Ketamine and ECT: better alone than together?

An exciting therapeutic advance in the treatment of severe mood disorders has been the discovery that the N-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine, a widely used anaesthetic agent, results in a rapid antidepressant effect in some patients with treatment-resistant unipolar or bipolar depression (with onset of this effect within 24 hours, lasting about 7 days after a single administration).\(^1\)\(^2\) However, the early adoption and enthusiasm surrounding the clinical use of ketamine in treatment-resistant depression greatly exceed its empirical support. The clinical enthusiasm is tempered by concerns that ketamine’s antidepressant activity is short lived and by uncertainty regarding long-term safety in repeated administrations, with unknown risks for long-term cognitive side-effects, psychotic symptoms, and substance abuse.\(^3\)

Given the need for anaesthesia during electroconvulsive therapy (ECT) and the excitement about ketamine’s acute effects in reducing depressive symptoms, combining the two therapies seemed a logical next step. However, the research on ketamine use in ECT has been starkly disappointing so far. The study by Ian Anderson and colleagues in *The Lancet Psychiatry*\(^4\) adds to the evidence base of adjunctive ketamine use with ECT, and to the disappointment of this pairing.

Ketamine has been used successfully as an alternative stand-alone anaesthetic in ECT for decades. Typically, it is a third-line or fourth-line choice (after methohexitol or thiopental, propofol, or etomidate), indicated when ECT-induced seizures have become short or difficult to elicit. In this context, it is a good ECT anaesthetic agent, with modest seizure-enhancing properties and a reasonable tolerability profile, albeit including some increased hypertension, tachycardia and occasional dissociative symptoms during the recovery period. This use involves bolus dosing in the range of 1–2 mg/kg.

When it became apparent from basic science and clinical investigations that low-dose ketamine has multiple, complex effects on cognition and mood,\(^1\)\(^2\)\(^5\) researchers began to study its use as adjunctive treatment in ECT, that is, so-called cutting the induction anaesthetic with small doses of ketamine. It has been combined with various agents, including barbiturates and etomidate, but probably most commonly with propofol, a combination referred to in the anesthesia literature as ketofol. The ketamine doses used in this combination are typically in the range used in stand-alone ketamine infusions (0.5 mg/kg), but the administration is as a bolus, not a slow infusion over 45 minutes. Additionally, a few patients have been given low-dose ketamine infusions before ECT with standard anaesthetics.

Ketamine might enhance (or accelerate) the antidepressant efficacy of ECT by the above-mentioned potentiation of the therapeutic seizure, or it might have intrinsic additive antidepressant properties. The antidepressant mechanism of ketamine is considered to be triggered by the acute, short-term surge in synaptic glutamate and GABA concentrations;\(^6\) these concentrations are in turn responsible for the downstream effects on multiple signalling pathways.\(^7\) However, ECT also acutely increases glutamate and GABA concentrations,\(^4\) and it is unclear that additional increases are possible or desirable.

At the level of clinical symptoms, ECT is already rapidly acting and effective, such that any added speed or magnitude of antidepressant effects will be hard to detect without very large sample sizes (in excess of 200 patients per group). One meta-analysis,\(^8\) which analysed data from about 400 patients, concluded that ECT might have a modest effect in enhancing antidepressant efficacy.\(^9\) Whether the benefit outweighs the increased side-effect burden is not yet clear.

Although clinical trials of intravenous ketamine have most frequently used a 0.5 mg/kg dose,\(^1\)\(^2\) the optimal antidepressant dose of ketamine is still unknown (an NIMH-funded dose-finding multicentre study is expected to report results in 2017: ClinicalTrials.gov, number NCT01920555). The uncertain dose and the unknown effects of combining ketamine with other anaesthetic agents with respect to antidepressant effects further complicate the interpretation of ketamine augmentation of ECT in clinical studies.

Anderson and colleagues reported that ketamine (mean 5·17, SD 2·92), when compared with saline (5·54, 3·42), had no benefit on the primary outcome (HVLT-R-DR; difference in means –0·43, 95%CI –1·73 to 0·87). Ketamine might improve the cognitive tolerability profile of ECT, but this too is uncertain. Assessing the cognitive effects of ECT is fraught with difficulty, with challenging choices related to the most relevant cognitive domains to target,
optimal neuropsychological instruments, and timepoints of assessments. We do know that most of the cognitive effects of ECT dissipate within days to weeks after the end of treatment and that retrograde autobiographical memory, the issue of greatest concern to patients, is remarkably difficult to measure accurately. The benign cognitive profile of ECT used in the Ketamine-ECT study (predominantly with bilateral electrode placement, a type of ECT typically associated with more cognitive effects) is reassuring, despite not shedding much light on whether ketamine has some protective effect.

The scientific literature on the combined use of ketamine in ECT comprises over 130 articles, but definitive studies are few. As for many clinical questions in psychiatry, and medicine in general, an adequately powered and well-designed study to test both the cognitive and antidepressant effects of ketamine in conjunction with ECT remains elusive and unlikely to receive funding support. Can the numerous small studies and case series take the place of such a definitive study when subjected to meta-analysis? Probably not, but it seems likely that if a powerful augmenting or synergistic effect of ketamine in ECT existed, a strong signal would have emerged by now. Anderson and colleagues state that their results excluded greater than a small to moderate benefit with 95% confidence. However, in our opinion, even a small-to-moderate benefit is worth pursuing. ECT remains the gold standard of antidepressant treatment and is essential for a large subgroup of patients who are seriously ill and resistant to treatment. Improving the efficacy and tolerability profile of ECT, even incrementally, remains a worthy research goal.

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Low dose imipramine for multiple functional somatic syndromes

Functional somatic syndromes are groups of symptoms without a clear medical explanation (also known as medically unexplained symptoms). They include chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome concomitantly; pain is commonly reported. Functional somatic syndromes represent a major challenge for health-care systems, professionals, and patients in terms of diagnosis and treatment. No strong evidence base exists beyond the experience and expertise of practitioners.