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Risk Factors for Psychotic Relapse After Dose Reduction or Discontinuation of Antipsychotics in Patients With Chronic Schizophrenia. A Meta-Analysis of Randomized Controlled Trials

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***Background and hypothesis*: Although maintenance treatment with antipsychotics protects against psychotic relapse, high doses may hamper recovery. Therefore, dose reduction or discontinuation may be considered in patients with chronic schizophrenia. Here, we identified risk factors for psychotic relapse when doses are reduced. *Study Design*: We systematically searched MEDLINE, EMBASE, and PsycINFO from January 1950 through January 2021 and reviewed randomized controlled trials (RCTs) that reported relapse rates after antipsychotic dose reduction or discontinuation in patients with chronic schizophrenia. We calculated relative risks (RRs) with 95% confidence intervals (CIs) per person-year and sought to identify potential risk factors for relapse. The study is registered with PROSPERO (CRD42017058296). *Study Results*: Forty-seven RCTs (54 patient cohorts, 1746 person-years) were included. The RR for psychotic relapse with dose reduction/discontinuation versus maintenance treatment was 2.3 per person-year (95% CI: 1.9 to 2.8). The RR was higher with antipsychotic discontinuation, dose reduction to less than 3–5 mg haloperidol equivalent (HE), or relatively rapid dose reduction (<10 weeks). The RR was lower with long-acting injectable agents versus oral antipsychotic dose reduction. Other factors that increased the risk of psychotic relapse were younger age and short follow-up time. *Conclusions*: Clinicians should take several risk factors for psychotic relapse into account when considering dose reduction in patients with chronic schizophrenia. Studies of a relatively fast reduction in antipsychotic dose support a minimum dose of 3–5 mg HE. However, if the dose is tapered more gradually, relapses related to medication withdrawal might be avoided, possibly enabling lower-end doses to be achieved.**

Key words: antipsychotic doses/maintenance treatment/withdrawal/gradual reduction/adverse events/recovery/tapering

Introduction

During the first years after a first psychotic episode, maintenance treatment with antipsychotics is more effective than placebo in preventing relapse.[1,2] There is, however, no consensus on the duration of maintenance treatment, and many patients and psychiatrists consider dose reduction or discontinuation in the long term.[3] In a large survey, 90% of patients reported antipsychotic-related side effects and more than 50% reported that their quality of life was worse after treatment.[4] Moreover, patients have reported that long-term antipsychotic use disturbs their individual efforts and their sense of agency in overcoming psychosis.[5] The dose of antipsychotic medication has been found to be positively associated with the severity of side effects.[6] Sedation, sexual dysfunction, extrapyramidal symptoms, metabolic syndrome,[7–9] diminished cognitive functioning, and loss of motivation and drive[10,11] are common during high-dose antipsychotic treatment and hamper recovery, and can also occur at lower doses, at least to some extent.[12] Several long-term naturalistic studies suggest that a considerable proportion of first-episode patients who undergo dose reduction or discontinue antipsychotics recover with better global functioning than those prescribed continuous antipsychotic treatment.[13–16]

Although these findings suggest it is worthwhile to consider dose reduction or discontinuation, schizophrenia tends to be a chronic disorder, with incomplete remission, functional impairment, and social disability.[17] Patients whose condition does not go into

remission are often prescribed high doses of antipsychotics.[18,19] If antipsychotics are stopped or the dose reduced, there is a subsequent higher risk of relapse and rehospitalization.[20,21] Recent meta-analyses found discontinuation and dose reduction to less than 4–5 mg haloperidol equivalents (HEs)/day to be associated with relapse, whereas gradual dose reduction reduced the risk of relapse.[22,23] However, these studies included cohort studies and a limited number of randomized controlled trials (RCTs), with high heterogeneity and a high risk of confounding and bias.

In the current study, we performed a systematic review and meta-analysis of RCTs, comparing dose reduction or discontinuation of antipsychotics with stable continuous antipsychotic medication use in patients with chronic schizophrenia. We intended to create more homogenous results by comparing the risk of relapse in different subgroups. On the basis of the literature and from a clinical point of view, we distinguished the following subgroups: (1) patients whose dose of antipsychotics is reduced or discontinued,[1,24] (2) male/female patients,[25,26] (3) inpatients or outpatients,[27,28] and (4) patients using long-acting injectable agents (LAI) or oral medication.[24,29] We aimed to determine the relative risk (RR) of relapse in patients with chronic schizophrenia and to identify risk factors for psychotic relapse in these subgroups.

Methods

This review was conducted following the PRISMA guidelines.[30] A protocol was published in the PROSPERO database under registration number CRD42017058296. We searched PubMed, EMBASE, and PsycINFO for studies of antipsychotic dose reduction from January 1950 through January 2021. This strategy included the following terms: ("Schizophrenia"[Mesh] OR "Schizophrenia"[tw] OR "Schizophrenic"[tw]) AND ("chronic"[tw] OR "clinical"[tw] OR "clinically"[tw]) AND ("Antipsychotic Agents"[Mesh] OR "Antipsychotic"[tw] OR "Antipsychotics"[tw] OR "Tranquilizing Agents"[Mesh] OR "Antipsychotic Agents" [Pharmacological Action] OR "Tranquilizing Agents" [Pharmacological Action] OR "dose reduction"[tiab] OR "dosage reduction"[tiab] OR "Therapeutic window"[tiab]). The reference lists of eligible articles and reviews were hand searched to identify eligible studies not previously identified through the database search (backward and forward tracking of literature).

Study Selection

Two reviewers (JPAMB and GH) independently screened the titles and abstracts of retrieved citations using the following inclusion criteria: (1) Patients were diagnosed with schizophrenia or schizoaffective disorder according to international classification systems (DSM, International Classification of Diseases and Related Health Problems (ICD) Research Criteria for Schizophrenia) or these disorders were explicitly mentioned as a clinical diagnosis, (2) Patients had chronic symptoms, ie, patients had been diagnosed as having chronic schizophrenia or patients lived in long-stay facilities or had received maintenance treatment for at least 5 years, (3) The dose reduction procedure was clearly described and data on relapse rates were provided, and (4) Studies were RCTs comparing dose reduction or discontinuation of antipsychotics with stable continuous use. Full-text articles were excluded if they involved reviews, studies with patients with different diagnoses and which did not provide separate data for schizophrenia patients, or studies involving patients with acute psychotic episodes. Differences in opinion between the reviewers about inclusion were settled in consensus meetings. Special effort was made to screen the reference lists of included articles and reviews to diminish the probability that we would miss a relevant RCT.

Data Extraction

Two authors (JPAMB, GH) extracted data independently and calculated RRs with 95% confidence intervals (95% CI) per person–year. We selected data on the basis of two earlier reviews,[22,23] namely: (1) dose reduction/discontinuation characteristics (starting dose before dose reduction, end dose after dose reduction, abrupt, or gradual dose reduction, where abrupt dose reduction was defined as oral medication stopped at once, duration of dose reduction in weeks), (2) patient characteristics (age, gender as a percentage of male subjects, inpatient or outpatient status, duration of illness, method of administration of antipsychotic medication, ie, LAI or oral medication), and (3) study characteristics (follow-up time after dose reduction, blinding, and relapse definition).

Relapse Criteria for Psychosis

The definition of psychotic relapse given in the original articles was used (Supplementary Table 1). Several researchers considered a 20% change in Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS) scores as clinically relevant. If such a rating was not available, clinical judgment, hospitalization, or an increase in antipsychotic dose was considered to reflect psychotic relapse.

Assessment of Risk of Bias

Two authors (GH, NWS) individually assessed all selected studies for risk of bias by using the Cochrane handbook, Risk of Bias 2 tool.[31] Any differences in opinion were discussed until a consensus was reached. Six potential sources of bias that could affect the association between exposure and outcome were investigated (Supplementary Table 2).

Statistical Analyses

All statistical analyses were performed using Comprehensive Meta-Analysis software, version 3.0.[32] For each study, we calculated the number of patients who underwent dose reduction or drug discontinuation (interventions), or maintenance therapy (control condition), and the number of relapses that occurred during the follow-up period as crude rates per person-years. RR was used as a measure to calculate and pool data on the RR of relapse (intervention vs control). RRs are more intuitive than odds ratios and since the risk of relapse is high, the statistical advantages of using odds ratios are limited.[33] Previous studies also used RR and therefore using this measure increased comparability.[34,35] Pooled estimates of RRs for continuous and dichotomous outcomes were calculated with two-sided 95% confidence intervals (95% CI) using a DerSimonian-Laird random effects model.[32] A 95% CI higher than 1.0 means that the rate of relapse in the intervention condition was significantly higher than in the control condition, and a 95% CI that includes 1.0 means that the relapse rate in the intervention condition was not significantly different from that in the control condition.

The influence of different variables, such as dose reduction, patient, and study characteristics, on the risk of relapse, was investigated by comparing differences between RRs of pools. If a variable was found to be associated with an increased RR of relapse, a subsequent subgroup analysis was conducted to see if other variables could explain the increased risk. As a rule of thumb, at least four groups in at least 2 strata were required to make comparisons meaningful. Since different antipsychotics were used in these studies, we converted doses to HE doses to enable group comparisons (Supplementary Table 3).

Between-study heterogeneity was assessed with Cochran's I^2-statistic. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance.[36,37] According to convention, a chi-squared test <0.05 or I^2 statistics >50% indicates high heterogeneity.

RR factor values for continuous variables were not normally distributed but showed clustering of data points. Therefore, meta-regression to identify RR factors was not deemed feasible. We analyzed all variables, dichotomous and continuous, by stratification. Continuous variables were divided into strata using median split. We analyzed all studies, and subgroups of studies based on specific discriminative variables, such as dose reduction or discontinuation,[1,24] gender (proportion of male patients),[25,26] inpatient or outpatient status,[27,28] and LAI or oral medication.[24,29] Additional analyses were performed to examine confounding. Publication bias was visually explored with funnel plots (Supplementary figure 1). Two-sided *P*-values <.05 were considered statistically significant.

Results

Study Selection

The initial search yielded 165 articles, of which 39 remained after the screening of titles and abstracts. Eighty-one articles were added after reviewing reference lists. After a full-text review of these 120 articles, 82 were discarded, mostly non-RCTs. By forwarding tracking we found another 9 articles, resulting in 47 RCTs, with 54 cohorts of patients (studies). Details of the selection process are shown in a flowchart (figure 1).

Study and Patient Characteristics

In total, 4571 patients were included, 2366 who underwent dose reduction/discontinuation and 2205 who received maintenance treatment, representing 1746 person-years, with a mean age of 42.2 years (SD 7.9). In total 66% (SD 22) were men, and the mean duration of illness was 14.7 years (SD 6.4). The mean follow-up time was 35 weeks (SD 23). The mean dose reduction was from 20.7 (SD 40.5) to 3.6 (SD 6.2) mg HE/day (Table 1).

Analysis of all studies (N = 54)

Overall, patients who underwent dose reduction or discontinuation had an increased risk of psychotic relapse (RR = 2.3 per person-year; 95% CI: 1.9 to 2.8; I^2 35%) relative to that of patients on antipsychotic maintenance treatment. Differences in RRs in different strata are given in Table 2. Heterogeneity was low in most analyses.

We found substantial differences in the RR of relapse when we compared the discontinuation group (RR = 2.6; 95% CI: 2.1 to 3.2; I^2 5%) with the dose reduction group (RR = 1.8; 95% CI: 1.3 to 2.4; I^2 42%) (P = .034). End dose significantly affected the RR of relapse. We found a comparable RR of relapse with dose reduction to less than 3 mg HE/day (RR = 2.9; 95% CI: 1.9 to 4.4; I^2 38%) and discontinuation (RR = 2.6; 95% CI: 2.1 to 3.2; I^2 5%), but a lower RR with end doses higher than 3 mg HE/day (RR = 1.2; 95% CI: 0.9 to 1.5; I^2 0%) (P < .001). The RR for the latter was not significantly different from that for maintenance treatment. The duration of dose reduction influenced the RR of relapse (P = .022): RR = 2.4 (95% CI: 1.9 to 3.0; I^2 0%) for dose reduction over 0 weeks or abrupt reduction, RR = 2.3 (95% CI: 1.6 to 3.2; I^2 52%) for dose reduction over 1–10 weeks, and RR = 1.0 (95% CI: 0.6 to 1.8; I^2 0%) for dose reduction over more than 10 weeks; the latter was not significantly different from that for the maintenance condition.

The RR of relapse was higher in studies involving men only (RR = 4.3; 95% CI: 2.5 to 7.2; I^2 0%) than in all other studies (RR = 2.0; 95% CI: 1.6 to 2.4; I^2 37%) (P = .006). However, the RR of relapse was not found to be higher in men when data were stratified according to the

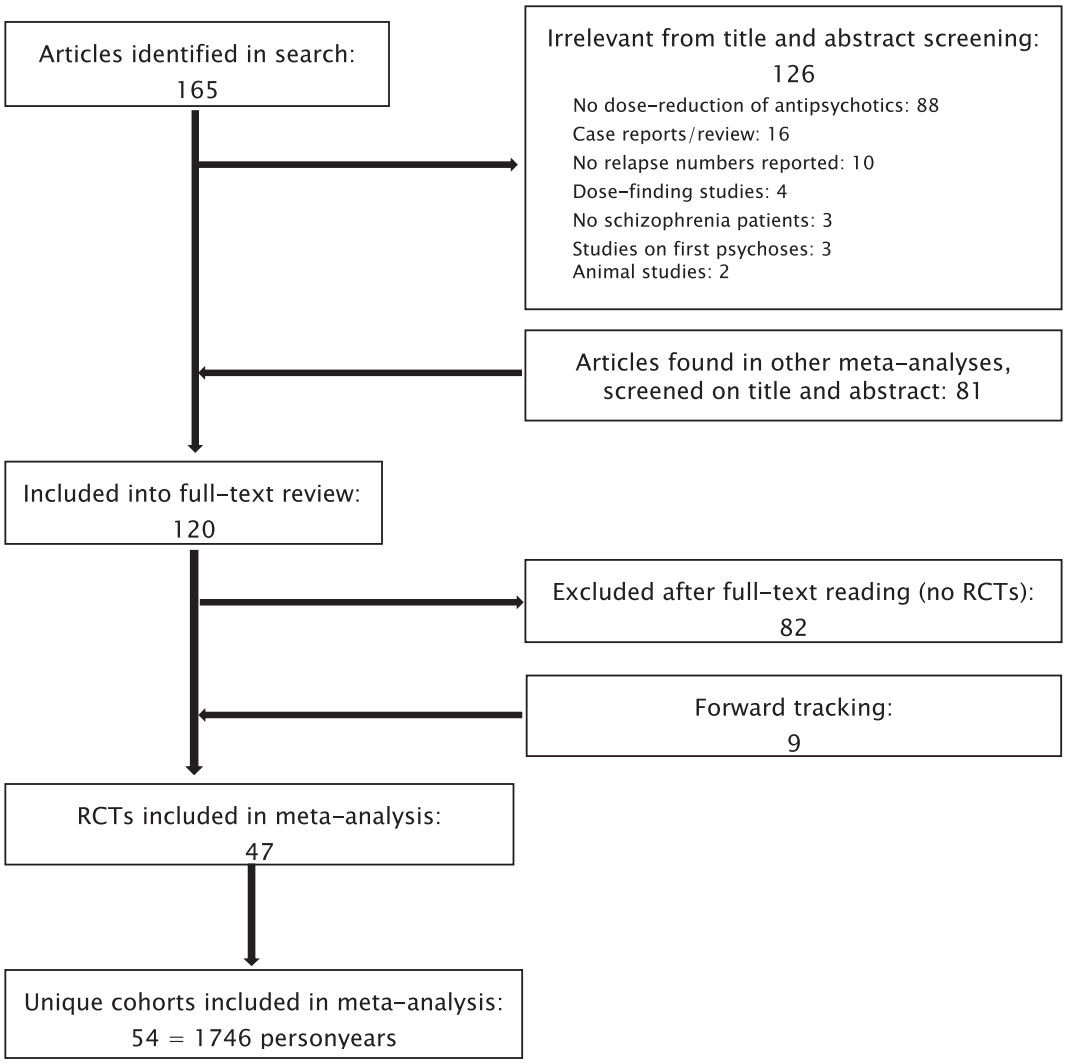

Fig. 1. Flowchart of study selection.

proportion of men in a study. Nearly all of the studies that included men only investigated abrupt cessation of medication or reduction of medication to doses lower than 3 mg HE/day.

The following characteristics did not significantly affect the overall RR of relapse: starting dose, age, inpatient or outpatient status, duration of illness, LAI or oral drug, follow-up time, blinding, or relapse definition.

Dose Reduction or Discontinuation Studies

In dose-reduction studies (n = 27*),* there was a more than double RR of relapse when the end dose was lower than 3 mg HE/day (RR = 2.9; 95% CI: 1.9 to 4.4; I^2 38%) than when it was higher than 3 mg HE/day (RR = 1.2; 95% CI: 0.9 to 1.5; I^2 0%) ($P < .001$), and an almost 2 times higher RR of relapse when the end dose was lower than 5 mg HE/day (RR = 2.2; 95% CI: 1.5 to 3.4; I^2 46%) than when it was higher than 5 mg HE/day (RR = 1.2; 95% CI: 0.9 to 1.6; I^2 0%) ($P = .016$). The risk of relapse was not significantly different between dose reduction to a dose higher than 3–5 mg HE/day and maintenance therapy. There were only 2 cohorts of patients in studies investigating abrupt dose reduction, so comparisons with gradual dose reduction could not be made. The same is true for studies with different durations of dose reduction. In post hoc analyses comparing dose reduction over 0–10 weeks and 10 weeks and longer, the risk of relapse was not significantly different between dose reduction over 10 weeks and longer and maintenance treatment (RR = 1.0; 95% CI: 0.6 to 1.8; I^2 0%). LAI seemed to protect against relapse during dose reduction (RR = 1.4; 95% CI: 0.9 to 2.1; I^2 47%) compared with oral antipsychotics (RR = 2.4; 95% CI: 1.7 to 3.3; I^2 7%) ($P = .046$). The risk of relapse with dose reduction with LAI was not significantly different from that with maintenance conditions. Starting dose, age, patient setting, duration of illness, follow-up time, blinding or relapse definition did not significantly affect the RR of relapse in dose-reduction studies.

Table 1. Patient and Study Characteristics

First Author and Cohort	Year	Cohort Size Exp (Participants)	Cohort Size Con (Participants)	Rate Ratio	FU (Weeks)	Blinding	Mean Age (Years)	Mean DOI (Years)	Patient Type	Male Percentage	Reduction Period (Weeks)	Medication Type	Pre Dose (mg)	Post Dose (mg)	Reduction Style	Relapse Definition
Diamond[38]	1960	20	20	3,7	26	Yes	46,6	11,0	Inpatients	nd	0	Oral	8,5	0,0	Abrupt	Clinical Judgment
Blackburn[39]	1961	14	25	4,8	16	No	nd	nd	Inpatients	100	0	Oral	nd	0,0	Abrupt	Rated on scales
Freeman[40]	1962	46	48	2,3	26	Yes	41,1	13,0	Inpatients	nd	0	Oral	4,6	0,0	Abrupt	Clinical Judgment
Whittaker 1[41]	1963	13	6	2,3	10	No	50,2	16,0	Outpatients	100	0	Oral	6,0	0,0	Abrupt	Clinical Judgment
Whittaker 2[41]	1963	13	7	2,7	10	Yes	49,5	15,0	Outpatients	100	0	Oral	6,0	0,0	Abrupt	Clinical Judgment
Marjerrison[42]	1964	171	44	10,9	22	Yes	47,0	20,0	Inpatients	48	0	Oral	nd	0,0	Abrupt	Rated on scales
Caffey 1[43]	1964	89	44	9,9	16	Yes	40,0	10,0	Inpatients	100	1	Oral	7,5	0,0	Gradual	Clinical Judgment
Caffey 2[43]	1964	31	26	3,2	16	Yes	40,0	10,0	Inpatients	100	1	Oral	7,5	4,3	Gradual	Clinical Judgment
Melnyk[44]	1966	16	9	21,0	6	Yes	42,8	12,0	Inpatients	65	0	Oral	7,0	0,0	Abrupt	Clinical Judgment
Garfield[45]	1966	20	20	2,8	22	Yes	42,6	11,0	Inpatients	0	1	Oral	12,8	0,0	Gradual	Clinical Judgment
Morton[46]	1968	20	20	2,8	26	Yes	nd	nd	nd	100	0	nd	nd	0,0	Abrupt	Clinical Judgment
Rassidakis[47]	1970	13	13	1,7	39	No	49,3	24,0	Inpatients	43	0	nd	nd	0,0	Abrupt	Clinical Judgment
Baro[48]	1970	43	41	27,0	10	Yes	nd	nd	Inpatients	100	1	LAI	50,1	0,0	Gradual	Clinical Judgment
Hershon[49]	1972	11	11	4,5	16	Yes	55,1	nd	Inpatients	52	1	LAI	11,3	0,0	Gradual	Clinical Judgment
Ota[50]	1973	49	49	4,0	13	Yes	42,9	nd	Inpatients	55	0	Oral	7,5	0,0	Abrupt	Clinical Judgment
Andrews[51]	1976	17	14	4,9	42	Yes	53,8	nd	Inpatients	100	0	Oral	4,6	0,0	Abrupt	Clinical Judgment
Lonowski[52]	1978	25	23	0,9	15	Yes	47,11	12,2	Inpatients	56	15	LAI	6,6	1,4	Gradual	Rated on scales
Levine 1[53]	1980	27	6	nd	15	No	31,2	nd	Inpatients	46	nd	Oral	24,2	0,0	Abrupt	Clinical Judgment
Levine 2[53]	1980	23	11	3,3	15	No	32,1	nd	Inpatients	52	nd	LAI	12,4	0,0	Gradual	Clinical Judgment
Lehmann[54]	1980	20	20	2,0	24	Yes	38,2	9,8	nd	68	2	LAI	270,0	30,0	Gradual	Clinical Judgment
Cheung[55]	1981	13	15	3,9	78	Yes	39,6	11,0	Outpatients	43	0	Oral	3.3	0,0	Abrupt	Clinical Judgment
Odejide[56]	1982	27	26	2,8	52	Yes	nd	nd	Outpatients	nd	6	LAI	20,0	0,0	Gradual	Rated on scales
Lehmann[57]	1983	60	56	3,0	48	No	47,7	nd	Outpatients	49	nd	Oral	7,3	1,5	Gradual	Clinical Judgment
Johnson[58]	1983	63	62	7,6	78	No	32,0	nd	Outpatients	52	2	LAI	nd	0,0	Gradual	Rated on scales
Kane[59]	1983	62	32	11,9	52	Yes	29,0	6,0	Inpatients	nd	3	LAI	20,0	2,0	Gradual	Clinical Judgement
Wistedt[60]	1983	16	22	1,7	24	Yes	44,4	11,7	Outpatients	50	3	LAI	11,0	0,0	Gradual	Rated on scales
Channabasavanna[61]	1987	14	14	13,3	12	Yes	36,0	11,0	Outpatients	64	0	Oral	6,1	0,0	Abrupt	Clinical Judgment
Cookson[62]	1987	28	31	3,0	44	Yes	46,0	14,0	Inpatients	67	2	LAI	nd	>0	Gradual	Rated on scales
Johnson[63]	1987	9	9	1,5	52	Yes	40,0	10,0	Outpatients	46	2	LAI	nd	>0	Gradual	Rated on scales
Hogarthy[64]	1988	30	25	1,3	54	Yes	28,3	7,0	Outpatients	57	2	LAI	25,8	4,6	Gradual	Rated on scales
Faraone[65]	1989	22	7	17,0	26	Yes	nd	nd	Outpatients	100	5	Oral	nd	>0	Gradual	Clinical Judgment
Sampath[66]	1992	12	12	1,9	12	Yes	57,6	31,0	Inpatients	nd	2	LAI	40,0	0,0	Gradual	Rated on scales
Inderbitzin[67]	1994	20	17	1,3	30	Yes	41,2	18,0	Outpatients	73	22	LAI	27,3	13,8	Gradual	Clinical Judgment
Hogarthy[68]	1995	38	41	0,2	13	Yes	33,7	9,7	Outpatients	66	2	LAI	22,3	12,6	Gradual	Clinical Judgment
Huttunen [69]	1996	9	10	1,1	104	No	nd	nd	Outpatients	53	4	Oral	nd	4,0	Gradual	Clinical Judgment
Hirschowitz 1[70]	1997	6	8	2,7	52	Yes	48,0	24,2	Inpatients	100	2	Oral	18,3	1,0	Gradual	Rated on scales
Hirschowitz 2 [70]	1997	8	8	0,5	52	Yes	43,1	23,2	Inpatients	75	2	Oral	20,0	11,0	Gradual	Rated on scales
Schooler[71]	1997	106	107	1,2	104	Yes	29,6	21,1	Inpatients	66	2	LAI	37,1	16,3	Gradual	Rated on scales
Carpenter[72]	1999	25	25	1,6	54	Yes	36,2	13,0	Outpatients	60	6	LAI	30	10,0	Gradual	Rated on scales
Volavka[73]	2000	11	12	1,1	16	Yes	40,2	20,4	Inpatients	87	12	Oral	32,9	19,4	Gradual	Clinical Judgment
Arato[74]	2002	71	206	1,8	52	Yes	48,8	22,0	Inpatients	83	0	Oral	nd	0,0	Abrupt	Rated on scales
Khazaie[75]	2005	25	25	1,2	54	Yes	34,0	12,0	Outpatients	72	6	LAI	20,7	10,0	Gradual	Rated on scales
Ushida[76]	2006	17	17	nd	24	Yes	40,1	15,8	Outpatients	53	12	Oral	14	8,0	Gradual	Clinical Judgment
Kramer[77]	2007	55	56	2,1	34	Yes	40,7	12,6	nd	51	0	Oral	10,8	0,0	Abrupt	Rated on scales
Rouillon[78]	2008	49	48	2,0	26	No	39,5	nd	Outpatients	65	nd	Oral	7,4	5,3	Gradual	Clinical Judgment
Hough[79]	2008	140	133	2,7	46	Yes	39,1	11,9	nd	54	4	LAI	6,6	0,0	Gradual	Rated on scales
Kane 1[80]	2010	203	205	2,3	24	Yes	37,7	nd	Outpatients	60	0	Oral	2,8	0,2	Abrupt	Rated on scales
Kane 2[80]	2010	144	133	4,5	24	Yes	39,5	nd	Outpatients	67	0	Oral	2,8	1,4	Abrupt	Rated on scales
Wang[81]	2010	245	129	2,6	52	No	32,0	6,4	Inpatients	45	8	Oral	4,3	2,1	Gradual	Rated on scales
Takeuchi[82]	2013	31	30	1,0	24	No	40,9	15,5	Outpatients	58	4	Oral	4,8	2,5	Gradual	Rated on scales
Yamanouchi[83]	2014	62	163	2,6	52	No	60,0	32,0	nd	57	24	Oral	20,0	15,0	Gradual	Clinical Judgment
Zhou[84]	2018	37	38	0,7	52	Yes	44,3	5,0	Outpatients	60	16	Oral	5,4	3,2	Gradual	Rated on scales
Ozawa[85]	2019	17	18	7,4	52	Yes	64,1	nd	Inpatients	37	4	nd	7,0	2,8	Gradual	Clinical Judgment
Huhn[86]	2021	10	8	0,4	14	Yes	44,7	16,8	Outpatients	55	14	Oral	5,8	3,5	Gradual	Rated on scales

Table 1. Continued

First Author and Cohort	Year	Cohort Size Exp (Participants)	Cohort Size Con (Participants)	Rate Ratio	FU (Weeks)	Blinding	Mean Age (Years)	Mean DOI (Years)	Patient Type	Male Percentage	Reduction Period (Weeks)	Medication Type	Pre Dose (mg)	Post Dose (mg)	Reduction Style	Relapse Definition
Total	—	2366	2205	—	1872	—	—	545	—	—	—	—	—	—	—	—
Mean	—	—	—	4.3	34.7	—	42,2	14,7	—	65,5	3,9	—	20,7	3,6	—	—
SD	—	—	—	5,2	22,5	—	7,9	6,4	—	21,6	5,7	—	40,5	6,2	—	—

Note: exp, experimental group = dose reduction or discontinuation condition; con, control group = maintenance condition; FU, follow-up period; DOI, duration of illness; nd, no data.

In discontinuation studies (n = 25), abrupt or gradual discontinuation did not significantly affect the RR of relapse. Studies with a duration of dose reduction of 10 weeks or longer were not available. Age 42 years or younger (RR = 3.4; 95% CI: 2.3 to 5.0; I^2 28%) was associated with a higher RR of relapse than age 42 years and older (RR = 2.0; 95%CI 1.6–2.7; I^2 0%)(P = .042). A shorter duration of illness was associated with a higher RR of relapse (<15 years, RR = 2.8; 95% CI: 2.1 to 3.7; I^2 0% vs >15 years RR = 1.8; 95% CI: 1.3 to 2.5; I^2 0%) (P = .038). A follow-up of less than 16 weeks was associated with higher RR of relapse (RR = 4.7; 95% CI: 2.8 to 7.9; I^2 0%) than a longer follow-up (RR = 2.3; 95% CI: 1.9 to 2.7; I^2 0%) (P = .016). Relapse defined on the basis of clinical judgment was also associated with a higher RR of relapse (RR = 3.5; 95% CI: 2.5 to 4.9; I^2 0%) than when relapse was assessed with rating scales (RR = 2.2; 95% CI: 2.1 to 3.1; I^2 0%) (P = .026). Gender, inpatient or outpatient status, LAI or oral antipsychotics, and blinding did not affect the RR of relapse in discontinuation studies.

Gender, Inpatients, or Outpatients, LAI or Oral Antipsychotics

The different subgroup analyses of males (there was 1 study with females only), inpatients/outpatients, and patients prescribed LAI or oral antipsychotics are presented in Supplementary Table 4. Most results are in line with the results for all studies and those for the dose reduction or discontinuation subgroups. Still, some results are worth mentioning. The end-dose analyses did not find a significant difference in risk of relapse between end doses above 3 mg or 5 mg HE/day and maintenance treatment. The risk of relapse was not significantly different from that of maintenance therapy if doses were reduced over 10 weeks or longer, whereas there was a significant difference when doses were reduced over 10 weeks or less.

In inpatients a short duration of illness affected the RR of relapse (0–10 years: RR = 5.1; 95% CI: 2.2 to 11.9; I^2 54%; 11–15 years: RR = 2.2; 95% CI: 1.1 to 4.3; I^2 23%; more than 15 years: RR = 1.5; 95% CI: 1.2 to 1.9; I^2 0%) (P = .015). In patients on oral antipsychotics, a follow-up of 26 weeks or less was associated with a higher risk of relapse (RR = 3.3; 95% CI: 2.4 to 4.6; I^2 0%) than a follow-up longer than 26 weeks (RR = 2.0; 95% CI: 1.5 to 2.6; I^2 0%) (P = .011). In patients on LAI antipsychotics, the risk of relapse was by and large not different from that of maintenance treatment.

Discussion

The current study is an extensive meta-analysis of RR factors for psychotic relapse following dose reduction or discontinuation of antipsychotics in patients with chronic schizophrenia. We found that the discontinuation

Table 2. Relative Risks (*RR*), Heterogeneity (I^2), Number of Studies (*n*), and *P*-Values After Stratification of Cohorts for Various Variables

		Cohort Name:	Total Group of Studies				Dose Reduction Group				Discontinuation (Stop) Group			
	Variable	Pools	*n*	RR (95%CI)	I^2 (%)	*P*	*n*	RR (95%CI)	I^2 (%)	*P*	*n*	RR (95% CI)	I^2 (%)	*P*
Reduction Characteristics	Medication	Discontinued	25	2.63 (2.14 to 3.22)	5	.034	na				na			
		Dose reduced	27	1.78 (1.32 to 2.39)	42									
	End-dose 3mg divide	0 mg	25	2.63 (2.14 to 3.22)	5	.000	na				na			
		0–3 mg	10	2.90 (1.90 to 4.44)	38		10	2.90 (1.90 to 4.44)	38	.000				
		3 mg+	14	1.16 (0.90 to 1.50)	0		14	1.16 (0.90 to 1.50)	0					
	End-dose 5mg divide	0 mg	25	2.63 (2.14 to 3.22)	5	.000	na				na			
		0–5 mg	14	2.22 (1.46 to 3.39	46		14	2.22 (1.46 to 3.39)	46	.016				
		5 mg+	10	1.20 (0.91 to 1.58)	0		10	1.20 (0.91 to 1.58)	0					
	Dose reduction style	Abrupt	17	2.42 (1.94 to 3.01)	0	.353					15	2.23 (1.75 to 2.85)	0	.093
		Gradual	35	2.05 (1.56 to 2.68)	44						11	3.27 (2.25 to 4.73)	15	
	Duration of dose reduction	0 week	17	2.42 (1.94 to 3.01)	0	.022	19	1.94 (1.33 to 2.84)#	52	.066	15	2.32 (1.75 to 2.85)	0	.099
		1–10 weeks	26	2.28 (1.64 to 3.17)	52						9	3.34 (2.21 to 5.05)	25	
		>10 weeks	6	1.02 (0.58 to 1.81)	0		6	1.02 (0.58 to 1.81)	0					
Patient Characteristics	Age	0–42 years	24	2.32 (1.72 to 3.14)	56	.303	16	1.85 (1.28 to 2.67)	54	.577	8	3.37 (2.25 to 5.04)	28	.042
		>42 years	22	1.90 (1.50 to 2.41)	0		9	1.54 (0.90 to 2.61)	13		13	2.04 (1.55 to 2.68)	0	
	Male percentage	0–49%	8	2.37 (1.64 to 3.44)	0	.016					4	2.12 (1.20 to 3.74)	0	.199
		50–99%	29	1.84 (1.42 to 2.38)	44						10	2.75 (1.92 to 3.95)	37	
		100%	10	4.26 (2.54 to 7.15)	0						7	4.45 (2.45 to 8.07)	0	
	Patient setting	Inpatients	25	2.58 (1.88 to 3.54)	41	.262	10	2.14 (1.20 to 3.82)	56	.401	15	2.72 (1.93 to 3.84)	16	.425
		Outpatients	22	1.98 (1.41 to 2.77)	41		15	1.59 (1.08 to 2.35)	42		7	3.50 (2.09 to 5.88)	4	
	Duration of Illness	0–10 years	9	2.14 (1.03 to 4.45)	66	.199	8	1.79 (0.85 to 3.75)	64	.592	11	2.79 (2.13 to 3.65)#	0	.038
		11–15 years	14	2.07 (1.53 to 2.81)	21		4	1.15 (0.72 to 1.83)	0					
		15+ years	13	1.50 (1.20 to 1.88)	0		8	1.22 (0.88 to 1.69)	0		5	1.80 (1.32 to 2.46)	0	
	Method of administration	Oral	30	2.48 (2.01 to 3.07)	4	.282	15	2.39 (1.74 to 3.27)	7	.046	8	3.00 (2.10 to 4.29)	8	.647
		LAI	19	1.97 (1.38 to 2.83)	58		11	1.39 (0.91 to 2.13)	47		15	2.68 (1.96 to 3.67)	10	
Study Characteristics	Follow-up 16	0–16 weeks	16	2.80 (1.54 to 5.10)	46	.433	5	0.87 (0.36 to 2.12)	31	.090	11	4.68 (2.76 to 7.94)	0	.016
		>16 weeks	36	2.18 (1.79 to 2.70)	31		22	1.97 (1.45 to 2.67)	41		14	2.34 (1.92 to 2.86)	0	
	Follow-up 26	0–26 weeks	28	2.70 (1.98 to 3.70)	22	.152	11	1.78 (0.99 to 3.19)	48	.925	17	3.39 (2.35 to 4.88)	0	.145
		>26 weeks	24	2.02 (1.59 to 2.58)	42		16	1.72 (1.23 to 2.41)	36		8	2.40 (1.80 to 3.20)	28	
	Blind	Yes	41	2.21 (1.74 to 2.79)	42	.475	21	1.67 (1.15 to 2.41)	51	.242	20	2.50 (2.04 to 3.06)	38	.462
		No	11	2.56 (1.85 to 3.53)	0		6	2.34 (1.52 to 3.63)	0		5	3.30 (1.63 to 6.70)	0	
	Relapse definition	Clinical judgement	28	2.98 (2.18 to 4.08)	17	.030	12	1.38 (1.31 to 4.33)	41	.218	16	3.11 (2.19 to 4.42)	0	.320
		Scales	24	1.93 (1.52 to 2.45)	43		15	1.56 (1.17 to 2.14)	537		9	2.47 (1.84 to 3.30)	25	

Note: Analyses have been done for the total group of studies, and for different subgroups of studies: dose-reduction studies, discontinuation studies, and other subgroups. The latter are presented in Supplementary Table 4. Blank Boxes Indicate an Insufficient Number of Studies (<4).
Note: na, not applicable; # rows combined because of insufficient number of studies in one of the rows (<4).

of antipsychotics and certain dose reduction characteristics substantially influenced the risk of psychotic relapse. Discontinuation of antipsychotic medication almost doubled the risk of relapse compared with dose reduction. This is in line with register studies and meta-analyses of dose reduction and discontinuation studies.[22,23,87–89] Previous uncontrolled cohort studies did not find an increased risk of relapse after antipsychotics were discontinued, which might be explained by the inclusion of relatively stable patients who would be less likely to relapse.[90]

End Dose

We found evidence to suggest that there is a threshold dose of antipsychotics above which patients are better protected against relapse. This dose is 3–5 mg HE/day for most patients, although there are interindividual differences. The greatest difference in RR was seen with doses lower and higher than 3 mg HE/day. Dose reduction to an end dose higher than 3 mg HE/day resulted in a substantially lower RR of relapse than with a lower end dose. In fact, the risk of relapse with a higher end dose (>3 mg HE/day) was comparable to that of maintenance treatment. This is in line with earlier studies.[23,34,89] Our previous meta-analysis of cohort studies found a threshold around 5 mg HE/day.[22] In a recent, methodologically different, meta-analysis of relapse rates in dose-response studies, prevention of relapse increased up to 5 mg/day risperidone equivalent, which is comparable with 5 mg HE/day.[34] Higher doses conferred little further advantage in reducing the relative relapse rate, while lower doses increased the relative relapse rate in a hyperbolic way.[34] In their meta-analysis of patients with schizophrenia in stable remission, Leucht et al. found that risperidone in doses higher than 2.5 mg provided better protection against relapse than in lower doses.[34] This suggests that the condition of patients with an optimal response to antipsychotics can remain stable on a relatively low dose. For first-generation antipsychotics, this effect could be seen with doses of 3 mg HE/day or higher.[34] Most of the studies included in our analyses concerned first-generation antipsychotics (90%). Another recent meta-analysis of RCTs of different maintenance doses compared standard, low, and very low doses. The risk of relapse was higher (+44%) with low daily doses (4–8 mg HE) and very low doses (<4 mg HE; +72%) than with a standard daily dose (8 mg HE).[35] The most recent network meta-analysis comparing continuing, reducing, switching, and discontinuing antipsychotics in patients with chronic psychosis found that fewer relapses occurred with continuing or switching at standard doses and more relapses when doses were lower than the standard dose or the drug was discontinued.[91] Taken together, findings suggest that an optimal maintenance dose of antipsychotics is 3–5 mg HE/day in patients with chronic schizophrenia. Lower doses, or no antipsychotics, are associated with an increased risk of relapse. Nevertheless, it should be borne in mind that the finding of a threshold might be an artifact due to the manner in which the drug dose was reduced or stopped in these studies. Other authors have already advocated the strategy of gradual dose reduction, pointing out that gradual dose reduction can prevent withdrawal-related relapse.[92] The idea that it is the process of reducing or discontinuing antipsychotics, rather than the actual dose used, that increases the risk of relapse, has gained traction in recent years. In this respect, it is worth mentioning that the dose-related pattern of relapse risk is hyperbolic, matching that for antipsychotic receptor occupancy, which strongly suggests that the risk of relapse corresponds to rate of change in receptor occupancy.[34] This implies that the risk of relapse is not only associated with the underlying health problem but also with the effect of drug withdrawal, which complicates the interpretation of findings from dose reduction or discontinuation trials.[93] Fast reduction of the dose of antipsychotics can cause withdrawal symptoms, such as anxiety, agitation, and insomnia, symptoms which may be mistaken for those of relapse of the underlying condition. Moreover, the experience of withdrawal effects might itself provoke psychotic relapse, especially when withdrawal is not gradual enough.[93,94] Somatic and psychiatric adverse events emerged 4 weeks after antipsychotic withdrawal, particularly after longer duration of treatment.[95] Furthermore, there is evidence that antipsychotic withdrawal in itself may be psychotogenic, as suggested by the effect of stopping antipsychotic-like drugs in formerly nonpsychotic patients or when clozapine is discontinued abruptly.[93]

The abovementioned mechanisms can be caused by rebound effects, which is consistent with the concept that neuro-adaptation occurs in various receptor systems during treatment; adaptation may take months or even years to resolve.[94] Dose reduction should therefore be gradual enough to negate the upregulation of density and sensitivity of receptors.[94–96] In other words, the process of dose reduction may have a larger impact on the risk of relapse than the end dose of antipsychotics.

Duration of Dose Reduction

Continuation of medication and gradual reduction both played a role in preventing relapse. The observation that a gradual withdrawal of medication was associated with a lower risk of relapse was mainly due to the effect of reducing doses over a period longer than 10 weeks. This is consistent with an additional analysis of Leucht et al., in which doses were gradually tapered to the lowest effective dose.[97] Gradual dose reduction may enable lower-end doses to be achieved. In this respect, it is worth mentioning that, with dose reduction, LAI antipsychotics

were protective against relapse when compared with oral antipsychotics. This is consistent with earlier findings, in which relapse occurred earlier and more often with reduction of oral (short half-life) versus reduction of LAI antipsychotics. The same was true for different LAI antipsychotics, comparing a once-monthly LAI, with a relatively short half-life, with a once-every-3-months LAI.[98] This suggests that gradual reduction, which is inherent to LAI medication dose reduction, and a long reduction time protect against relapse.

We included only 6 studies in which the dose of antipsychotics was reduced over 10 weeks or longer, which limits the power to draw firm conclusions. None of these studies were discontinuation studies, and in a further survey the end dose in these studies turned out to be relatively high (>5 mg HE/day).

Other Outcomes

The risk of relapse appeared to be higher when reducing the dose of oral antipsychotics than when reducing the dose of LAI antipsychotics. This is probably because of the inherently gradual and slower reduction with LAI reduction. At the same time, the lower risk of relapse with LAI may also indicate better adherence to treatment with these drugs.[34,98]

The finding that the RR of relapse was significantly higher in young patients and in patients with a short duration of illness underlines the need to take these factors into account when clinicians consider antipsychotic dose reduction or discontinuation.

While end dose and duration of dose reduction were risk factors for relapse overall and in dose-reduction studies, various factors were associated with the risk of relapse in studies in which antipsychotic medication was stopped. We speculate that potential risk factors become stronger if antipsychotics are discontinued, because discontinuation causes greater disruption of a stable equilibrium in receptor occupancy after years of antipsychotic therapy than dose reduction, and might give rise to greater withdrawal effects. This is in line with our finding that the RR of relapse was higher in discontinuation studies than in dose reduction studies.

The risk of relapse was high in discontinuation studies with a short follow-up (less than 16 weeks), which suggests that most relapses occur relatively soon after medication discontinuation and that relapses are associated with withdrawal symptoms. Young patients and patients with a short duration of illness who stopped their medication were at the highest risk of relapse, which is in line with previous findings.[22,23] A possible explanation for the lower risk of relapse in older patients is the decline in hyperdopaminergic functioning with age, with a decrease in dopaminergic receptor availability.[99,100] In studies in which medication was stopped, clinical judgment rather than objective testing was associated with the highest risk of relapse. This might be explained by expectation bias on the part of clinicians.

Adverse Events and Relapse Risk

In this meta-analysis, we found evidence that withdrawal effects might play a role in relapse and therefore might have influenced the results. First, a short follow-up was associated with a higher RR of relapse, suggesting that relapse occurs more often shortly after dose reduction, while there is no reason to expect this because relapses normally occur divided over time.[101] Second, there were fewer relapses when the antipsychotic dose was reduced slowly. However, it should be borne in mind there were no studies with a long duration of reduction and only 6 with a reduction duration longer than 10 weeks, and these studies had a high-end dose. Still, it is possible that a more gradual dose reduction causes fewer relapses, even when the dose is reduced to less than 3–5 mg HE/day. Third, that drug withdrawal may play a role in relapses is supported by the finding that reducing the dose of LAI antipsychotics, it itself gradual, was associated with fewer relapses than reducing the dose of oral antipsychotics. A study has been started to investigate the effect of tapering antipsychotic medication over a long period of time, possibly even more than 1 year, in patients with schizophrenia (not first episode).[102] Fourth, the risk of relapse is higher with drug discontinuation than with dose reduction, which can be explained by discontinuation causing a greater disruption of receptor equilibrium, what may indicate withdrawal. This is in line with other studies where relapse rates with (very) low doses increase steeply,[34] similar to the inverse hyperbolic pattern of dopamine receptor occupancy with lowest doses (below 2.5–5 mg HE/day).[103]

Strength and Limitations

We carried out an extensive database search covering several decennia to produce a comprehensive overview of RCTs of risk factors for psychotic relapse in chronic schizophrenia and supplemented the search by screening reference lists from other publications and adding relevant publications, resulting in a relatively large number of RCTs. We controlled for confounding and heterogeneity by carrying out a number of sensitivity analyses. Overall heterogeneity was low in most analyses, which makes findings more reliable and robust. Funnel plots showed a scattered distribution of rate ratios, indicating that the likelihood of publication bias was low. The differences in risk of relapse we found between studies of dose reduction and dose discontinuation, studies with male patients only, studies with male and female patients, and studies of oral medication and LAI medication support our initial choice to analyze these groups of studies separately.

Several limitations should be considered when interpreting the results. This is a meta-analysis of trials that were not set up to identify risk factors for relapse or to find the best way to perform dose reduction. This limitation should be kept in mind when interpreting our findings. Although comparisons were statistically significant, some comparisons between RRs had overlapping 95% CIs, which is acceptable but limits the power of comparisons.

Bias by indication can affect RRs. The selection of patients for dose reduction trials may be affected by the stability of their mental condition, and stabilized patients may be included more often than unstable patients. In addition, caregivers and patients might refrain from participating in a dose reduction trial, because they do not want to change the patient's stable condition. The use of a dose reduction protocol with more intense monitoring of patients may have induced performance bias (more close monitoring and expectation to find relapse may influence relapse rates).

Conventional antipsychotics were prescribed in most studies, whereas clozapine was not used in any of the studies, which limits the generalizability of findings. Multiple subgroup analyses might result in false negative and false positive significance tests that increase in likelihood as more subgroup analyses are performed. We used the criteria for relapse used by the authors of studies, but there are several definitions in use, which limits study comparison and the drawing of practical implications of findings.[104] Residual confounding cannot be ruled out. In conclusion, we identified a number of RR factors for psychotic relapse when doses were reduced or discontinued in patients with schizophrenia with a long duration of illness and treated with antipsychotics for several years. We found the end dose to be an important factor in relapse occurrence. Stopping the medication or reducing the dose to less than 3–5 mg HE/day increased the risk of relapse. However, there are many, not mutually exclusive, explanations for this finding. That said, a relatively fast reduction in antipsychotic dose, which was the case in most of the included studies, might have had a pronounced influence by inducing relapse or relapse-like symptoms that can be ascribed to the effect of antipsychotic withdrawal rather than to the underlying psychosis vulnerability of the patient. Other factors that increased the risk of relapse were younger age, shorter duration of illness, and short follow-up time. Reducing the dose of LAI antipsychotics was associated with a lower relapse rate than reducing the dose of oral medication, such that the relapse rate of the former was often not significantly different from that of maintenance treatment.

Patients tend to be ambivalent about using antipsychotics long-term. We need to discuss with patients or their caregivers the potential negative effects of long-term antipsychotic use, balancing these effects against the increased risk of relapse when doses of antipsychotic medication are reduced too quickly or by too much. In this way, shared treatment plans can be made as safe as possible.

Implications for Practice

Our data suggest that the dose of antipsychotic medication should not be reduced to less than 3–5 mg HE/day in patients with chronic schizophrenia, although it might be possible to lower the dose further while avoiding relapse if the dose is tapered carefully and (very) slowly, preferably over more than 10 weeks, and probably longer, considering the hyperbolic pharmacology of antipsychotics. Arguments not to reduce doses to below 3–5 mg HE may be outweighed by other considerations, such as side effects or patient preference. Gradual tapering might prevent withdrawal symptoms, which might be perceived as a psychotic relapse.[94,96] Patients should be closely monitored after every dose reduction step.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

Conflict of Interest

The authors report no financial interests or conflicts of interest.

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