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META-ANALYSIS

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Meta-Analysis: Relapse Prevention Strategies for Depression and Anxiety in Remitted Adolescents and Young Adults

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Objective: Depression and anxiety cause a high burden of disease and have high relapse rates (39%-72%). This meta-analysis systematically examined effectiveness of relapse prevention strategies on risk of and time to relapse in youth who remitted.

Method: PubMed, PsycInfo, Embase, Cochrane, and ERIC databases were searched up to June 15, 2021. Eligible studies compared relapse prevention strategies to control conditions among youth (mean age 13-25 years) who were previously depressed or anxious or with ≥30% improvement in symptoms. Two reviewers independently assessed titles, abstracts, and full texts; extracted study data; and assessed risk of bias and overall strength of evidence. Random-effects models were used to pool results, and mixed-effects models were used for subgroup analyses. Main outcome was relapse rate at last follow-up (PROSPERO ID: CRD42020149326).

Results: Of 10 randomized controlled trials (RCTs) that examined depression, 9 were eligible for analysis: 4 included psychological interventions (n = 370), 3 included antidepressants (n = 80), and 2 included combinations (n = 132). No RCTs for anxiety were identified. Over 6 to 75 months, relapse was half as likely following psychological treatment compared with care as usual conditions (k = 6; odds ratio 0.56, 95% CI 0.31 to 1.00). Sensitivity analyses including only studies with ≥50 participants (k = 3), showed similar results. Over 6 to 12 months, relapse was less likely in youth receiving antidepressants compared with youth receiving pill placebo (k = 3; OR 0.29, 95% CI 0.10 to 0.82). Quality of studies was suboptimal.

Conclusion: Relapse prevention strategies for youth depression reduce risk of relapse, although adequately powered, high-quality RCTs are needed. This finding, together with the lack of RCTs on anxiety, underscores the need to examine relapse prevention in youth facing these common mental health conditions.

Key words: anxiety disorders; depressive disorders; intervention; meta-analysis; relapse prevention

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Depressive and anxiety disorders cause a high burden of disease,[1] with crossover from one to the other,[2] substantial overlap, frequent co-occurrence,[3] and an early onset before the age of 25 in most people.[4] Even after reaching remission, the burden of these disorders is high owing to reduced quality of life[5] and high risk of relapse (39%-72%).[6-11] For major depressive disorder (MDD), the risk of relapse increases with every episode, with estimates of approximately 60% after two or more episodes.[6] Relapse rates of MDD in youth range from 47% to 67% over 6 to 24 months[5,6] and are up to 72% over 15 years.[7] For anxiety disorders, the risk of relapse differs among disorders, ranging from 39% to 58% over 12 years.[2,10,11]Anxiety disorders have an estimated relapse rate of 48% over 4 years in youth[12] and may recur as a different anxiety disorder or as MDD at a later stage in life.[2,10] Despite the early onset and risk of relapse, research focusing on relapse prevention strategies for youth in remission is scarce.[8] The current study therefore aimed to examine the effectiveness of relapse prevention strategies for youth.

Remission of MDD is defined as a period of at least 2 months in which a patient no longer meets criteria for MDD, after previously meeting the criteria.[6,13] Recovery means a person is no longer in an episode after a longer period of remission (6-12 months).[6,13] Remission of anxiety disorders may best be defined as not meeting the criteria after previously meeting the criteria for at least one anxiety disorder, without consensus on the duration.[2] Relapse is defined as a return of the disorder during remission, and recurrence refers to a new episode after recovery.[4,11] For ease of communication, and because clear definitions for

anxiety are lacking, relapse will be used to denote both relapse and recurrence.

Two main relapse prevention strategies are often used: antidepressant medication (ADM) continuation (ADMc) (eg, see [11,14]) and psychological interventions (or the combination) (eg, see [15-18]). ADMc and psychological strategies started after remission are associated with reduced risk of relapse and prolonged time to relapse in adults remitted from MDD (eg, see [6,17,19-21]). There is even meta-analytic evidence that psychological relapse prevention strategies (ie, mindfulness-based cognitive therapy and preventive cognitive therapy) are an alternative for ADMc in recurrent MDD (eg, see [18,21]). The use of ADMc in adults remitted from anxiety disorders showed a benefit over ADM discontinuation in terms of relapse rate and time to relapse up to 1-year follow-up.[11] The effectiveness is not yet established for psychological relapse prevention strategies (eg, see Scholten *et al.*[22]). However, psychological strategies used in the acute phase of illness seem to have long-term protective effects in MDD and anxiety disorders,[23] including in youth.[24]

To our knowledge, only one prior meta-analysis[8] examined relapse prevention strategies in adolescents aged 8 to 18 years. Based on 3 randomized controlled trials (RCTs) with 164 participants, ADMc outperformed pill placebo on MDD relapse rates (41% vs 67%), but not depressive symptoms, at last follow-up.[8] The meta-analysis was limited to RCTs of ADMc in MDD, and the number of studies was marginal (n = 3). Thus, to date, the evidence for relapse prevention strategies, other than ADMc in MDD, remains unclear in youth. For anxiety disorders, there is no meta-analysis to our knowledge examining relapse prevention strategies in youth.

This is the first systematic review and meta-analysis to our knowledge to examine all possible relapse prevention strategies (including ADMc and guided and unguided psychological and mind-body strategies) for youth (age 13-25 years) in remission of MDD or anxiety disorders. To examine the effectiveness, we compared relapse prevention strategies for youth in remission to control conditions on relapse rate, time to relapse, and depressive and anxiety symptoms.

METHOD

This review was preregistered in PROSPERO (PROSPERO ID: CRD42020149326) and followed the PRISMA reporting guidelines (Supplement 1, available online). PubMed, PsycInfo, Embase, Cochrane, and ERIC electronic databases were searched for articles published from database inception up to June 15, 2021, using search terms related to "depression," "anxiety," "adolescents," "young adults," "relapse," "treatment," and study type (Table S1, available online). Additionally, senior experts in the review team provided potentially eligible studies and reference lists of included studies, and prior meta-analyses were screened for relevant studies.

Using a flow diagram with inclusion and exclusion criteria, each record was selected based on title/abstract by 2 reviewers independently. Two reviewers independently assessed full-text articles. Decisions were registered in Rayyan, an online tool for systematic reviews (www.rayyan.ai). Any disagreement was resolved in consensus meetings, optionally by consulting a third reviewer.

Inclusion criteria were RCTs including participants with a mean age of 13 to 25 years who were in remission or showed at least 30% improvement in symptoms from at least 1 unipolar depressive or anxiety disorder as defined in *DSM-III*, *DSM-IV*, *DSM-5*, or *ICD-10*. The cutoff of at least 30% improvement was based on a recent RCT that included 30% to 50% improved participants to continue with a relapse prevention strategy. Inclusion of these participants did not meaningfully change conclusions.[25] By using the cutoff of 30%, this recent RCT could be included in the meta-analysis too. If randomization occurred before remission or 30% improvement (eg, only before the acute phase), the study was excluded. Control conditions could be care as usual (CAU) (including assessment only and ADMc), waitlist control, attention control, and (pill) placebo. Studies needed to report number of relapses, time to relapse, or symptoms at last follow-up and be published in peer-reviewed journals in English or Dutch. Additional data were requested for subgroups when the mean age of a study covered (part of) the range of 13-25 years and met all other eligibility criteria. Data were also requested for remitted (or 30% improved) participants when the study included participants with and without history of disorders or when randomization occurred regardless of remission status. Studies examining bipolar disorder or non–*DSM-5* anxiety disorders were excluded (eg, posttraumatic stress disorder, obsessive-compulsive disorder).

Two reviewers independently extracted data using a precoded Excel (Microsoft Corp., Redmond, Washington) form. Consensus meetings were held, and if necessary, a third reviewer was consulted to reach agreement. Extracted data were age, sex, previous disorder, number of previous episodes, sample size, relapse definition, experimental and control condition, duration of study and strategy, relapse rate, time to relapse, and mean symptoms at randomization and last-follow-up. Study authors were contacted for unreported data.

Risk of bias was assessed by 2 reviewers independently using the Cochrane Collaboration Risk of Bias tool version 2.[26] Any disagreement was resolved in consensus meetings. During risk of bias assessment, each study could score "low" (score = 0), "some concerns" (score = 1), or "high" (score = 2) on 5 domains: randomization procedures, deviations from the intended interventions, handling of missing data, consistent measurement of the outcome, and (nonselective) reporting of results. A total continuous score for the study could range from 0 (low risk of bias) to 10 (high risk of bias). Strength of evidence for the pooled outcome effect sizes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool (https://gradepro.org/).

Comprehensive Meta-Analysis version 3 was used to calculate the main outcomes of this meta-analysis: relapse rates (odds ratio [OR]), pooled relapse rates (event rates), time to relapse (hazard ratio [HR]), and mean symptoms at last follow-up (Hedges' *g*). Random-effects models were used owing to anticipated heterogeneity between studies. When available, intention-to-treat data were used. To allow for comparison of time to event data, originally reported HRs were reanalyzed to include the experimental group as reference group, or the inverse of the HR was calculated using 1/HR, $1/CI_{low}$, and $1/CI_{high}$. If studies included 2 similar control conditions, number of relapses per condition and number of participants were added to calculate the OR. To calculate Hedges' *g*, means and standard deviations of symptoms at last follow-up were pooled between the control groups.

Forest plots, heterogeneity between studies (expressed in I^2 with 95% CI calculated using the HETEROGI Stata module),[27] funnel plots, and subgroups were calculated for each outcome. Potential publication bias was assessed using visual inspection of funnel plots and with Egger's test and Duval and Tweedie trim and fill technique. Number needed to treat was calculated for relapse rates using the inverse of the risk difference.[28] Subgroup analyses on risk of bias and type of disorder were prespecified. Subgroup analyses based on remission status and symptoms at randomization were additionally performed. If a minimum of 3 studies with ≥50 participants were available for an outcome, sensitivity analyses were also conducted.

RESULTS

A total of 9,120 records were identified. Inclusion criteria were met by 20 articles, constituting 10 unique studies (Supplement 2, available online). No RCTs were identified that examined relapse prevention strategies as started after remission or 30% improvement for youth remitted from anxiety disorders. None of the RCTs investigated tapering antidepressants. One eligible study was excluded owing to unavailable outcome data.[29] All other studies reported at least 1 of the outcomes (events, time to relapse, or symptoms). This resulted in 9 included studies with a total of 582 participants (Figure 1).

Table 1 summarizes the characteristics of included studies. Four studies included a cognitive-behavioral therapy (CBT)–based strategy (n = 370) added to CAU (which could include ADMc). Two studies examined CBT as add-on to ADMc (with planned discontinuation in one; n = 132). Three studies compared ADMc with pill placebo (n = 80). Only selective serontonin reuptake inhibitors for pediatric MDD have been studied in the RCTs, which are the only MDD medications approved by the U.S. Food and Drug Administration. CBT-based relapse prevention strategies were relapse prevention CBT, cognitive-behavioral prevention, CBT booster sessions, and rumination-focused CBT. Relapse was assessed by a clinical interview in 7 studies and by clinical judgment in 2 studies. Follow-up time from baseline ranged from 6 to 75 months. Weighted mean age at randomization was 15.6 years (range, 11-24 years). Five studies did not report ethnicity or race. The 4 studies that reported on race/ethnicity were predominantly conducted among White populations (range, 52%-81%). Other ethnicities included African American, Asian, Hispanic, and multiracial. Participants could have comorbid anxiety disorders in 5 studies. In 1 study, generalized anxiety disorder was an exclusion criterion. The risk of bias was low in 2 studies, moderate in 2 studies, and high in 5 studies (Figure S1, available online). The total risk of bias score for each study is provided in the last column of Table 1.

The included studies were assumed to examine strategies that have different underlying mechanisms, and therefore separate meta-analyses were performed for psychological strategies (as add-on to ADMc; k = 6; n = 502) and for ADMc compared with pill placebo (k = 3; n = 80). When psychological relapse prevention strategies were compared with CAU control conditions, relapse in psychological treatment conditions was half as likely (OR 0.56, 95% CI 0.31 to 1.00) (Table 2) over 6 to 75 months of follow-up. The pooled relapse rates were estimated at 42% for the experimental (95% CI 26% to 60%) and 52% for the control (95% CI 32% to 71%) conditions, with number needed to treat of 9. Statistical heterogeneity was low to substantial (I^2 = 38% [95% CI 0 to 76]), and publication bias was suggested based on visual inspection of the funnel and forest plot (Figure S2, available online). When ADMc strategies were compared with pill placebo

conditions, relapse was less likely in ADMc conditions (OR 0.29, 95% CI 0.10 to 0.82) (Table 2) over 6 to 12 months of follow-up. The pooled relapse rates for ADMc trials were estimated at 42% (95% CI 23% to 63%) for the experimental and 67% (95% CI 32% to 88%) for the control conditions, with number needed to treat of 4. Statistical heterogeneity was low to substantial (I^2 = 0% [95% CI 0 to 90]), and publication bias was suggested based on visual inspection of the funnel and forest plot (Figure S2, available online). Owing to limited power in meta-analyses with <10 studies, tests for asymmetry in the funnel plots were not conducted.[38] Sensitivity analysis including only studies with >50 participants (k = 3) did not change results (OR 0.56, 95% CI 0.37 to 0.85) (Table 2). All these studies examined psychological relapse prevention strategies.

The HR was pooled across 4 studies examining psychological relapse prevention strategies that reported time to relapse data. In one additional study, no HR was calculated because of insufficient information.[30] Pooled HR was 0.64 (95% CI 0.46 to 0.91) (Table 3), suggesting that

FIGURE 1 Flowchart for Inclusion of Studies

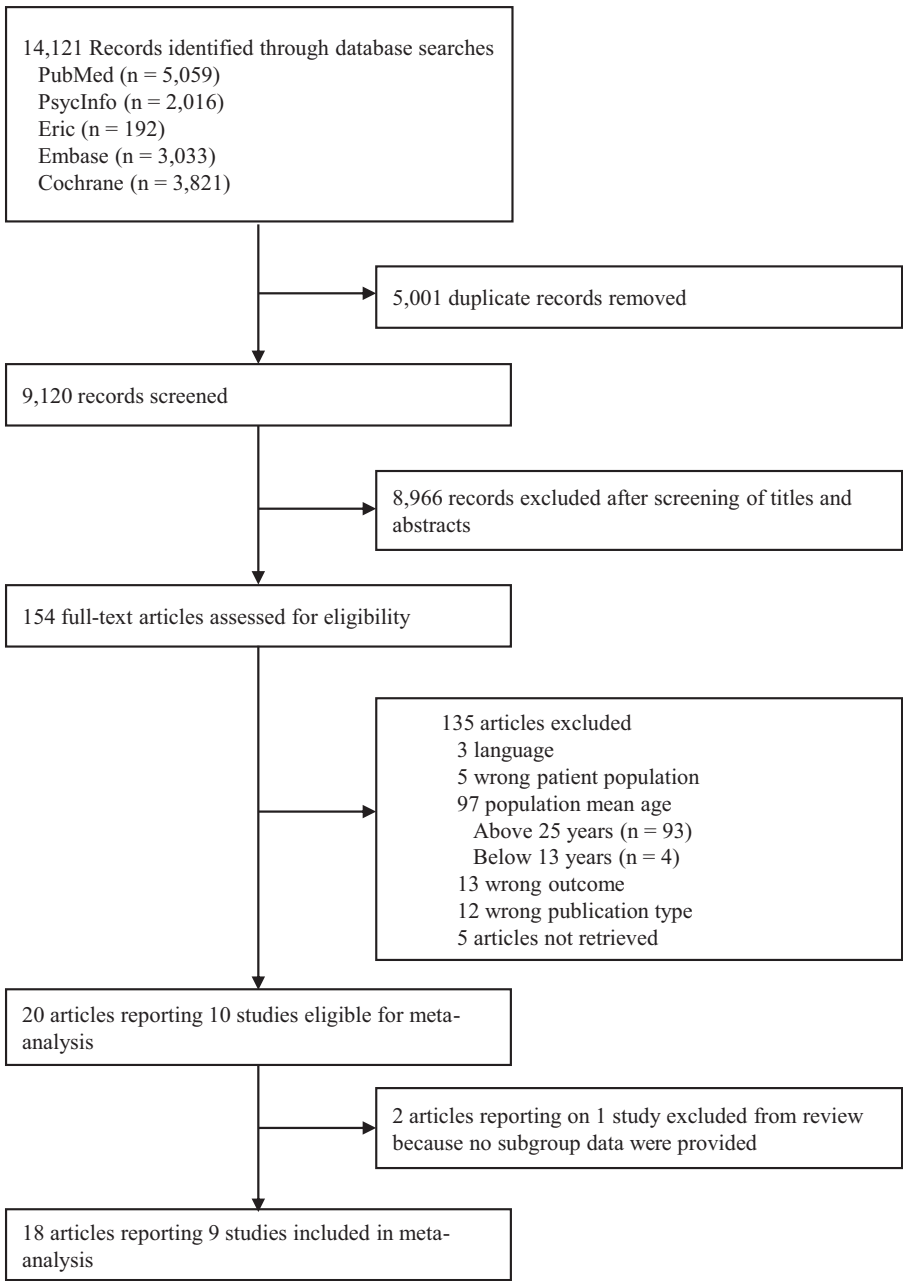

TABLE 1 Characteristics of Included Studies

First author, year of publication	Country	Intervention vs comparator	Duration of intervention and dose	Last assessment (mo)	Previous disorder	Depression severity at randomization (diagnostic tool, mean (SD))	Remission status (diagnostic tool)
Psychological relapse prevention interventions							
Bessette, 2020[30,b,c]	USA	CBT + CAU vs CAU	8 wk, weekly sessions (45-60 min)	24	MDD	CDRS-R, 27.73 (5.42)	Remission and partial remission (K-SADS)
Brent, 2015[31,b]	USA	CBT + CAU vs CAU	8 wk, weekly sessions (90 min) and 6 mo, monthly booster session	75	MDD or dysthymia	DSR, 1.50 (0.79)	Remission for at least 2 mo + subsyndromal symptoms (K-SADS)
Clarke, 1999[32,b]	USA	CBT + CAU vs CAU	Duration: NR (1-2 booster sessions)	24	MDD or dysthymia	HAM-D, 5.01 (5.81)	Remission for at least 2 wk (K-SADS)
Cook, 2019[33,b,c]	United Kingdom	CBT + CAU vs CAU	6 online guided modules (60 min, 1-2 wk per module)	15	MDD	PHQ-9, 5.97 (4.12)	Remission for at least 1 mo (SCID-I)
Psychological relapse prevention interventions + antidepressant medication continuation							
Kennard, 2008[34,b]	USA	CBT + medication vs medication	6 mo, 8-11 CBT sessions (60 min) and medication discontinuation after 12 wk	6	MDD	CDRS-R, 26.60 (5.19)	At least 50% response (CDRS-R + CGI)
Kennard, 2014[25,b,c]	USA	CBT + fluoxetine vs fluoxetine	6 mo, CBT sessions and continued medication	6	MDD	CDRS-R, 31.27 (5.64)	At least 50% response (CDRS-R)
Antidepressant medication continuation							
Cheung, 2008[35,c]	Canada	Sertraline vs placebo	1 y, 25-200 mg sertraline	12	MDD	NR	At least 50% response (HAM-D) + HAM-D <9
Cheung, 2016[36]	Canada	Citalopram vs placebo	6 mo, 10-40 mg citalopram	6	MDD	HAM-D, 1.64 (1.80)	At least 50% response (HAM-D) + HAM-D <9
Emslie, 2008[37,c]	USA	Fluoxetine vs placebo	6 mo, 10-40 mg fluoxetine	6	MDD	CDRS-R, 24.03 (4.75)	At least 50% response (CDRS-R) or remission (CDRS-R <28)

Note: CAU = care as usual; CBT= cognitive-behavioral therapy; CDRS-R = Children Depression Rating Scale–Revised; CGI = Clinical Global Impressions; DSR = depression symptom rating scale; HAM-D = Hamilton Rating Scale for Depression; K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children; MDD = major depressive disorder; NR = not reported; PHQ-9 = Patient Health Questionnaire-9; SCID-I, Structured Clinical Interview for DMS-IV *Axis I Disorders.*[a]*Scores of 0 or 1 are considered as low to moderate risk of bias, and scores above 1 are considered as high risk of bias.*[b]*Psychological intervention studies, but medication as co-intervention was allowed (or it was part of the study design).*[c]*Included participants with comorbid anxiety disorder.*

TABLE 1 Continued

Relapse definition	Age, mean (SD)	Age range	Sample (N)	Female participants, n (%)	Race/ethnicity	Risk of bias score[a]
Psychological relapse prevention interventions						
DSM-5 diagnostic criteria for any unipolar depressive disorder	15.59 (1.92)	12 to 18	29	15 (52)	4 (14%) African American; 1 (3%) Asian; 5 (17%) Hispanic; 4 (14%) Other; 15 (52%) White	0
DSR ≥4 for at least 2 wk	14.89 (1.35)	13 to 17	253	142 (56)	NR	1
DSM-III-R diagnostic criteria for any unipolar depressive disorder	NR	14 to 18	46	NR	NR	4
DSM-IV-TR diagnostic criteria for any depressive episode	20.64 (1.51)	18 to 24	63	53 (84)	NR	0
Psychological relapse prevention interventions + antidepressant medication continuation						
CDRS-R ≥40 + worsening of symptoms for at least 2 wk or clinical judgment of deterioration	14.3 (1.90)	11 to 18	46	22 (48)	12 (26%) Non-White; 34 (74%) White	4
CDRS-R ≥40 + worsening of symptoms for at least 2 wk or clinical judgment of deterioration	15.17 (1.44)	13 to 17	103	64 (62)	13 (13%) African American; 1 (1%) American native or Alaskan native; 1 (1%) Asian; 5 (5%) multiracial; 83 (81%) White	4
Antidepressant medication continuation						
Clinical judgment by treating physician (HAM-D scores were available) or intervention beyond what was permitted	15.9 (NR)	13 to 19	22	17 (77)	NR	5
Clinical judgment by treating physician or intervention beyond what was permitted	15.32 (1.25)	13 to 18	25	15 (60)	NR	4
CDRS-R ≥40 + worsening of symptoms for at least 2 wk or clinical judgment of deterioration	14.79 (1.78)	13 to 18	33	12 (36)	3 (9%) African American; 7 (21%) Hispanic; 1 (3%) Other; 22 (67%) White	1

psychological relapse prevention strategies were associated with increased time to relapse compared with CAU control groups over 6 to 75 months. Heterogeneity between studies was low to considerable ($I^2 = 11\%$ [95% CI 0 to 86]), and publication bias could not be ruled out (Figure S2, available online). One study that examined ADMc in 25 participants reported time to relapse data. The HR was 0.51 (95% CI 0.11 to 2.36) over 6 months. When pooling the HR including this ADMc study, pooled HR was 0.67 (95% CI 0.51 to 0.87). Sensitivity analysis including only studies with >50 participants (k = 3)[25,31,33] did not change results (HR = 0.69, 95% CI 0.52 to 0.91) and included only psychological relapse prevention strategies (Table 3).

Mean symptoms at last follow-up were pooled across 6 studies examining psychological relapse prevention strategies. Hedges' *g* was estimated at 0.26 (95% CI 0.08 to 0.45) (Table 4) over 6 to 75 months, indicating that psychological relapse prevention strategies were associated with lower MDD symptoms as compared to CAU control groups, although the difference was small. Statistical heterogeneity between studies was low to substantial ($I^2 = 0\%$ [95% CI 0 to 75]). Visual inspection of the funnel and forest plot suggested some publication bias in the data because all favored the experimental conditions (Figure S2, available online). One study that reported ADMc in 25 participants as compared to pill placebo reported symptoms at last follow-up. Hedges' *g* was 0.12 (95% CI −0.70 to 0.94) over 6 months. Sensitivity analysis was not performed, as only 2 studies included ≥50 participants with symptoms outcome. When combining psychological relapse prevention strategies and ADMc (k = 7), Hedges' *g* was estimated at 0.25 (95% CI 0.07 to 0.43) over 6 to 75 months.

Even though there was quite a bit variability in the strength of the outcomes, none of the subgroup analyses revealed a characteristic that could explain the variability (Tables 2-4). Subgroup analyses are reported because of clinical value. As no study was identified that primarily examined anxiety disorders, the planned subgroup analysis for difference between anxiety and depressive disorders was not performed.

Strength of the evidence (GRADE) was assessed as very low for all 3 pooled outcomes. Uncertainty in risk of bias, possible publication bias, inconsistency, and imprecision in the outcome led to downgrading of evidence. Strengths of included studies were the design (RCTs) and directness of the data (assessment of relapse with an established clinical interview or clinical assessment).

DISCUSSION

This systematic review and meta-analysis is the first to our knowledge to compare relapse prevention strategies to CAU and pill placebo control conditions in youth remitted from MDD and anxiety disorders. Nine RCTs focused on MDD, while, surprisingly, no RCTs on anxiety relapse were identified. Results suggest that overall in psychological treatment conditions (CBT-based or combined with ADMc), relapse was half as likely, time to relapse was increased, and the mean depressive symptoms at last follow-up were lower compared with the control conditions. In addition, relapse rates were substantial, with pooled relapse rates of 42% to 52% in the psychological treatment conditions and control conditions respectively. The overall time to stay well was significantly increased in the psychological treatment conditions compared with control conditions, as the hazard of experiencing a relapse was 0.64 at any given time point. The 3 studies that examined ADMc indicated that relapse was less likely when receiving ADMc as compared to pill placebo over 6 to 12 months of follow-up. Nonetheless, relapse rates were substantial as well, with 42% for ADMc and 67% for control conditions. There were insufficient data to analyze time to relapse and changes in symptoms for ADMc.

Our results of ADMc studies corroborate the results from the previous meta-analysis in youth[8] that found a reduction in relapse rates (41% vs 67%) in 164 adolescents receiving ADMc over 6 to 12 months. With regard to the psychological relapse prevention strategies, we found a substantially smaller reduction in relapse rates in 502 participants (42% vs 52%) over 6 to 75 months. This could be explained by a time effect, as risk of relapse increases with time.[19] A sensitivity analysis of all studies that included ≥50 participants (k = 3) included only psychological strategies. The results of the sensitivity analysis resembled the results of the analysis based on all 6 psychological relapse prevention strategies. This suggests that the relapse prevention strategies may indeed significantly reduce the risk of relapse by half. This is in line with relapse rates that are reported in adults who remitted who received psychological relapse prevention strategies (combined with ADM). Relapse rates ranged from 29% over 14 months to 60% over 6 years and up to 87% over 10 years follow-up.[18]

Next to improved relapse rates, we found that CBT-based strategies (combined with ADMc) are associated with increased time to relapse, which is closely comparable to findings in previous meta-analyses in adults (eg, see [6,17-21]). There was a small difference between CBT-based strategies and CAU control conditions on mean depressive symptoms at last follow-up, which was not found in the previous meta-analysis in youth.[8] This might be an effect of increased statistical power (N = 451 vs N = 164) or be explained by the different strategies (CBT-based vs ADMc). CBT-based strategies are suggested to target different

TABLE 2 Results for Odds Ratio Meta-analyses and Subgroup Analyses

	Studies	Participants	OR	(95% CI)	I^2	(95% CI)	p^a	NNT
Overall								
CBT-based vs CAU	6	502	0.56	(0.31 to 1.00)	38%	(0 to 76)		9
ADMc vs pill placebo	3	80	0.29	(0.10 to 0.82)	0%	(0 to 90)		4
Subgroups CBT-based vs CAU								
Inclusion criteria							.31	
Remission	4	370	0.70	(0.29 to 1.72)	53%	(0 to 84)		
At least 50% response	2	132	0.38	(0.18 to 0.81)	NA			
Risk of bias							.80	
High	3	169	0.69	(0.18 to 2.67)	69%	(0 to 91)		
Low-moderate	3	333	0.57	(0.36 to 0.91)	0%	(0 to 90)		
Symptoms at randomization							.61	
Above remission cutoff	1	86	0.44	(0.18 to 1.05)	NA			
Below remission cutoff	5	416	0.59	(0.27 to 1.29)	48%	(0 to 81)		
Subgroups ADMc vs pill placebo								
Inclusion criteria								
Remission	3	80	0.29	(0.10 to 0.82)	0%	(0 to 90)		
At least 50% response	0	NA	NA	NA	NA			
Risk of bias							.82	
High	2	47	0.32	(0.06 to 1.65)	NA			
Low-moderate	1	33	0.25	(0.06 to 1.07)	NA			
Symptoms at randomization[b]							1.00	
Above remission cutoff	0	NA	NA	NA	NA			
Below remission cutoff	2	58	0.34	(0.11 to 1.04)	NA			
Sensitivity analysis (≥50 participants)								
CBT-based vs CAU[25,31,33]	3	390	0.56	(0.37 to 0.85)	0%	(0 to 90)		

Note: ADMc = antidepressant medication continuation; CAU = care as usual; CBT-based = cognitive-behavioral therapy–based strategy; OR = odds ratio; NA = not applicable; NNT = number needed to treat.

[a]p *value significance between subgroups.*

[b]*Symptoms at randomization could not be retrieved for Cheung* et al. *study*[35]*; therefore, the last subgroup analysis is based on 1 study less.*

underlying mechanisms than ADMc, thereby potentially reducing symptoms that cannot be achieved by receiving ADMc only.[18]

Although none of the subgroups could explain heterogeneity between studies, they can be used to form hypotheses for further research. For example, one subgroup division based on remission and response suggests that the subgroup of participants in remission at randomization (k = 4) has a lower effectiveness than the effectiveness based on all 6 psychological strategies (Table 2). The 2 studies that are left out are those examining the add-on of a CBT-based strategy to ADM and included participants who responded and remitted. Possibly, effectiveness is higher when participants responded to treatment in the acute phase of illness and then receive an additional treatment in the relapse prevention phase. Unfortunately, use of ADMc was not randomized in identified studies of CBT-based strategies. This means CAU could include ADMc. Moreover, the difference in CAU and pill placebo as control conditions may influence the interpretation of the OR. It would be important to further study the effect of adding a psychological strategy to ADMc vs ADMc only as well as tapering of ADM combined with a psychological strategy in youth. A recent 3-arm RCT including these comparison conditions in adults with recurrent MDD demonstrated that adding a psychological strategy (ie, preventive cognitive therapy) was superior in reducing relapse risk (41% risk reduction) compared with ADMc alone, whereas ADMc alone was not superior to tapering ADM with preventive cognitive therapy.[15] Based on RCTs in adults, evidence suggests that people can taper antidepressants with a psychological relapse prevention intervention. These trials in youth are currently lacking. Nonetheless, studies in adults suggest that tapering is an option in MDD and that clinicians need to be mindful

TABLE 3 Results for Hazard Ratio Meta-analyses and Subgroup Analyses

	Studies	Participants	HR	(95% CI)	I^2	(95% CI)	p^a
Overall							
CBT-based vs CAU	4	436	0.64	(0.46 to 0.91)	11%	(0 to 86)	
Subgroups CBT-based vs CAU[b]							
Remission status							.23
Remission	2	304	0.71	(0.53 to 0.95)	NA		
At least 50% response	2	132	0.33	(0.09 to 1.12)	NA		
Risk of bias							.23
High	2	132	0.33	(0.09 to 1.12)	NA		
Low-moderate	2	304	0.71	(0.53 to 0.95)	NA		
Symptoms at randomization							.61
Above remission cutoff	1	86	0.48	(0.18 to 1.29)	NA		
Below remission cutoff	3	350	0.63	(0.39 to 1.04)	30%	(0 to 93)	
Sensitivity analysis (≥50 participants)							
CBT-based vs CAU[25,31,33]	3	390	0.69	(0.52 to 0.91)	0%	(0 to 90)	

Note: CAU = care as usual; CBT-based = cognitive-behavioral therapy–based strategy; HR = hazard ratio; NA = not applicable.
[a]*p value significance between subgroups.*
[b]*Subgroup analyses were not performed for antidepressant medication continuation owing to insufficient studies.*

of the pace of tapering, owing to potential withdrawal symptoms and (subsequent) relapse.[21,39]

Effective early interventions have the potential to reduce the long-term burden of disease in youth. When time to relapse is increased and functioning is better after relapse prevention, youth have the opportunity to become more autonomous and build meaningful relationships with others, which may in itself protect against MDD[40] and potentially against MDD relapse. Because there was variability in the strength of the outcomes, clinical and statistical heterogeneity between studies, possible publication bias and risk of bias, the strength of the evidence (GRADE) was characterized as very low for all 3 outcomes. Moreover, the studies were conducted in youth of predominantly White ethnicity, which may limit the generalizability of the findings to other ethnic groups. This means the quality of the majority of studies is suboptimal, and adequately powered, high-quality RCTs among diverse populations are needed to improve recommendations for relapse prevention in youth with these common mental health conditions.

The current results are promising and based on a couple of well-designed and well-executed trials. Therefore, first recommendations for clinical practice are to consider relapse prevention for youth depression. Given that relapse rates are as high as 52% in control conditions and remain high (42%) in the group that received CBT-based strategies (that could include ADMc), more research into relapse prevention strategies is necessary to strengthen the evidence, lower the long-term burden of disease, and further guide conclusions and recommendations for clinical practice. Even though RCTs in youth are challenging, time intensive, and often expensive, it is important to further explore relapse prevention interventions. With regard to which relapse prevention strategies should be studied, psychological strategies could be a more desirable alternative for youth. Individuals may prefer psychological strategies over ADM.[41] Moreover, negative side effects of ADM use have been reported, specifically in youth, including increased risk of suicidality and aggression.[42] Therefore, clinicians and youth may be reluctant to make a choice for ADM use in the first place, and continuation of ADM is then no option for the prevention of relapse. Moreover, youth of childbearing age may be hesitant to use ADMc owing to the potential effects of ADM on future pregnancy and offspring.[43] Use of ADM is often continued for longer periods, sometimes years, thereby causing a dilemma for youth with a desire to have a child or during pregnancy. During pregnancy, antidepressants have been associated with hypertension and diverse adverse offspring outcomes, including preterm birth, lower birth weight, and developmental problems.[44-46] Therefore, among other reasons, women often prefer psychotherapy over medications.[47]

To better understand the course of MDD and anxiety disorders in youth and how relapse prevention strategies affect it, longer follow-up lengths, regular reporting of concurrent disorders, (number of) previous mental disorders, service use and medication, and bigger samples are recommended for future RCTs. More research that studies the effectiveness of relapse prevention strategies for youth is

TABLE 4 Results for Depressive Symptoms at Last Follow-up Meta-analyses and Subgroup Analyses

	Studies	Participants	Hedges' *g*	(95% CI)	I^2	(95% CI)	*p*[a]
Overall							
CBT-based vs CAU	6	451	0.26	(0.08 to 0.45)	0%	(0 to 75)	
Subgroups CBT-based vs CAU[b]							
Remission status							.73
Remission	4	328	0.24	(0.03 to 0.46)	0%	(0 to 85)	
At least 50% response	2	123	0.31	(−0.04 to 0.67)	NA		
Risk of bias							.42
High	4	182	0.35	(0.06 to 0.65)	0%	(0 to 85)	
Low-moderate	2	269	0.20	(−0.04 to 0.44)	NA		
Symptoms at randomization							.75
Above remission cutoff	1	77	0.20	(−0.25 to 0.64)	NA		
Below remission cutoff	5	374	0.27	(0.07 to 0.48)	0%	(0 to 79)	

Note: *CAU = care as usual; CBT-based = cognitive behavioral therapy–based strategy; NA = not applicable.*
[a]*p value significance between subgroups.*
[b]*Subgroup analyses were not performed for antidepressant medication continuation owing to insufficient studies.*

needed to strengthen the evidence. Further recommendations are to register RCT study protocols, to define outcome measures using internationally recognized definitions of remission and relapse, and to assess relapse with gold-standard diagnostic interviews administered by outcome assessors blinded to randomization.

Some strengths and limitations should be noted. Strengths of our systematic review and meta-analysis are the independent assessments and specific inclusion criteria (eg, RCTs to raise certainty in the outcomes), inclusion of different strategies (including ADMc and psychological and mind-body strategies), both MDD and anxiety disorders, and a wide age range. Moreover, we expected heterogeneity and used random-effect models (which take heterogeneity into account) for the meta-analysis. Limitations are that we excluded studies reported in languages other than English or Dutch, and we did not search for unpublished studies, which may have resulted in missed studies. However, we consider the chance of missed studies low owing to the elaborate search string and examination of reference lists of included studies, which we consider strengths of the study. Owing to fairly strict inclusion criteria, generalizability is limited to studies that used re-randomization after reaching remission or 30% response. This resulted in a homogeneous sample of substantially improved participants before receiving a relapse prevention strategy (with only 1 sample that included mean symptoms above a remission cutoff), which in fact increased generalizability of our results. Additionally, some subgroups were defined after data collection, which can be viewed as a limitation. However, we deemed it necessary to disentangle studies based on baseline symptoms because this allowed us to examine differences between responders and remitters. Although the subgroups could not explain heterogeneity between studies, our results may provide input for future RCTs.

In conclusion, relapse prevention strategies seem to significantly reduce the risk of MDD relapse by half in adolescents and young adults. This is supported by sensitivity analyses including only larger studies. This finding is promising; however, together with the total lack of evidence for relapse preventive strategies in anxiety disorders, it underscores the urgent need to further study relapse prevention strategies with adequately powered, high-quality RCTs in youth facing these common mental health conditions.

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