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Ultrabrief pulse electroconvulsive therapy for depression: a systematic review and meta-analysis

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Ultrabrief pulse (<0.5 millisecond pulse width) electroconvulsive therapy (ECT) is regarded as a cognition-sparing form of ECT. Contrary to some early research, recent randomised trials have reported low remission rates with ultrabrief pulse high-dose right unilateral ECT. The aim of the present systematic review and meta-analysis was to assess acute and long-term outcomes following right unilateral and bilateral forms of ultrabrief pulse ECT in depression. We searched PubMed, Embase, PsycINFO, CENTRAL and ClinicalTrials.gov databases from 01 January 2007 to 17 September 2024 for randomised controlled trials and observational studies reporting on one or more relevant outcomes. Remission, response, relapse and switching rates to other forms of ECT were pooled using random effects models. 30 studies provided data on one or more outcomes. The pooled remission rate ($k = 23$, $n = 1478$) was 32.2% (95% CI 26.1%-39.0%) with ultrabrief pulse high-dose right unilateral ECT. Less than half of patients (45.3% [95% CI 39.0%-51.7%]) treated with this form of ECT achieved therapeutic response. Switching to brief-pulse ECT due to perceived inadequate response was common and occurred in 28.1% of patients (95% CI 20.6%-37.0%). Of remitters with ultrabrief pulse high-dose right unilateral ECT treated with continuation pharmacotherapy, 44.1% (95% CI 34.4%-54.3%) relapsed or withdrew within six months of completion of an acute course of ECT. The results of this meta-analysis indicate that acute outcomes following ultrabrief pulse ECT fall short of those expected with conventional brief-pulse ECT. As such, ultrabrief pulse ECT cannot be regarded as "state-of-the-art" ECT.

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INTRODUCTION

Electroconvulsive therapy (ECT) is the most effective somatic treatment for depression [1, 2] but its use is curtailed by adverse cognitive effects. In use for almost 90 years, numerous refinements to technique have been proposed to minimise cognitive side effects, including optimisations of stimulus waveform, electrode placement, pulse width and amplitude [3]. As a result of these technical advancements, cognitive side effects have been substantially reduced, though not eliminated, over time. The infrequency with which this highly effective treatment is utilised speaks to the reservations regarding its cognitive safety among patients and healthcare providers alike.

Brief-pulse (typically 0.5-1.5 millisecond [ms]) ECT is more effective than other brain stimulation techniques [2], with remission rates in meta-analyses of contemporary randomised controlled trials (RCTs) of 52-53% [4, 5]. Until recently, brief-pulse was the default mode of ECT administration in Western countries since it superseded sine wave ECT decades ago. Over the past decade, however, the therapeutic landscape has undergone a major shift, with some centres now using ultrabrief pulse ECT, conventionally defined as ECT administered with pulse widths shorter than 0.5 ms, as their default method of right unilateral ECT administration due to it being viewed as a cognition-sparing form of ECT [6]. A 2022 survey of global ECT practice found that right unilateral electrode placement was the preferred method for treating a major depressive episode (56% of respondents) [7]. Most respondents in the United States (74%) and Canada (67%) used ultrabrief pulse width when administering right unilateral ECT; meanwhile, only a small minority (13%) of European respondents did [7].

Early experiments with ultrabrief pulse widths suggested reduced efficacy of such ECT administered bilaterally [8, 9]. The first modern-era RCTs of unilaterally delivered ultrabrief pulse ECT were published in a predominantly schizophrenia sample in the Czech Republic in 1998 [10] and depression in the United States in 2008 [11]. These landmark studies showed similar therapeutic efficacy compared to brief-pulse unilateral ECT in small sample sizes ($n = 29$ [10] and $n = 22$-23 [11] per group, respectively). In 2013, the largest to date ($n = 58$ per group) randomised comparison of high-dose ultrabrief vs. brief-pulse right unilateral ECT reported significantly lower remission and response rates with ultrabrief pulse ECT and no advantage in autobiographical memory recall in the ultrabrief pulse group [12]. No head-to-head trials of ultrabrief vs. brief-pulse right unilateral ECT in depression have been published since 2015 [13], and only four such RCTs have been carried out to date [11–14]. These trials used a range of stimulus doses relative to seizure threshold (5-8x), some of which are not typically used in clinical practice, and which cannot be directly compared due to the strong dose-response relationship in unilateral ECT. Only two RCTs [11, 14] to date have

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compared ultrabrief and brief-pulse right unilateral ECT administered at the conventional 6x seizure threshold stimulus dose in both groups, with a combined sample size of only 84 randomised participants treated with right unilateral ECT.

Despite a precarious evidence base, ultrabrief pulse right unilateral ECT has been characterised as "state-of-the-art" ECT [15] and is currently being used as an active comparator in studies examining novel therapies for treatment-resistant depression, such as focal electrically-administered seizure therapy [16], frontoparietal ECT [17], magnetic seizure therapy [15, 18] and serial ketamine infusions [19]. However, a 2023 noninferiority trial in which 403 participants were randomised to a course of nine ketamine infusions or nine ECT sessions starting with ultrabrief pulse right unilateral ECT [19], and a superiority trial (conducted between 2007 and 2012 but published in 2024) in which 73 participants were randomised to a course of magnetic seizure therapy or ultrabrief pulse right unilateral ECT [15], both reported remarkably low observer-rated remission rates in their ECT arms (21.8% and 26.3%, respectively). Experts have noted that these remission rates are similar to those in historical samples treated with ineffective forms of ECT, such as low-dose brief-pulse right unilateral ECT, or anaesthesia-only simulated ECT [20]. A large nationwide registry study in Sweden had previously reported a similarly low self-reported remission rate of 29% with ultrabrief pulse ECT [21].

Prior reviews [22–24] on this topic were carried out a decade ago, a time when ultrabrief pulse ECT was beginning to be implemented in clinical practice and only a handful of studies were available. As ultrabrief pulse ECT is now routinely used clinically and increasingly used as an active comparator in clinical trials of new treatments for depression, providing an up-to-date review of outcomes using this ECT modality is essential. Herein, we report a quantitative synthesis of this growing literature. The aims of this systematic review and meta-analysis were to estimate remission, response and relapse rates following ultrabrief pulse ECT for depression and rates of switching to brief-pulse ECT.

METHODS

Search strategy

The conduct of this meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [25]. The protocol was preregistered on PROSPERO (CRD42023445613). Electronic databases (PubMed, Embase, PsycINFO, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov) were searched from 01 January 2007 to 17 September 2024 without language or publication type restrictions using search terms provided in the Supplementary Table S1. The year 2007 was chosen as the starting point for literature searches based on prior systematic reviews identifying a 2007 study [26] as the earliest contemporary published report evaluating ultrabrief pulse ECT in depression. We manually searched reference lists of previous reviews, eligible studies and studies citing eligible studies. We also contacted key investigators in the ECT field, identified by a bibliometric analysis of the relevant decade [27], to identify any additional studies. Records were imported into, de-duplicated and managed using the reference management application Covidence.

Two reviewers (A.J., D.M.M.) independently screened abstracts and full texts, carried out data extraction and assessed the risk of bias using an adapted version of the Newcastle-Ottawa scale [28]. Disagreements were resolved through discussion and consensus. Where publications contained overlapping samples, we extracted data from the publication with the most complete information. In case of unclear eligibility or missing outcome information in published reports, we contacted original investigators at least twice in an attempt to obtain the necessary information.

Study selection criteria

Studies met eligibility criteria if they included adults (age ≥18) meeting operationalised criteria (*Research Diagnostic Criteria*, *Diagnostic and Statistical Manual of Mental Disorders* [DSM] or *International Statistical Classification of Diseases and Related Health Problems*) for a major depressive episode (unipolar or bipolar) where depression symptom severity was assessed using a validated depression rating scale (e.g., Hamilton Rating Scale for Depression [HRSD], Montgomery-Åsberg Depression Rating Scale [MADRS], etc.). Studies reporting outcomes solely based on clinical impression were excluded. Where studies reported continuous outcome data only (e.g., mean depression rating scale scores), they were not automatically excluded. In such cases, we asked authors to provide binary outcomes (e.g., remission rate) where available. If an original study did not define remission or response using a validated depression rating scale, we applied the most common definitions of the relevant outcomes to individual participant data provided by study authors (i.e., ≥50% reduction in depression rating scale score from baseline to end-of-treatment for treatment response and score of ≤10 on MADRS/HRSD-24 at end-of-treatment for remission). Where studies reported outcomes using more than one validated depression rating scale, we prioritised outcomes derived from observer-rated scales (i.e., HRSD and MADRS).

We included ultrabrief pulse ECT arms of RCTs, ultrabrief pulse ECT groups from nonrandomised comparative studies and single-arm ultrabrief pulse ECT prospective or retrospective cohort studies. Studies were eligible for inclusion if they contained one or more samples where participants received a twice- or thrice-weekly acute course of ECT with an ultrabrief pulse width (<0.5 ms). We included the three most widely used electrode placements: right unilateral (d'Elia), bitemporal and bifrontal. We included bilateral samples treated with any dose relative to seizure threshold. On the other hand, as the efficacy of right unilateral ECT is highly dose-dependent, only studies using a high dose (here operationalised as doses ≥4x individually titrated seizure threshold in line with a previous meta-analysis [2]) were included. Samples treated with non-standard ECT administration schedules (e.g., daily ECT) or experimental ECT parameters (e.g. low amplitudes outside of the conventional 800-900 milliampere range) were excluded. Concomitant antidepressant treatment with oral monoaminergic antidepressants and augmenting agents was permitted since this reflects the standard of care in many countries. However, we excluded samples where patients were concurrently receiving another somatic intervention for depression alongside ECT (e.g., subanaesthetic or anaesthetic doses of ketamine, transcranial direct current stimulation, transcranial magnetic stimulation). Case reports or series with ≤10 participants were excluded, as were nonhuman studies, conference abstracts, unpublished theses, editorials and reviews.

Data extraction

Data were extracted into a structured template. The following information was recorded: study author; year of publication; country; study design (randomised or nonrandomised); baseline ultrabrief pulse group sample size; demographic and clinical characteristics (age, gender, ethnicity, proportion of patients with bipolar depression, and proportion of patients with psychotic features); depression diagnostic criteria; depression rating scale(s); criteria for remission, response, switching to other forms of ECT, and relapse; electrode placement; stimulus dose relative to individually titrated seizure threshold; weekly frequency of ECT sessions; anaesthetic type; use of concomitant antidepressants; the number of remitters and responders; the number of switchers to brief-pulse forms of ECT; and the number of relapses following remission.

Outcomes

The pooled remission rate at the end of an acute ECT course was prespecified as the primary outcome since a full resolution of a depressive episode is the recognised therapeutic goal of ECT. Secondary outcomes included: response rate at the end of an acute ECT course; the rate of switching from ultrabrief pulse to another form of ECT, typically brief-pulse bilateral, when the former was deemed to not be sufficiently effective; and cumulative relapse rate at six-month follow-up. Definitions of these outcomes were retained from the original studies. End-of-treatment outcomes were typically assessed within a week of the final ECT session; we excluded studies where the end-of-treatment assessment was carried out weeks or months, rather than days, after the final ECT session. We also excluded studies where repeat assessment was carried out before completion of a full course of ECT (e.g., after only 5 or 6 sessions).

Outcomes were analysed on an intention-to-treat basis. The number of participants who initiated their treatment with ultrabrief pulse ECT served as the denominator for calculation of remission, response and switching rates. In studies where ultrabrief pulse ECT nonresponders were permitted to switch to other forms of ECT, based on clinical judgement of inadequate response or formal study criteria for inadequate response, such switchers were classified as nonresponders and nonremitters to ultrabrief pulse ECT. Participants who discontinued the treatment early due to adverse events or withdrew from the study protocol for other reasons were assumed to have had a negative outcome (e.g., nonremission).

Data analysis

Single proportions were pooled using generalised linear mixed models for logit-transformed proportions [29], with corresponding Clopper-Pearson 95% confidence intervals and 95% prediction intervals. Prediction intervals estimate the range within which effects in a future similar study are expected to fall. Random-effects models were used for all meta-analyses regardless of heterogeneity estimates. Statistical heterogeneity was assessed using the I^2 statistic, which should be interpreted with caution in meta-analyses of prevalence [30]. In sensitivity analyses, we repeated all main analyses using the variance-stabilising Freeman-Tukey double-arcsine transformation for proportions [31]. Subgroup analyses were carried out where at least 10 studies were available. Planned subgroup analyses included comparisons of outcomes in randomised vs. nonrandomised studies, observer-rated vs. self-reported outcome measures and studies with lower vs. higher risk of bias. In post hoc analyses, we compared outcomes between studies permitting vs. not permitting concomitant pharmacotherapy, and between geographical regions (Australia, Europe and North America). We also recalculated main outcomes following exclusion of outliers [32], as well as following exclusion of studies that enrolled only older adults as older age is associated with enhanced therapeutic response to ECT [33]. Where more than 10 studies were available, we assessed small-study effects with funnel plots of sample size plotted against logit-transformed proportions, which may be more appropriate in meta-analyses of proportions [34]. Statistical analyses were carried out using the *meta* [35] and *dmetar* [36] packages in R version 4.4.1 [37].

RESULTS

Search results

A PRISMA flow diagram of the study selection process is shown in Fig. 1. The literature search yielded 7437 nonduplicate records. Following title and abstract screening, 215 studies were retained for full-text screening, 30 of which were deemed eligible for inclusion and provided data on one or more relevant outcomes. Reasons for ineligibility of the remaining 185 records are provided in Supplementary Table S2. Risk of bias assessment for the included studies is reported in Supplementary Table S3.

Acute outcomes following ultrabrief pulse high-dose right unilateral ECT

Data were available from 26 samples totalling 1717 patients for one or more acute outcomes (remission, response and/or switching) following ultrabrief pulse right unilateral ECT [11, 13–16, 19, 22, 38–56]. Key study characteristics are summarised in Supplementary Table S4. The mean sample size was 66.0 (range 12-240). Participants in all studies met DSM-IV or DSM-5 criteria for a major depressive episode and received ultrabrief pulse (0.25-0.3 ms) right unilateral ECT with a stimulus dose typically at 6x seizure threshold (range 4-10x).

We were unable to include five eligible studies in meta-analyses of remission and response following ultrabrief pulse right unilateral ECT due to being unable to obtain information unavailable in published reports from the authors. Reasons for not providing the requested information were: information not recorded [42, 57, 58], no response from the corresponding author [59] and the corresponding author refused to provide the requested information [19].

The pooled remission rate with ultrabrief pulse high-dose right unilateral ECT ($k = 23$, $n = 1478$) was 32.2% (95% CI 26.1%-39.0%) (Table 1; Fig. 2) while the pooled response rate ($k = 22$, $n = 1466$) was 45.3% (95% CI 39.0%-51.7%) (Table 1; Fig. 3). Sensitivity analyses yielded similar estimates (Table 1). The I^2 values were substantially reduced following exclusion of outliers, with corresponding narrowing of prediction intervals, while point estimates for both pooled remission and response rates remained very similar to the primary analyses (Table 1). There was no evidence of funnel plot asymmetry (Supplementary Figures S1 and S2). In 17 studies ($n = 1212$), nonresponders to ultrabrief pulse high-dose right unilateral ECT could be switched to another form of ECT, typically brief-pulse bilateral, according to clinical judgment (16 studies) or formal study criteria (1 study). The switching rate was 28.1% (95% CI 20.6%-37.0%; prediction interval 6.5-68.7; $I^2 = 82.3\%$).

Results of subgroup analyses are presented in Table 2. Neither remission nor response rates following ultrabrief pulse high-dose right unilateral ECT significantly differed depending on study design (randomised vs. nonrandomised), risk of bias (higher vs. lower), type of depression outcome measure (observer-rated vs. self-reported), concomitant pharmacotherapy use (permitted vs. not permitted), or geographic region (North America vs. Australia vs. Europe) (Fig. 4).

Long-term outcomes following ultrabrief pulse high-dose right unilateral ECT

Six studies investigated relapse following a successful acute course of ultrabrief pulse high-dose right unilateral ECT [11, 15, 19, 60–62]. Three studies with six-month follow-up [15, 60, 61] and a combined sample size of 93 remitters were meta-analysed; the remaining three eligible studies could not be included as the corresponding authors did not respond to requests for information not extractable from the published reports [11, 62] or refused to provide the requested information [19].

For characteristics of the three included relapse studies, see Supplementary Table S5. Cumulative relapse (including withdrawal) rate at six months with continuation pharmacotherapy was 44.1% (95% CI 34.4%-54.3%) (Fig. 5). As only one study [61] measured six-month relapse rate with continuation ECT following an acute course of ultrabrief pulse right unilateral ECT, this outcome was not meta-analysed.

Outcomes following ultrabrief pulse bilateral ECT

Four studies [11, 52, 63, 64] ($n = 101$) used a form of bilateral (i.e. bitemporal or bifrontal) ultrabrief pulse ECT. As only one of these

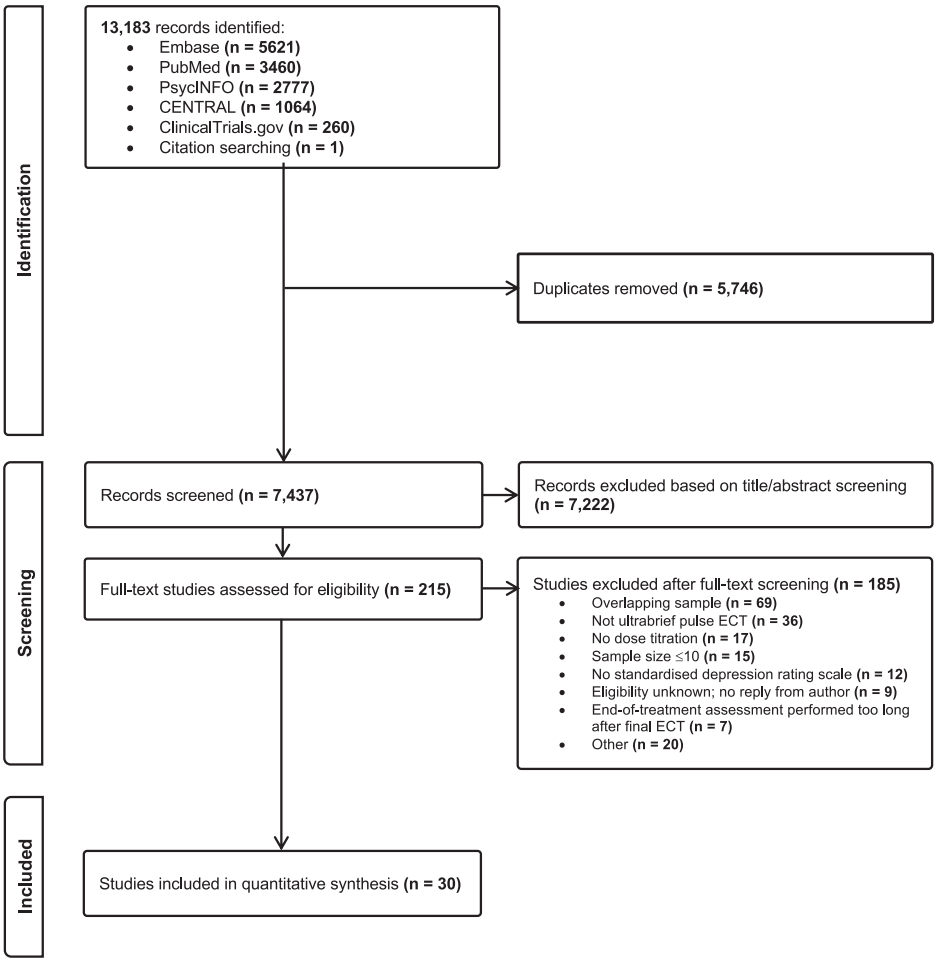


Fig. 1 PRISMA flow diagram.

studies evaluated bifrontal ECT [52], we pooled all bilateral samples into one analysis. We also performed a sensitivity analysis where the bifrontal ECT sample was excluded, analysing the three remaining bitemporal samples [11, 63, 64]. For characteristics of included ultrabrief pulse bilateral ECT studies, see Supplementary Table S6. Remission and response rates are provided in Table 1 and Supplementary Figures S3 and S4. There were insufficient data to analyse switching rates from ultrabrief bilateral to brief-pulse ECT. No published reports provided extractable data on six-month relapse rate following ultrabrief pulse bilateral ECT.

DISCUSSION

Our meta-analysis found that approximately a third of patients with a major depressive episode treated with ultrabrief pulse high-dose right unilateral ECT achieved remission and less than a half responded to this therapy. The practice of switching to more effective (brief-pulse) forms of ECT due to inadequate treatment response was common and occurred in 28.1% of patients initiated on ultrabrief pulse high-dose right unilateral ECT. The pooled remission rate of 32.2% reported herein, analysed on an intention-to-treat basis using data from 23 samples with 1478 participants, is similar to the pooled estimate of 33.8% reported in a 2015 meta-analysis [23], based on a largely per-protocol analysis of the early ultrabrief pulse right unilateral ECT literature featuring head-to-head studies where ultrabrief pulse ECT was shown to be significantly less effective than brief-pulse ECT. As no new head-to-head trials of ultrabrief vs. brief-pulse ECT have been published since 2015, the finding of significantly reduced clinical efficacy of ultrabrief pulse ECT remains valid. However, ultrabrief pulse right unilateral ECT has since been used in several RCTs examining other research questions. Therefore, we were able to provide an updated meta-analytic estimate of remission rate from nine randomised trials, all of which included participants drawn from populations of patients specifically referred for ECT. The pooled remission rate across these nine trials was identical (33.8%) to that reported in the 2015 meta-analysis of head-to-head ultrabrief vs. brief-pulse ECT studies [23]. Overall, our findings relating to acute outcomes following ultrabrief pulse high-dose right unilateral ECT compare unfavourably to previous meta-analytic estimates of 52-53% remission rates with brief-pulse high-dose right unilateral and bilateral ECT [4, 5].

Our meta-analysis also found that 44.1% of patients who remitted with ultrabrief pulse high-dose right unilateral ECT relapsed or withdrew from the study protocol within six months of completion of an acute course. Thus, longer-term outcome was similar to the previously reported pooled six-month relapse rate following other forms of ECT [65]. Two previous RCTs [61, 66] have suggested that continuation ECT with ultrabrief pulse high-dose right unilateral ECT delivered at 6x seizure threshold, used in conjunction with continuation pharmacotherapy, may be more effective than pharmacotherapy alone in depression relapse prevention. We were unable to pool these two trials in the present meta-analysis of relapse following ultrabrief pulse ECT due to a range of ECT parameters being used during the acute phase of treatment in one trial [66], which included patients treated with brief-pulse ECT. However, since long-term outcomes following ECT using continuation pharmacotherapy alone are

Table 1. Pooled remission and response rates with ultrabrief pulse ECT.

Analysis	Remission					Response				
	k	*n*	Remission rate (95% CI)	Prediction interval	I^2	*k*	*n*	Response rate (95% CI)	Prediction interval	I^2
Ultrabrief pulse right unilateral ECT analyses										
All UBP-RUL ECT samples, GLMM model	23	1478	32.2% (26.1%-39.0%)	11.0%-64.8%	84.4%	22	1466	45.3% (39.0%-51.7%)	20.9%-72.1%	80.7%
All UBP-RUL ECT samples, FT model	23	1478	32.6% (26.3%-39.3%)	7.8%-64.0%	86.4%	22	1466	45.3% (38.9%-51.8%)	18.8%-73.2%	83.5%
UBP-RUL ECT special populations excluded[a]	20	1150	30.4% (24.6%-37.0%)	11.2%-60.4%	70.1%	19	1138	43.6% (37.7%-49.8%)	22.4%-67.5%	64.8%
UBP-RUL ECT outliers excluded[b]	19	1134	31.5% (27.4%-35.8%)	19.5%-46.5%	52.5%	19	1124	46.3% (42.1%-50.6%)	33.5%-59.7%	48.0%
UBP-RUL ECT lower risk of bias studies only[c]	15	977	34.0% (28.6%-39.8%)	18.0%-54.7%	64.0%	14	958	47.4% (42.3%-52.7%)	32.5%-62.8%	54.7%
Ultrabrief pulse bilateral ECT analyses										
All UBP-BL ECT samples, GLMM model	4	101	28.7% (20.7%-38.3%)	13.5%-50.9%	32.4%	4	101	51.3% (34.7%-67.6%)	6.0%-94.6%	68.9%
All UBP-BL ECT samples, FT model	4	101	28.1% (17.2%-40.2%)	0.6%-70.6%	39.9%	4	101	51.2% (32.3%-70.0%)	0.0%-100.0%	69.8%
UBP bitemporal samples only[d]	3	60	29.1% (16.5%-46.2%)	0.0%-99.7%	50.9%	3	60	47.0% (26.5%-68.6%)	0.0%-100.0%	73.3%

FT Freeman-Tukey double arcsine model, *GLMM* generalised linear mixed model, *UBP-BL ECT* ultrabrief pulse bilateral electroconvulsive therapy, *UBP-RUL ECT* ultrabrief pulse high-dose right unilateral electroconvulsive therapy.

[a]Analyses using GLMM models excluding three samples which included only older adults (Abbott 2021; Kellner 2016a; Sun 2020 [University of New Mexico site]).

[b]Analyses using GLMM models excluding four outlier studies (Kellner 2016a; Loureiro 2020; Quante 2011; Sackeim 2008) from meta-analysis of remission and three outliers (Kellner 2016a; Loureiro 2020; Quante 2011) from meta-analysis of response.

[c]Analyses using GLMM models excluding eight studies with higher risk of bias. For details of risk of bias assessment for individual studies, see Supplementary Table S3.

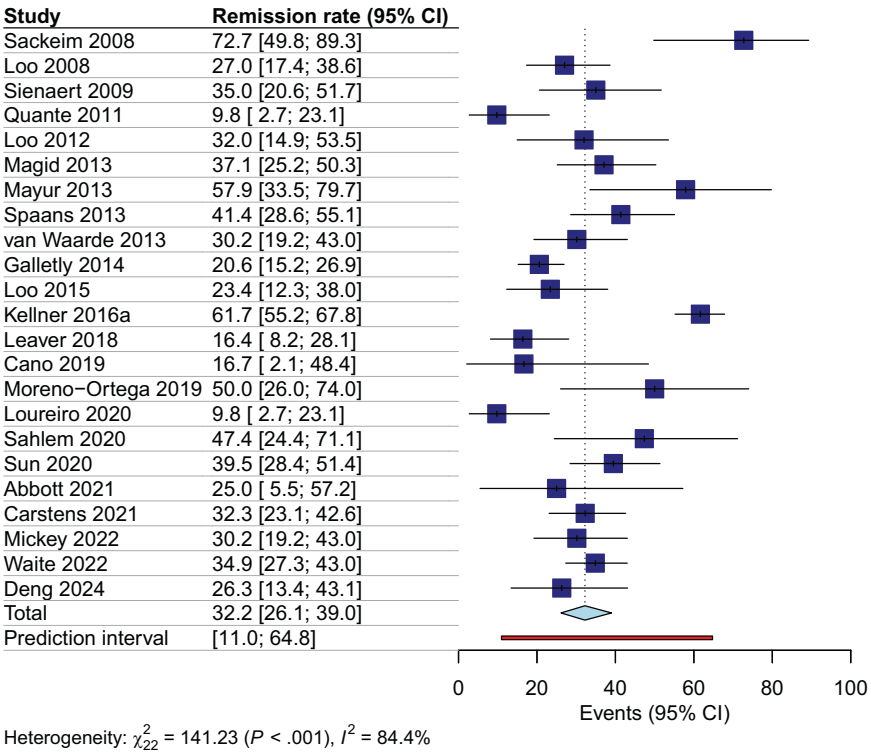
[d]Analyses using GLMM models excluding Sienaert 2009 sample which used bifrontal electrode placement.

widely acknowledged to be unfavourable, ultrabrief pulse high-dose right unilateral ECT may have a useful role in relapse prevention. To definitively answer this question, an adequately powered multicentre trial of continuation ECT is needed.

Of note, several studies have previously reported conspicuously poor outcomes with right unilateral ultrabrief pulse ECT, starting as early as 2007 with an observational study reporting a 13.3% remission rate [26] and a 2011 randomised trial with an overall 9.8% remission rate [51]. However, such outcomes have gone largely unnoticed and undebated until the recent publications of two major multicentre RCTs carried out in the United States involving ultrabrief pulse as the active comparator against other therapies for depression reporting observer-rated remission rates of only 21.8% [19] and 26.3% [15]. There are several possible explanations for why poor outcomes with ultrabrief pulse ECT have been overlooked until recently. Firstly, in the majority of included studies, as well as routine clinical practice, switching to brief-pulse forms of ECT is permitted, thus increasing the overall remission rate and masking the unfavourable therapeutic outcome with ultrabrief pulse ECT. Secondly, some studies, including some RCTs [14, 52], have analysed outcomes in study completers, rather than on an intention-to-treat basis. Such analyses have thus excluded patients who dropped out of the ultrabrief pulse ECT protocol due to perceived inadequate response, complications, or other reasons, thus overestimating the effectiveness of the treatment.

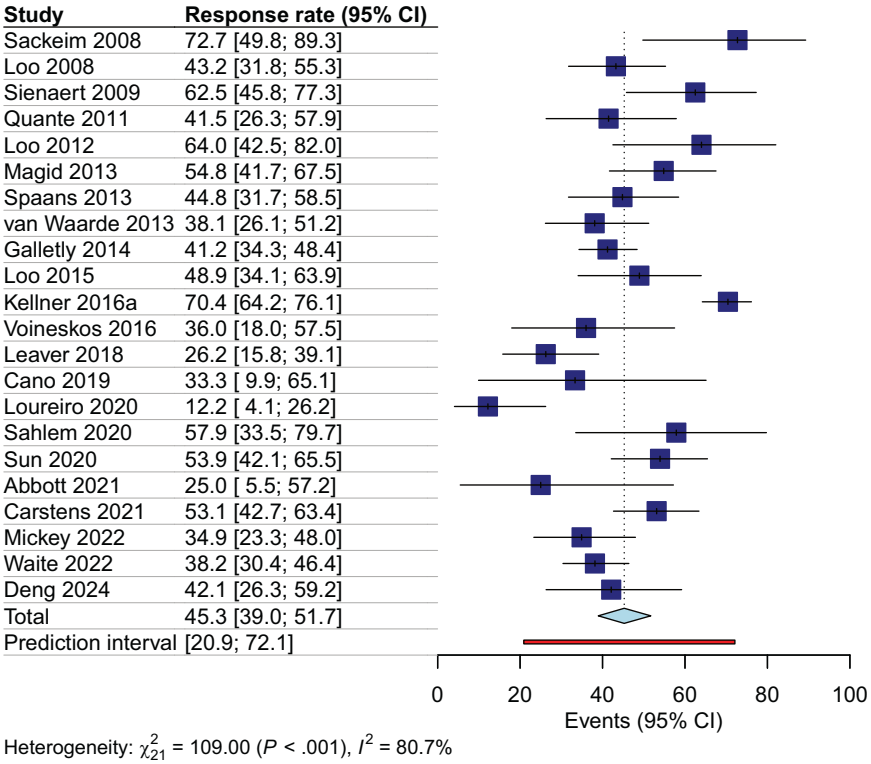
Two outlier studies [11, 43], identified as such in the present meta-analysis, are commonly cited in the literature as evidence in support of efficacy of ultrabrief pulse high-dose right unilateral ECT. The first contemporary trial of this modality for depression [11] used typical ECT trial inclusion criteria, resulting in a representative sample of general adult ECT patients who had the capacity to provide informed consent for trial participation. The study reported a remission rate of 73%, which has not been subsequently replicated elsewhere, as shown in the forest plot presented in Fig. 2. Unfortunately, this study had a sample size of 22 ultrabrief pulse right unilateral ECT participants, making the results susceptible to small-study effects. In meta-analyses, smaller studies often report more extreme effect sizes, and it is common in medicine for implausibly optimistic effect sizes reported in early pilot trials to be tempered over time as larger studies become available. On the other hand, the PRIDE Phase 1 [43] study was a large-sample, open-label observational study where older adults (threshold for study entry was age ≥60, resulting in a mean age of 70) received combination therapy with ultrabrief pulse right unilateral ECT at 6x seizure threshold and newly initiated venlafaxine. This study also reported an unusually high remission rate of 61.7%. However, older age is associated with significantly better ECT therapeutic outcomes [33]. As such, the results of the PRIDE Phase 1 study may not necessarily be applicable to general adult populations who receive ECT. While individual studies have reported a range of outcomes with ultrabrief pulse ECT, ranging from very poor to very robust, when formulating treatment guidelines for ECT, it is important to focus on the totality of available evidence, preferably from high-level evidence such as systematic reviews.

Outcomes with ultrabrief pulse right unilateral and bilateral ECT reported in the present meta-analysis are similar to those of classic experiments, previously reviewed elsewhere [67], using forms of ECT that induce a generalised tonic-clonic seizure but result in little-to-no appreciable therapeutic benefit, namely brief-pulse low- and moderate-dose right unilateral ECT. Pooled remission rates in our meta-analysis are also similar to those seen in treatment-resistant depression samples treated with anaesthetics alone, including ketamine [68], propofol [69] and nitrous oxide [70]. Similar remission rates as those reported in the present meta-analysis have also been observed using nonconvulsive forms of brain stimulation. A recent large registry ($n = 7215$) study [71] of



Heterogeneity: χ^2_{22} = 141.23 (P < .001), I^2 = 84.4%

Fig. 2 Remission following ultrabrief pulse high-dose right unilateral ECT.



Heterogeneity: χ^2_{21} = 109.00 (P < .001), I^2 = 80.7%

Fig. 3 Response following ultrabrief pulse high-dose right unilateral ECT.

transcranial magnetic stimulation recorded an overall remission rate of 30.9%, while a 2023 meta-analysis [72] of transcranial magnetic stimulation trials for treatment-resistant depression reported a 35.7% remission rate. In summary, remission rates following treatment with intravenous and gas anaesthetics, as well as nonconvulsive forms of brain stimulation, are similar to our pooled remission rates with ultrabrief pulse ECT.

While previous meta-analyses of RCTs have demonstrated that other types of ECT are significantly more effective than general anaesthesia-only simulated ECT with large effect sizes [1, 73], no

Table 2. Subgroup analyses for remission and response outcomes following ultrabrief pulse high-dose right unilateral ECT.

Subgroup analysis	Remission				Response			
	k	Remission rate (95% CI)	I^2	*p*	*k*	Response rate (95% CI)	I^2	*p*
Study design				0.740				0.166
Randomised	9	33.8% (22.7%-47.1%)	73.5%		8	50.6% (42.7%-58.5%)	50.1%	
Nonrandomised	14	31.4% (24.5%-39.3%)	88.3%		14	42.5% (34.5%-50.8%)	86.2%	
Depression rating scale type				0.847				0.357
Observer-rated	21	32.5% (26.0%-39.8%)	85.7%		20	45.1% (38.4%-52.0%)	82.2%	
Self-reported	2	33.8% (24.0%-45.2%)	42.8%		2	51.4% (40.1%-62.5%)	44.1%	
Risk of bias				0.317				0.200
Lower risk of bias	15	34.0% (28.6%-39.8%)	64.0%		14	47.4% (42.3%-52.7%)	54.7%	
Higher risk of bias	8	25.8% (14.4%-41.8%)	91.1%		8	37.1% (24.3%-52.1%)	90.4%	
Concomitant pharmacotherapy				0.881				0.373
Permitted	16	32.8% (26.7%-39.6%)	85.7%		16	47.6% (42.0%-53.3%)	78.8%	
Not permitted	7	31.4% (17.5%-49.7%)	82.1%		6	38.2% (21.5%-58.3%)	84.8%	
Geographic region				0.737				0.439
North America	12	34.5% (24.2%-46.5%)	86.6%		12	43.1% (32.1%-54.8%)	86.9%	
Australia	6	29.6% (22.6%-37.7%)	70.5%		5	42.5% (38.2%-46.8%)	38.9%	
Europe	5	29.5% (21.0%-39.7%)	61.5%		5	47.9% (40.8%-55.0%)	47.7%	

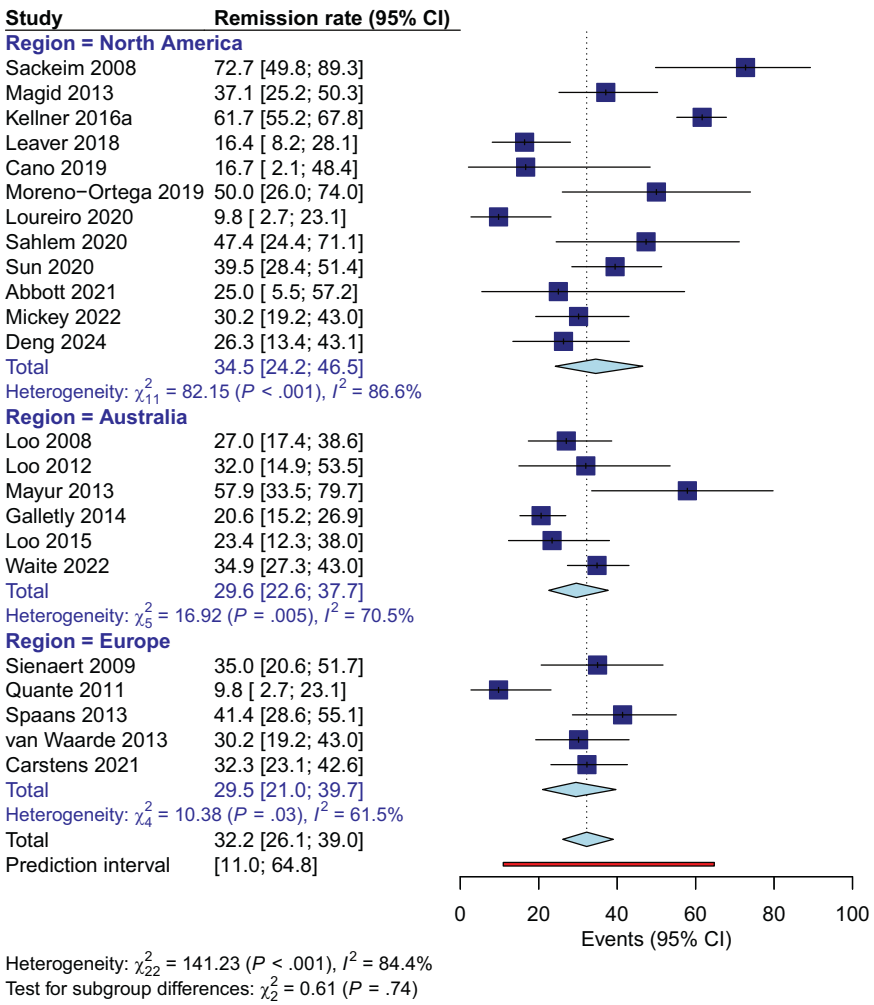


Fig. 4 Remission following ultrabrief pulse high-dose right unilateral ECT by geographical region.

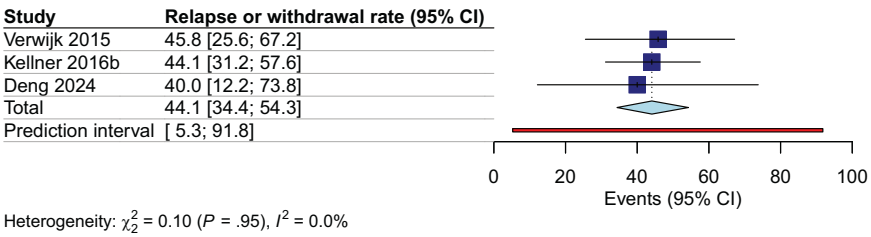


Fig. 5 Relapse following ultrabrief pulse high-dose right unilateral ECT.

such trials have been conducted using ultrabrief pulse ECT. Given the absence of a general anaesthesia-only control group in any of the studies identified by our systematic review, it cannot be concluded that the effect observed is caused by the treatment effect of ultrabrief ECT per se since within-group change can also include regression to the mean and placebo effect. Of the nine major psychiatric disorders examined in a 2024 meta-analysis, major depression had the greatest effect size for pre-post treatment within-group change in placebo arms of RCTs (Cohen's $d = 1.40$) [74]. However, while placebo-controlled trials are lacking, ultrabrief pulse ECT has been compared to active interventions for treatment-resistant depression. In randomised comparisons of ECT and subanaesthetic ketamine infusions, notable differences in outcomes have emerged depending on pulse width: brief-pulse ECT is significantly more effective than serial ketamine infusions [75] while ultrabrief pulse ECT is not [19]. The largest RCT of brief-pulse right unilateral ECT vs. serial ketamine infusions to date, KetECT [75], found a significantly higher remission rate with ECT (63 vs. 46%). To our knowledge, the only adequately powered RCT to date where ketamine has been found to be noninferior to ECT is the ELEKT-D trial [19] where almost all ECT participants (169 out of 170) in the modified intention-to-treat sample initiated their treatment with ultrabrief pulse high-dose right unilateral ECT.

The present meta-analysis has some limitations. Due to inconsistent reporting of essential study characteristics, including ECT parameters and outcomes in the primary literature, we were unable to determine eligibility of some studies and could not include several eligible studies in our meta-analysis due to authors being unable or unwilling to provide the missing information. Only a handful of studies have examined longer-term outcomes following ultrabrief pulse ECT which is concerning given the high propensity for post-ECT relapse in patients maintained on usual-care pharmacotherapy following ECT [65]. Likewise, very few studies using ultrabrief pulse bilateral ECT were identified, resulting in imprecise estimates of outcomes which should not be used to inform clinical practice. Substantial heterogeneity observed in some of our analyses was not explained by the examined study-level characteristics. Future work, preferably an individual participant data meta-analysis to avoid the risk of ecological fallacy, is needed to examine associations between potentially relevant patient-level characteristics (e.g., age, presence of psychotic features, duration of illness and/or index episode, psychiatric and/or medical comorbidities etc.) and clinical outcomes following ultrabrief pulse ECT.

In conclusion, the low remission rates with ultrabrief pulse right unilateral ECT reported in recent RCTs are not "anomalous" [20]. Rather, they are close to the norm. As such, ultrabrief pulse ECT cannot reasonably be considered "state-of-the-art" ECT. Reducing adverse cognitive effects, the main impetus for using ultrabrief pulse ECT, is an important consideration when deciding which ECT modality to use. However, while improving tolerability of this treatment is a laudable goal, it should not come at the expense of severe loss of therapeutic efficacy [76]. Failure to treat severe or prolonged depressive episodes aggressively carries the risk of nonremission and the accompanying risks of continued impairment in social and occupational functioning and premature death. Thus, the minimisation of risks must always be weighed against the maximisation of therapeutic benefit. There is currently no one-size-fits-all approach to prescribing ECT that is suitable for all clinical scenarios.

DATA AVAILABILITY

Data are available from the authors at reasonable request.

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AUTHOR CONTRIBUTIONS

Ana Jelovac: Conceptualisation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. Declan M. McLoughlin: Conceptualisation, Formal analysis, Writing – original draft, Supervision, Writing – review & editing.

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COMPETING INTERESTS

DMM has received speaker's honoraria from MECTA, Otsuka, and Janssen and an honorarium from Janssen for participating in an esketamine advisory board meeting. AJ has no competing interests to declare.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was not sought or required as the study was based on previously reported data.

ADDITIONAL INFORMATION

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