Time-dependent effect of antipsychotic discontinuation and dose reduction on social functioning and subjective quality of life–a multilevel meta-analysis

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eClinicalMedicine 2023;65: 102291
Published Online xxx
https://doi.org/10.1016/j.eclinm.2023.102291

Summary

Background Meta-analyses indicate superiority of antipsychotic maintenance treatment over discontinuation within up to 24 months after treatment initiation for patients with schizophrenia-spectrum disorders. In terms of functional recovery, long-term trials show improved functioning after discontinuation, suggesting a time-dependent effect of antipsychotic maintenance. However, these trials were not included in previous meta-analyses. We therefore investigated whether the effect of antipsychotic maintenance treatment vs. discontinuation on social functioning and quality of life varies by trial length.

Methods The study was preregistered with PROSPERO (CRD42021248933). PubMed, PsycINFO, Web of Science, Embase and trial registers were systematically searched on 8th November 2021 and updated on 25th June, 2023 and 10th August, 2023 for studies that compared antipsychotic maintenance to discontinuation and reported data on social functioning or subjective quality of life in patients with schizophrenia-spectrum disorders. Risk of bias was assessed with the RoB 2, the ROBINS-I and the RoB-ME tools. Quality of evidence was rated using the Grading of Recommendations Assessment, Development, and Evaluation approach.

Findings. We included k = 35 studies (N = 5924) with follow-ups between one month and 15 years. Overall, maintenance and discontinuation did not differ on social functioning (k = 32; n = 5330; SMD = 0.204; p = 0.65; 95% *CI* [–0.69, 1.10]) or quality of life (k = 10; n = 943; SMD = –0.004; p = 0.97; 95% *CI* [–0.22, 0.21]), whilst subgroup analyses of middle- (2–5 years; k = 7; n = 1032; SMD = 0.68; 95% *CI* [0.06, 1.28]) and long-term follow-ups (>5 years; k = 2; n = 356; SMD = 1.04; 95% *CI* [0.82, 1.27]) significantly favoured discontinuation. However, the quality of evidence was rated as very low.

Interpretation Although our findings suggest a time-dependent decrease in the effect of maintenance treatment on social functioning, interpretation of these findings is limited by the serious risk of bias in middle- and long-term trials. Therefore, any conclusions regarding the long-term benefits of antipsychotic treatment or discontinuation for functional recovery are premature and more high-quality trials tailored to comparing state of the art maintenance treatment vs. discontinuation are needed.

Funding None.

Keywords: Schizophrenia; Neuroleptics; Cessation; Dose-reduction; Social functioning; Quality of life

Introduction

Schizophrenia-spectrum disorders can be associated with severe functional impairment. For instance, many people with schizophrenia-spectrum disorders show an increasing decline in cognitive functions.[1] Compared to the general population, they reach lower educational degrees and are less likely to be employed.[2] In the social domain, many patients face a loss of social

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Research in context

Evidence before this study

Long-term studies comparing antipsychotic maintenance treatment against discontinuation suggest improved functional recovery associated with discontinuation, which may suggest a time-dependent and decreasing effect of antipsychotic maintenance treatment. However, previous reviews included only short-term trials and focused on relapse rates or symptomatic remission. To investigate the putative time-dependent effect of antipsychotic maintenance treatment vs. discontinuation on social functioning and subjective quality of life, PubMed, PsycINFO, Web of Science and Embase were systematically searched on 8th November, 2021 and updated on 25th June, 2023 and 10th August, 2023. Search terms included (*schizophreni** OR *psychosis* OR *psychotic disorder* OR *schizoaffective*) AND (*neuroleptic** OR *antipsychotic**) AND (*discontinu** OR *withdraw** OR *maintain** OR *reduc** OR *stop** OR *cessation* OR *halt**). Studies were included if they compared antipsychotic maintenance to discontinuation and reported data on social functioning or subjective quality of life in patients with schizophrenia-spectrum disorders. Risk of bias was assessed with the RoB 2, ROBINS-I and RoB-ME tools, which were indicative of low study quality, and low risk of bias due to missing evidence. Our results showed that whilst short-term follow-ups (<2 years) on social functioning did not yield significant differences between maintenance and discontinuation, middle- and long-term follow-ups significantly favoured discontinuation. However, interpretation of this effect is limited by the small number and high risk of bias in middle- and long-term studies.

Added value of this study

This is the first meta-analysis aggregating the long-term effects of antipsychotic maintenance vs. discontinuation on functional recovery in people with schizophrenia-spectrum disorders.

Implications of all the available evidence

Our meta-analysis extends previous reviews as it tentatively supports findings of long-term studies indicating that discontinuation after two years of maintenance treatment may benefit functional recovery. However, one should refrain from drawing definite conclusions as this finding might be driven by the high risk of bias in available long-term studies.

relationships[3] and an insecure housing situation.[4] These and further types of functional impairments diminish quality of life[5] and are likely to hamper patients' long-term recovery.

Current evidence on the treatment of patients with schizophrenia-spectrum disorders leaves no doubt about the beneficial effects of antipsychotic maintenance treatment for stabilised patients within the first 12–24 months after stabilisation from an acute psychotic episode. For this timeframe, several meta-analyses confirm the superiority of antipsychotic maintenance treatment over discontinuation in terms of control over positive symptoms,[6] relapse prevention as well as improved social functioning and quality of life.[7,8]

Despite the benefits on symptomatology, many patients do not wish to continue antipsychotic treatment after remission from an acute psychotic episode,[9] which is reflected in high rates of self-initiated discontinuation.[10] Also, some researchers question the long-term advantage of antipsychotic maintenance treatment for functional recovery.[11] One reason for a more cautious attitude are the adverse medication effects such as weight gain, sedation, insomnia,[12] and metabolic and cardio-vascular complications[13–15] that have a negative impact on patients' quality of life[16,17] and impede long-term social functioning.[18,19] Moreover, a recent meta-analysis of prospective randomised controlled trials (RCTs) revealed preliminary evidence of improved neurocognition in patients following dose-reduction of antipsychotics[20] although it is important to note that this effect was based on a sub-analysis of only two RCTs. Similarly, long-term studies tentatively indicate improved functional recovery in favour of discontinuation. For instance, a 7-year follow-up on a randomised cohort study found that rates of functional remission were higher in the discontinuation group (46% vs. 20%).[18] A 20-year non-randomised observational cohort study, in which 35% of the patients discontinued their medication, revealed non-significant differences at the 2-year follow-up in recovery (including symptom remission, social functioning, and work performance), but significantly higher recovery rates in patients who discontinued their medication at the 20-year follow-up.[19]

In sum, both RCTs and non-randomised studies (NRS) tentatively point to a time-dependent effect of antipsychotic maintenance treatment. Whilst short-term follow-ups with less than 24 months provide compelling evidence for broad benefits of antipsychotic maintenance, longer follow-ups seem to suggest superiority of discontinuation for functional recovery. However, existing meta-analyses did not include studies with follow-ups beyond 24 months. Moreover, previous reviews investigated relapse rates and symptomatic remission as primary outcomes and therefore may not be showing the full picture of evidence on functional recovery. Finally, previous meta-analyses investigated maintenance vs. discontinuation effects by means of standardised withdrawal schemes. Yet, evidence on discontinuation converges in that this constitutes the riskiest approach in terms of risk for relapses,[21]

therefore a gradual and individualised reduction is generally recommended.[22]

Aiming to gain a better understanding of the risks and benefits of antipsychotic maintenance treatment vs. discontinuation for functional recovery, we performed this meta-analysis

(1) to update previous meta-analyses on the overall effect of antipsychotic maintenance treatment vs. discontinuation on functional recovery in terms of social functioning and subjective quality of life by including a larger study pool,
(2) to test whether the effect between maintenance treatment vs. discontinuation is moderated by a preregistered set of study (e.g., abrupt vs. gradual discontinuation) and patient characteristics (e.g., severity of positive symptoms), and
(3) to examine the effects of antipsychotic maintenance treatment vs. discontinuation on social functioning and subjective quality of life as a function of follow-up duration.

Methods

Study design

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] The protocol was preregistered with PROSPERO (CRD42021248933). The systematic literature review was performed based on the PICO strategy[24] (patients: schizophrenia spectrum disorders, intervention: antipsychotic discontinuation/dose-reduction, comparator: antipsychotic maintenance treatment, outcome: social functioning and subjective quality of life). All deviations from protocol are listed for transparency (see Supplement S1). All study materials including quality ratings, data and analysis scripts are available online (https://osf.io/msq6k/).

Search strategy and selection criteria

PubMed, PsycINFO, Web of Science and ClinicalTrials.gov were systematically searched on 8th November 2021 and 25th June 2023 with the following search terms: (*schizophreni** OR *psychosis* OR *psychotic disorder* OR *schizoaffective*) AND (*neuroleptic** OR *antipsychotic**) AND (*discontinu** OR *withdraw** OR *maintain** OR *reduc** OR *stop** OR *cessation* OR *halt**). Additional searches were performed with Embase using the same search terms on 10th August 2023. Reference lists of included studies, relevant reviews,[7,8,20,25] and Google Scholar were used for supplementary manual searches.

Titles and abstracts of identified records were screened by LB, BS, and MP. LB, BS, and MP independently performed full-text screenings and applied inclusion criteria. Studies were eligible if they (1) assessed social functioning and/or subjective quality of life in patients with schizophrenia-spectrum disorders (i.e., schizophrenia, schizoaffective disorder, schizophreniform or delusional disorder) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD), (2) applied either full cessation or a partial reduction (min. 10%) of previously administered antipsychotic medication, (3) reported data on group differences between patients who discontinued/reduced antipsychotic medication compared to those who were continuously treated with antipsychotics, and (4)—in case of quality of life studies—used scales that assessed subjective quality of life independent of symptom severity (i.e., scales assessing symptomatology as part of quality of life were excluded to prevent confounding).

Risk-of-bias & overall quality of evidence evaluation

Risk of bias was assessed by LB and BS independently according to the guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions.[26] Randomised controlled trials (RCTs) were evaluated with the RoB 2 tool.[27] Non-randomised studies (NRS) were evaluated with the ROBIN-I tool.[28] Risk of bias due to missing evidence was rated by LB and AB independently using the ROB-ME tool.[29] Discrepancies in any risk of bias assessment were resolved by discussion with MP. The overall quality of evidence was rated by AB and MP for each outcome and separately for RCTs and NRS using the Grading of Recommendations Assessment, Development and Evaluation approach.[30]

Data extraction and effect size calculation

LB and RM independently extracted data. The final dataset was checked for inconsistencies by MP. In case of missing data, corresponding authors were contacted to obtain additional information. In NRS, adjusted effect sizes were preferred when available.

For the main outcomes, means and standard deviations of social functioning and/or subjective quality of life were transformed into standardised mean differences (SMD)[31] and corrected for overestimation using Hedge's *g*.[32] Positive SMDs indicate better outcomes in discontinuing patients, while negative SMDs reflect outcomes favouring maintenance treatment. Outcomes that were reported as categorical variables (e.g., odds ratio for functional remission) were converted to standardised mean differences ($k = 2$, see Supplement S2).[33]

If a study reported multiple outcome measures for social functioning or subjective quality of life at one follow-up assessment, these were combined at study level by calculating composite mean scores and study-level variances adjusted for dependency of observations.[33] In $k = 2$ cases[34,35] for social functioning and $k = 1$ case[36] for quality of life, composite scores were calculated based on the correlation between measures reported in the literature, whereas in $k = 3$ cases[37–39] for social functioning and $k = 2$ cases[40,41] for quality of life,

composite mean scores were calculated with the assumption of a covariation of $r = 1.0$ in lieu of any data on their covariation. Sensitivity analyses were performed testing this assumption against $r = 0.9$, $r = 0.7$, and $r = 0.5$ with no considerable changes in study effect sizes or model estimates (see Supplement S3).

Secondary outcomes included the number of adverse events (e.g., mean number of relapses and hospitalisation, adverse drug effects, somatic symptoms, general psychopathology), employment status (employed vs. unemployed), and living situation (independent vs. assisted living).

For employment status, living situation and relapse, log odds ratios were calculated and analysed. For adverse events, some studies reported continuous outcomes (i.e., adverse event questionnaire scores), for which effect sizes were converted to log odds ratios (see Supplement S2).[33]

Coding of sample characteristics and covariates

Sample characteristics included sample size, attrition rates, age, gender, illness duration (years), length of previous antipsychotic treatment (years), positive and negative symptom severity at baseline, and differences in antipsychotic mean daily dose (chlorpromazine equivalents[42]). Study characteristics included design (RCT vs. NRS), type of effect size (based on endpoint data vs. change scores from baseline), type of antipsychotic agent (first vs. second generation), degree of antipsychotic dose reduction (full vs. partial), timing of antipsychotic discontinuation (abrupt vs. gradual) and discontinuation strategy (standardised vs. individualised). Based on the length of follow-up, each study was classified as either short-term (<2 years), middle-term (2–5 years) or long-term (>5 years).

Statistics

Statistical analyses were carried out using the "metafor" package implemented in RStudio.[43] Based on the decision algorithm for the synthesis of NRS and RCTs by the International Society for Pharmacoepidemiology, three-level hierarchical random-effect models were preferred to estimate the summary effect sizes.[44] Next to the standard meta-analysis structure of participants (level 1) nested into studies (level 2), these models also nest studies into study design (RCT vs. NRS, level 3). As RCTs and NRS are likely to produce different estimates for treatment effects, these models use the first level to estimate variation within individual studies, the second level to estimate variation between studies, and the third level to estimate variation between RCTs and NRS. This allows to disentangle potential sources of between-study heterogeneity that are attributable to differences in study designs by yielding a summary effect for each distinct study design and an overall treatment effect across all study designs.

For all our outcomes that were based on RCTs and NRS, three-level mixed effect models with restricted maximum likelihood estimation (REML) and confidence intervals based on *t*-distributions were calculated. To prevent statistical overfitting, the fit of each three-level model was tested against the fit of the respective two-level solution using the Likelihood ratio test. Publication bias was assessed by visual inspection of funnel plots and Egger's regression test.[45] Sensitivity analyses were done according to the outlier and influence diagnostics procedure for meta-analyses.[46] Where analyses were indicative of significant outliers, the leave-one-out method was applied. Between-study heterogeneity was assessed using the multilevel I^2 index.[47] Moderator analyses were carried out by calculating three-level mixed effect models including the interaction term of treatment and the respective moderator variable. Models including subsamples of only RCTs or NRS were calculated using the standard 2-level structure for meta-analysis. All cases where 2-level meta-analyses were calculated are highlighted as such.

For the test of the overall effect of antipsychotic maintenance vs. discontinuation as well as for the moderator analyses, effect sizes from the latest follow up per study were analysed. To test for a time-dependent effect of antipsychotic maintenance vs. discontinuation, subgroup analyses were performed for each follow-up period (short-term, middle-term, long-term). To account for potential confounding between trial design and follow-up duration, additional two-level linear meta-regression models with random effects and REML were calculated to predict effect-size magnitudes as a function of follow-up duration and the interaction between length of follow-up duration and study design (RCT vs. NRS).

All main analyses were repeated with two-level random effects models with equally weighted effects to test robustness of findings against small subgroup analyses.[48] Results from these stability analyses are reported in case of divergence from the corresponding weighted analysis (see Supplement S21 for full stability analyses).

Role of funding source

This study did not receive any external funding or financial support.

Results

A total of $k = 35$ studies ($N = 5924$; 41% female) were included. The PRISMA flow-chart is depicted in Fig. 1. Twenty-six studies were RCTs and nine were NRS. Twenty-two studies deployed full discontinuation (63%), eight a partial dose-reduction (23%), and five a combination of both (14%). Observation periods ranged from one month to 15 years. Twenty-six studies (74%) reported short-term follow-ups (i.e., <2 years), seven (20%)

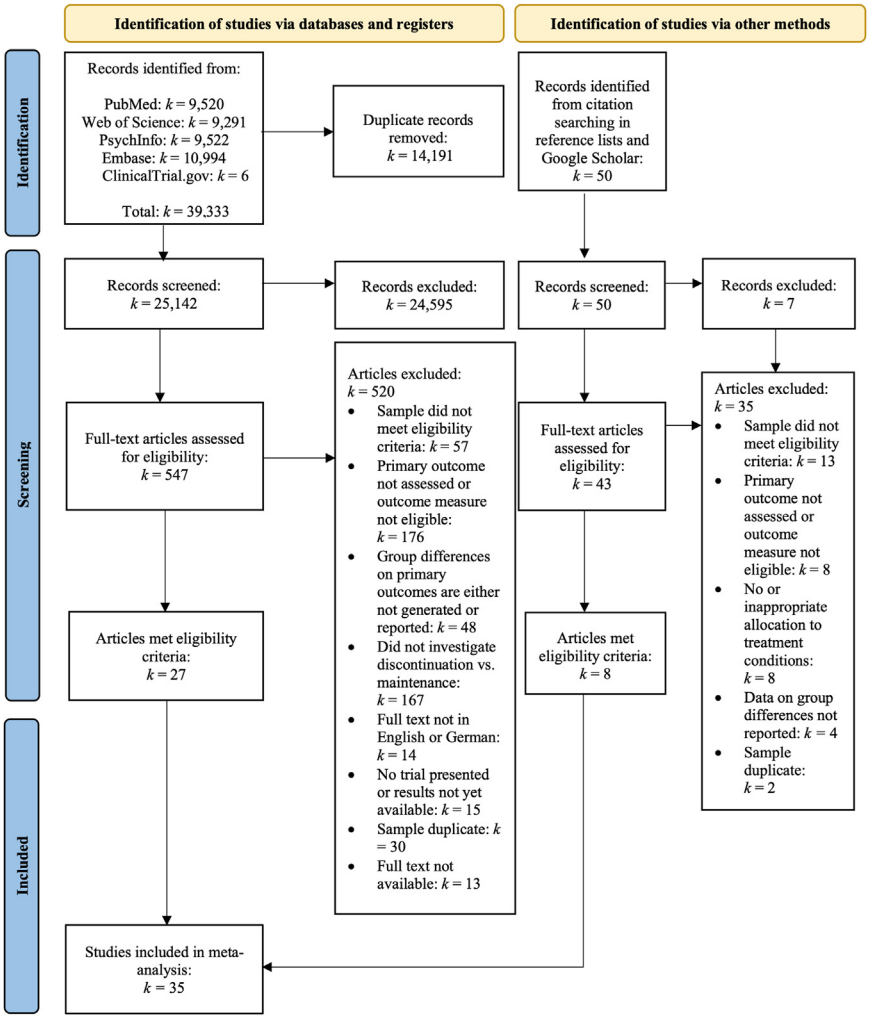

Fig. 1: PRISMA flow chart.

and two (6%) reported middle- and long-term follow-ups, respectively. Most study sites were located in European (24 sites), North American (17 sites), and Asian countries (17 sites). African and South American countries and Australia were represented with five, two and one study sites, respectively. Detailed study characteristics can be found in Table 1.

Examination of the study designs revealed that NRS primarily comprised naturalistic comparisons between patients who discontinued their medication and those continuing maintenance treatment. NRS in our study pool typically have significantly longer follow-up periods than RCTs. Therefore, most studies with middle-term follow-up (2–5 years, k = 4 of 7) and long-term follow-up (>5 years, k = 2 of 2) are NRS. In contrast, about half of the RCTs (k = 12, n = 2850) are placebo-controlled efficacy trials that examined the effect of antipsychotic medication on relapse prevention. These trials[34,36,49–54,56,59,62,65] included only patients who (1) were successfully treated with an antipsychotic during a prior stabilisation phase and (2) abruptly discontinued this medication after randomisation to the placebo/discontinuation group. In addition, unlike the NRS, (3) study participation was terminated for participants experiencing relapse (usually defined as an increase in psychotic symptoms, suicidality, or aggression, or admission to a psychiatric hospital). In these cases, the last assessment of social functioning or subjective quality of life at the time of relapse was included as the endpoint.

Thirty-two studies (N = 5330; discontinuing: n = 2351; maintaining: n = 2979; 41% female; age: M = 34.89 years, SD = 7.63, illness duration: M = 11.94 years, SD = 8.12) provided data on social functioning using eleven different scales (see Supplement S4). The likelihood ratio test indicated a better fit of a three-level

Study	*n* [% female]	Effect size *SMD* [95% CI]	Design	Follow-up[a]	Antipsychotic agent(s)	Study procedure	Degree of discontinuation	Outcome	Scale	Risk of bias
Randomised controlled trials										
Beasley et al. (2006)[49]	304 [47%]	−0.95 [−1.20 to −0.69]	RCT	Short-term	Olanzapine (oral)	Double-blind placebo treatment after 8-week stabilisation on Olanzapine	Full dose reduction	Social functioning	QLS	Serious
Berwaerts et al. (2015)[50]	305 [25%]	−0.45 [−0.68 to −0.22]	RCT	Short-term	Paliperidone palmitate (3-month formulation)	Double-blind placebo injection after 12-week open-label maintenance phase	Full dose reduction	Social functioning	PSP	Moderate
Carpenter et al. (1999)[38]	50 [28%]	0.50 [−0.11 to 1.10]	RCT	Short-term	Fluphenazine decanoate Injections	Double-blind injection either every 2 or placebo with active injection every 6 weeks	Partial dose reduction	Social functioning	LSF, QLS	Moderate
Durgam et al. (2016)[51]	200 [34%]	−0.55 [−0.83 to −0.27]	RCT	Short-term	Cariprazine (oral)	Double-blind placebo treatment after 2–4 weeks of hospitalization and open-label stabilisation	Full dose reduction	Social functioning	PSP	Serious
Fleischhacker et al. (2014)[52]	385 [40%]	−0.23 [−0.44 to −0.02]	RCT	Short-term	Aripiprazole (once monthly)	Double-blind placebo injection after 12–36-week stabilisation phase	Full dose reduction	Social functioning	PSP	Serious
Fleischhacker et al. (2017)[34]	197 [39%]	−0.42 [−0.70 to −0.14]	RCT	Short-term	Brexpiprazole (oral)	Double-blind placebo treatment after 12–36-week stabilisation phase	Full dose reduction	Social functioning	PSP	Serious
Fu et al. (2015)[53]	334 [49%]	−0.14 [−0.35 to 0.08]	RCT	Short-term	Paliperidone (once monthly)	Double-blind placebo injection after 12-week open-label stabilisation phase	Full dose reduction	Social functioning	PSP	Serious
Gaebel et al. (2011)[40]	44 [43%]	−1.24 [−1.89 to −0.60]	RCT	Short-term	Risperidone or haloperidol	Stepwise dose reduction (3 months) with intermittent treatment	Full dose reduction	Social functioning	GAF	Serious
		−0.40 [−1.00 to −0.19]						Quality of life	LQo, LP, SWN	
Herz et al. (1991)[37]	54 [47%]	−0.12 [−0.68 to 0.45]	RCT	Middle-term	First generation antipsychotics	Double-blind placebo treatment with intermittent antipsychotic medication	Full dose reduction	Social functioning	GAF, PAS	Serious
Hough et al. (2010)[54]	408 [46%]	−0.46 [−0.66 to −0.27]	RCT	Short-term	Paliperidone palmitate (once monthly)	Double-blind placebo injection after 12-week open-label maintenance phase	Full dose reduction	Social functioning	PSP	Serious
Howard et al. (2018)[36]	34 [73%]	0.04 [−0.53 to 0.61]	RCT	Short-term	Amisulpride (oral)	Abrupt withdrawal from amisulpride and switch to placebo	Full dose reduction	Quality of life	EQ-5D, WHOQOL-BREF	Moderate
Huhn et al. (2021)[55]	19 [40%]	−0.24 [−1.15 to −0.68]	RCT	Short-term	No restrictions (excl. clozapine)	Gradual dose reduction adapted for each patient individually and complete withdrawal if possible	Partial dose reduction	Social functioning	PSP	Low
		−0.15 [−1.03 to −0.73]						Quality of life	SWN	
Kramer et al. (2007)[56]	205 [41%]	−0.43 [−0.71 to −0.16]	RCT	Short-term	Paliperidone (ER)	Double-blind placebo treatment after 6-week open-label stabilisation phase	Full dose reduction	Social functioning	PSP	Serious
		−0.30 [−0.58 to −0.02]						Quality of life	S-QoL	
Liu et al. (2023)[57,c]	75 [54%]	1.28 [0.75–1.80]	RCT	Middle-term	Chlorpromazine equivalent	Patients were randomised 2:1 into guided dose reduction group vs. maintenance treatment group and a group of naturalistic maintenance controls	Mixed	Social functioning	PSP	Serious
								Quality of life	EQ-5D-VAS	
Mueser et al. (2001)[58]	313 [34%]	0.09 [−0.15 to 0.32]	RCT	Middle-term	Fluphenazine decanoate (every 2 weeks)	Low-dose or intermittent treatment (placebo) after 16–24-week stabilisation phase	Mixed (targeted treatment/low dose)	Social functioning	SAS-II	Serious
NCT01435928 (2011)[59]	246 [38%]	−0.24 [−0.49 to 0.01]	RCT	Short-term	Lurasidone (oral)	Double-blind placebo treatment after a stable dose of lurasidone for at least 4 weeks	Full dose reduction	Social functioning	SLOF (modified)	Serious
		−0.26 [−0.49 to −0.02]						Quality of life	EQ-5D	
Ozawa et al. (2019)[60]	35 [34%]	0.50 [−0.18 to 1.17]	RCT	Short-term	Risperidone, olanzapine (oral)	Model-guided dose reduction to individually estimated target dose	Partial dose reduction	Social functioning	GAF	Moderate
Rouillon et al. (2008)[61]	97 [32%]	0.16 [−0.24 to 0.56]	RCT	Short-term	Olanzapine (oral)	Partial dose reduction adapted for each patient individually	Partial dose reduction	Quality of life	S-QoL	Serious
Rui et al. (2014)[62]	135 [59%]	−0.55 [−0.90 to −0.21]	RCT	Short-term	Paliperidone (ER)	Double-blind placebo treatment following a 6-week open-label stabilisation phase	Full dose reduction	Social functioning	PSP	Serious

(Table 1 continues on next page)

Study	*n* [% female]	Effect size *SMD* [95% CI]	Design	Follow-up[a]	Antipsychotic agent(s)	Study procedure	Degree of discontinuation	Outcome	Scale	Risk of bias
(Continued from previous page)										
Shenoy et al. (1981)[63]	28 [0%]	−1.23 [−2.04 to −0.41]	RCT	Short-term	Fluphenazine decanoate (every 3 weeks)	6-week "drug holiday" (double-blind placebo treatment) after 2-year treatment	Full dose reduction	Social functioning	GAF	Moderate
Stürup et al. (2022)[39]	25 [59%]	0.31 [−0.34 to 0.96]	RCT	Short-term	Antipsychotic medication (oral or long-acting injection)	25% monthly reduction of baseline dose	Mixed	Social functioning	PSP	Low
		0.41 [−0.38 to 1.20]						Quality Of life	WHO-5	
Takeuchi et al. (2014)[41]	61 [39%]	−0.04 [−0.45 to 0.37]	RCT	Short-term	Risperidone and olanzapine (oral)	Gradual dose reduction after clinical stabilization for at least 4 months	Partial dose reduction	Quality of life	SW, EQ-HRQOL EQ-VAS	Moderate
Uchida et al. (2006)[64]	34 [59%]	−0.12 [−0.79 to 0.56]	RCT	Short-term	*Not reported*	Dose reduction for 12 weeks (41.3% reduction) followed by low dose maintenance treatment for 24 weeks	Partial dose reduction	Social functioning	GAF	Moderate
Weiden et al. (2016)[65]	301 [41%]	−0.28 [−0.51 to −0.06]	RCT	Short-term	Iloperidone (oral)	Double-blind placebo treatment after 14–24-week open-label stabilization phase	Full dose reduction	Social functioning	SDS	Serious
Wiedemann et al. (2001)[35]	51 [39%]	−0.03 [−0.50 to 0.44]	RCT	Short-term	49% clozapine, 51% typical antipsychotics	Gradual dose reduction of 50% every two weeks (intermittent treatment)	Partial dose reduction	Social functioning	SAS GAF	Serious
Yamanouchi et al. (2014)[66]	105 [41%]	−0.10 [−0.48 to 0.28]	RCT	Short-term	First and second generation antipsychotics	Gradual dose reduction for a period of 12 weeks based on the judgments of the attending physician	Partial dose reduction	Social functioning	GAF	Serious
		0.06 [−0.32 to 0.45]						Quality of life	EQ-5D-TTO	
Non-randomised studies										
Albert et al. (2019)[67,b]	189 [50%]	0.63 [0.32–0.94]	NRS	Short-term	95% second generation antipsychotics	No antipsychotic treatment within the last month prior to follow-up	Full dose reduction	Social functioning	PSP	Serious
Álvarez-Jiménez et al. (2012)[68]	209 [27%]	1.13 [0.75–1.51]	NRS	Middle-term	*Not reported*	No antipsychotic medication for at least 2 years	Full dose reduction	Social functioning	QLS	Serious
Fountoulakis et al. (2019)[69]	98 [42%]	0.04 [−0.56 to 0.64]	NRS	Short-term	*Not reported*	Antipsychotic treatment at baseline/not naïve and without antipsychotic treatment at follow-up	Full dose reduction	Social functioning	GAF	Serious
Harrow & Jobe (2007)[70]	53 [34%]	1.02 [0.42–1.62]	NRS	Long-term	*Not reported*	Not on any psychiatric medication at the respective follow-up assessment	Full dose reduction	Social functioning	LKP	Serious
Malla et al. (2022)[71]	221 [57%]	0.46 [0.19–0.73]	NRS	Middle-term	Chlorpromazine equivalent	Between months 4 and 24 of treatment, 107 patients discontinued medication as compared to 146 who stayed on medication	Mixed	Social functioning	SOFAS	Serious
Moilanen et al. (2013)[72]	70 [46%]	1.03 [0.51–1.55]	NRS	Short-term	*Not reported*	Patients are grouped into 'non-medicated' vs. 'medicated' according to the previous 3 months	Full dose reduction	Social functioning	SOFAS	Serious
Mustafa et al. (2018)[73]	230 [29%]	−0.14 [−0.45 to 0.17]	NRS	Short-term	Second generation antipsychotics	Antipsychotics were not prescribed for at least one month	Full dose reduction	Social functioning	SOFAS	Serious
Wils et al. (2017)[74]	303 [45%]	1.05 [0.80–1.29]	NRS	Long-term	*Not reported*	Patients without antipsychotic medication at the 10-year follow-up of the Danish OPUS trial	Full dose reduction	Social functioning	GAF	Serious
Wunderink et al. (2013)[18]	103 [31%]	0.69 [0.21–1.18]	NRS	Middle-term	*Not reported*	Patients who were originally allocated to antipsychotic dose reduction	Mixed (targeted treatment)	Social functioning	GSDS	Moderate

Note. EQ-5D = EuroQol 5 dimensions; EQ-HRQOL = EuroQol-health Related Quality of Life; EQ-5D-TTO = EuroQol-5D with time-trade-off evaluation; EQ-5D-VAS = EuroQol-5D Visual Analog Scale; EQ-VAS = EuroQol-Visual Analogue Scale; ER = Extended Release Tablets; GAF = Global Assessment of Functioning; GSDS = Groningen Social Disability Schedule; LKP = Levenstein-Klein-Pollack Scale; LQoLP = Lancashire Quality of Life Profile; LSF = Level of Functioning Scale; NRS = Non-Randomised Study; PAS = Problem Appraisal Scale; PSP = Personal and Social Performance Scale; QLS = Heinrich-Carpenter Quality of Life Scale; RCT = Randomised-Controlled Study; SAS = Social Adjustment Scale; SDS = Sheehan Disability Scale; SF-36-MH = 36-item short form—mental health; SLOF = Specific Levels of Functioning Scale; SOFAS = Social and Occupational Functioning Scale; S-QoL = Schizophrenia Quality of Life Scale; SWN = Subjective Well-Being Under Neuroleptic Treatment Scale; WHO-5 = World Health Organization Wellbeing Index; WHOQOL-BREF = World Health Organization Quality of Life-BREF. [a]Short-term = less than 2 years; Middle-term = 2–5 years; Long-term = more than 5 years. [b]The study by Albert et al.[67] only entered the analysis of short-term follow-ups because of a sample duplicate with Wils et al.[74] [c]Naturalistic cohort was not included in this meta-analysis.

Table 1: **Table of study characteristics.**

model than of a two-level model ($\chi^2 = 11.45$, $p < 0.001$). The pooled three-level effect between maintenance vs. discontinuation/dose-reduction was not significant ($k = 32$; $N = 5330$; $SMD = 0.20$; $SE = 0.44$; $T = 0.46$; $p = 0.646$; 95% CI [–0.69 to 1.10]). The estimated variance components were $\tau^2_{Level\ 3} = 0.369$ and $\tau^2_{Level\ 2} = 0.194$, indicating that $I^2_{Level\ 3} = 62.5\%$ of the total variation can be attributed to the study design (RCT vs. NRS), and $I^2_{Level\ 2} = 32.85\%$ to within-study heterogeneity. As can be seen in Fig. 2, the effect was significantly moderated by study design with RCTs significantly favouring maintenance and NRS significantly favouring discontinuation (2-level meta-analysis testing study design as moderator: $SMD_{Mod} = -0.89$: $SE = 0.19$; $T = -4.69$; $p < 0.001$; 95% CI [–1.27 to –0.50]). Visual inspection of the funnel plot (see Supplement S5) did not indicate publication bias and Egger's regression test (using a 2-level meta-analysis model) did not suggest funnel plot asymmetry ($Z = 0.59$, $p = 0.557$). Results of sensitivity analyses did not reveal any significant outliers (see Supplement S6).

Results of moderator analyses for social functioning are summarised in Table 2. Significant moderator effects were found for timing of discontinuation (abrupt vs. gradual) and degree of dose reduction (full vs. partial vs. mixed). Subgroup analyses revealed that abrupt discontinuation showed effect sizes favouring maintenance treatment and that a mixed approach including guided reduction or target medication strategies favours reduction. The equal weight stability analyses confirmed the moderation effect by timing of discontinuation ($k = 24$; $N = 3957$; $SMD = 0.48$; $p = 0.026$) and degree of dose-reduction ($k = 32$; $N = 4706$; $SMD_{full\text{-}vs\text{-}mixed} = 0.56$; $p = 0.033$) and yielded a significant moderation effect by discontinuation strategy ($k = 32$; $N = 5330$; $SMD = 0.53$; $p = 0.014$), indicating that studies with individualised dose-reduction schemes favour discontinuation and studies with standardised dose-reduction favour maintenance.

Twenty-six studies (discontinuing: $n = 1951$; maintaining: $n = 2415$; study-type: $k_{RCT} = 22$, $k_{NRS} = 4$; risk of bias: $k_{low} = 7$, $k_{moderate} = 11$, $k_{serious} = 7$, $k_{NI} = 1$) provided data on social functioning with follow-ups of less than 2 years. The three-level summary effect did not indicate a significant difference in social functioning between antipsychotic maintenance and discontinuation ($k = 26$; $n = 4366$; $SMD = -0.01$; $SE = 0.34$; $T = 0.04$; $p = 0.965$; 95% CI [–0.68 to 0.71]). The estimated variance

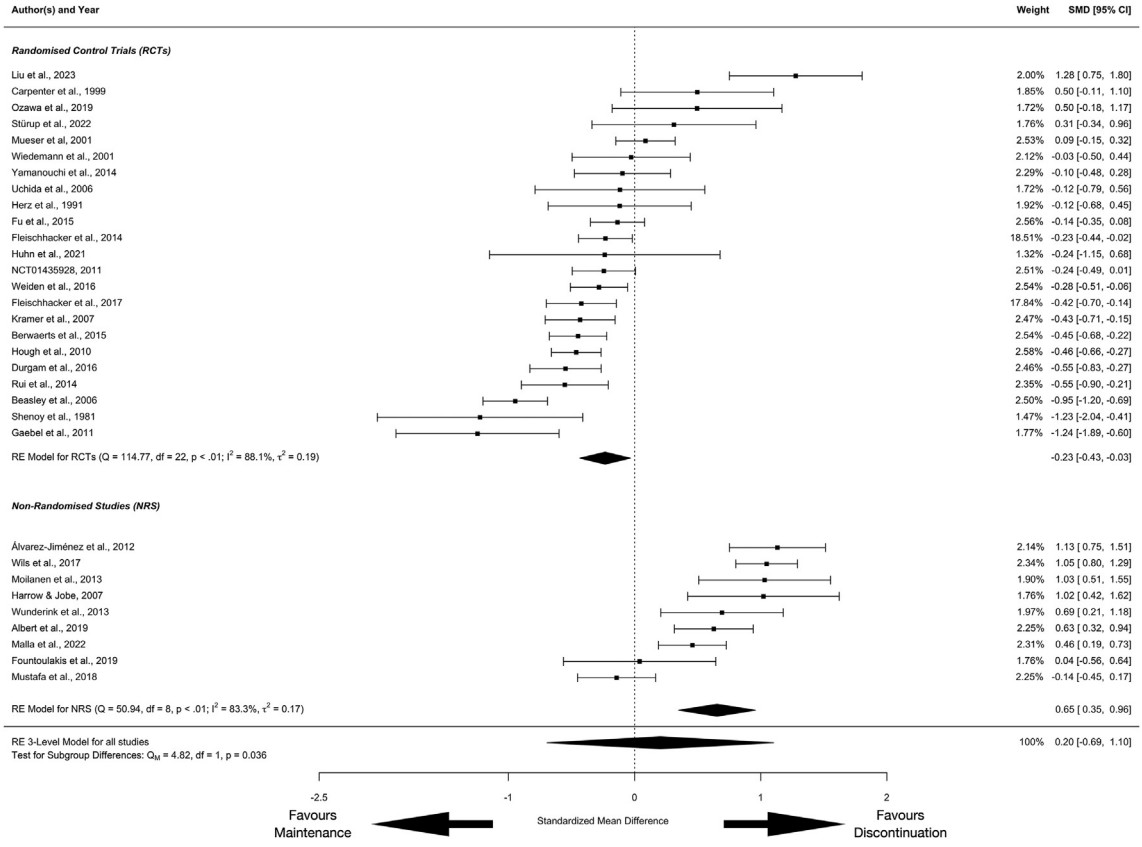

Fig. 2: Summary effect of antipsychotic maintenance vs. discontinuation/dose-reduction on social functioning, SMD = Standardised Mean Difference, $k = 31$, $N = 5141$.

Test of moderator effect estimate								Follow-up tests for subgroups (significant moderation only)			Test of effect				
Moderator	k	n	SMD	SE	T	95% CI	p[a]	Subgroup name	k	n	SMD	SE	T	95% CI	p[a]
Type of effect size	32	5330	0.19	0.13	1.44	−0.08, 0.45	0.129	Pre-to-post change difference	15	3221	–				
								Difference at endpoint	17	2109	–				
Antipsychotic agent discontinued	21	4066	−0.26	0.23	−1.14	−0.73, 0.21	0.226	1st gen. AP	4	445	–				
								2nd gen. AP	17	3621	–				
Timing of discontinuation	24	3957	**0.46**	**0.20**	**2.27**	**0.04, 0.89**	**0.034**	Abrupt discontinuation[b]	14	3411	**−0.38**	**0.09**	**−4.45**	**−0.57, −0.20**	**0.001**
								Tapering off	10	546	0.11	0.21	0.52	−0.37, 0.58	0.616
Route of administration	19	2928	−0.20	0.13	−1.47	−0.48, 0.09	0.161	Oral AP	12	2105	–				
								Depot AP	7	1823	–				
Discontinuation strategy[c]	32	5330	−0.18	0.22	−0.79	−0.63, 0.28	0.440	Individualised strategy	17	2132	0.26	0.39	0.67	−0.57, 1.10	0.513
								Standardised strategy[b]	15	3198	−0.26	0.13	−1.90	−0.55, 0.03	0.078
Degree of dose reduction[c]	32	4706						Full discontinuation	21	4298	0.09	0.58	0.16	−0.41, 0.17	0.975
Full vs. partial			0.23	0.12	1.95	−0.01, 0.48	0.061	Partial reduction[b]	6	295	0.06	0.11	0.50	−0.24, 0.35	0.641
Full vs. mixed			**0.56**	**0.09**	**6.59**	**0.39, 0.73**	**<0.001**	Mixed	5	737	0.54	0.20	2.68	−0.02; 1.09	0.055
CPZ	22	3153	−0.00	0.00	−0.59	−0.00, 0.01	0.562	–	–	–	–				
Illness duration	24	4354	−0.00	0.10	−0.04	−0.22, 0.22	0.970	–	–	–	–				
Positive symptom severity	18	2452	0.07	0.13	0.52	−0.21, 0.34	0.614	–	–	–	–				
Negative symptom severity	17	2399	0.11	0.12	0.91	−0.15, 0.36	0.377	–	–	–	–				

Note. RCT = Randomised-Controlled Trials; NRS = Non-Randomised Studies; SMD = Standardised Mean Difference; SE = Standard Error; AP = Antipsychotic; CPZ = Chlorpromazine equivalents. [a]The level of statistical significance was set at $p < 0.05$. Significant effects are printed in bold. [b]Moderator analyses were done without a three-level nested structure. [c]Significance of this moderation effect was limited to the main analyses or the stability analyses only. Subgroups were calculated even when the significance was only found in one of the two approaches.

Table 2: **Summary of moderator analyses for social functioning.**

components were $\tau^2_{Level\ 3} = 0.202$ and $\tau^2_{Level\ 2} = 0.117$, indicating that $I^2_{Level\ 3} = 58.49\%$ of the total variation can be attributed to the study design (RCT vs. NRS), and $I^2_{Level\ 2} = 33.82\%$ to within-study heterogeneity. The moderator test for study design was not significant ($Q_M = 3.20$, $p = 0.086$). However, subgroup analyses revealed that short-term RCTs significantly favoured maintenance ($SMD = -0.30$; $SE = 0.08$; $Z = -3.98$; $p = 0.001$; 95% CI [−0.45 to −0.15]), whereas the difference between maintenance and discontinuation/dose-reduction was non-significant in short-term NRS ($SMD = 0.38$; $SE = 0.27$; $Z = 1.43$; $p = 0.249$; 95% CI [−0.14 to 0.91]).

Seven studies (discontinuing: $n = 504$; maintaining: $n = 528$; study-type: $k_{RCT} = 3$, $k_{NRS} = 4$; risk of bias: $k_{serious} = 6$, $k_{moderate} = 1$) provided data on social functioning with follow-ups between 2 and 5 years. The three-level summary effect indicated a significant effect on social functioning in favour of discontinuation/dose-reduction ($k = 7$; $n = 1032$; $SMD = 0.68$; $SE = 0.25$; $T = 2.70$; $p = 0.036$; 95% CI [0.06 to1.28]). The estimated variance components were $\tau^2_{Level\ 3} = 0.034$ and $\tau^2_{Level\ 2} = 0.267$, indicating that $I^2_{Level\ 3} = 10.11\%$ of the total variation can be attributed to the study design (RCT vs. NRS), and $I^2_{Level\ 2} = 78.56\%$ to within-study heterogeneity. The moderator test for study design was not significant ($Q_M = 0.81$, $p = 0.409$). However, subgroup analyses revealed that middle-term NRS significantly favoured discontinuation/dose-reduction ($SMD = 0.89$; $SE = 0.21$; $Z = 4.09$; $p = 0.026$; 95% CI [0.20 to 1.58]), whereas the difference between maintenance and discontinuation/dose-reduction was non-significant in middle-term RCTs ($SMD = 0.41$; $SE = 0.42$; $Z = 0.96$; $p = 0.026$; 95% CI [−0.43 to 1.24]).

Two studies (discontinuing: $n = 139$; maintaining: $n = 217$; study-type: $k_{NRS} = 2$; risk of bias: $k_{serious} = 2$) provided data on social functioning with follow-ups beyond 5 years. Because both long-term studies were NRS, a two-level model was calculated. The summary effect indicated a significant difference in social functioning in favour of antipsychotic discontinuation/dose-reduction ($k = 2$, $n = 356$; SMD = 1.04; SE = 0.12; Z = 9.03; $p < 0.001$; 95% CI [0.82 to 1.27]). Between-study heterogeneity was not significant ($Q = 0.01$; $p = 0.94$) with $I^2 = 0.0\%$. Forest plots of subgroup analyses can be found in the Supplement S7–S9.

The interaction between follow-up duration and study design on effect size magnitude was significant (2-level meta-regression: $k = 32$; $n = 5330$; $b = 0.04$; $SE = 0.01$; $Z = 2.75$; $p = 0.010$; 95% CI [0.01 to 0.07]). For RCTs, effect sizes at short-term follow-ups were significantly negative, favouring maintenance ($k = 23$; $n = 3854$; intercept: $b = -0.65$; $SE = 0.15$; $Z = -4.23$; $p < 0.001$; 95% CI [−0.95 to −0.35]). With increasing follow-up length, RCT effect sizes increased significantly in favour of discontinuation/dose-reduction (slope: $b = 0.04$; $SE = 0.01$; $Z = 3.18$; $p = 0.002$; 95% CI [0.02 to 0.07]). For NRS, effect sizes were in favour of discontinuation/dose-reduction with no significant change over follow-up length ($k = 9$; $n = 1476$; intercept:

$b = 0.53$; $SE = 0.19$; $Z = 2.84$; $p = 0.005$; 95% CI [0.17 to 0.90]; slope: $b = 0.003$; $SE = 0.003$; $Z = 1.10$; $p = 0.272$; 95% CI [–0.003 to 0.010]). See Fig. 3 for a depiction of effect-size magnitudes by follow-up length and study design.

Ten studies (N = 943; discontinuing: n = 484; maintaining: n = 459; 42% female; age: M = 43.05 years, SD = 10.05; illness duration: M = 16.91 years, SD = 8.14) provided data on subjective quality of life using seven different scales (see Supplement S10). As all studies had a RCT design and since all but one trial[57] were classified as short-term trials (<2 years), two-level models were calculated without further subgroup analyses on follow-up length. As can be seen in Fig. 4, the summary effect did not indicate a significant difference in subjective quality of life between antipsychotic maintenance and discontinuation/dose-reduction (k = 10; n = 943; SMD = –0.004; SE = 0.11; Z = 0.94; p = 0.971; 95% CI [–0.22 to 0.21]). Between-study heterogeneity was significant (Q = 20.14; $p < 0.05$) with I^2 = 57.60%. Visual inspection of the funnel plot (see Supplement S11) did not indicate publication bias and Egger's regression test did not suggest funnel plot asymmetry (Z = 1.15, p = 0.25). Sensitivity analyses identified the Liu et al. study as a significant outlier (see Supplement S12). Leave-one-out analyses showed a similar pattern with no difference between discontinuation/dose-reduction and maintenance (k = 9; n = 868; SMD = –0.12; p = 0.14; 95% CI [–0.27 to 0.04]).

As for our secondary outcomes, reporting of adverse events varied significantly across studies from broad descriptions to standardised assessment of treatment emergent adverse events (see Supplement S13 for detailed adverse event reporting). Overall, the probability of experiencing an adverse event did not differ significantly between the discontinuation/dose-reduction and the maintenance treatment groups (k = 27, n = 3,662, OR = 0.79; p = 0.248; 95% CI [–0.52 to 1.20]).

Participants who discontinued antipsychotic medication were more likely to be employed compared to participants who maintained antipsychotic treatment (k = 3, n = 426, OR = 3.84, $p < 0.001$; 95% CI [2.13 to 6.93]).

Given the major concerns regarding relapses following discontinuation, we also included a separate analysis of risk of relapse (relapse vs. no relapse at follow up) as an additional secondary outcome post-hoc. The risk for a relapse following discontinuation did not differ between participants who discontinued vs. maintained antipsychotic treatment (k = 29, n = 4662, OR = 1.50, p = 0.603; 95% CI [0.31 to 7.33]). However, subgroup 2-level meta-analyses showed that whilst no differences were found for NRS (k = 5, n = 692, OR = 0.66, p = 0.343; 95% CI [0.28 to 1.57]), relapse was more likely after discontinuation than maintenance in RCTs (k = 24, n = 3970, OR = 3.26, $p < 0.001$; 95% CI [2.33 to 4.56]). This difference became smaller, yet remained significant when all of the 12 aforementioned abrupt-switch placebo controlled efficacy trials were removed (k = 13, n = 933, OR = 1.65, p = 0.017; 95% CI [1.11 to 2.45]).

Forest plots for adverse events, employment status and risk of relapse can be seen in Supplement S14–S16. An integrated effect on patients' living condition could not be calculated as only one study provided corresponding data.[67]

During risk of bias evaluation, 25 studies (71%) were rated as at serious, eight studies (23%) as at moderate and two studies (6%) as at low risk of bias. For RCTs, the overall risk of bias was high in 65% of the trials and low in only 8%. Most common concerns were based on potential bias due to missing outcome data (item D3) and bias in measurement of the outcome (item D4). For NRS, risk of bias was high for 89% of the studies. Most common concerns were based on potential bias due to confounding (item D1) and bias due to missing data (item D5). Risk of bias did not moderate the effect of maintenance vs. discontinuation/dose-reduction on social functioning ($F_{(2,29)}$ = 0.933; p = 0.405) or subjective quality of life (Q_M = 0.189; p = 0.910).

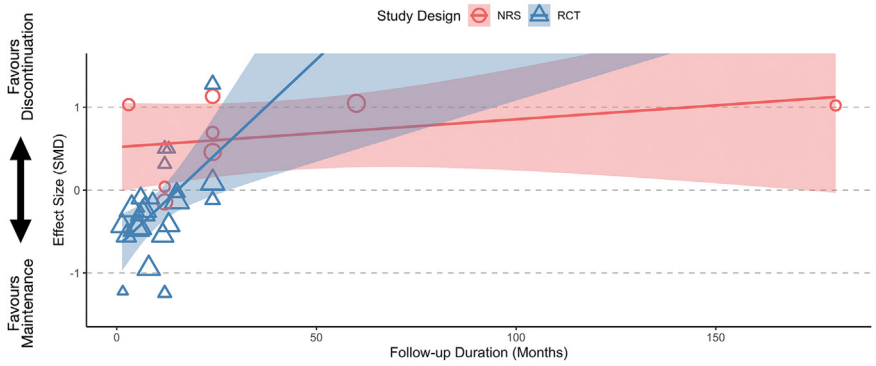

Fig. 3: Time-dependent effect of antipsychotic maintenance by study design. Size of data points indicates study weights. RCT = Randomised-Controlled Trial, NRS = Non-Randomised Study.

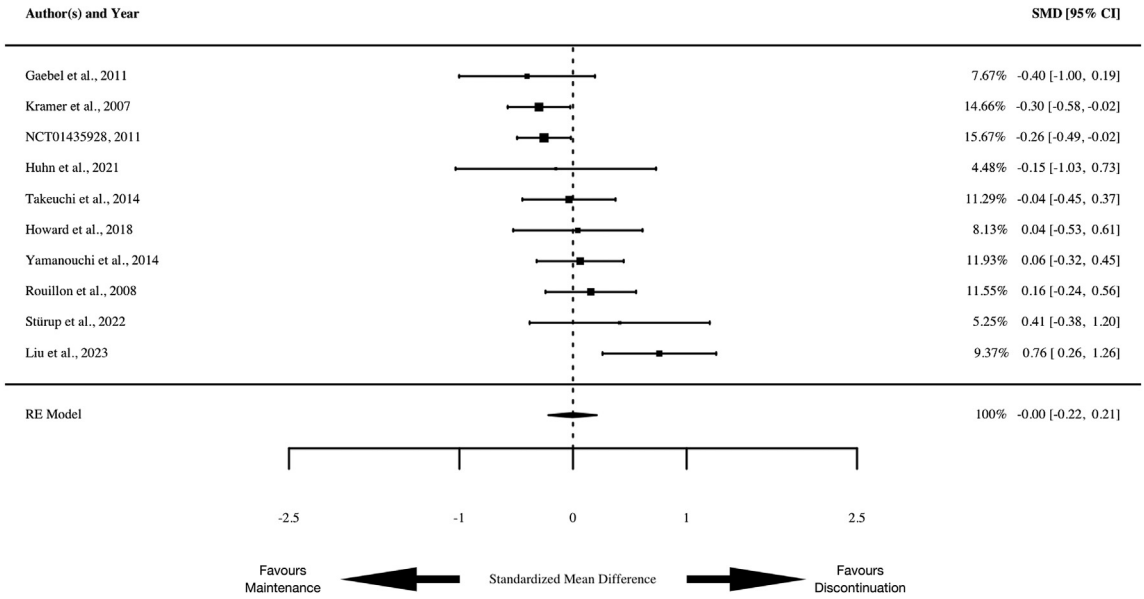

Fig. 4: Summary effect of antipsychotic maintenance vs. discontinuation/dose-reduction on subjective quality of life. SMD = Standardised Mean Difference.

With respect to the follow-up length subgroups, it needs noting that for moderate follow-up length, six[37,57,58,68,70,71] of the seven studies were rated at high and one at a moderate risk of bias.[18] For long follow-up lengths, all included studies[70,74] were rated as at serious risk of bias (see Supplement S17 and S18 for details). Thus, risk of bias is more extreme for longer follow-up intervals.

The risk of bias due to missing evidence was rated as low for both social functioning and subjective quality of life. Although we identified signs of potentially missing evidence in 28 studies (k = 17 social functioning, k = 7 quality of life, k = 4 both outcomes), non-reporting was likely attributable to non-significant p-values (i.e., null-findings), matching the current meta-analytic findings. Thus, it is unlikely that these missing studies biased the pooled effect size estimates of the present meta-analyses (see Supplement S17–S19 for detailed risk of bias ratings).

The certainty of evidence was rated as very low for all outcomes and for both study types (RCTs and NRS), with the dimension of risk of bias, inconsistency and imprecision being rated negatively for all/most of the outcomes (see Supplement S20 for more details).

Discussion

This meta-analysis sought to investigate the time-dependent effect of antipsychotic maintenance treatment vs. discontinuation/dose-reduction and to update previous meta-analyses on the overall effect of antipsychotic maintenance vs. discontinuation/dose-reduction on social functioning and subjective quality of life in patients with schizophrenia-spectrum disorders.

The subgroup analyses by length of follow-up were indicative of a time-dependent effect on social functioning in favour of discontinuation/dose-reduction. Whilst short-term studies (<2 years) favoured maintenance treatment, antipsychotic discontinuers showed increased social functioning in middle- and long-term follow-ups. However, caution is warranted as the number of studies with middle-term (k = 7) and long-term follow-ups (k = 2) was critically low. In addition, most of the middle- and all of long-term studies had a non-randomised study design and a high risk of bias. Typical reasons for this are the inherent possibilities of self-selection bias in naturalistic study designs. For example, less severely impaired participants might opt for or persist with discontinuation more frequently, show more favourable outcomes at baseline than participants in RCTs, which could account for the association of discontinuation and favourable outcomes in these studies. Finally, it needs noting that GRADE ratings indicated the overall quality of evidence to be very low for all main outcomes. Thus, there is a substantial possibility that the true effects diverge from the estimated effects.

In support of the validity of our effects, however, we did not find evidence that the study design or the risk of bias moderated the effect of maintenance vs. discontinuation/dose-reduction on social functioning in the subgroup analyses. Furthermore, the stability analyses confirmed the robustness of effects and the meta-regression analyses predicting effect sizes on social

functioning by months of follow-up supported the putative time-dependent effect in favour of discontinuation/dose-reduction with increasing follow-up length. Notably, this was predominantly evident in the RCT subgroup, yet with a limited maximum follow-up length of seven, but mostly less than two years.[37,58] Specifically, RCTs with short follow-ups favoured maintenance, whereas RCTs with longer follow-ups reported increased effect sizes in favour of discontinuation/dose-reduction. Taken together, our findings extend the picture provided by previous short-term meta-analyses[7,8] and complement findings of a systematic review[75] suggesting a time-dependent decrease in the effect of antipsychotic maintenance treatment on functional recovery. This pattern seems to indicate that negative discontinuation/dose-reduction effects may be of short-term nature, whilst with increasing time, discontinuation/dose-reduction could benefit long-term recovery in terms of improved social functioning.

However, some important limitations of existing studies became evident: Almost half of the RCTs were placebo-controlled efficacy trials for antipsychotic medication, in which the discontinuation condition was operationalised as an abrupt switch to placebo. As these trials do not compare maintenance therapy with a state-of-the-art discontinuation procedure, which would at the very least include a tapering plan, these trials do not compare maintenance and discontinuation in the sense of guided, medical interventions. Rather, antipsychotic maintenance is compared to sham-maintenance, which may bias the effects in favour of maintenance. Furthermore, all but three of these trials have only short follow-ups. The observation periods in these trials are often additionally narrowed by an analysis plan that stops the trial once a critical number of relapses occurred. Commonly, these trials show an increased rate of relapses in the "discontinuation"/sham-treatment condition that is then interpreted as evidence for the efficacy of medication. For each individual participant experiencing a relapse, this also means that follow-up outcome measures are assessed at the time of relapse and then used in a last-observation carried forward approach to impute the respective outcome at the trial's end. Consequently, outcomes such as social functioning or quality of life could be biased in either direction: On the one hand, carrying forward a mental health related assessment from a time-point of a possibly temporary symptomatic deterioration that is more prevalent in the "discontinuation"/sham-treatment condition could exaggerate the difference between maintenance and discontinuation in favour of maintenance. On the other hand, cumulative effects of repeated or prolonged phases of symptomatic deterioration that might follow relapses could take a further toll on social functioning and quality of life. In this case, the assessed outcome levels would underestimate the true difference between maintenance and discontinuation. This highlights the necessity of further high-quality RCTs with a more elaborate assessment plan and both maintenance and discontinuation conditions defined in accordance with state-of-the-art treatment recommendations to further explore possible positive and negative effects of discontinuation.

When including the entire study pool and the respective latest follow-ups, the overall effects in the present meta-analysis do not suggest significant differences in social functioning, subjective quality of life, or adverse events between patients who discontinued antipsychotic medication and those who maintained antipsychotic treatment. This contradicts previous meta-analyses that found superiority of antipsychotic maintenance treatment on social functioning and quality of life.[7,8] However, authors of previous reviews defined relapse rates and symptomatic remission as primary outcomes and therefore included fewer studies providing data on quality of life (k = 7) or social functioning (k = 15). Furthermore, previous meta-analyses explicitly focused on the comparison of maintenance vs. placebo,[7,8] whereas the aim of this meta-analysis was to evaluate discontinuation as a medical treatment option. This led to the active search for and inclusion of studies that compared antipsychotic maintenance to discontinuation in the form of guided tapering or individualised dose-reduction, which were not included in previous meta-analyses. For example, Cesaro and colleagues[7] list multiple studies that were excluded due to 'lacking an adequate placebo condition' but were eligible for our meta-analysis.[18,35,39,57] Thus, our review may provide a more comprehensive picture with a larger study pool and longer follow-up durations.

Nevertheless, the significant moderation of the overall effect by study design (RCT vs. NRS) clearly indicates that RCTs, in particular RCTs with a brief follow-up interval, favoured maintenance treatment. Additionally, there is a clear trend in the available evidence showing a decrease of the superiority of maintenance over discontinuation/dose-reduction with increasing follow-up length. However, the negative effect of discontinuation on relapse found in previous meta-analyses of RCTs[7,8] was replicated as a secondary outcome. Of importance, this result remained stable, albeit with a reduced effect size, when maintenance vs. placebo RCTs were excluded from the analysis, suggesting it is not merely the result of a sudden cessation of antipsychotic medication. Taken together, this supports the evidence of superiority of maintenance therapy within an immediate timeframe of about one year, but a delayed benefit of discontinuation on social functioning. Of note, however, such a delayed benefit of discontinuation in social functioning may still come at the cost of increased risk for symptomatic deterioration and relapse. In light of the low quality of the available evidence, there is an urgent need for high-quality studies with multiple follow-ups beyond two years to examine

the effect of maintenance vs. discontinuation/dose-reduction on functional recovery before definitive conclusions can be drawn.

Finally, moderator analyses on the overall effect on social functioning indicated that individualised and gradual procedures as well as mixed approaches of discontinuation and dose-reduction (including targeted treatment and guided reduction strategies) are the most promising methods. These therefore warrant further investigation. This is particularly interesting since meta-analyses comparing dose-reduction with discontinuation[76] or with maintenance[76,77] showed that although dose reduction is inferior to maintenance in relapse prevention, it is superior to complete discontinuation. Furthermore, a recent network meta-analysis of mostly short-term trials (83.6% with follow-ups of ≤1 year)[76] showed that reduction has an equally beneficial effect as maintenance on social functioning (vs. discontinuation, respectively). Thus, there is some tentative evidence that antipsychotic dose-reduction does not share the same short-term risks as full discontinuation. However, further research is needed to examine the effects of dose-reduction compared to full discontinuation on social functioning. This type of research could add crucial information to improve current discontinuation guideline recommendations that to date have a focus on symptomatology and relapses.[78,79]

The following limitations need to be considered: Fourteen studies were excluded because full texts were not available in English or German. Despite intercontinental distribution of study sites, we cannot rule out that this has introduced language bias in the study selection. Although our stability analyses indicated robustness of our summary effect sizes, the number of studies with middle- and long-term follow-ups, especially of RCTs, was critically low, questioning the generalisability of our findings. In addition, a third of the RCTs were evaluated at serious risk of bias. This was in large parts due to the fact that most RCTs reported only last-observation carried-forward data, because they were designed to examine relapse rates in maintenance treatment. Therefore, discontinuation groups showed a disproportionally high amount of missing data, which introduced a bias in these RCTs in favour of maintenance treatment. Also, patients with unsuccessful discontinuation/dose-reduction attempts are not adequately represented in the overall sample as these were either treated as study drop-outs in RCTs or were assigned to treatment groups in NRS.

In conclusion, this meta-analysis tentatively supports the notion of a time-dependent effect of antipsychotic maintenance treatment on functional recovery. However, due to high risk of bias and critically low number of the middle- and long-term studies, one should refrain from drawing definite conclusions on the long-term effect of antipsychotic maintenance treatment vs. discontinuation/dose-reduction on functional recovery. Therefore, our review strongly emphasizes the need for further high-quality RCTs with follow-ups beyond two years to investigate the long-term effect of antipsychotic maintenance treatment vs. discontinuation or dose reduction.

Contributors

Björn Schlier: Data curation, formal analysis, methodology, visualisation, writing–review & editing, verification of the underlying data.
Laura Buck: Conceptualisation, data curation, formal analysis, methodology, visualisation, writing–original draft, verification of the underlying data.
Rebecca Müller: Visualisation, writing–original draft.
Tania M. Lincoln: Conceptualisation, methodology, writing–review & editing.
Antonia Bott: Data curation, writing–review & editing.
Matthias Pillny: Conceptualisation, data curation, methodology, writing–original draft, supervision, project administration, verification of the underlying data.
All authors read and approved of the final version of this manuscript.

Data sharing statement

All study materials including quality ratings, data and analysis scripts (written in Rstudio) are available online (https://osf.io/msq6k/).

Declaration of interests

The authors declare that there are no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102291.

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