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Review

A systematic review and meta-analysis of randomized controlled trials of adjunctive ketamine in electroconvulsive therapy: Efficacy and tolerability

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ABSTRACT

Background: Electroconvulsive therapy (ECT) remains one of the most effective tools in the psychiatric treatment armamentarium, particularly for refractory depression. Yet, there remains a subset of patients who do not respond to ECT or for whom clinically adequate seizures cannot be elicited, for whom ketamine has emerged as a putative augmentation agent.

Methods: We searched EMBASE, PsycINFO, CENTRAL, and MEDLINE from 1962 to April 2014 to identify randomized controlled trials evaluating ketamine in ECT (PROSPERO #CRD42014009035). Clinical remission, response, and change in depressive symptom scores were extracted by two independent raters. Adverse events were recorded. Drop-outs were assessed as a proxy for acceptability. Meta-analyses employed a random effects model.

Results: Data were synthesized from 5 RCTs, representing a total of 182 patients with major depressive episodes (n = 165 Major Depressive Disorder, n = 17 Bipolar Disorder). ECT with ketamine augmentation was not associated with higher rates of clinical remission (Risk Difference (RD) = 0.00; 95%CI = −0.08 to 0.10), response (RD = −0.01; 95%CI = −0.11 to 0.08), or improvements in depressive symptoms (SMD = 0.38; 95%CI = −0.41 to 1.17). Ketamine augmentation was associated with higher rates of confusion/disorientation/prolonged delirium (OR = 6.59, 95%CI: 1.28–33.82, NNH = 3), but not agitation, hypertension or affective switches.

Conclusion: Our meta-analysis of randomized controlled trials of ketamine augmentation in the ECT setting suggests a lack of clinical efficacy, and an increased likelihood of confusion. Individuals for whom adequate seizures or therapeutic response cannot be obtained have not been studied using randomized controlled designs. Additional research is required to address the role of ketamine in this population.

1. Background

Electroconvulsive therapy (ECT) remains one of the most effective tools in the psychiatric treatment armamentarium, particularly for refractory depression. Indeed, rates of response as high as 90% are reported in major depressive disorder (Petrides et al., 2001), and even in the context of treatment resistant depression up to 60% of patients achieve clinical response following ECT (Prudic et al., 1996).

Nevertheless, there remains a subset of patients who do not respond to ECT, or for whom clinically adequate seizures cannot be elicited. This population has spurred substantial research on stimulation parameters (Krystal and Weiner, 1994) as well as optimal electrode placement (Kellner et al., 2010). Even with treatment optimization, a substantial portion of patients show limited or

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partial response. This has in turn stimulated interest in augmentation strategies in order to improve clinical response to ECT. Several augmentation strategies have been employed (Loo et al., 2010), including hyperventilation, caffeine, and remifentanil.

More recently, ketamine has become a focus of research and attention in the ECT setting and recently systematically reviewed (Fond et al., 2014). Ketamine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic subpopulation of glutamate receptors. At high doses it acts as a dissociative anesthetic, but has antidepressant effects with lower doses (McGirr et al., in press). It is unclear whether adjunctive ketamine improves rates of remission and response when used in conjunction with ECT.

Ketamine is an attractive adjunctive agent in the ECT setting given that it is an anesthetic agent with limited anticonvulsant properties (Krystal et al., 2003). Indeed, adjunctive ketamine was associated with early case reports of effectiveness in patients receiving ECT (Ostroff et al., 2005). This was followed by open-label trials suggestive of increased effectiveness in the initial ECT sessions, but no benefit compared to treatment as usual after six sessions (Okamoto et al., 2010). Ketamine has also garnered attention for its putative ability to temper the cognitive side-effects associated with ECT, and has been associated with improvements in time to re-orientation (Krystal et al., 2003) and word recall (McDaniel et al., 2006).

We performed a systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials to assess the efficacy of ketamine as an adjunctive agent to ECT. In order to maximize the clinical relevance of our findings, we focused on clinical remission and response as outcomes, but we also examined changes in clinician-rated depression scores. Adverse events were recorded in order to determine safety and tolerability, while acceptability was assessed using drop outs as a proxy measure.

2. Methodology of the literature review

2.1. Search strategy

This protocol was registered in the PROSPERO registry (CRD42014009035). We identified articles for inclusion by searching MEDLINE, EMBASE, PsycINFO, and the Cochrane Central Register of Controlled Trials (CENTRAL) until April 15th, 2014. The search procedures (including syntaxes, parameters, and results) are described in detail in the Supplementary Material. Briefly, the search terms “ketamine”, “ketofol”, “electroconvulsive therapy” and “ECT” were utilized to identify randomized controlled trials. We also reviewed the bibliographies of published trials retained in this study for additional unidentified studies.

2.2. Study selection

Studies were identified on the basis of their title, abstract and full text, and were included if they satisfied all of the following criteria (Higgins and Green, 2008): 1) Study Validity: Random allocation; double-blind (i.e., patients and clinical raters blinded to treatment conditions); controlled; parallel arm design; ≥5 subjects randomized per study arm; 2) Sample Characteristics: Subjects aged 18–75 years with a diagnosis of primary major depressive episode (unipolar or bipolar) according to DSM-IV(APA, 1994) or ICD (WHO, 1992) criteria; 3) Treatment Characteristics: Ketamine given as an adjunct to ECT; 4) Publication-Related: Articles written in English.

Studies were excluded if they:

1) Enrolled subjects with “narrow” diagnoses (e.g., postpartum depression) or secondary depression (e.g., vascular depression); 2) Did not report raw data or the authors did not provide raw data. In cases where potentially eligible studies were missing key data, their corresponding authors were contacted at least twice by e-mail at 2-week intervals. Additional data was provided by the corresponding authors of all trials, with one exception (Wang et al., 2012).

2.3. Data extraction

Data were recorded by two independent observers with subsequent review and consensus in a structured fashion as follows:

Sample Characteristics – Mean age, sex, and primary diagnosis
ECT related – Electrode placement, number of sessions
Ketamine related – Dose and administration
Control condition – The control condition and its associated characteristics were recorded
Primary Outcome Measure – Clinical Remission, defined as a Hamilton Depression Rating Scale [HRDS](Hamilton, 1960) score of ≤7 for the 17-item version, of ≤8 for the 21-item version, ≤9 for the 25-item version, or a score of ≤8 for the Montgomery–Asberg Depression Rating Scale [MADRS](Montgomery and Asberg, 1979). These definitions were those employed in the RCTs at the conclusion of ECT treatment.
Secondary Outcome Measures – Clinical response, defined as a ≥50% reduction in post-treatment scores based on the study's primary efficacy measure (HRDS or MADRS) at study end; Change in clinician-rated depressive symptoms pre- and post-intervention were recorded, as was seizure duration and cognitive testing. Secondary outcomes were defined at the conclusion of ECT treatment.
Acceptability and Tolerability– Adverse events and overall dropout rates at study end.

2.4. Data synthesis and analyses

Analyses were performed using Comprehensive Meta-Analyses Version 2.0 (Biostat, Englewood, NJ, USA).

Given that true treatment effects were likely to vary between studies given different methodological characteristics including patient selection, ketamine doses, anesthetic agents and electrode placements, we used a random-effects model (Riley et al., 2011). Intention-to-treat data were analyzed (Fergusson et al., 2002). The efficacy of ketamine, as well as its acceptability, was investigated by Risk Difference (RD) as well as Odds Ratio (OR) and the Number Needed to Treat (NNT) or Number Needed to Harm (NNH). We utilized Standardized Mean Differences (SMD) to quantify changes in depression scores pre- and post-treatment. With respect to SMDs, as we could not retrieve the correlations between pre- and post-ketamine measures from the individual RCTs we followed the recommendation of Rosenthal (Rosenthal, 1993) and assumed a conservative estimation of $r = 0.7$.

Heterogeneity was assessed using the Q statistics and I^2 (Cooper et al., 2009) and two-tailed p-values reported. Values of $p < 0.1$ for the former and >35% for the latter were deemed as indicative of study heterogeneity (Borenstein et al., 2009). Finally, we used Funnel Plots and Egger's Regression Intercept (Egger et al., 1997) to test for the presence of publication bias (Borenstein et al., 2009; Cooper et al., 2009).

3. Results

3.1. Literature search

Our literature search is detailed in Fig. 1 and the Supplementary material (SupplFigs. 1–4; STable1). Study quality was assessed