted for rates of relapse or hospitalization, and score changes in symptoms or adverse effects between pre- and post-dose reduction in single-arm prospective trials and between the dose reduction and maintenance groups in RCTs. Two authors (H.T. and S.T.) independently extracted the data. Any discrepancies in data extraction were resolved by consensus with the senior corresponding author (H.T.).

For meta-analysis of RCTs. We extracted the following clinical outcome data for both dose reduction and maintenance groups from the included RCTs: (1) number of patients who relapsed (primary outcome) and were hospitalized, (2) number of patients who discontinued the study due to all causes, inefficacy, and intolerability, (3) mean ± standard deviation (SD) changes from baseline to endpoint in psychopathology scores (total, and positive and negative symptom subscale scores) [12–15], and (4) mean ± SD changes in the scores for adverse effects (EPSs [15–18], body weight, neurocognition [19, 20], and quality of life (QOL) [21–23]). The detailed scales included in this meta-analysis are described in Supplementary Figure S1A. Two authors (H.T. and S.T.) independently extracted the data. Any discrepancies in data extraction were resolved by consensus with the senior corresponding author (H.T.). If the articles did not provide sufficient data, we contacted the corresponding authors to request additional data.

Data analysis

Qualitative analysis of prospective trials. We conducted qualitative analyses of the identified prospective clinical trials. A successful dose reduction was defined as (1) any significant improvement or no significant change in symptom severity between pre- and post-reduction along with any significant improvement or no significant change in adverse effects after dose reduction, or (2) any significant superiority or no significant difference in relapse rates or changes in symptom severity (if relapse rates were not available) between the dose reduction and maintenance groups along with any significant superiority or no significant difference in adverse effects. We counted the number of successful and unsuccessful studies for each item of the study information and the factors related to patients' demographic and clinical characteristics, antipsychotic use, and dose reduction procedures. The cut-off was set to obtain the highest sensitivity and specificity to differentiate the factor in terms of the proportion of successful studies (Supplementary Fig. S1B). A factor was considered a predictor of successful dose reduction if it satisfied both of the following criteria: (1) all included studies identified a particular factor as a predictor of successful dose reduction and (2) more than half of the unsuccessful studies did not identify that specific factor as a predictor of unsuccessful dose reduction (i.e., less than half of the unsuccessful studies were grouped as "not available") to increase the certainty of the findings (Supplementary Fig. S1C).

Meta-analysis of RCTs. We performed meta-analyses of RCTs using Review Manager (RevMan) version 5.3. We combined and compared the outcome data between the dose reduction and maintenance groups for each extracted outcome. Pooled estimates of risk ratios (RRs) for dichotomous outcomes and standardized mean differences (SMDs) for continuous variables were calculated with 2-sided 95% confidence intervals (CIs) using a random-effects model. Antipsychotic doses reported in the included studies were converted to chlorpromazine equivalent (CPZE) doses [24].

In addition, we conducted subgroup analyses with the following factors using the cut-off identified as described above: publication year, study duration, illness stability, age, treatment setting, duration of illness and treatment, baseline symptom severity, antipsychotic type and formulation, pre- and post-reduction doses of antipsychotics, reduction rates, and duration and speed of reduction. When some factors were found to be significantly associated with an increased risk of relapse, we conducted further subgroup analyses classified by factors related to antipsychotic dose to see if there were other variables independent of antipsychotic dose (Supplementary Fig. S1D). Sensitivity analyses were performed if there were studies that included a factor just right on the threshold dividing the subgroups (Supplementary Fig. S1E). All effect sizes with $P < 0.05$ were considered statistically significant. Study heterogeneities were quantified by using the I^2 statistic with $I^2 \geq 50\%$ indicating significant heterogeneity. Publication bias was assessed by visual inspection of funnel plots.

RESULTS

A total of 37 prospective clinical trials involving 2,080 subjects that met our eligibility criteria were identified for the systematic review [25–61]. The characteristics of all the included studies are shown in Table 1. The PRISMA flow diagram of the literature search is shown in Supplementary Fig. S2. Of these studies, 18 RCTs involving 1,385 subjects were included in the meta-analysis. The risk of bias for the RCTs is shown in Supplementary Fig. S3A.

Six studies assessed a change in symptom severity after dose reduction and 18 RCTs compared relapse rates or changes in symptom severity between the dose reduction and maintenance groups. Of these 24 studies, 20 (83.3%) showed a significant improvement or no significant difference in symptom severity or

Table 1. Characteristics of included studies.

Author (year)	Outcome: overall	Outcome: symptoms	Outcome: adverse effects	*n*	Study design	Study duration	Age, year	DOI, year	Baseline symptoms		APs	Baseline CPZE dose, mg/day[d]	CPZE dose after reduction, mg/day[d]	Reduction duration	Relapse rate in reduction group (that in non-reduction group)
Zhou et al. [25]	Success	No change	Improved	75	SBRCT	52 w	44.3	NA	PANSS	66.2	RIS OLZ	510 585	330 234	16 w	10.8% (15.8%)
Yamanouchi et al. [26]	Success	No change	No change	163	OLRCT	RP + 3 m	60	32	MS	12.7	FGAs/ SGAs	1012	763	12–24 w	NA
Takeuchi et al. [27]	Success	No change	Improved	61	OLRCT	28 w	40.9	15.5	PANSS	56.4	RIS OLZ	370 414	210 213	4 w	3.2% (3.3%)
Wang et al. [28]	Failure	Deteriorated	Improved	264	OLRCT	1 y	32.7	6.7	PANSS	39.6	RIS	420	200	≤8 w[g]	15.8% (7.8%)
Rouillon et al. [29]	Success	No change	No change	97	OLRCT	6 m	39.5	NA	PANSS	61.3	OLZ	528	399	6 m	8.2% (6.3%)
Uchida et al. [30]	Success	No change	Improved	34	OLRCT	36 w	40.1	15.8	PANSS	55.0	NA	703	413	12 w	0% (0%)
Kinion et al. [31]	NA	NA	No change	27	SBRCT	RP + 6 m	73	35[a]	NA	NA	FGAs	370	173	≤6 m	NA
Volavka et al. [32]	Success	No change	No change	23	DBRCT	28 w	40.1	20.4[a]	PANSS	82.7	HPD	1974	1164	12 w	NA
Hirschowitz et al. [33]	Success	No change	No change	24	DBRCT	RP+1 y	43.1	19.9[a]	PANSS	82.1	HPD	1200	666	1 w	NA
Schooler et al. [34]	Success	No change	NA	212	DBRCT	2 y	29.6	8.5	BPRS	29.4	FPZ-LAI	300–1200	215	0	25%[h] (25%)
Hogarty et al. [35]	NA	NA	No change	79	DBRCT	12 w	NA	NA	NA	NA	FPZ-LAI	446.4[e] 396.0[f]	256.8 242.4	12 w	NA
Inderbitzin et al. [36]	Success	No change	Improved	37	DBRCT	1 y	41.2	18.2[a]	BPRS	32.9	FPZ-LAI	545	276	5 m	25.0% (23.5%)
Newcomer et al. [37]	NA	NA	Improved	24	DBRCT	4 w	39	15.8	BPRS	35.7	HPD	1704	NA	4 w	21.4% (NA)
Faraone et al. [38]	Success	No change	NA	29	DBRCT	6 m	37–74	NA	NA	NA	NA	NA	NA	2 w/8 w	36.4% (0%)
Hogarty et al. [39]	Success	No change	No change	70	DBRCT	2 y	28.3	7	BPRS	NA	FPZ-LAI	516	91	2 y	24.3% (18.2%)
Cookson et al. [40]	NA	NA	NA	18	DBRCT	44 w	46	14	BPRS	20.2	FUL-LAI	3540	1770	0	33.3% (11.1%)
Johnson et al. [41]	Failure	Deteriorated	No change	59	DBRCT	1 y	40	10	BPRS	1.0	FUL-LAI	NA	90	1 y	32.1% (9.7%)
Kane et al. [42]	Failure	Deteriorated	Improved	126	DBRCT	1 y	28.9	6.1[a]	BPRS	NA	FPZ-LAI	300–1200	30–120	0	56.0% (7.0%)
Bogers et al. [43]	Success	No change	No change	24	Prospective	RP + 1 y	53	NA	PANSS	104	FGAs	1086	300	0–24 w	20.8%
Graff-Guerrero et al. [44]	Success	Improved	Improved	35	Prospective	RP + 5.9 w	60.1	33.1	PANSS	61.3	RIS OLZ	440 624	300 405	2.0 w	NA
Uchida et al. [45]	NA	NA	NA	9	Prospective	3 m	58	34	PANSS	43.4	RIS	340	NA	NA	NA
Kawai et al. [46]	Success	No change	Improved	23	Prospective	21.3 w	42.4	23.8	PANSS	92.4	FGAs	2253	1315	21.3 w	NA
Tsuruta et al. [47]	Failure	Deteriorated	No change	170	Prospective	2 y	NA	NA	BPRS	NA	NA	NA	NA	≤5 m	59.5% (12.5%)
	NA	NA	NA	5	Prospective	35 w	33.4	NA	BPRS	52.0	QTP	600/360	360/240	1 w	NA

Table 1 continued

Author (year)	Outcome: overall	Outcome: symptoms	Outcome: adverse effects	*n*	Study design	Study duration	Age, year	DOI, year	Baseline symptoms		APs	Baseline CPZE dose, mg/day[d]	CPZE dose after reduction, mg/day[d]	Reduction duration	Relapse rate in reduction group (that in non-reduction group)
Gefvert et al. [48]															
Nyberg et al. [49]	NA	NA	Improved	8	Prospective	2 w	30.9	5.5	PANSS	85.6	RIS	600	300	0	NA
Harris et al. [50]	Success	No change	Improved	49	Prospective	11 m	61.8	26.2	PANSS	59.5	NA	190	108	NA	0%[h] (0%)
Canuso et al. [51]	NA	NA	No change	5	Prospective	12.2 w	39.4	17.0	NA	NA	NA	1980	631	12.2 w	100%
Dale et al. [52]	NA	NA	NA	22	Prospective	1 y	33.4	9.9	NA	NA	FGA-LAIs	318	NA	6 m	54.5%
Leblenc et al. [53]	Success	Improved	Deteriorated	32	Prospective	1 y	37	11.7[b]	BPRS	38.1	FGA-LAIs	3702	1800	5 m	18.8%
Smith et al. [54]	Success	No change	NA	16	Prospective	10.3 m	46.5	11.5[c]	BPRS	NA	NA	1290	437	10.3 m	NA
Solgaard et al. [55]	Success	No change	NA	23	Prospective	NA	45.7	18.8	BPRS	9.8	ZUC-LAI	656	599	NA	4.3%
Heresco-Levy et al. [56]	NA	NA	NA	41	Prospective	2 y	41.6 39.6	19.3 16.7	BPRS	31.4 33.5	FPZ-LAI FPZ-LAI	258 665	120 420	2 m 2 m	36.0% 78.0%
Van Putten et al. [57]	Success	Improved	Improved	13	Prospective	1 y	32.6	NA	BPRS	NA	HP	3786	1410	32 w	NA
Hirschowitz et al. [58]	NA	NA	No change	16	Prospective	NA	53	22	SAPS	NA	HPD	1680	NA	NA	NA
Kistrup et al. [59]	NA	NA	NA	44	Prospective Prospective	5–14 m 3–9 m	45.8 44.1	16.8 16.6	BPRS BPRS	10.0 9.5	PPZ-LAI FUL-LAI	700 975	596 900	8.0 m 5.1 m	NA NA
Faraone et al. [60]	NA	NA	NA	29	Prospective	1 y	48	23	BPRS	32.6	FGAs	NA	NA	2 w	44.8%
Lehman et al. [61]	Success	No change	NA	94	Prospective	48 w	45	NA	BPRS	25.9 32.6	NA	266 475	50 100	1 m	25.8–32.3% (21.9%)

APs antipsychotics, *BPRS* Brief Psychiatric Rating Scale, *CGI-S* Clinical Global Impressions – Severity scale, *CPZE* chlorpromazine equivalent, *DBRCT* double-blind randomized controlled trial, *DOI* duration of illness, *FPZ* fluphenazine, *FGAs* first-generation antipsychotics, *FUL* flupentixol, *HPD* haloperidol, *LAI* long-acting injection, *MS* Manchester Scale, *n* number of subjects, *NA* not available, *m* months, *OLRCT* open-label randomized controlled trial, *OLZ* olanzapine, *PANSS* Positive and Negative Syndrome Scale, *PPZ* perphenazine, *RIS* risperidone, *RP* reduction period, *SAPS* Scale for the Assessment of Positive Symptoms, *SBRCT* single-blind randomized controlled trial, *SGAs* second-generation antipsychotics, *w* weeks, *y* years, *ZUC* zuclopenthixol

[a]Duration from the first hospitalization to study participation

[b]Duration of antipsychotic treatment

[c]Duration of current hospitalization

[d]CPZE dose was calculated according to Gardner et al.[24]

[e]Distressed group

[f]Defect group

[g]Dose was maintained for 26 weeks before reduction

[h]Hospitalization rate

relapse rates between pre- and post-dose reduction or between the dose reduction and maintenance groups, along with no worsening or no inferiority of adverse effects, which was considered to indicate a successful dose reduction by our definition. Nine studies reported a significant improvement in adverse effects after dose reduction, including EPSs and neurocognitive impairment.

Factors related to successful dose reduction identified by qualitative analysis of prospective trials

Table 2 shows the number of studies classified by outcome for each of the factors related to study design, patient characteristics, and antipsychotic dose reduction strategy. Relapse definition varied among the studies and included exceeding a certain threshold score on a scale ($N = 9$), an increase in antipsychotic dose ($N = 4$), hospitalization ($N = 2$), or a combination of them (i.e., an increase in antipsychotic doses or hospitalization) ($N = 4$), whereas relapse was not clearly defined in 18 studies. In addition, 21 (56.8%) and 11 (29.7%) studies targeted first-generation antipsychotics (FGAs) and LAI-APs only, respectively. Only 8 studies (21.6%; 4 RCTs and 4 non-RCTs) focused on second-generation antipsychotics (SGAs) and no studies examined dose reduction of LAI-SGAs. Sixteen studies (43.2%) included patients receiving a mean CPZE ≥ 600 mg/day at baseline. In 7 out of 8 studies (87.5%), patients who experienced clinical deterioration were re-stabilized by increasing the doses back to the pre-reduction baseline.

Factors that satisfied the criteria for predicting successful dose reduction were study duration < 1 year, age > 40 years, duration of illness > 10 years, and a post-reduction antipsychotic CPZE dose > 200 mg/day. Other factors including illness stability or antipsychotic dose at baseline did not fulfill the criteria for predicting successful dose reduction.

Factors related to an increased risk of relapse after dose reduction identified by meta-analysis of RCTs

The quantitative results of the meta-analyses are summarized in Table 3 and the corresponding forest plots are shown in Supplementary Fig. S4. Relapse rate was significantly higher in the dose reduction group than in the maintenance group ($N = 13$; $n = 902$; RR = 1.96; 95% CI, 1.23–3.12; $P = 0.005$; $I^2 = 27\%$). In contrast, a significantly greater improvement in neurocognition was found in the dose reduction group compared with the maintenance group ($N = 2$; $n = 136$; SMD = 0.69; 95% CI, 0.25–1.12; $P = 0.002$; $I^2 = 34\%$). There were no significant differences in hospitalization, study discontinuation, psychopathology, EPSs, body weight, or QOL between the 2 groups.

The subgroup analyses of relapse rate are summarized in Table 4 and the corresponding forest plots are shown in Figs. 1–4 and Supplementary Figs. S5–7. The following factors were associated with an increased risk of relapse: publication before 2002, study duration ≥ 1 year, stable illness at enrollment, mean age ≤ 40 years, outpatient setting, mean illness duration ≤ 10 years, mean treatment duration ≤ 10 years, use of FGAs, use of LAI-APs, mild or lower symptom severity, post-reduction CPZE dose ≤ 200 mg/day, and duration of reduction ≤ 2 months. However, after the sensitivity analyses, study duration and duration of illness were no longer significant (Supplementary Table S1). Moreover, when the further subgroup analyses of studies with a post-reduction CPZE dose > 200 mg/day were conducted, no factors remained significant (Supplementary Table S2).

The results of the subgroup analyses of studies with a post-reduction CPZE dose > 200 mg/day are shown in Figs. 1–4. Negative symptoms ($N = 4$; $n = 256$; SMD = −0.45; 95% CI, −0.86 to −0.04; $P = 0.03$; $I^2 = 59\%$), EPSs assessed with the Simpson-Angus Scale ($N = 2$; $n = 195$; SMD = −0.37; 95% CI, −0.65 to −0.08; $P = 0.01$; $I^2 = 0\%$), and neurocognition ($N = 2$; $n = 136$; SMD = 0.69; 95% CI, 0.25–1.12; $P = 0.002$; $I^2 = 34\%$) were improved to a significantly greater extent in the dose reduction group than in the maintenance group. Funnel plots showed no significant publication bias in these findings (Supplementary Fig. S3B, C).

DISCUSSION

Our qualitative analyses of prospective trials suggested that study duration < 1 year, age > 40 years, duration of illness > 10 years, and post-reduction CPZE dose > 200 mg/day were associated with a successful antipsychotic dose reduction in patients with schizophrenia. Our quantitative results from a meta-analysis of RCTs showed that dose reduction increased the risk of relapse but improved neurocognitive function. A subgroup analysis confirmed that an antipsychotic reduction that remained above the minimum effective dose (i.e., CPZE 200 mg/day) did not increase the risk of relapse compared with a maintained dose.

Factors related to a successful dose reduction identified by qualitative analysis of prospective trials

Although studies with a shorter duration were associated with greater success of antipsychotic dose reduction, these studies may underestimate the risk of relapse because it increases over time [1, 62]. Older age was another factor associated with a successful dose reduction, which suggests that elderly patients may need lower antipsychotics doses, given that an age-related decline in the dopaminergic system has been consistently reported; for example, dopamine receptor availability decreases by about 10% per decade [63, 64]. Moreover, a longer duration of illness was another factor associated with a successful dose reduction, which may indicate that chronic patients are a good candidate for dose reduction. Because functional deterioration as an index of illness severity is supposed to plateau 10 years after the onset of illness [65–67], patients with chronic schizophrenia may be treated with lower doses of antipsychotics once their illness has stabilized. Alternatively, in younger patients with a shorter illness duration, antipsychotic dose reduction should be more carefully implemented with close monitoring.

A moderate dose reduction seems to be a reasonable treatment option in the maintenance phase of schizophrenia. This approach is consistent with the results of a previous meta-analysis examining the effectiveness of antipsychotic low-dose vs. standard-dose treatment [68], although there are substantial differences in study design between low-dose treatment trials and dose reduction trials. This meta-analysis found no significant difference in relapse between low-dose treatment (i.e., 0.5–1.0 defined daily dose [DDD]) and standard-dose treatment (i.e., >1.0 DDD) but significant inferiority of very low-dose treatment (i.e., <0.5 DDD) vs. standard-dose treatment. This is in line with the concept of minimum effective dose, which is defined as the lowest dose that shows superiority over placebo [1, 69, 70]. Moreover, it is reassuring that, even if symptoms deteriorate, the patient's condition can generally be re-stabilized by simply increasing the doses back to those at baseline.

Antipsychotic discontinuation is the most straightforward approach to nullify the exposure to antipsychotics. A systematic review suggested that older age, maintenance on a lower antipsychotic dose before discontinuation, shorter duration of untreated psychosis, older age at the onset of illness, lower severity of positive symptoms at baseline, better social functioning, and fewer previous relapses were associated with a lower risk of relapse after antipsychotic discontinuation [71]. These factors, except for older age, were not identified as risk factors in antipsychotic dose reduction in our results. Another review focusing on first-episode psychosis found no replicated predictive factors for continuing remission after discontinuation of antipsychotics [72]. These findings highlight the difference between antipsychotic discontinuation and dose reduction.

Table 2. Number of studies classified by outcome in each factor.

		Number of studies			
		Total	By outcome classification		
			Success (%)	Failure (%)	NA
Factors related to study design					
Publication year	2003–	10	8 (89)	1 (11)	1
	–2002	27	12 (80)	3 (20)	12
Study design	Randomized controlled trial	18	11 (79)	3 (21)	4
	Blind	13	7	2	4
	Open label	5	4	1	0
	Prospective trial	19	9 (90)	1 (10)	9
Study duration	≥1 year	14	7 (64)	4 (36)	3
	≥6 months and <1 year	14	10 (100)	0 (0)	4
	<6 months	7	2 (100)	0 (0)	5
	NA	2	1	0	1
Inclusion criteria: illness stability	Stable condition	19	9 (69)	4 (31)	6
	Less than a certain score on a scale	4	2	2	0
	Longer than a certain period	5	2	1	2
	≥3 months	4	1	1	2
	<3 months	1	1	0	0
	Mixed (less than a certain score and longer than a certain period)	4	2	1	1
	Unstable condition	5	4 (100)	0 (0)	1
	NA	13	7	0	6
Inclusion criteria: antipsychotic dose	Stable dose for a certain period	7	2 (100)	0 (0)	5
	More than a certain dose	3	0 (0)	2 (100)	1
	More than a certain dose and period	15	12 (92)	1 (8)	2
	NA	12	6	1	5
Relapse definition	More than a certain score on a scale	9	5 (57)	3 (43)	1
	Increase in antipsychotic dose	4	2 (67)	1 (33)	1
	Hospitalization	2	2 (100)	0 (0)	0
	Mixed (hospitalization or increase in antipsychotic dose)	4	2 (100)	0 (0)	2
	NA	18	9	0	9
Factors related to patients' demographic and clinical characteristics					
Mean age	>40 years	21	14 (100)	0 (0)	7
	≤40 years	13	5 (63)	3 (38)	5
	NA	3	1	1	1
Treatment setting	Outpatients only	15	9 (82)	2 (18)	4
	Inpatients only	10	5 (100)	0 (0)	5
	Mixed (outpatients and inpatients)	7	6 (100)	0 (0)	1
	NA	5	0	2	3
Mean illness duration[a]	>10 years	17	8 (100)	0 (0)	9
	≤10 years	7	2 (40)	3 (60)	2
	NA	13	10	1	2
Mean treatment duration	>10 years	11	8 (100)	0 (0)	3
	≤10 years	2	0 (0)	2 (100)	0
	NA	24	12	2	10
Antipsychotics: type	FGAs only	21	10 (83)	2 (17)	9
	SGAs only	8	4 (80)	1 (20)	3
	Mixed (FGAs and SGAs)	1	1 (100)	0 (0)	0
	NA	7	5	1	1
Antipsychotics: formulation	Oral	14	6 (86)	1 (14)	7
	LAI	11	4 (67)	2 (33)	5
	Mixed (oral and LAI)	3	2 (100)	0 (0)	1
	NA	9	8	1	0
Antipsychotics: mean CPZE dose	≥430 mg/day	22	16 (100)	0 (0)	6
	>600 mg/day	15	9	0	6
	<430 mg/day	9	2 (67)	1 (33)	6
	NA	6	2	3	1
Mean symptom severity	>Mild	14	10 (100)	0 (0)	4
	PANSS total >58	9	8	0	1
	BPRS total >31	5	2	0	3
	CGI-S >3	0	0	0	0

Table 2 continued

		Number of studies			
		Total	By outcome classification		
			Success (%)	Failure (%)	NA
	≤Mild	10	5 (71)	2 (29)	3
	PANSS total ≤58	4	2	1	1
	BPRS total ≤31	6	3	1	2
	CGI-S ≤3	0	0	0	0
	NA	13	5	2	6
Factors related to antipsychotic dose reduction strategy					
Goal of reduction	% reduction	17	9 (75)	3 (25)	5
	50% reduction	11	6	2	3
	To target dose	7	4 (100)	0 (0)	3
	Mixed (% reduction and to target dose)	1	1 (100)	0 (0)	0
	To MED for each patient	6	3 (100)	0 (0)	3
	NA	5	3	0	2
Actual proportion of reduction	>52%	11	6 (75)	2 (25)	3
	>80%	3	2	1	0
	≤52%	17	12 (100)	0 (0)	5
	NA	9	2	2	5
Antipsychotic dose after reduction (CPZE)	>600 mg/day	8	6 (100)	0 (0)	2
	>200 mg/day and ≤600 mg/day	14	10 (100)	0 (0)	4
	≤200 mg/day	8	3 (50)	3 (50)	2
	NA	7	1	1	5
Duration of reduction	>2 month	21	12 (86)	2 (14)	7
	≤2 month	9	4 (67)	2 (33)	3
	NA	7	4	0	3
Speed of reduction	<6.5%/week	16	11 (100)	0 (0)	5
	≥6.5%/week	8	4 (67)	2 (33)	2
	NA	13	5	2	6

BPRS Brief Psychiatric Rating Scale, *CGI-S* Clinical Global Impressions – Severity scale, *CPZE* chlorpromazine equivalent, *FGAs* first-generation antipsychotics, *LAI* long-acting injectable, *MED* minimum effective dose, *NA* not available, *PANSS* Positive and Negative Syndrome Scale, *SGAs* second-generation antipsychotics
[a]Duration of illness or since first hospitalization

Table 3. Effect estimate of each outcome.

	Studies	Participants	Statistics	Effect estimate	Overall effect	Heterogeneity	
				[95% CI]	*P*-value	I^2 (%)	*P*-value
Relapse/Hospitalization							
Relapse (primary outcome)	13	902	RR	1.96 [1.23–3.12]	0.005*	27	0.18
Hospitalization	5	350	RR	1.79 [0.60–5.30]	0.30	30	0.22
Study discontinuation							
due to all causes	11	857	RR	1.11 [0.86–1.42]	0.42	0	0.54
due to inefficacy	12	914	RR	1.36 [0.86–2.14]	0.19	0	0.75
due to intolerability	9	797	RR	1.17 [0.48–2.82]	0.73	0	0.64
Psychopathology							
Total	6	668	SMD	−0.16 [−0.53–0.21]	0.40	80	0.0002
Positive symptoms	6	523	SMD	0.01 [−0.26–0.29]	0.92	50	0.07
Negative symptoms	5	505	SMD	−0.29 [−0.72–0.13]	0.18	79	0.0009
CGI-S	3	473	SMD	−0.05 [−0.24–0.15]	0.65	9	0.33
Adverse effects							
SAS	4	444	SMD	−0.20 [−0.52–0.12]	0.23	55	0.08
BARS	1	97	SMD	0.04 [−0.36–0.44]	0.84	NA	NA
AIMS	1	97	SMD	0.18 [−0.22–0.58]	0.38	NA	NA
DIEPSS	2	224	SMD	−0.36 [−0.87–0.15]	0.16	66	0.09
Body weight	3	407	SMD	−0.00 [−0.20–0.19]	0.98	0	0.87
Neurocognition	2	136	SMD	0.69 [0.25–1.12]	0.002*	34	0.22
QOL	3	321	SMD	0.07 [−0.15–0.29]	0.54	0	0.75

AIMS Abnormal Involuntary Movement Scale, *BARS* Barnes Akathisia Rating Scale, *CGI-S* Clinical Global Impression – Severity scale, *DIEPSS* Drug-Induced Extrapyramidal Symptoms Scale, *NA* not applicable, *QOL* quality of life, *RR* risk ratio, *SAS* Simpson-Angus Scale, *SMD* standardized mean difference
*$P < 0.05$ overall effect

Table 4. Subgroup analysis of effect estimate in relapse rate.

Factors	Subgroup	Studies	Participants	Effect estimate	Overall effect	Heterogeneity	
				[95% CI]	*P*-value	I^2 (%)	*P*-value
Overall		13	902	1.96 [1.23–3.12]	0.005*	27	0.18
Publication year	2003–−2002	5	516	1.45 [0.83–2.54]	0.19	0	0.47
		8	386	2.59 [1.33–5.05]	0.005*	35	0.15
Study duration	≥1 year	6	616	1.96 [1.00–3.84]	0.05*	61	0.02
	<1 year	7	286	1.95 [0.80–4.77]	0.14	0	0.84
Illness stability	Stable	8	761	2.06 [1.13–3.74]	0.02*	45	0.08
	Unstable	3	70	2.70 [0.67–10.95]	0.16	0	0.66
Mean age	>40 years	6	248	1.02 [0.50–2.07]	0.96	0	0.83
	≤40 years	6	625	2.56 [1.38–4.75]	0.003*	41	0.13
Treatment setting	Outpatient only	6	418	2.37 [1.10–5.11]	0.03*	53	0.06
	Inpatient only	1	23	1.09 [0.08–15.41]	0.95	NA	NA
Mean illness duration	>10 years	6	197	1.44 [0.62–3.36]	0.40	0	0.79
	≤10 years	4	504	2.79 [1.29–6.03]	0.009*	60	0.06
Mean treatment duration	>10 years	2	60	1.07 [0.37–3.05]	0.90	0	0.99
	≤10 years	2	185	5.55 [2.06–14.94]	0.0007*	30	0.23
Antipsychotics: type	FGAs	7	357	2.48 [1.21–5.07]	0.01*	41	0.12
	SGAs	4	482	1.45 [0.83–2.54]	0.19	0	0.47
Antipsychotics: formulation	Oral	6	529	1.50 [0.88–2.56]	0.14	0	0.65
	LAI	5	310	2.53 [1.09–5.90]	0.03*	58	0.05
Antipsychotics: mean dose	≥430 mg/day	8	378	1.22 [0.72–2.06]	0.46	0	0.84
	<430 mg/day	2	310	1.94 [0.97–3.92]	0.06	0	0.60
Mean symptom severity	>Mild	5	256	1.05 [0.54–2.06]	0.88	0	0.77
	≤Mild	5	421	2.28 [1.28–4.07]	0.005*	0	0.82
Actual proportion of reduction	≥52%	3	445	2.73 [0.99–7.51]	0.05	73	0.03
	<52%	6	270	1.28 [0.60–2.73]	0.52	0	0.94
Antipsychotic dose after reduction	>200 mg/day	7	345	1.07 [0.57–2.02]	0.83	0	0.90
	≤200 mg/day	4	504	2.79 [1.29–6.03]	0.009*	60	0.06
Duration of reduction	>2 months	7	395	1.32 [0.80–2.17]	0.28	0	0.61
	≤2 months	4	460	3.39 [1.22–9.41]	0.02*	47	0.13
Speed of reduction	<6.5%/week	6	336	1.08 [0.62–1.88]	0.78	0	0.93
	≥6.5%/week	3	436	3.20 [0.93–11.00]	0.07	64	0.06

FGAs first-generation antipsychotics, *LAI* long-acting injectable, *NA* not applicable, *SGAs* second-generation antipsychotics
*$P < 0.05$ for overall effect

Factors related to an increased risk of relapse after dose reduction identified by meta-analysis of RCTs

The subgroup meta-analyses found that the following factors were associated with an increased risk of relapse: publication before 1999, study duration of ≥1 year, stable illness, age ≤ 40 years, outpatient setting, illness or treatment duration ≤ 10 years, use of FGAs or LAI-APs, mild or lower symptom severity, reduction rate ≥ 50%, post-reduction CPZE dose ≤ 200 mg/day, and reduction duration ≤ 2 months. Because older studies often used FGAs or LAI-APs and reduced the doses aggressively (e.g., by 80–90%), these factors seem to be closely related to each other. An inpatient setting would be advantageous for clinicians to closely monitor patients and more precisely detect signs of imminent worsening, which can avert a full-blown relapse. Stable or less severe illness was also associated with an increased risk of relapse, which means that patients with more severe illness are more likely to experience successful dose reduction. This seemingly paradoxical finding may indicate that the antipsychotic drugs used for these patients did not work in the first place and therefore dose reduction did not result in any symptom change. It may also be possible that clinicians were less likely to recognize relapse when a patient was already symptomatic. A shorter duration of dose reduction was related to an increased risk of relapse, suggesting that gradual dose reduction should be recommended to ensure stabilization before the next step of dose reduction and to avoid withdrawal/rebound symptoms. The speed of the reduction was not statistically significant but did show a similar trend in which a gradual dose reduction may be more favorable. This finding is supported by a meta-analysis indicating that gradual withdrawal for at least 3 weeks was associated with a lower risk of relapse [73], although the result was not consistent with a recent meta-analysis [1]. Further research is warranted to elucidate the relationship between the speed of reduction and risk of relapse. Reduction in the number of antipsychotics (e.g., switching from antipsychotic polypharmacy to monotherapy) is another clinically important issue because antipsychotic dose is associated with the number of antipsychotics. A recent meta-analysis showed that conversion of polypharmacy to monotherapy was related to an increased risk of study discontinuation [74], which should be taken into consideration when clinicians simultaneously reduce the dose and the number of antipsychotics.

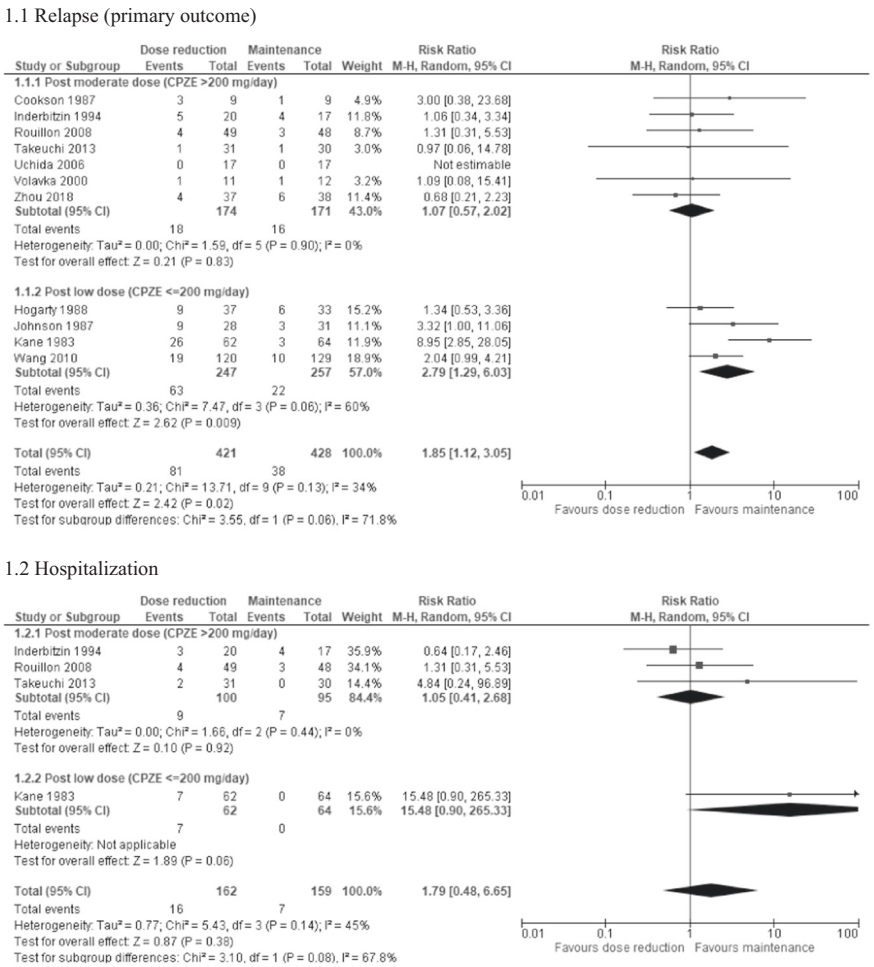


Fig. 1 Forest plot: relapse/hospitalization, subgroup analysis by antipsychotic dose after reduction. *CPZE* chlorpromazine equivalent.

Given that the sensitivity analyses did not find any significance for study duration, illness duration, and reduction rate, they do not seem to be robust factors for successful dose reduction. Moreover, antipsychotic dose before reduction was not associated with the risk of relapse, even when the cut-off was set beyond the upper end of the therapeutic dose range (i.e., CPZE dose > 600 mg/day). Furthermore, in the further subgroup analyses of studies with the predictive factor identified by the aforementioned subgroup analyses (i.e., a post-reduction CPZE dose > 200 mg/day), no other factors remained significant, suggesting that post-reduction CPZE dose is a robust factor for successful dose reduction.

Other outcomes of the meta-analysis

Our meta-analysis found that antipsychotic dose reduction significantly improved neurocognitive function, which aligns with the recent evidence indicating that neurocognitive impairment is a dose-dependent adverse effect of antipsychotics [5, 6]. Both studies included in the meta-analysis conducted a 50% dose reduction of risperidone and olanzapine, indicating that dose reduction of SGAs is still beneficial, even though they are considered to have fewer risks of neurocognitive dysfunction than FGAs [75, 76]. Impaired neurocognition is related to disturbances in the dopaminergic and cholinergic systems in the brain. All antagonist antipsychotic drugs are believed to exert their effects by blocking mesolimbic dopamine D_2 receptors; however, they also block dopamine receptors in the prefrontal cortex, which can lead to impairment in cognitive control and working memory [77]. In addition, some antipsychotics, in particular olanzapine and clozapine, have marked anticholinergic effects, which can be associated with impairment in attention and memory [78]. An excessive blockade of dopaminergic and cholinergic transmission with antipsychotics can be relieved by antipsychotic dose reduction, which can ameliorate neurocognitive adverse effects. However, this finding in our meta-analysis was from only 2 RCTs and further studies are clearly needed to identify a strategy to counteract this problematic adverse effect of antipsychotics.

The subgroup analyses found that an antipsychotic dose reduction that did not exceed the minimum effective dose (i.e., CPZE 200 mg/day) was not associated with an increased risk of relapse. Moreover, such a reduction improved not only neurocognitive function but also EPSs and negative symptoms. EPSs are another dose-dependent adverse effect of antipsychotics [79]. Negative symptoms are one of the core features of schizophrenia, although some of them are represented by secondary negative symptoms due to excessive exposure to antipsychotics. Furthermore, given that (1) EPSs are correlated with negative symptoms [80], (2) negative symptoms are associated with neurocognitive impairment [81], and (3) poor neurocognitive performance is linked to severe EPSs [82], there is a close relationship among EPSs, neurocognitive impairment, and negative symptoms. Antipsychotic dose reduction may be a viable strategy for these domains, given that currently available treatment options for negative symptoms and neurocognitive impairment are limited both in quality and quantity [83, 84].

It should be emphasized that 2 studies revealed worsened clinical symptoms but improved adverse effects after dose

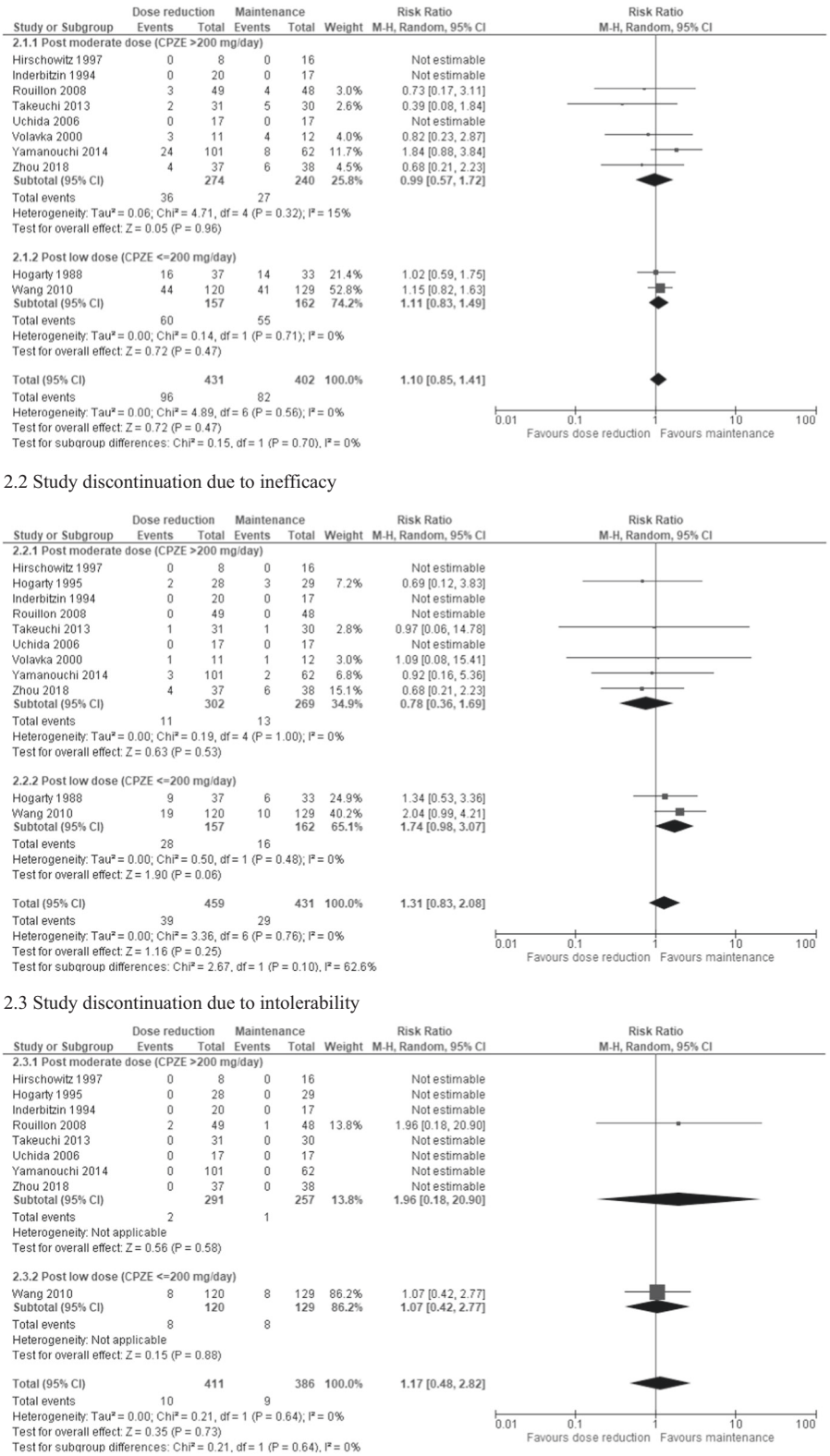
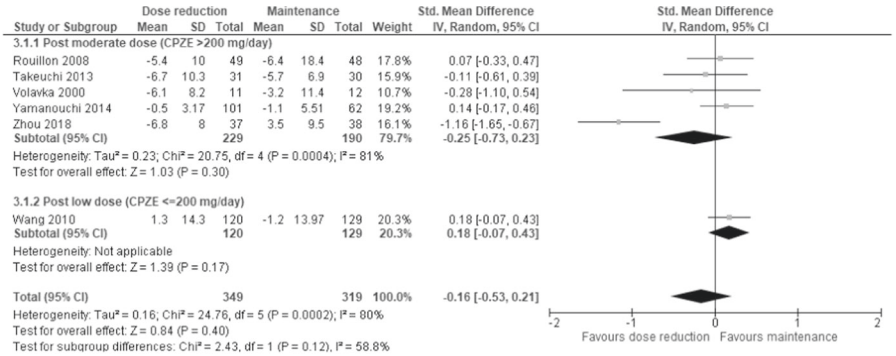


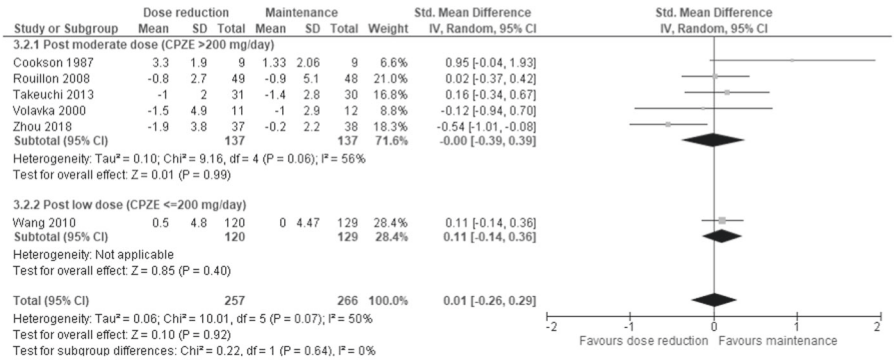
Fig. 2 Forest plot: study discontinuation, subgroup analysis by antipsychotic dose after reduction. *CPZE* chlorpromazine equivalent.

reduction [28, 42], whereas 1 study showed a paradoxical finding in which symptoms improved but adverse effects worsened [53]; tardive adverse effects may worsen upon antipsychotic dose reduction. Physicians should consider this clinical dilemma during the therapeutic decision-making process. Although we also investigated QOL as an index of functioning, there was no difference between the dose reduction and maintenance groups.

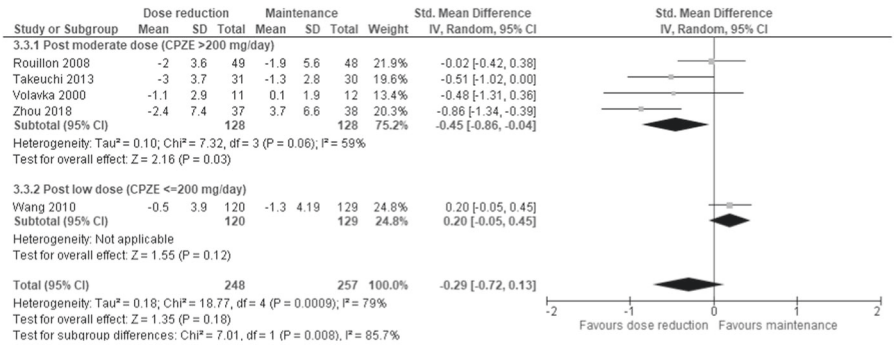
3.1 Total



3.2 Positive symptoms



3.3 Negative symptoms



3.4 CGI-S

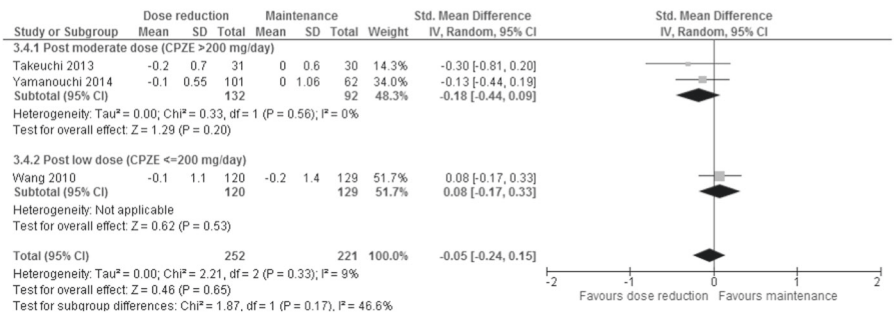
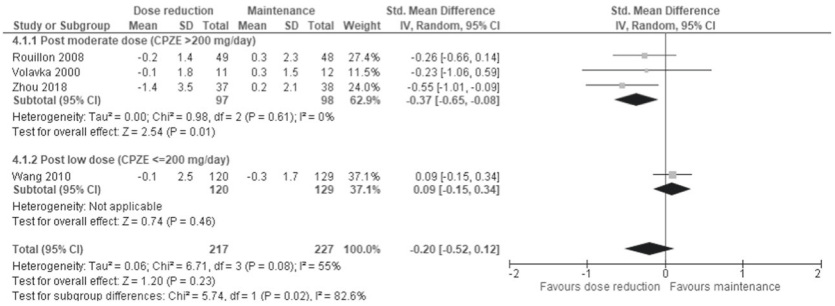


Fig. 3 Forest plot: psychopathology, subgroup analysis by antipsychotic dose after reduction. *CGI-S* Clinical Global Impressions – Severity scale, *CPZE* chlorpromazine equivalent.

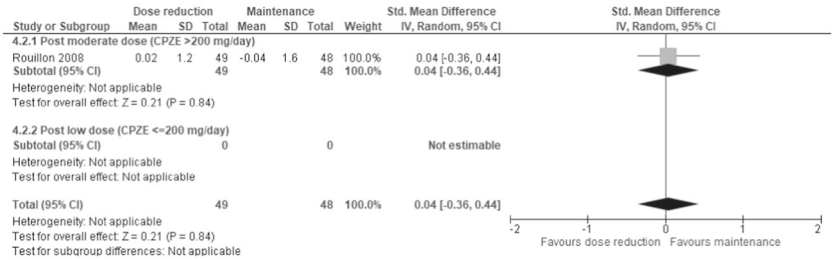
Limitations

This systematic review should be interpreted in light of some limitations. First, the heterogeneity of the study design made comparisons among the studies difficult; however, the aim of this study was to identify factors associated with successful dose reduction rather than to simply synthesize relapse rates in dose reduction studies. For this purpose, we sorted the studies by study design, participants' demographic and clinical

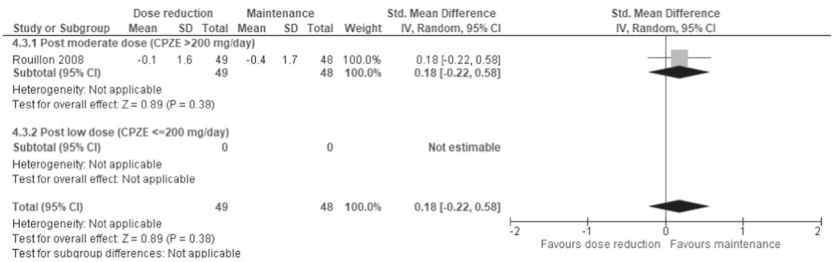
4.1 SAS



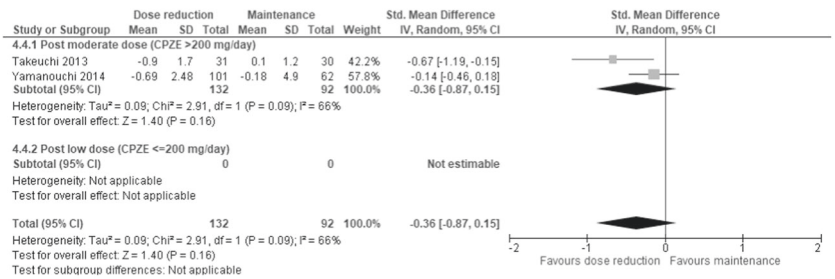
4.2 BARS



4.3 AIMS



4.4 DIEPSS



4.5 Body weight

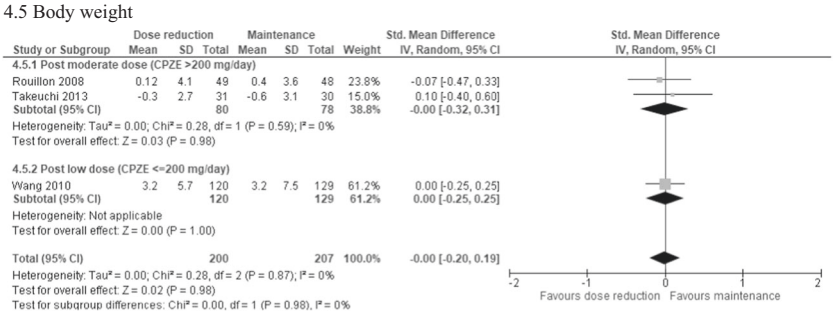


Fig. 4 Forest plot: adverse effects, subgroup analysis by antipsychotic dose after reduction. *AIMS* Abnormal Involuntary Movement Scale, *BARS* Barnes Akathisia Rating Scale, *CPZE* chlorpromazine equivalent, *DIEPSS* Drug-Induced Extrapyramidal Symptoms Scale, *QOL* quality of life, *SAS* Simpson-Angus Scale.

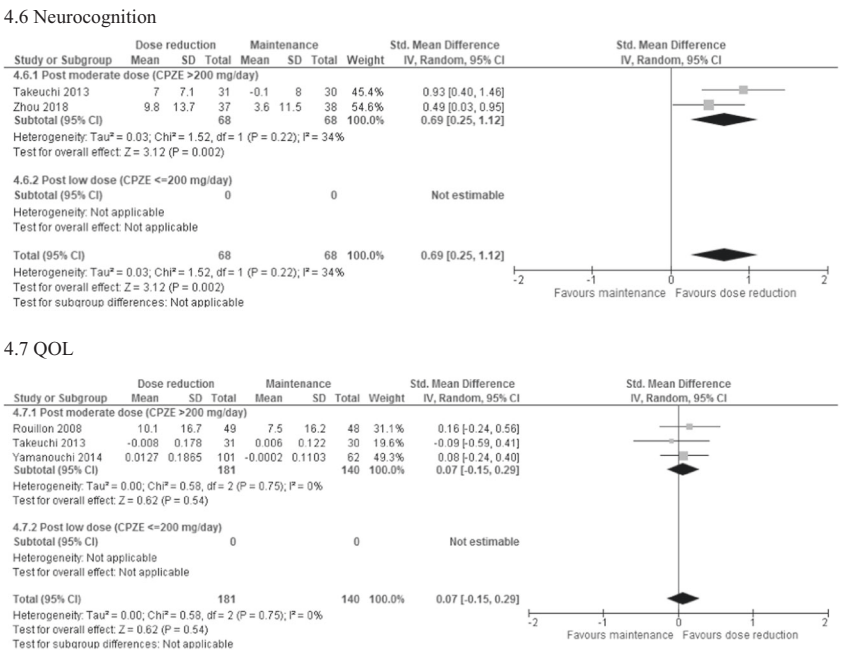


Fig. 4 Continued

characteristics, and dose reduction procedures that were potentially related to successful dose reduction. Second, the definition of relapse was not consistent across the studies; a temporary deterioration was managed by an increase in antipsychotics in some studies, whereas other studies recognized it as a relapse. Moreover, the results of 3 possible causes of study discontinuation could overlap with relapse and may not be independently interpreted because 10 studies included relapse in the criteria of withdrawal from the study. Third, an arbitrary definition of successful dose reduction was adopted in the qualitative analysis. Fourth, half of the included RCTs were conducted with an open-label design that is susceptible to biases such as patient and rater expectations. Fifth, the small number of studies included in the subgroup analysis is prone to a potential type II error for predictors of successful dose reduction. It should be emphasized that only 4 studies used SGAs and that no study examined dose reduction of LAI-SGAs. Further trials with a double-blind design examining antipsychotic dose reduction with oral SGAs or LAI-SGAs are certainly warranted to support the findings in this meta-analysis.

CONCLUSIONS

Antipsychotic dose reduction increased the risk of relapse but improved neurocognitive function. In most studies, patients were re-stabilized by increasing the doses back to the baseline level, even when their symptoms worsened. A subgroup analysis indicated that modest dose reduction not exceeding the minimum effective dose (i.e., CPZE 200 mg/day) was the only robust predictor of successful dose reduction; modest dose reduction was associated with improvements in EPSs and negative symptoms in the maintenance treatment of schizophrenia. Given a lack of RCTs of SGAs, clinicians are advised to closely monitor patients when reducing the doses of these antipsychotics. Considering substantial heterogeneity in study designs and insufficient quality of the data, optimal antipsychotic dose reduction strategies should currently be guided by individual patient characteristics.

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ADDITIONAL INFORMATION

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