Effects of Discontinuation of Drugs Used for Augmentation Therapy on Treatment Outcomes in Depression: A Systematic Review and Meta-analysis

Authors
Hideo Kato[1], Teruki Koizumi[1, 2], Hiroyoshi Takeuchi[1], Hideaki Tani[1, 3], Masaru Mimura[1], Hiroyuki Uchida[1]

Affiliations
1 Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan
2 Department of Psychiatry, Shimofusa Psychiatric Medical Center, Chiba, Japan
3 Kimel Family Translational Imaging-Genetics Laboratory, Centre for Addiction and Mental Health, Toronto, ON, Canada

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Hiroyuki Uchida
Department of Neuropsychiatry
Keio University School of Medicine
35 Shinanomachi
Shinjuku-ku
160-8582 Tokyo
Japan
hiroyuki_uchida@keio.jp

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ABSTRACT

Introduction There has been no consensus on whether and how long add-on drugs for augmentation therapy should be continued in the treatment of depression.

Methods Double-blind randomized controlled trials that examined the effects of discontinuation of drugs used for augmentation on treatment outcomes in patients with depression were identified. Meta-analyses were performed to compare rates of study withdrawal due to any reason, study-defined relapse, and adverse events between patients who continued augmentation therapy and those who discontinued it.

Results Seven studies were included (n = 841 for continuing augmentation therapy; n = 831 for discontinuing augmentation therapy). The rate of study withdrawal due to any reason was not significantly different between the 2 groups (risk ratio [RR] = 0.86, 95 % confidence interval [CI] = 0.69–1.08, p = 0.20). Study withdrawal due to relapse was less frequent in the continuation group than in the discontinuation group (RR = 0.61, 95 % CI = 0.40–0.92, p = 0.02); however, this statistical significance disappeared when one study using esketamine as augmentation was excluded. Analysis of the data from 5 studies that included a stabilization period before randomization found less frequent relapse in the continuation group than in the discontinuation group (RR = 0.47, 95 % CI = 0.36–0.60, p < 0.01). This finding was repeated when the esketamine study was excluded.

Discussion No firm conclusions could be drawn in light of the small number of studies included. Currently available evidence suggests that add-on drugs, other than esketamine, used for augmentation therapy for depression may be discontinued. This may not be the case for patients who are maintained with augmentation therapy after remission.

Introduction

Antidepressant drugs play a major role in the treatment of depression through significant improvement of acute symptoms and reduction in the risk of relapse [1, 2]. However, only one-third of the patients with depression respond to the first-line antidepressant treatment [3], which indicates the need of augmentation therapy (i. e., adding another psychotropic drug to the current regimen) for this difficult-to-treat population. Evidence indicates the efficacy of such augmentation therapy with several psychotropic drugs, such as lithium [4], olanzapine [5–7], aripiprazole [8–11], quetiapine [12, 13], and risperidone [14, 15]. Hence, recent guidelines suggest the use of augmentation therapy with another psychotropic drug,

such as antipsychotics and mood stabilizers, if series of monotherapies with antidepressant drugs are not successful [16–18]. Interestingly, while many efforts have been devoted to the investigation of add-on treatment for depression, the issue remains unaddressed as to whether and how long such augmentation therapy should be maintained in terms of efficacy and safety. The lack of consensus on this issue may expose patients to drugs used for augmentation for a longer period of time than necessary. This issue is especially important to avoid the adverse events of psychotropic drugs used for augmentation therapy, including motor [19, 20], metabolic [21], cognitive [22], and cardiovascular adverse events [23] caused by antipsychotics, or thyroid dysfunction caused by lithium [24]. We therefore undertook a systematic review of randomized controlled trials (RCTs) that examined the effects of the discontinuation of drugs used for augmentation therapy on treatment outcomes in depression and conducted a meta-analysis to address this relevant issue in clinical practice.

Methods

A study protocol was registered at PROSPERO before commencing data collection (Registration number: CRD42018103621). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement was followed to ensure transparent and complete reporting (**Table S1**). The study protocol is available on reasonable request. Two independent authors (H.K. and T.K.) conducted the literature search, assessed eligibility, and extracted data. Any discrepancies during these procedures were resolved through discussion.

Study Selection

RCTs to examine the effects of discontinuing medications that had been introduced to augment antidepressant treatment were identified. The MEDLINE (1950 to January 2020) and EMBASE (1950 to January 2020) databases were searched by using the following search terms: depressi * AND (withdraw * OR * OR continu *) AND (combin * OR augment * OR adjunct * OR cotreatment * OR coadministrat *). Unpublished trials were searched using Clinical Trials.gov (http://clinicaltrials.gov/); the following search terms were used: "depression" for "condition or disease" and "augmentation" for "other terms." In addition, reference lists of relevant articles identified in the electronic search for published trials were hand-searched for additional trials.

Inclusion Criteria

Clinical trials fulfilling the following 2 conditions were included: (1) RCTs to examine the effects of discontinuing versus continuing medications that had been introduced to augment antidepressant treatment after failure to pharmacotherapy with antidepressants alone, and (2) RCTs with more than half of the participants with the diagnosis of depression according to study-defined diagnoses. If several publications were found from the same investigators using overlapping samples, data from the publication with the largest number of patients were included.

Outcome Parameters

The primary outcome of interest was overall treatment failure, which was defined as withdrawal from the study for any reason. The secondary outcomes included study withdrawal due to relapse defined by the individual studies and changes in symptomatology scores. When those patients who relapsed stayed in the study until the endpoint according to the protocol, they were considered to have withdrawn from the study due to relapse in this analysis. Additionally, study withdrawal due to adverse events was analyzed as a measure of tolerability. All these parameters were obtained based on an intention-to-treat basis.

Data Extraction

Outcomes in terms of withdrawal from the study due to any reason, study-defined relapse, adverse events, changes in symptomatology scores, hospitalization, and suicide were extracted. Information on each adverse event was also extracted when available. Demographic and clinical characteristics of the subjects such as age, sex, durations of illness and treatment, study design, and interventions were extracted. Information regarding the sources of funding was also collected. We used the WebPlotDigitizer software (available at https://automeris.io/WebPlotDigitizer/) if the included studies provided the data only in the form of graphs. In the studies where relevant data were unreported, we contacted the authors for additional data.

Data Analysis

Prior to the meta-analysis, risk of bias of the included studies was assessed using the Cochrane risk of bias tool [25]. Meta-analyses were performed using the Review Manager software, version 5.3 (The Cochrane Collaboration, http://ims.cochrane.org/revman). Mean difference (MD) was estimated for continuous outcomes. We calculated pooled estimates of standardized mean difference (SMD) to compile different symptomatology scales. The inverse-variance statistical method and random-effects model to adjust for study heterogeneity were used in each estimation. Two-sided 95 % confidence intervals (CIs) were used to assess significance, according to whether the CIs included the null value. The Mantel test and random-effects model were used to calculate pooled estimates of risk ratios (RRs) for dichotomous outcomes. These analyses were also performed in a subgroup of studies that included a stabilization period before randomization and studies that did not use esketamine as an augmentation therapy, since esketamine has a unique mechanism of action and efficacy compared to other drugs. Subgroup analyses were also conducted for studies using lithium and second-generation antipsychotics, respectively, when relevant data were available in 2 or more studies. Adverse events that were assessed in 2 or more studies were meta-analyzed. Study heterogeneity was quantified using the I^2 statistics [26], with $I^2 \geq 50\,\%$ indicating significant heterogeneity. The possibility of publication bias was assessed by visual inspection of funnel plots [27]. We used 2-tailed p-values of < 0.05 to assess significance.

Results

Included Studies

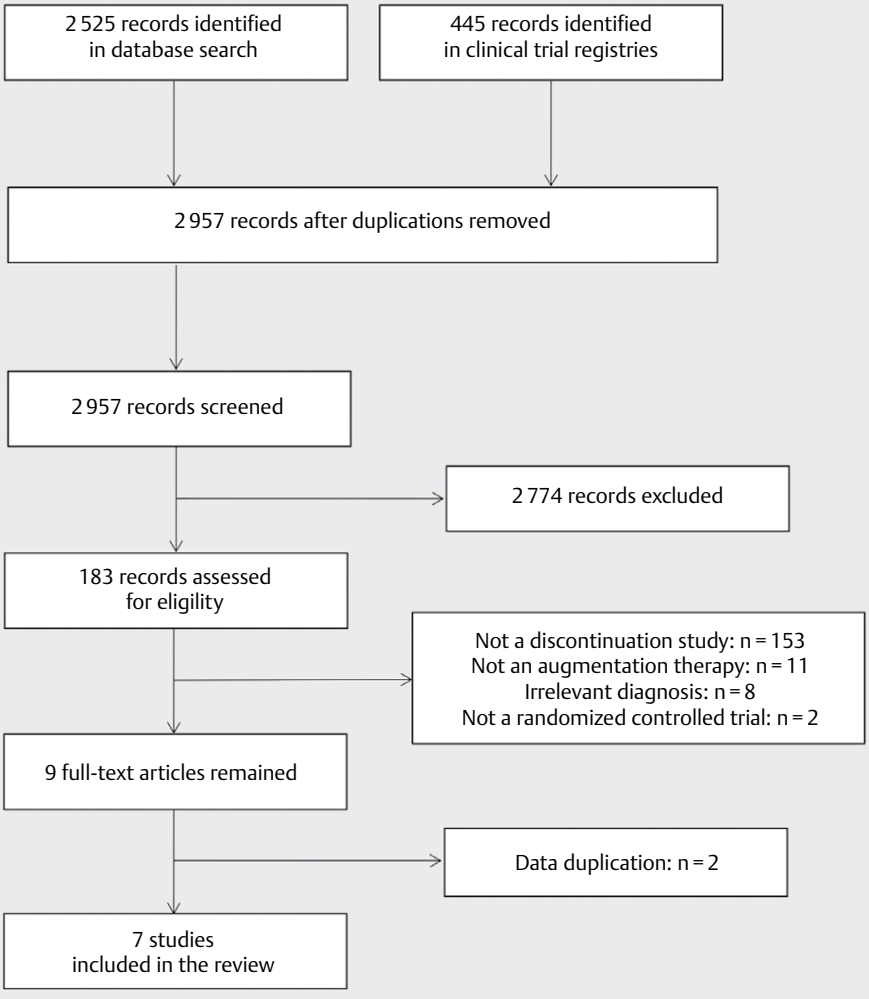
The systematic literature search yielded 2957 reports; 7 of these studies (n = 1672) fulfilled the inclusion criteria and were therefore included in the meta-analysis (n = 841 for continuing augmentation therapy; n = 831 for discontinuing the augmentation therapy) (▶ **Fig. 1**) [28–34]. The characteristics of these studies are shown in ▶ **Table 1** and ▶ **Table 2**. In 6 studies, patients were diagnosed with study-defined treatment-resistant depression (▶ **Table 2**). Five studies in this meta-analysis included a stabilization period in which patients were maintained on both antidepressants and augmentation drugs, after they exhibited remission before the RCT phase [28, 29, 32–34] (▶ **Table 2**). The stabilization period ranged between 2 weeks and 1 year; the study by Hardy et al. [28] had the longest stabilization period of 1 year. Antidepressants used varied depending on the studies; however, selective serotonin reuptake inhibitors were most frequently prescribed. Lithium (n = 2), risperidone (n = 2), esketamine (n = 1), olanzapine (n = 1), and edivoxetine (n = 1) were used for augmentation therapy. Previous use of electroconvulsive therapy before study entry was described only in 1 study [28].

Risk of Bias

Risks of bias of the included studies are summarized in **Table S2**. All studies were double-blind RCTs. The methodology of random sequence generation and allocation concealment was unclear in all the included studies. Furthermore, blinding of outcome assessment was often unreported, leading to "unclear risk" for detection bias in all studies. Withdrawal cases were adequately explained. Two studies (29 %) did not report full data on adverse effects and were judged to have "high risk" of selective reporting.

Withdrawal from the Study

Overall withdrawal rates from the study were comparable between the patients who continued the augmentation drug added on to the antidepressant and those who discontinued it (n = 7, n = 1.672, RR = 0.86, 95 % CI = 0.69–1.08, p = 0.20) (▶ **Fig. 2a**). Also, when the



▶ **Fig. 1** PRISMA flow diagram of the literature search. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomized controlled therapy.

▶ **Table 1** Characteristics of included studies at the beginning of randomized controlled trail phase.

First author (Year)	Augmentation drug	Sample size	Male sex	Age, years[a]	Age at first episode, years[a]	Number of previous episodes[a]	Duration of current episode, years[a]	MADRS total score[a]	CGI-S score[a]	Presence of psychotic features
Hardy (1997)	Lithium	6	0%	79 (6)	63 (12)	N/A	N/A	5.2 (2.2)	N/A	N/A
	Placebo	6	50%	74 (5)	59 (8)	N/A	N/A	2.3 (2.1)	N/A	N/A
Bauer (2000)	Lithium	14	21%	47.4 (16.9)	43.0 (15.2)	1.7 (2.2)[b]	0.54 (0.34)	N/A	2.4 (0.5)	N/A
	Placebo	15	60%	47.4 (11.4)	41.3 (10.9)	2.2 (1.0)[b]	0.68 (0.40)	N/A	2.6 (0.5)	N/A
Rapaport (2006)	Risperidone	122	28.7%	47.8 (11.4)	29.9 (12.6)	N/A	2.0 (3.7)	6.8 (4.7)	N/A	0.8%
	Placebo	119	43.7%	48.4 (12.0)	30.8 (14.0)	N/A	2.0 (3.8)	8.1 (4.6)	N/A	3.4%
Alexopoulos (2008)	Risperidone	32	31%	62.3 (7.2)	38.1 (13.6)	N/A	1.4 (1.9)	9.2 (5.0)	N/A	3.1%
	Placebo	31	58%	62.9 (7.3)	40.0 (17.3)	N/A	2.4 (5.7)	8.7 (5.2)	N/A	9.7%
Brunner (2014)	Olanzapine	221	35.3%	44.9 (11.3)	31.7 (12.4)	3.5 (4.2)	1.50 (2.66)	5.4 (3.8)	1.7 (0.7)	0%
	NA	223	31.4%	44.1 (12.3)	31.7 (13.4)	3.8 (9.7)	1.75 (3.21)	5.4 (4.0)	1.7 (0.8)	0%
Oakes (2015)	Edivoxetine	294	24.1%	47.5 (11.9)	N/A	N/A	N/A	4.4 (2.9)	1.7 (0.7)	N/A
	Placebo	292	22.6%	46.9 (12.3)	N/A	N/A	N/A	4.4 (2.9)	1.7 (0.7)	N/A
Daly[c] (2019)	Esketamine	90	35.6%	45.2 (12.12)	32.5 (11.42)[e]	N/A	2.15 (3.29)	3.7 (3.7)[f]	N/A	0%
	Placebo	86	31.4%	46.2 (11.16)	33.4 (11.41)[e]	N/A	2.12 (2.83)	4.6 (5.3)[f]	N/A	0%
Daly[d] (2019)	Esketamine	62	38.7%	47.2 (11.00)	36.2 (13.25)[e]	N/A	2.33 (3.72)	10.8 (5.5)[f]	N/A	0%
	Placebo	59	61.3%	46.7 (9.76)	34.0 (10.54)[e]	N/A	2.72 (4.88)	10.5 (4.8)[f]	N/A	0%

[a] Values are shown as mean (standard deviation). [b] Including the current episode. [c] Stable remission group. [d] Stable response group. [e] Age when diagnosis of major depressive disorder was confirmed. [f] Extracted from the figure in the report. CGI-S, Clinical Global Impressions-Severity of illness; MADRS, Montgomery-Asberg Depression Rating Scale; NA, not applicable; N/A, not available; RCT, randomized controlled trial; SD, standard deviation.

▶ **Table 2** Study design of included studies.

First author (Year)	Stabilization period after remission before RCT	Duration of RCT phase	Major inclusion criteria regarding age and illness severity	Augmentation drug	Dose ofaugmentation drug	Antidepressants used	Definition of relapse
Hardy (1997)	1 year	2 years	– >65 years of age – Diagnosis of major unipolar depressive episode according to DSM-III-R – "Refractory" depression (failed to show improvements after ≥ 6 months at maximal doses of 1 antidepressant) – GDRS score of < 20 – MADRS score of < 15 – MMSE score of > 20 – Responded to lithium augmentation – Absence of depressive symptoms for at least 1 year on lithium augmentation	Lithium	150 mg (n = 1) 300 mg (n = 10) 900 mg (n = 1)	Amitriptyline (n = 6) Doxepine (n = 3) Imipramine (n = 1) Tranylcypromine (n = 1) Nortriptyline (n = 1)	– Hospitalization for depression – Need of adjustment of antidepressant medication – MADRS score of ≥ 15 or change from baseline of ≥ 10 – GDRS score of > 20 or change from baseline of ≥ 10
Bauer (2000)	2–4 weeks	4 months	– ≥ 18 years of age – Diagnosis of major depressive episode according to DSM-III-R – "Refractory" depression (failed to respond to an adequate trial of 1 antidepressant) – HAMD-21 score of ≤ 10, CGI-S score of ≤ 3 or CGI-I score of 2 or 3 following a 6-week lithium augmentation phase, and being judged by 2 independent psychiatrists as asymptomatic	Lithium	– Doses to achieve lithium blood levels of 0.5–1.0 mmol/L	Amitriptyline (n = 16) Clomipramine (n = 3) Nortriptyline (n = 3) Dibenzepin (n = 2) Trazodone (n = 1) Paroxetine (n = 1) Clomipramine (n = 1) Imipramine (n = 1) Maprotiline (n = 1) Venlafaxine (n = 1)	– HAM-D-21 score of ≥ 15 – CGI-S score of ≥ 4
Rapaport (2006)	None	24 weeks	– 18–85 years of age – Diagnosis of MDD, single or recurrent episode, with or without psychotic features according to DSM-IV – "TRD" (resistant to respond to ≥ 1 adequate antidepressant trials for ≥ 6 weeks) – HAMD-17 score of ≤ 7 or CGI-S score of 1 or 2	Risperidone	– Open-label augmentation phase, 1.1 ± 0.6 mg/day (mean ± SD) – Double-blinded phase, 1.2 ± 0.6 mg/day	Citalopram	– CGI-I score of 6 or 7 – HAMD-17 score of ≥ 16 – Discontinuation due to lack of therapeutic effect – Self-injury or suicidal intent
Alexopoulos (2008)	None	24 weeks	– ≥ 55 years of age – Diagnosis of MDD, single or multiple episode, with or without psychotic features according to DSM-IV – "Resistant depression" (resistant to respond to ≥ 1 adequate antidepressant trials for ≥ 6 weeks) – HAMD-17 score of ≤ 7 or CGI-S score of 1 or 2	Risperidone	– Acute treatment phase, 0.7 ± 0.3 mg/day – Double-blind phase, 0.8 ± 0.3 mg/day	Citalopram	– CGI-I score of 6 or 7 – HAMD-17 score of ≥ 16 – Discontinuation due to lack of therapeutic effect – Self-injury or suicidal intent

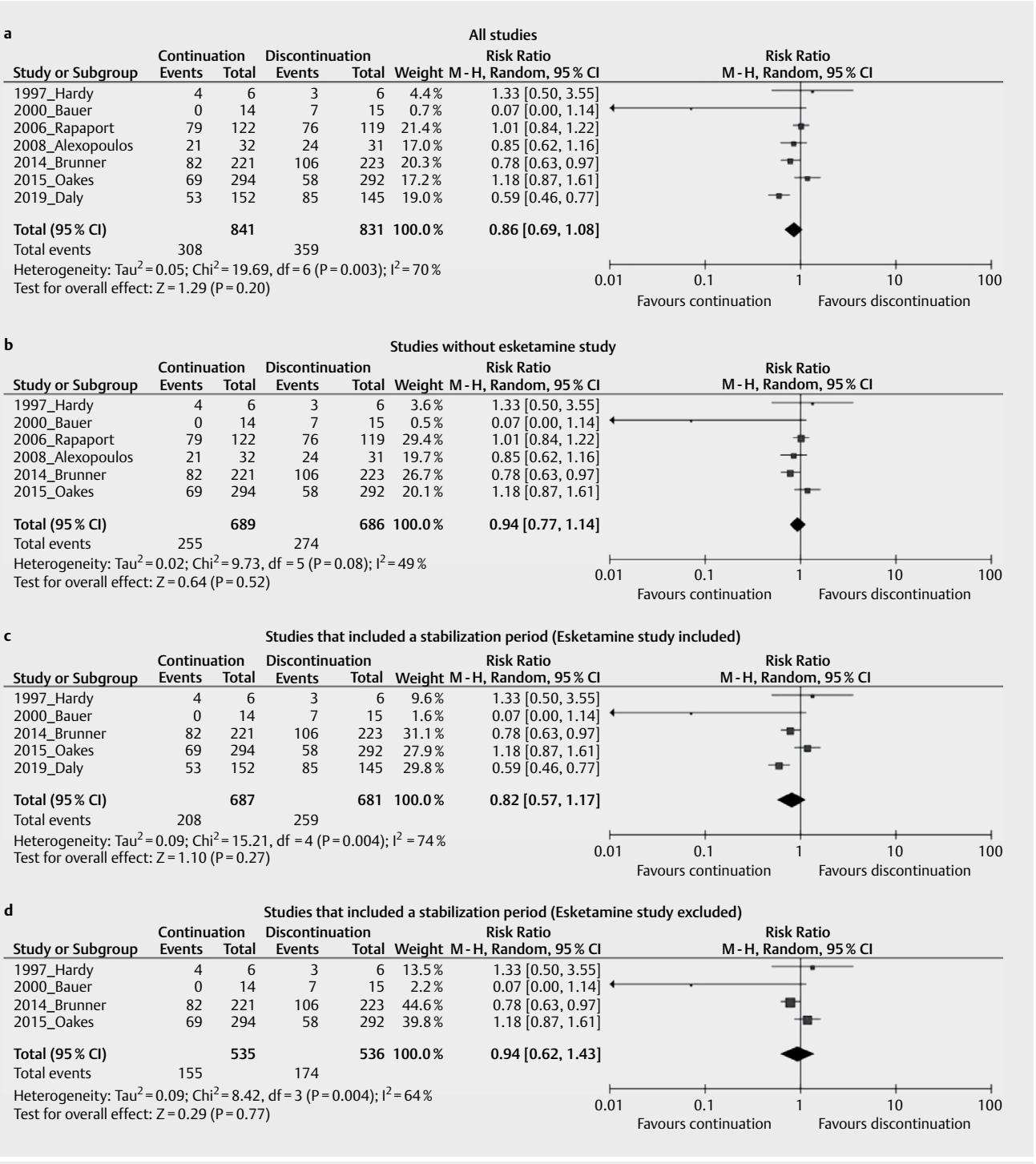
▶ **Table 2** Continued.

First author (Year)	Stabilization period after remission before RCT	Duration of RCT phase	Major inclusion criteria regarding age and illness severity	Augmentation drug	Dose ofaugmentation drug	Antidepressants used	Definition of relapse
Brunner (2014)	12 weeks	27 weeks	– 18–65 years of age – Diagnosis of single or recurrent unipolar MDD without psychotic features according to DSM-IV-TR – "TRD" (resistant to respond to ≥ 2 different antidepressants, for ≥ 6 weeks for each medication) – Absence of psychotic features – Maintained ≥ 50 % improvement with augmentation therapy compared to baseline on MADRS and CGI-S score of ≤ 3 during 12-week stabilization phase	Olanzapine	3–18 mg/day	Fluoxetine	– 50 % increase in the MADRS score from randomization with concomitant CGI-S score increase to ≥ 4 – Hospitalization for depression or suicidality – Discontinuation due to lack of efficacy or worsening of depression or suicidality
Oakes (2015)	12 weeks	2 weeks	– ≥ 18 years of age – Diagnosis of MDD according to DSM-IV-TR – MADRS score of ≤ 10 for ≥ 2 weeks following SSRI + edivoxetine treatment	Edivoxetine	12 or 18 mg/day	Escitalopram (n = 167) Citalopram (n = 114) Fluoxetine (n = 107) Sertraline (n = 106) Paroxetine (n = 80) Fluvoxamine (n = 12)	– MADRS score of ≥ 14 or CGI-S score increase of ≥ 2 – Discontinuation due to lack of efficacy, worsening of depression, or suicidality
Daly (2019)	12 weeks	Variable duration[a]	– 18–64 years of age – Diagnosis of current or single- episode (≥ 2 years) MDD according to DSM-5 – "TRD" (resistant to respond to ≥ 1 different antidepressants, for ≥ 4 weeks for each medication) – Absence of psychotic features – MADRS score of ≤ 12 during the last 4 weeks of the maintenance phase (stable remission group) – ≥ 50 % reduction from baseline in MADRS score in the last 2 weeks of the maintenance phase but not achieving remission (stable response group)	Esketamine	– Open-label augmentation phase, 56 mg or 84 mg for 2 times per week – Maintenance phase, once weekly for the first 4 weeks and then individualized to weekly or biweekly based on the severity of depressive symptoms – Double-blinded phase, weekly or biweekly based on the severity of depressive symptoms	SNRI (n = 191) SSRI (n = 86)	– MADRS score of ≥ 22 at 2 consecutive assessments with an interval of 5 to 15 days or hospitalization due to symptom worsening – Suicide attempt, suicide prevention, or completed suicide – Another clinically relevant event suggestive of relapse

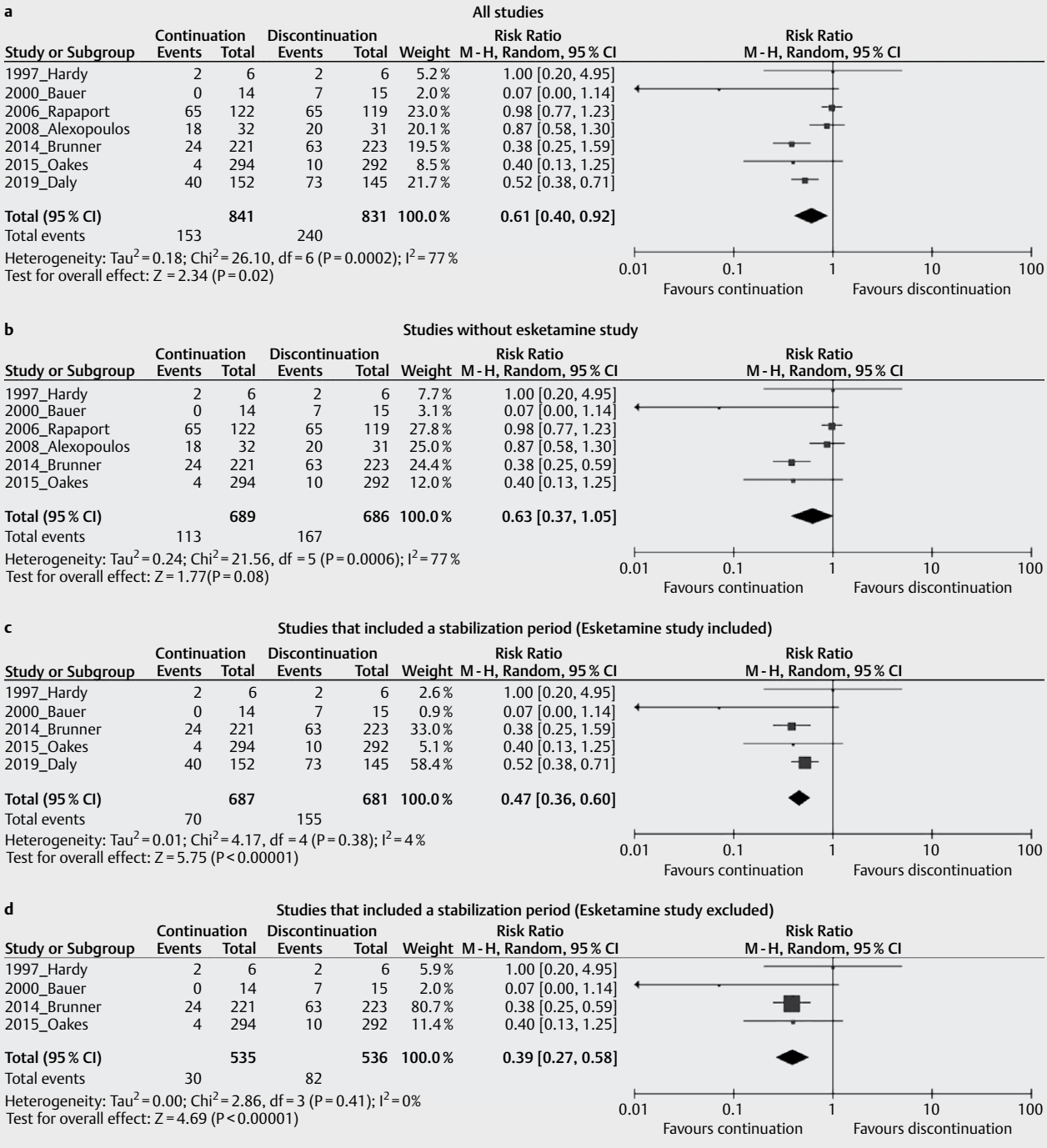
CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impressions-Severity of illness; DSM, Diagnostic and Statistical Manual of Mental Disorders; GDRS, Geriatric Depression Rating Scale; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, Major Depressive Disorder; MMSE, Mini-Mental State Examination; SNRI, serotonin norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TR, Text Revision; TRD, treatment-resistant depression; RCT, randomized controlled trial. [a] From 10.1 weeks to 19.4 weeks as a median duration in each treatment group; the intervention was continued until the required number of relapse was achieved or until the study was recommended to be stopped based on the results of interim analysis.

study by Daly et al. [34] which used esketamine for augmentation therapy was excluded, there was no significant difference between the 2 groups (n = 6, n = 1.375, RR = 0.94, 95 % CI = 0.77–1.14, p = 0.52) (▶ **Fig. 2b**). Subgroup analysis of the data from 5 studies [28, 29, 32–34] that included a stabilization period before RCT found no significant difference between the 2 groups (n = 5, n = 1.368, RR = 0.82, 95 % CI = 0.57–1.17, p = 0.27) (▶ **Fig. 2c**). This finding remained unchanged when the esketamine study [34] was excluded (n = 4, n = 1.071, RR = 0.94, 95 % CI = 0.62–1.43, p = 0.77) (▶ **Fig. 2d**). Subgroup analyses for lithium and second-generation antipsychotics also failed to find statistical differences, respectively (lithium: n = 2, n = 41, RR = 0.37, 95 % CI = 0.01–15.49, p = 0.60; second-generation antipsychotics: n = 3, n = 748, RR = 0.89, 95 % CI = 0.74–1.06, p = 0.18).

The rate of study withdrawal due to relapse was significantly lower in the continuation group than that in the discontinuation group



▶ **Fig. 2** Study withdrawal due to all causes in the continuation and discontinuation groups.



▶ **Fig. 3** Study withdrawal due to relapse in the continuation and discontinuation groups.

(n = 7, n = 1.672, RR = 0.61, 95% CI = 0.40–0.92, p = 0.02) (▶**Fig. 3a**). When the esketamine study [34] was excluded, the difference showed a trend level without any statistical significance (n = 6, n = 1.375, RR = 0.63, 95% CI = 0.37–1.05, p = 0.08) (▶**Fig. 3b**). Subgroup analysis of the data from studies that included a stabilization period found a significantly lower relapse rate in the continuation group than that in the discontinuation group (n = 5, n = 1.368, RR = 0.47, 95% CI = 0.36–0.60, p < 0.00001) (▶**Fig. 3c**). This finding was unchanged when the esketamine study [34] was excluded (n = 4, n = 1.071, RR = 0.39, 95% CI = 0.27–0.58, p < 0.00001) (▶**Fig. 3d**). When the trial by Hardy et al. [28] that included the longest stabilization phase of 1 year was excluded from these 5 studies, the significant difference was not affected (n = 4, n = 1.356, RR = 0.45, 95% CI = 0.34–0.60, p < 0.00001). On the other hand, subgroup analyses for lithium and second-generation antipsychotics did not find statistical differences between the continuation and discontinuation

groups, respectively (lithium: n = 2, n = 41, RR = 0.32, 95 % CI = 0.02–6.11, p = 0.45; second-generation antipsychotics: n = 3, n = 748, RR = 0.70, 95 % CI = 0.40–1.24, p = 0.22).

No significant differences were found in the study withdrawal rates due to adverse events between the 2 groups in the whole dataset (n = 4, n = 1.334, RR = 1.41, 95 % CI = 0.84–2.36, p = 0.20) (**Fig. S1a**) or in a subgroup studies that included a stabilization period (n = 2, n = 1.030, RR = 0.72, 95 % CI = 0.09–6.10, p = 0.76) (**Fig. S1b**).

Symptomatology Scores

There were no significant differences in score changes in the Montgomery-Asberg Depression Rating Scale (MADRS) (n = 4, n = 1.334, MD = − 0.60, 95 % CI = − 3.08–1.88, p = 0.64) (**Fig. S2a**), Hamilton Depression Rating Scale-17 items (HAMD-17) (n = 2, n = 304, MD = 0.20, 95 % CI = − 1.66–2.06, p = 0.83) (**Fig. S3a**), the Clinical Global Impression-Severity of Illness (CGI-S) scale (n = 3, n = 1.051, MD = − 0.07, 95 % CI = − 0.41–0.27, p = 0.68) (**Fig. S4a**), Hamilton Depression Rating Scale-21 items (HAMD-21) (n = 1, n = 21, MD = 0.30, 95 % CI = − 3.02–3.62, p = 0.86) (**Fig. S5a**), and 2 rating scales (i. e., the MADRS and HAMD-21) combined (n = 5, n = 1.355, SMD = − 0.05, 95 % CI = − 0.28–0.18, p = 0.66) (**Fig. S6a**) between the continuation and discontinuation groups. With reference to the subgroup analysis of the data from studies that included a stabilization period, no significant differences were found in the MADRS (n = 2, n = 1.030, MD = − 1.77, 95 % CI = − 5.54–2.01, p = 0.36) (**Fig. S2b**), CGI-S scale (n = 3, n = 1.051, MD = − 0.07, 95 % CI = − 0.41–0.27, p = 0.68) (**Fig. S4b**), HAMD-21 (n = 1, n = 21, MD = 0.30, 95 % CI = − 3.02–3.62, p = 0.86) (**Fig. S5b**), and 2 rating scales (i. e., the MADRS and HAMD-21) combined (n = 3, n = 1.051, SMD = − 0.14, 95 % CI = − 0.47–0.18, p = 0.38) (**Fig. S6b**) between the 2 groups. Symptomatology scores were available in only 1 study for lithium and 3 studies for second-generation antipsychotics. A subgroup analysis for the second-generation antipsychotics found no significant differences in score changes of the MADRS (n = 3, n = 748, MD = − 0.67, 95 % CI = − 4.64–3.30, p = 0.74) or HAMD-17 (n = 2, n = 304, MD = 0.20, 95 % CI = − 1.66–2.06, p = 0.83) between the continuation and discontinuation groups.

Adverse Events

Twenty-two adverse events were assessed in 2 or more studies. Among these 22 adverse events (**Fig. S7a–b**), only 3 showed statistically significant differences as follows: less frequent depression (n = 2, n = 1.030, RR = 0.34, 95 % CI = 0.13–0.87, p = 0.02) (**Fig. S7c** and frequent headache (n = 6, n = 1.660, RR = 1.59, 95 % CI = 1.12–2.25, p = 0.009) (**Fig. S7k**) and hyperhidrosis (n = 2, n = 615, RR = 5.13, 95 % CI = 1.16–22.76, p = 0.03) (**Fig. S7l**) in the continuation group than that in the discontinuation group. Subgroup analysis of the 3 studies in which second-generation antipsychotics were used as augmentation drugs [30–32] compared the incidence rates of 16 adverse events between the continuation and discontinuation groups (**Fig. S8a–p**) and found no significant differences between them.

Publication Bias

A funnel plot of the included 7 studies with respect to overall withdrawal from the study indicated the low possibility of publication bias (**Fig. S9**).

Discussion

This meta-analysis of double-blind RCTs found no significant differences in study withdrawal rates due to any reason or due to the majority of adverse events between patients with depression who continued adjunctive psychotropic drugs used for augmentation therapy and those who discontinued these drugs. We found a significantly lower study withdrawal rate due to relapse in the continuation group than that in the discontinuation group; however, this statistical significance became insignificant when one trial using esketamine as an augmentation therapy was excluded. In contrast, in a subgroup of studies that included a stabilization period after remission before entering the RCT phase, the rate of study withdrawal due to relapse was lower in the continuation group than that in the discontinuation group, regardless of whether esketamine study was included or not. These findings suggest that augmentation therapy may be discontinued, but this may not be the case for patients who were maintained with augmentation therapy after remission. Moreover, the results of this analysis indicate the need for continuing esketamine for relapse prevention in the treatment of depression although the available data are still limited.

When relapse was focused as a treatment outcome, a subgroup analysis of studies that included a stabilization period after remission found a lower study withdrawal rate in the continuation group than in the discontinuation group, regardless of whether esketamine study was included or not. This finding seems reasonable since these 5 studies included the patients who benefited from such augmentation therapy in terms of relapse prevention. Moreover, the mean number of previous depressive episodes was up to 3.7 in these 4 studies. Since repetitive episodes of depression are characteristic of bipolar depression [35], potential patients who could later develop bipolar disorder may have been included in these studies. In fact, 2 of the 3 drugs used for augmentation therapy in these 4 studies are indicated for bipolar disorder. The results in this meta-analysis provide important knowledge for further discussions with regard to similarities and differences between treatment-resistant depression and bipolar depression.

Ketamine, an N-methyl-D-aspartate receptor-modulating anesthetic, has a rapid-onset, strong antidepressant efficacy for patients with treatment-resistant depression [36–41]. However, the duration of its efficacy is only a few days [37]. Ketamine has a unique mechanism of action via the glutamatergic system, which is different from other conventional antidepressants. Therefore, the response and remission of depression achieved by the use of ketamine could be essentially transient and qualitatively different from those by other antidepressants. In fact, relapse after discontinuation of ketamine in the treatment of depression was frequently observed in the study included in this meta-analysis [34]. On the other hand, it should be noted that there has been only one RCT that examined the effect of discontinuing ketamine used as an augmentation therapy on relapse in the treatment of depression. Moreover, this study included an antidepressant switch when esketamine was introduced, whereas other studies included in this review [28–33] continued the same antidepressants. These issues clearly warrant further investigations on whether and how ketamine treatment should be continued for relapse prevention in depression.

One systematic review reported frequent adverse events associated with adjunctive treatment with antipsychotics for depres-

sion as follows: akathisia, sedation, abnormal metabolic laboratory results, and weight gain [42]. In contrast, we did not find any significantly different incident rates of these symptoms between the 2 treatment strategies although the discontinuation rate due to adverse events was numerically lower in the discontinuation group than that in the continuation group. However, in the light of a variety of adverse events, including motor [19, 20], metabolic [21], cognitive [22], and cardiovascular [23] caused by antipsychotics and thyroidal and parathyroidal dysfunction caused by lithium [24], physicians should be aware of these potential adverse events in the maintenance treatment of depression. This is especially true for patients with mood disorders due to increased sensitivity to antipsychotics in these patients [43].

There are several limitations of this study. First, the number of studies included in this meta-analysis, especially those examining efficacy of ketamine, was small. The results of our analysis highly depend on which trials are included. Moreover, it should be noted that edivoxetine has not been approved for adjunctive treatment for major depressive disorder because of negative findings in phase II and III trials [44]. Second, the study design was different among the 7 studies included. The definitions of relapse, treatment resistance, study durations, subject characteristics, durations of adjunctive therapy, augmentation drugs, and methods of discontinuing drugs used for augmentation therapy varied among them. Among them, various definitions of treatment resistance as detailed in ▶ **Table 2** should be especially acknowledged since the degree of treatment resistance could affect both the likelihood of acute response and the probability of relapse [3]. Moreover, the trial duration varied from 2 weeks to 2 years; the period of 2 weeks may be short to evaluate long-term outcomes of this chronic illness and side effects of drugs used for augmentation. Third, adverse events were not comprehensively or thoroughly assessed in the majority of the trials, which clearly limits the interpretation of the findings of this meta-analysis. Lastly, 6 of the 7 studies were funded by pharmaceutical companies, which needs to be acknowledged when the results in favor of the continuation strategy are interpreted.

It should be noted that no firm conclusions could be drawn in the light of the small number of studies included. In addition, no clear answer was obtained as to how long augmentation therapy should be continued for the maintenance treatment of depression. Still, currently available evidence suggests that add-on drugs used for augmentation therapy for depression may be discontinued with the exception of esketamine. However, for patients who are maintained with augmentation therapy after remission, discontinuation of augmentation therapy may need to be carefully considered.

Conflicts of Interest

H. K. has nothing to declare. T. K. has nothing to declare. H. Tak. has received research grants from Japan Society for the Promotion of Science (JSPS), Japan Agency for Medical Research and Development (AMED), SENSHIN Medical Research Foundation, and Novartis Pharma; Fellowship grants from Astellas Foundation for Research on Metabolic Disorders, the Canadian Institutes of Health Research (CIHR), Centre for Addiction and Mental Health (CAMH) Foundation, and the Japanese Society of Clinical Neuropsychopharmacology (JSCNP); Speaker's fees from Kyowa, Janssen, Meiji Seika Pharma, Mochida, Otsuka, Sumitomo Dainippon Pharma, and Yoshitomiyakuhin; and manuscript fees from Sumitomo Dainippon Pharma. H. Tan. has received grants from Eli Lilly, the Japanese Society of Clinical Neuropsychopharmacology, and Canadian Insitutes of Health Research; manuscript or speaker's fees from Otsuka, Sumitomo Dainippon Pharma, Wiley, and Yoshitomi Yakuhin. M. M. has received grants or consultant fees from Eisai, Astellas Pharma, GlaxoSmithKline, and Meiji, and received speaker's honoraria from Astellas Pharma, Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, Meiji, Otsuka Pharmaceutical, Pfizer, and Yoshitomi Yakuhin within the past 3 years. H. U. has received grants from Eisai, Otsuka Pharmaceutical, Dainippon-Sumitomo Pharma, and Meiji-Seika Pharmaceutical; speaker's honoraria from Otsuka Pharmaceutical, Dainippon-Sumitomo Pharma, Eisai, and Meiji-Seika Pharma; and advisory panel payments from Dainippon-Sumitomo Pharma within the past 3 years.

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