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Relapse Following Electroconvulsive Therapy for Schizophrenia: A Systematic Review and Meta-analysis

Nobuatsu Aoki[1,2,3], Aran Tajika[4], Taro Suwa[5], Hirotsugu Kawashima[5], Kazuyuki Yasuda[6], Toshiyuki Shimizu[1], Niina Uchinuma[6], Hirotaka Tominaga[7], Xiao Wei Tan[8], Azriel H. K. Koh[8], Phern Chern Tor[8], Stevan Nikolin[2,3], Donel Martin[2,3], Masaki Kato[1], Colleen Loo[2,3], Toshihiko Kinoshita[1], Toshi A. Furukawa[4], and Yoshiteru Takekita[1,*]

[1]Department of Neuropsychiatry, Faculty of Medicine, Kansai Medical University, Osaka, 570-8506, Japan; [2]Discipline of Psychiatry and Mental Health, University of New South Wales, Sydney, NSW, 2031, Australia; [3]Black Dog Institute, Sydney, NSW, 2031, Australia; [4]Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, 606-8501, Japan; [5]Department of Neuropsychiatry, Kyoto University Graduate School of Medicine, Kyoto, 606-8507, Japan; [6]Department of Neuropsychiatry, University of Yamanashi Faculty of Medicine, Yamanashi, 409-3898, Japan; [7]Department of Psychiatry, Mojimatsugae Hospital, Fukuoka, 800-0112, Japan; [8]Department of Mood and Anxiety, Institute of Mental Health, 539747, Singapore

[*]To whom correspondence should be addressed; Yoshiteru Takekita, Department of Neuropsychiatry, Faculty of Medicine, Kansai Medical University, 10-15 Fumizono-cho Moriguchi, Osaka 570-8506, Japan (takekity@takii.kmu.ac.jp)

***Background*: Evidence regarding schizophrenia relapse following acute electroconvulsive therapy (ECT) is sparse compared with that for depression, and we have no clear consensus on relapse proportions. We aimed to provide longitudinal information on schizophrenia relapse following acute ECT. Study Design: This systematic review and meta-analysis included randomised controlled trials (RCTs) and observational studies on post-acute ECT relapse and rehospitalization for schizophrenia and related disorders. For the primary outcome, we calculated the post-acute ECT pooled relapse estimates at each timepoint (3, 6, 12, and 24 months post-acute ECT) using a random effects model. For subgroup analyses, we investigated post-acute ECT relapse proportions by the type of maintenance therapy. *Study Results*: Among a total of 6413 records, 29 studies (3876 patients) met our inclusion criteria. The risk of bias was consistently low for all included RCTs (4 studies), although it ranged from low to high for observational studies (25 studies). Pooled estimates of relapse proportions among patients with schizophrenia responding to acute ECT were 24% (95% CI: 15-35), 37% (27-47), 41% (34-49), and 55% (40-69) at 3, 6, 12, and 24 months, respectively. When continuation/maintenance ECT was added to antipsychotics post-acute ECT, the 6-month relapse proportion was 20% (11-32). Conclusion: Relapse occurred mostly within 6 months post-acute ECT for schizophrenia, particularly within the first 3 months. Relapse proportions plateaued after 6 months, although more than half of all patients could be expected to relapse within 2 years. Further high-quality research is needed to optimise post-acute ECT treatment strategies in patients with schizophrenia.**

Key words: electroconvulsive therapy/schizophrenia/systematic review/meta-analysis/relapse/rehospitalisation

Introduction

Electroconvulsive therapy (ECT) is a somatic treatment strategy widely used for treatment-resistant depression and catatonia.[1] Generally, antipsychotics (APs) are used to treat schizophrenia, although their effects are limited.[2–4] When treatment with multiple APs fails, ECT may be an effective treatment option.[5]

Several reviews evaluating the role of ECT in schizophrenia have shown that acute ECT is effective at achieving short-term improvements in psychiatric symptoms for up to 6 weeks, reduction of relapse and rehospitalization risk, and early hospital discharge.[1,5–7] However, insufficient evidence exists to determine whether these benefits can be maintained over medium- to long-term timeframes.[5,7] Hence, considerable variation can be observed in the guidelines for the use of ECT for schizophrenia among countries worldwide. In Asia, the technique is widely used for schizophrenia, unlike in Western countries, where it is not as proactively recommended.[1,5,8–15]

An acute course of ECT involves treatments twice or thrice weekly, typically for a total of 6-12 treatments, although in cases of schizophrenia, a longer treatment

period is sometimes necessary.[16–19] If the patient is not fully well after acute ECT, even with AP maintenance therapy, or if multiple severe relapse episodes occur, continuation/maintenance ECT (C/M-ECT) once a week or less may be considered to maintain remission and prevent relapse.[20] C/M-ECT must be reviewed every 6-12 months to tailor treatment to individual patient needs while assessing the risks and benefits. Nevertheless, there are no absolute guidelines on the timing of its termination.[1]

Relapse and hospitalization for schizophrenia necessitate enormous costs at both the individual and societal levels; its chronic and persistent repetition leads to poor social functioning.[21–23] More than 80% of patients with first-episode schizophrenia experience a relapse within 5 years of their initial recovery.[24] Similarly, 63% of such individuals relapse within 2 years of discharge from the hospital, and most of those who relapse are rehospitalized.[25] Thus, understanding how likely relapse is after acute ECT is a critically important clinical issue. However, consistent findings regarding medium- to long-term changes in schizophrenia relapse proportions following acute ECT have not yet been obtained.[7,20]

To properly evaluate the benefits of acute ECT in treating schizophrenia, we conducted the first systematic review and meta-analysis reporting medium- to long-term relapse and rehospitalization proportions following acute ECT.

Methods

Search Strategy and Selection Criteria

In accordance with the PRISMA guidelines (Supplementary Materials, pp. 2-3), we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) and observational studies reporting relapse after acute ECT treatment for schizophrenia.[26] The study protocol was registered at PROSPERO (CRD42022341402).

We searched Embase, PubMed, Web of Science, and Cochrane Library databases for studies published in English from database inception until the last search on March 7, 2024. Using the aforementioned databases and the ClinicalTrials.gov registry and similar repositories, we also searched for unpublished studies.

The search keywords included "electroconvulsive therapy," 'schizophrenia', and synonyms thereof, referring to related disorders. Detailed search methods including search terms and search strings are described in Supplementary Materials (pp. 4-12).

We also searched the reference lists of relevant publications. In some cases, multiple reports referred to the same study or to overlapping patient populations (eg, studies published in different years with study periods that overlapped with nationwide observational studies). In these situations, only the newest or largest studies were included.

Two independent researchers (NA and YT) conducted the literature search. Titles and abstracts of the retrieved studies were screened to identify potentially eligible publications. Disagreements were resolved by consensus or via a third researcher's opinion (ToS).

The eligibility criteria were applied in the screening phase. The full texts of all potentially relevant articles were screened. Criteria for inclusion in this meta-analysis were:

(a) Schizophrenia and related disorders patient after acute ECT;
(b) RCTs and observational studies that reported on rehospitalization due to relapse or worsening of symptoms;
(c) Studies reporting remission to non-remission outcomes post-acute ECT;
(d) Relapse proportion (or raw data enabling calculation of the relapse proportion) were provided or could be obtained by contacting the authors;
(e) Four or more participants[27];

Data Extraction and Primary Outcomes

Summary estimate data for each study were extracted independently by 2 researchers (NA and YT). Extracted data were compared and inconsistencies were resolved through consensus or a third researcher's (AT) opinion. Duplicate reports were identified and excluded during the review process using study titles, trial numbers, methodologies, and specific patient characteristics. If the study in question involved interventions other than acute ECT, only the acute ECT group was included. Studies using the same data reporting different timepoints were included as one study.[28,29] Data extraction from published figures was performed using Engauge Digitizer 12.1.[30] The first data extraction was performed on August 25, 2022.

The primary outcome was defined as the pooled relapse proportion estimate for patients post-acute ECT with schizophrenia. Relapse data was extracted at 4 different timepoints: 3 months (≥2 months and <4 months), 6 months (≥4 months and <9 months), 12 months (≥9 months and <18 months), and 24 months (≥18 months). When RCTs compared different maintenance therapies, we pooled all the arms: differences in maintenance therapies were examined through subgroup analyses. Both relapse and rehospitalization were considered as relapse events. If both were reported, we opted to use relapse. Studies that did not report on relapse or rehospitalization were excluded during the primary analysis phase. To the greatest extent possible, we extracted data on the aforementioned outcomes from each study's endpoint data. However, participants with unclear post-acute ECT responses or who were not discharged were excluded from the denominator when calculating the relapse proportions.

Data Synthesis, Analysis, and Quality Assessment

For the primary outcome, the relapse proportion after acute ECT was combined for each timepoint; 3 months, 6 months, 12 months, and 24 months.

We used the command *metan* of Stata/IC 18.0 (Stata Corporation, College Station) to estimate pooled relapse proportions according to a random effects model.[31–33] We pooled the relapse estimates, assuming relapse approximated risk, with a meta-analysis weighting each series on the overall pooled estimate according to its standard error. To normalise the sampling distribution and stabilise the variance, a double arcsine square root transformation was used.[32,34–36] This transformation was chosen due to the small sample size and extreme proportions.[35,36] After analysis, the final pooled estimates with 95% confidence intervals (CIs) were back-transformed to facilitate interpretation.[37] The recommended DerSimonian Laird random effects models were run to account for variation between studies and increase the generalizability of conclusions.[31] We explored between-study heterogeneity using τ^2 and I^2 statistics, with a P value of less than .05 and I^2 greater than 50% taken to indicate significant heterogeneity.[38,39] However, although I^2 is a measure developed to estimate heterogeneity in comparative data, there is no specific test to assess heterogeneity in meta-analyses using proportional data. Therefore, I^2 is recommended to be used with caution, noting that there are some issues with its application to this type of data.[36,40] It should be noted that I^2 is usually high in meta-analyses of this type, owing to the small sample sizes, and the characteristics of proportional data that result in high variance. Thus, we reinforced our evaluations of heterogeneity by investigating the 95% prediction interval (PrI), based on the prediction distribution of future research taking into account the heterogeneity of the random effects model.[41]

We conducted the following pre-planned subgroup analyses. The first was the change in relapse proportions by maintenance therapy type post-acute ECT. Maintenance therapy with APs alone and that with APs and C/M-ECT combined were evaluated separately. We excluded studies in which 20% or more of the target population in each maintenance treatment group received a different maintenance therapy.[42]

We also examined the following subgroups: study design (RCTs/observational studies), outcome type (relapse/rehospitalization), publication year (1999 or earlier/2000-2009/2010 or later), location (North America/Asia/Europe/Oceania), diagnosis (schizophrenia/schizoaffective disorder/other), and indication for ECT (treatment-resistant schizophrenia/clozapine-resistant schizophrenia/other).

The risk of bias was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist, which is a recommended assessment tool for systematic reviews of prevalence and incidence (Supplementary Materials, p. 21).[43,44] Two evaluators (NA and YT) used the JBI Checklist to evaluate the risk of bias. In the event of differences in opinion, a consensus was reached through discussion, or a third researcher (AT) was brought in to resolve the difference.

Results

Search Results

Our initial search yielded 6413 records. Title screening revealed that 5287 of these were unrelated or duplicates and were excluded (Figure 1). Of the remaining 1126 records, 1097 were excluded during further screening and evaluation of the abstract/full text, leaving 29 records (3876 patients) (4 RCTs [141 patients], 25 observational studies [3735 patients]). We were also able to include 5 unpublished datasets (from 5 observational studies) (see Supplementary References[98,106,107,113,115], [pp. 44, 45]). Included studies were published or conducted between 1993 and 2023. The number of reports for each timepoint was: 15 at 3 months (1143 patients), 20 at 6 months (1502 patients), 17 at 12 months (2821 patients), and 6 at 24 months (443 patients).

The studies, patients, and treatment characteristics are summarised in Supplementary Table S4 (pp. 17-20). A list of the studies is given in Supplementary References.

Studies, Patients, and Treatment Characteristics

Fourteen studies reported only relapse as the primary outcome (9.0%; 347 patients), 12 reported only rehospitalization (87.4%; 3389 patients), and 3 reported both (3.6%; 140 patients). Of the 3811 individuals whose sex was indicated, 1818 (47.7%) were female and 1993 (52.3%) were male. The mean age of the participants was 38.1 (standard deviation [s.d.] 12.2) years, and the mean disease duration was 9.5 (s.d. 5.9) years. The mean reported baseline severity scores were 51.7 (s.d. 9.9; 10 studies, 271 patients) on the Brief Psychiatric Rating Scale and 110.4 (s.d. 12.3; 3 studies, 61 patients) on the Positive and Negative Syndrome Scale. The average sample size per study was 133.7 (range 4-2074); the average follow-up period was 14.7 months (range 2-36). Supplementary Table S4 (pp. 17-20) summarizes study, patient, and maintenance therapy characteristics.

Risk of Bias Assessment

In terms of overall risk of bias, 4 (13.8%), 14 (48.3%), and 11 (37.9%) studies had high, moderate, and low risks of bias, respectively. RCTs consistently had low bias risks, whereas observational studies were quite varied, ranging from low to high (4 RCTs [low: 3 studies, moderate: 1 study], 25 observational studies [low: 8 studies, moderate: 13 studies, high: 4 studies]). Among the items with particularly low percentages of low ratings was "sample size" (17.2%) (Supplementary Tables S5, S6 and Figure S1; [pp. 21-24]).

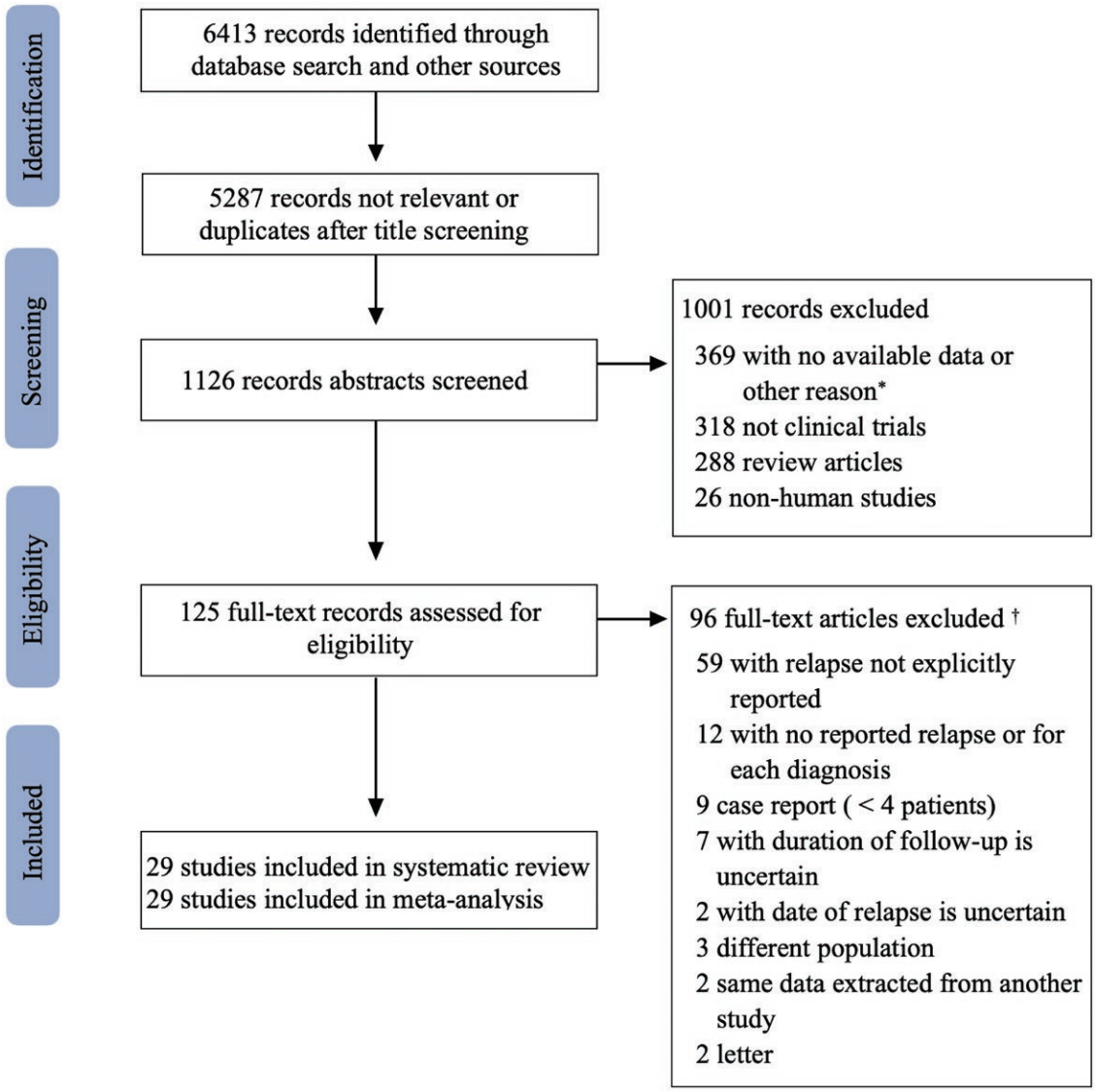

Figure 1. Search and Selection Process. PRISMA Flow Diagram. *242 Records Without Available Data, 79 Trial Registries Without Results, 29 Non-ECT Studies, and 19 Records Not Involving Patients with Schizophrenia and Related Disorders. †Reasons for Exclusion Detailed After Full-Text Screening are Described in Supplementary Table S2 (pp. 13-15). ECT, Electroconvulsive Therapy

Primary Outcome

The post-acute ECT pooled relapse estimates at each timepoint were as follows: 24% (95% CI, 95% PrI: 15-35, 0-67) at 3 months, 40% (27-47, 4-79) at 6 months, 41% (34-49, 17-68) at 12 months, and 55% (40-69, 12-94) at 24 months (Figure 2). There was high heterogeneity at all timepoints (3 months: $P < .001$, $I^2 = 89.0\%$, $\tau^2 = 0.149$; 6 months: $P < .001$, $I^2 = 90.8\%$, $\tau^2 = 0.160$; 12 months: $P < .001$, $I^2 = 82.8\%$, $\tau^2 = 0.060$; 24 months: $P < .001$, $I^2 = 82.6\%$, $\tau^2 = 0.095$).

Subgroup Analyses

With regard to the type of maintenance therapies, of the 29 studies included, the number of studies reporting on APs alone as maintenance therapy after acute ECT therapy at each timepoint were as follows: 11 (949 cases), 15 (1062 cases), 12 (2548 cases), and 4 (287 cases) studies at 3, 6, 12, and 24 months, respectively. In contrast, the number of studies that reported on APs + C/M-ECT maintenance therapy following ECT at each timepoint were as follows: 9 (174 cases), 10 (184 cases), 10 (172 cases), and 3 (78 cases) studies at 3, 6, 12, and 24 months, respectively. Supplementary Table S7 (pp. 25-26) lists the demographic characteristics and various clinical parameters of these studies, subgrouped by maintenance therapy. Post-acute ECT pooled relapse proportion estimates by the type of maintenance therapy were as follows. APs alone group: 33% (95% CI, 95% PrI: 20-47, 0-82), 47% (34-59, 6-90), 47% (39-55, 22-72), and 51% (45-57, 39-64) at 3, 6, 12, and 24 months, respectively, (Supplementary Figure S2, p. 28). APs + C/M-ECT group: 12% (5-22, 0-48), 20%

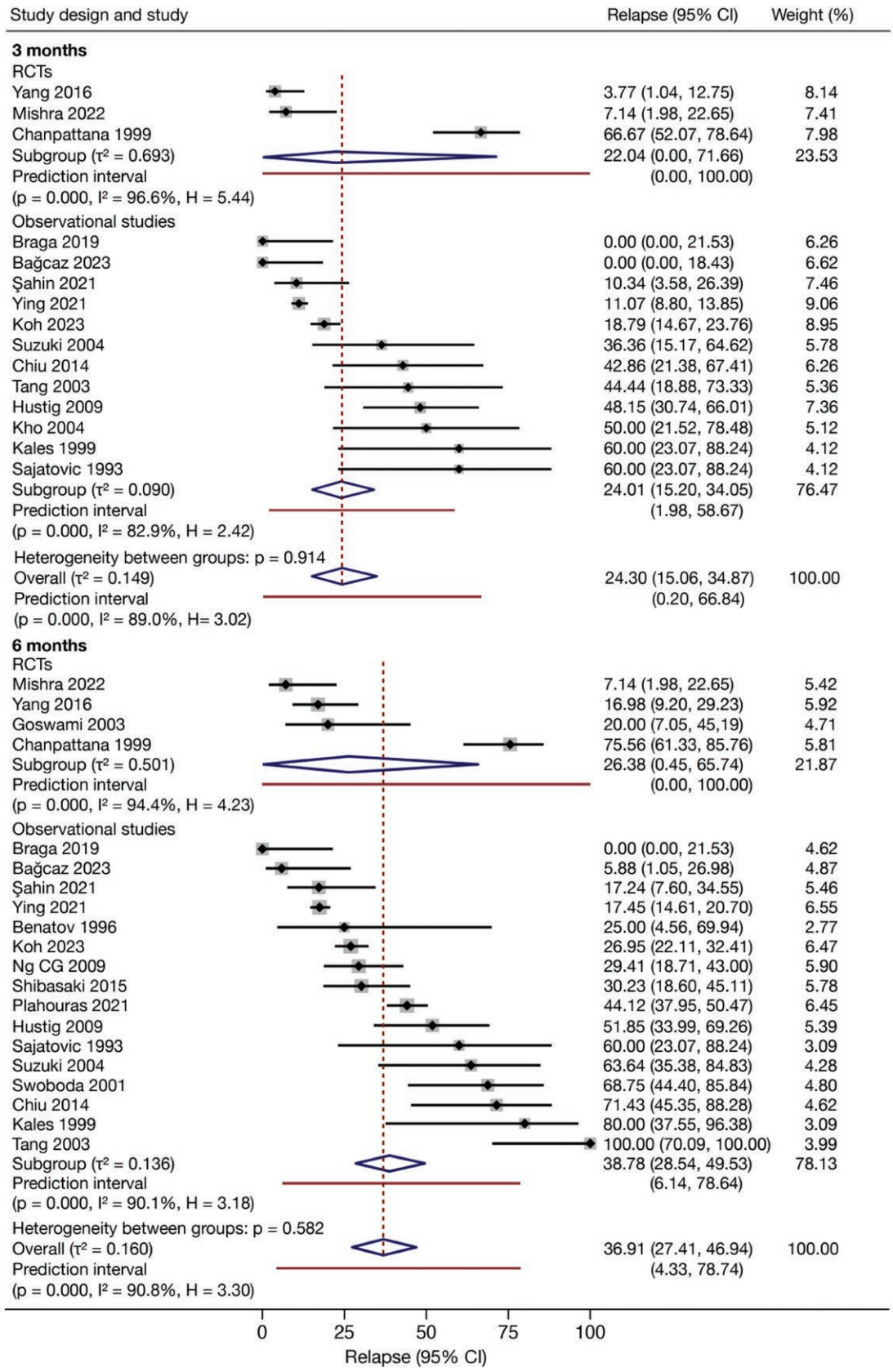

Figure 2. Forest Plot: Pooled Relapse Proportion Estimates at 3, 6, 12, and 24 Months After Acute ECT. ECT, Electroconvulsive Therapy

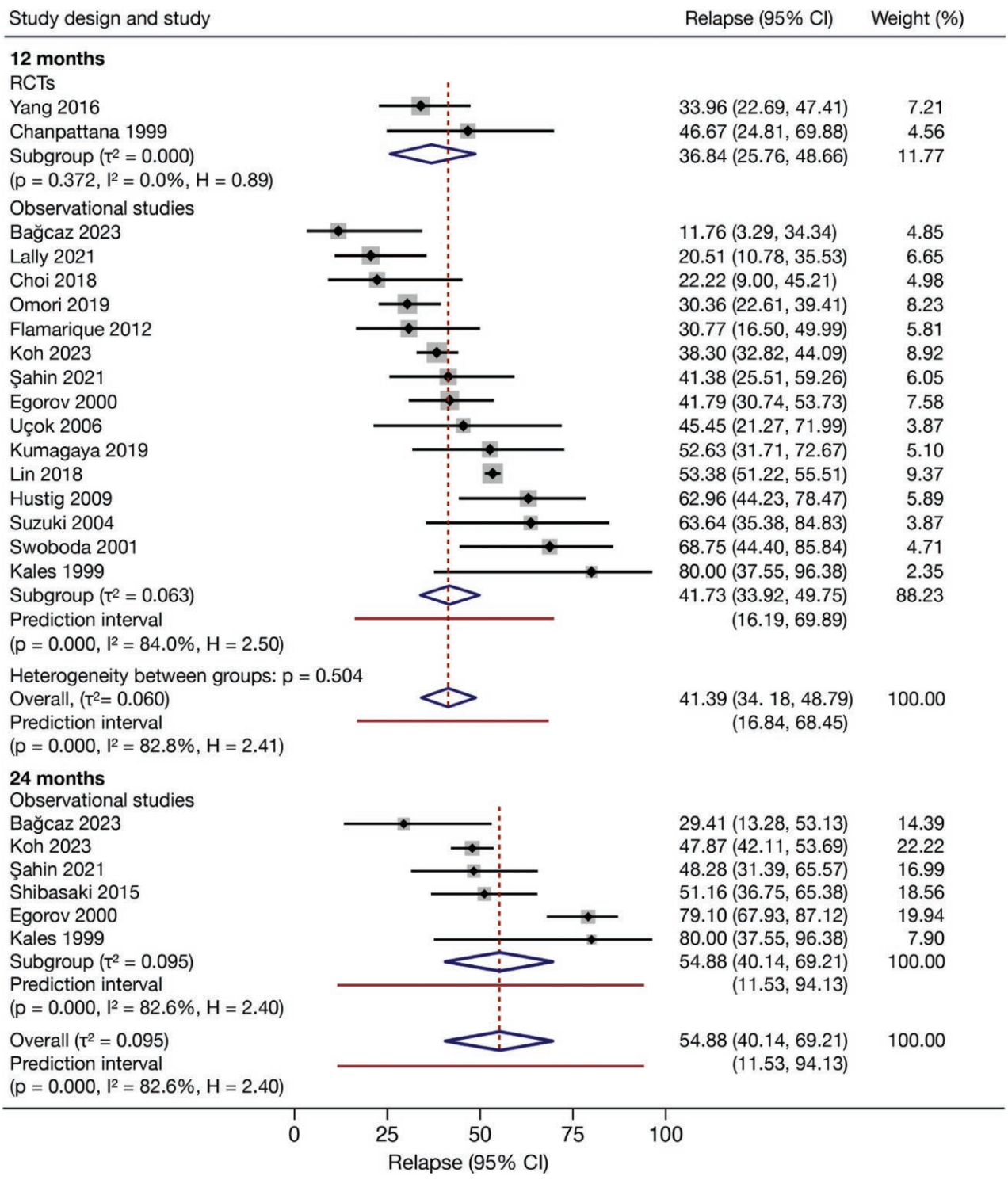

Figure 2. Continued

(11-32, 0-60), 30% at (21-40, 10-57), and 40% (29-51, 0-98) at 3, 6, 12, and 24 months, respectively, (Supplementary Figure S3, p. 29). Figure 3 and Supplementary Table S8 (p. 27) show the pooled relapse estimates for both maintenance therapies at each timepoint.

In the subgroup analysis, while heterogeneity was observed across publication years at all timepoints, no intergroup heterogeneity was detected for study design, outcome type, and location (Supplementary Table S9 and Figures S4-S8; pp. 30-40). Finally, due to the difficulty of determining strict grouping guidelines and an insufficient number of samples, we were unable to conduct a subgroup analysis on diagnosis and ECT indication criteria.

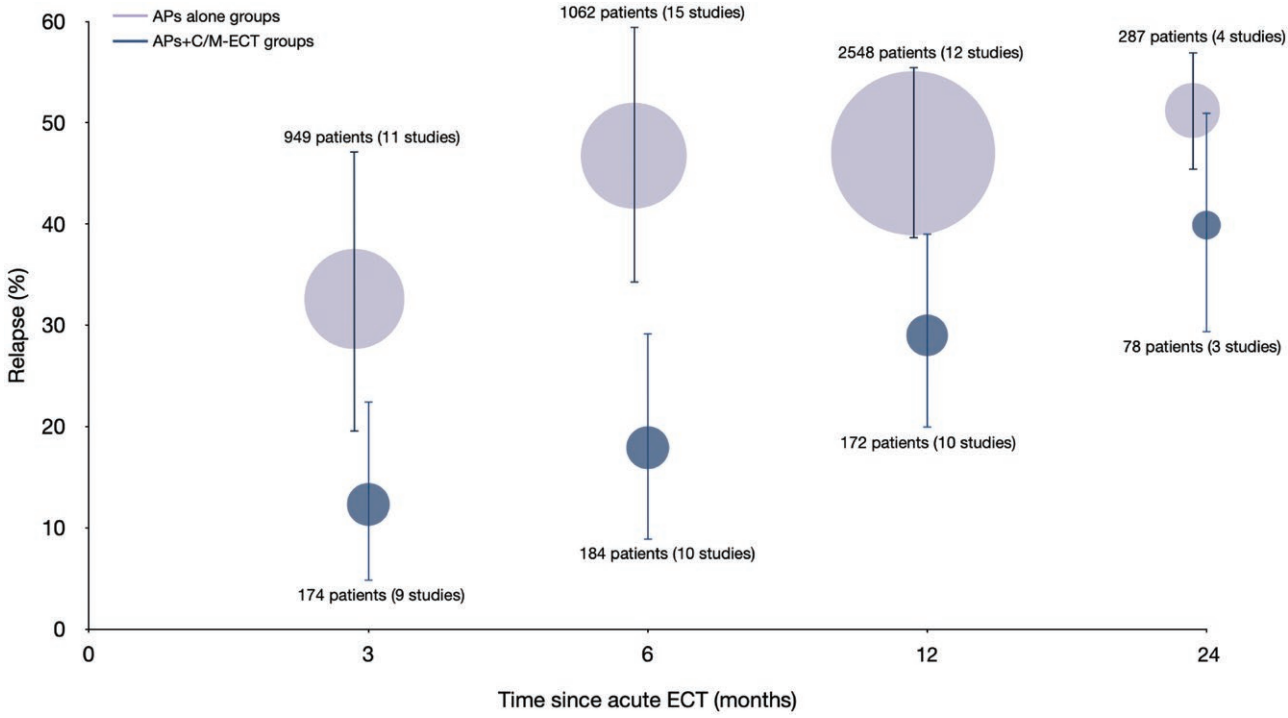

Figure 3. Pooled Relapse Proportion Estimates From APs Alone and C/M-ECT + APs Groups at 3, 6, 12, and 24 Months. The Size of Each Circle is Proportional to the Total Number of After Acute ECT Patients at the Start of all the Studies Contributing to That Pooled Estimate. Aps, Antipsychotics; C/M-ECT, Continuation/Maintenance ECT; ECT, Electroconvulsive Therapy

Discussion

Main Findings

To the best of our knowledge, this is the first systematic review and meta-analysis to characterize short- and medium- to long-term relapse proportions after acute ECT for patients with schizophrenia. We conducted a broad literature search across a variety of evidence sources, ranging from highly structured research such as RCTs to real-world approaches with observational studies, and identified 29 studies (3876 patients) to include in this analysis. The main finding of this study was that relapse after acute ECT for schizophrenia was observed in 25% of patients in the first 3 months, was approximately 40% after 6 months, and plateaued afterward to reach approximately 55% after 2 years.

Our results support those of a previous study indicating that schizophrenia relapse within 6 months of acute ECT is common[45] and suggest that reducing relapse in the first 6 months following acute ECT may be an important clinical goal. A meta-analysis by Leucht et al. demonstrated that, after treatment of acute symptoms with common APs, continuing AP therapy is highly effective at preventing schizophrenia relapse. When AP maintenance therapy was continued, the relapse proportion was approximately 12% for up to 3 months, 18% for 4-6 months, 27% for 7-12 months, and 44% for 13-36 months; in contrast, when APs were discontinued, the proportions were 37%, 50%, 64%, and 79%, respectively.[46] The group who discontinued APs after successful acute therapy with APs had similar outcomes to the results shown in this study. In other words, after discontinuing a therapy to which patients had demonstrated a response in the acute phase, relapse within 6 months was common; in particular, the highest likelihood of relapse was seen within the first 3 months. Unlike other treatments for major mental illnesses, acute ECT is often terminated once the efficacy goals have been achieved, and therefore relapse prevention has been a major clinical challenge for ECT.[47–50] Although a Cochrane Review concluded that acute ECT is effective at improving clinical symptoms of treatment-resistant schizophrenia,[5] our results show that, unfortunately, relapse is all too common following successful acute ECT. This tendency to relapse following acute ECT was similar to findings of studies in patients with depression. Jelovac et al.[50] used data from RCTs up to 2013 to conduct a meta-analysis on relapse after acute ECT for depression and found that the relapse proportion was approximately 25% at 3 months, 40% at 6 months, and 50% at 2 years. However, in recent years large-scale multicenter RCTs and meta-analyses have provided robust evidence that concomitant use of antidepressants and lithium, concomitant use of antidepressants and C/M-ECT, optimization of C/M-ECT treatment strategies, and other post-acute ECT approaches can prolong treatment response and further suppress relapse.[51–55] Although the combination of APs and C/M-ECT and the use of mood stabilisers are reportedly effective for preventing relapse

after acute ECT in schizophrenia, most reports were from observational studies, and knowledge regarding effective treatment strategies is still lacking.[20,45,56–58]

Subgroup Analyses

In the subgroup analysis, we investigated how to maximise treatment effects after acute ECT. With maintenance therapy using APs alone, the relapse proportions after acute ECT at 3, 6, 12, and 24 months were 33%, 47%, 47%, and 51%, respectively. In contrast, relapse proportions with maintenance therapy using APs + C/M-ECT combined were consistently lower at 12%, 20%, 30%, and 40%, respectively. In other words, the effects of acute ECT may be sustained by concomitant use of APs + C/M-ECT. This finding agrees with that of a systematic review by Ward et al.,[20] which suggested that the use of APs and C/M-ECT combined was effective in preventing relapse. Notably, maintenance therapy using APs + C/M-ECT maintained the relapse proportions within the first 6 months, the period during which relapse was most common, at approximately 20%. A proportion of the population does not relapse even on maintenance therapy using APs alone, although no clinical indices or biomarkers have yet been identified that clearly differentiate these individuals. Unfortunately, based on our systematic review, we are unable to provide specific guidance as to which maintenance therapies are optimal for maximising post-acute ECT treatment effects for a given patient group.

In other subgroup analyses, we found that, compared with observational studies, relatively few RCTs involved long-term follow-ups after acute ECT treatment; in particular, evidence at or beyond the 12-month timepoint was lacking. Hence, whether differences in relapse proportion estimates between RCTs and observational studies are due to biases originating in differences in study design is unclear. In the analysis of relapse and rehospitalization, estimates of rehospitalization were consistently lower than those of relapse. Although little subjective heterogeneity was observed in definitions of hospitalisation, many studies in this analysis included hospitalisation in the definition of relapse, with varying thresholds for hospitalisation, primarily reflecting differences in health insurance systems and the year/period in which the study was conducted. Therefore, both results were possibly affected. In terms of publication year, relapse proportions and heterogeneity were consistently low across all timepoints after the publication year 2010, because multiple studies after 2010 included patients that received APs + C/M-ECT or were supplemented with mood stabilisers (1999 or earlier: 2 studies; 2000-2009: 1 study; 2010 or later: 13 studies). Based on these results, post-acute ECT maintenance therapy strategies for schizophrenia may improve, similar to trends reported for depression.[20,45,56–58] By location, our analysis revealed that the majority of the participants in this meta-analysis were recruited from Asian countries (Asia, 86.46%; North America, 6.76%; Europe, 5.65%; Oceania, 1.19%). As noted previously, ECT is not proactively recommended for schizophrenia in North America and Europe, whereas it is widely used in Asia, underscoring this regional asymmetry.[1,15]

Strengths and Limitations

The present review had several strengths, including its inclusive and comprehensive design, predefined inclusion criteria, and realistic interpretation of relapse proportions that account for clinical progress at each timepoint.

However, the study must be interpreted considering the following limitations. First, due to the nature of this study being a proportional meta-analysis that summarises relapse proportions, we are unable to provide recommendations on the use of ECT for schizophrenia per se.

Second, irrespective of the study design, results at all timepoints were highly heterogeneous. This suggested that criteria for study parameters, populations, and treatment variables differed between the studies included in this meta-analysis. Unfortunately, no specific statistical test exists to evaluate heterogeneity in meta-analyses that use proportional data. While considering that there are several issues with applying such a metric to this type of data, the literature recommends that the I^2 statistic be applied.[34,35] Thus, in the context of the current meta-analysis, I^2 values must be interpreted carefully. We used PrI, which incorporates and assesses both the uncertainties in the combined effects and the potential heterogeneity to predict likely distributions of future studies.

Third, the sample sizes of many of the studies included in our analysis were small, likely owing to the limitations unique to the field of ECT research. Patients with severe schizophrenia warranting ECT are a highly selective and limited population, and the prevalence of such disease in the general population, especially compared with that of other mental illnesses, is low. We decided to comprehensively pool together all studies from which post-acute ECT relapse proportions for schizophrenia and other related disorders following acute ECT could be calculated.

Fourth, ECT treatment is commonly accompanied by concomitant antipsychotics with or without other medicines. Owing to the nature of the large amount of retrospective data included, this meta-analysis was unable to separate the impact of concurrent medication and ECT on outcome events of patients' relapse and rehospitalization.

Fifth, the studies included in this analysis had different designs, used different diagnostic criteria, had different definitions of relapse, and employed different recruitment criteria. However, because the outcome here was the prognosis-related event of relapse, the results obtained from integrating the data used in this study are within a clinically meaningful range.

To overcome these limitations, multicenter trials with detailed information on the clinical assessment of patients, ECT settings, and pharmacotherapy in both acute and maintenance treatment phases could be conducted. A common definition of relapse and a long-term observation period are necessary. In addition to clinical outcome assessment, studies of the mechanisms of ECT-associated neurobiological/behavior changes and the specific brain processes underlying post-ECT relapse and relapse prevention effects are helpful.

In addition to other research designs, these studies should also investigate the mechanisms of change and specific processes underlying post-ECT relapse and relapse prevention effects. These findings are of critical importance in sustaining and individualising medical care for patients with schizophrenia.

Conclusion

In conclusion, our results indicated that relapse within 6 months is common following acute ECT for schizophrenia, particularly within the first 3 months. Relapse proportions plateau somewhat after 6 months, although ultimately, after 2 years, more than half of all patients can be expected to relapse. Further, our results suggest that, following successful acute ECT, concomitant use of APs + C/M-ECT may reduce relapse proportions, although this finding should be confirmed with higher-quality evidence. The findings of this study have important implications for expected outcomes following acute ECT for patients with schizophrenia.

Supplementary Material

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

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Authors' contributions

NA, AT, and YT designed the study, with input from TS, KY, and HT. NA set up the database, with help from NU. NA, YT, and ToS screened the literature search, acquired reports of the relevant trials, identified multiple publications of individual studies, selected included studies, and extracted data. NA contacted trial investigators for additional information and did the statistical analyses, with inputs from XWT, AHKK, and PCT. NA, AT, YT, SN, DM, and TAF analysed and interpreted the data. NA and HK verified the underlying data. NA, AT, and YT wrote the paper the draft, and the final version of the manuscript. MK, CL, TK, TAF, and YT provided supervision to NA at all stages. All authors critically reviewed the report for important intellectual content and approved the final submitted version. All authors had full access to all the data in the study and accepted responsibility to submit for publication.

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The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Conflicts of interest

NA reports grants from the Japan Society for Promotion of Science and the Japanese Society of Clinical Neuropsychopharmacology, during the conduct of the study; has received honoraria from Lundbeck and Sumitomo Pharma, outside the submitted work. AT has received honoraria from Eisai, Janssen, Meiji-Seika Pharma, Mitsubishi Tanabe, Otsuka, Shionogi, Sumitomo Pharma, and Takeda Pharmaceutical. TS reports grants from Shionogi; and has received honoraria from EA Pharma, Otsuka, Sumitomo Pharma, Takeda, and Viatris Pharmaceutical, outside the submitted work. HK has received honoraria from Lundbeck, Otsuka, and Sumitomo Pharma. KY has received honoraria from Sumitomo Pharma, Otsuka, Eisai, MSD, and Viatris Pharmaceutical, outside the submitted work. ToS has received honoraria from Janssen, Meiji-Seika, Mochida Pharmaceutical, and Sumitomo Pharma, outside the submitted work. NU has received honoraria from Eisai, Janssen, Lundbeck, Otsuka, Sumitomo Pharma, and Viatris, outside the submitted work. DM has received honoraria for consultancy work from Douglas Pharmaceuticals, outside the submitted work. MK has received consulting fees from Lundbeck, Otsuka, Shionogi, Sumitomo Pharma and Takeda Pharma; honoraria from Eisai, Eli Lilly,

Janssen, Kyowa Pharmaceutical, Lundbeck, Meiji-Seika Pharmaceutical, Mitsubishi Tanabe, MSD, Ono Pharmaceutical, Otsuka, Pfizer, Shionogi, Sumitomo Pharma, Takeda Pharmaceutical and Viatris, outside the submitted work. CL has received honoraria as an advisor board member from Douglas Pharmaceuticals and book royalties from Springer, outside the submitted work. TK has received honoraria from Eisai, Janssen, Meiji-Seika Pharma, Otsuka, and Sumitomo Pharma, outside the submitted work. TAF reports personal fees from Boehringer Ingelheim, Daiichi Sankyo, DT Axis, Kyoto University Original, Shionogi, SONY, and UpToDate, and a grant from Shionogi, outside the submitted work; In addition, TAF has patents 2020-548587 and 2022-082495 pending, and intellectual properties for Kokoro-app licensed to Mitsubishi Tanabe. YT reports grants from the Japan Society for Promotion of Science; and has received honoraria from Boehringer Ingelheim, Daiichi Sankyo, Eisai, Janssen, Lundbeck, Meiji-Seika, Novartis, Ono Pharmaceutical, Otsuka, Sumitomo Pharma, Teijin Pharma and UCB Japan, outside the submitted work. NA, TS, HK, KY, and YT are ECT committee members of the Japanese Society of General Hospital Psychiatry. TS and YK are Psychiatric Devices committee members of the Japanese Society of Psychiatry and Neurology. All other authors declare no competing interests.

Data Sharing

Please contact the corresponding author if you would like to see any data that are not included in the Article or Supplementary Materials.

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