ECT is Evidence-Based - a Commentary on Depression: Why drugs and electricity are not the answer

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In their narrative review Read and Moncrieff (this issue) query the concept of depression and the efficacy and safety of two cornerstone treatments for severe illness: antidepressants and electroconvulsive therapy (ECT). Regarding their concept of depression, as "misery and sadness", they ignore historical psychopathological descriptions of depression, presenting with features such as impaired cognition, psychomotor disturbance and psychosis (Kendler, 2016). This fundamental reframing of what depression is (and is not) colours any subsequent arguments made by the authors. Antidepressants are covered elsewhere in this issue, and we focus here on ECT, an internationally recognised evidence-based treatment for severe, sometimes life-threatening, depression (Kirov et al, 2021). We have already drawn attention to substantial methodological limitations in previous narrative reviews of ECT by Read and colleagues (Meechan et al., 2022). These are repeated in the narrative by Read and Moncrieff and can be summarised as: selective citing and biased reporting of results. Briefly, the main arguments put forward relate to the mechanism of ECT, efficacy and side-effects.

Mechanism of ECT

As with many effective medical treatments, the precise mechanism of action of ECT is not yet fully understood (Kirov et al, 2021). Bizarrely, Read and Moncrieff (2022) draw on historical hypotheses *predating* ECT, accompanied by inflammatory language, "some doctors treated epilepsy by injecting the blood of 'schizophrenics'…". They quote doctors from the early 1940s, one of which clearly refers to brain damage from historical treatments such as insulin coma therapy rather than ECT. Additionally, it is unclear how, in stating "A similar line of argument was resurrected, 70 years later, by researchers who reported that ECT reduces the 'functional connectivity' of the brain", the authors can imply change in Blood-Oxygen-Level-Dependent (BOLD) signal is some kind of marker for 'brain damage'. These erroneous historical and conceptual references are accompanied by a vernacular (e.g., "electrocutions") that does little to advance scientific debate or assuage concerns about impartiality.

Efficacy of ECT

Read and Moncrieff focus almost exclusively on older sham ECT (sECT) trials, going back to the 1980s. While older sECT trials have limitations, they consistently identify large reductions of depression

symptoms following ECT (g=0.85; Meechan et al 2022). The authors suggest ECT proponents are arguing "RCTs aren't necessary" and "non-placebo studies [are] sufficient". Such straw-man arguments side-step the abundance of well-conducted and converging evidence from contemporary trials demonstrating the superiority of ECT over antidepressants and other brain stimulation therapies and different modes of ECT (unilateral vs bilateral) (Meechan et al 2022). These findings are important because, where possible, 'active comparators' rather than 'placebo' are the best and most ethical comparator arms.

With no evidence, the authors claim expectation effects in those previously treated with ECT would exaggerate efficacy. We compared effect sizes in those who previously received ECT versus those who had not or where previous ECT was not ascertained: the effect size was significantly *smaller* in those with known prior exposure (indeed almost half the size) (Meechan et al 2022). This directly opposes the expectation claim. If ECT encompasses a placebo effect, then the placebo occupies a unique place in science by working *against* expectation.

Another argument is lack of benefit at follow-up in older sECT trials, which is hardly surprising. These studies did not optimally use continuation therapies, which have evidence for decreasing relapse, a feature of the underlying illness (Jelovac et al., 2013).

Safety of ECT

The authors allude to ECT causing brain damage in discussion of its impact on memory. As above, cited evidence is historical, irrelevant, and involves backward inference. They conflate weaker neuropsychological test performance with brain damage and refer to functional rather than structural magnetic resonance imaging (MRI) changes. They selectively cite Sackeim et al. (2007), conflating cognitive test performance with brain damage. This observational study, which included use of outmoded sine-wave ECT, demonstrated a small mean reduction in autobiographical memory (<0.2 Z-scores) at 6 months for bilateral ECT. However, this was substantially less for unilateral ECT and did not factor in the effects of depression itself on cognition or the normal rate of forgetting autobiographical memories, key areas of contemporary research. While cognitive function was poorer

immediately following ECT, the authors fail to mention that Sackeim et al. (2007) reported improved cognitive performance (including memory) on 29 of 33 assessments at 6 months, compared with pre-ECT scores. Presumably, Read & Moncrieff would not want to equate improved cognitive test performance in the longer-term with the presence of brain damage? Nor do they acknowledge ECT does not increase risk for stroke or dementia, which might be expected if it caused "brain damage" (Kirov *et al.*, 2021).

Furthermore, the authors selectively cite a systematic review of subjective memory in seven questionnaire-based studies (Rose et al., 2003), three of which failed to meet Rose et al's own inclusion criteria. By contrast, Read & Moncrieff ignore a subsequent meta-analysis that demonstrated short-term reduction in cognition in the first three days after completing a course of ECT, followed by overall improvement after 15 days, with 57% of cognitive variables assessed showing positive effect sizes, ranging from 0.35 [95% CI 0.07 to 0.63] to 0.75 [95% CI 0.43 to 1.08] with the remaining variables similar to pre-ECT scores (Semkovska & McLoughlin, 2010).

Concerning their assertions about adverse psychological and emotional effects following ECT, Read & Moncrieff cite one small (n=20) study that "targeted people who had had negative reactions to ECT…recruited by posters and flyers asking, `Have you been given ECT? Did you find it upsetting or distressing in any way?" This is hardly an even-handed representation of psychological and emotional responses to ECT. They further cite Wells et al (2021) as evidence of negative psychological and emotional effects, ignoring the fact that these authors clearly document both positive *and* negative effects in 23 individuals (largely a sample of peer supporters). In a recent qualitative study, Wells et al also pointed out that most who had received ECT reported it as a positive experience, stating "ECT should be raised as a potential treatment option earlier in the treatment process. Participants suggested that this may help to reduce the stigma associated with ECT."

Read and Moncrieff quote statistics on safety, suicide, and mortality, though again are remarkably selective. They state, "Numerous studies have found ECT recipients are more likely than other patients to kill themselves". They cite one study by Munk-Olsen et al (Munk-Olsen et al., 2007), which actually states "Although ECT patients are psychologically and physically severely ill, the decrease in mortality

from natural causes implies that the treatment does not endanger but rather may have a positive effect on physical health. …The increased suicide rate among ECT patients shortly after treatment is probably a result of bias…" Read and Moncrieff omit crucial details that the increased suicide rate is a result of bias, while decrease in overall mortality is, as Munk-Ollsen et al state, "unlikely to be a result of bias".

Read and Moncrieff state "Another recent study, using the Swedish national registry, claimed its findings 'support the continued use of ECT to reduce suicide risk in hospitalised patients who are severely depressed' (Ronnqvist, Nilsson, & Nordenskjold, 2021). The overall difference in suicides over 12 months between the ECT group (1.1%) and non-ECT group (1.6%) was small." This is not an issue of '*claimed*'. The study of 28,557 showed lower suicide rate amongst those who had received ECT compared to those who had not. The rates per group are naturally small because it is a low-incidence event; but, of the 152 who committed suicide, it equated to 28 fewer suicides in the ECT group.

Regarding mortality from physical causes, Read and Moncrieff cite Duma et al. (2019) who report 25.8 per 1000 experience major cardiac events. However, they neglect to mention that the same study reported all-cause mortality was low at 0.42 (0.11 to 1.52) deaths per 1,000 patients and 0.06 (0.02 to 0.23) deaths per 1,000 electroconvulsive therapy treatments.

Given the problems of confounding by indication, it is worth noting results of two large recent studies comparing safety, suicidality and mortality between people receiving and not receiving ECT, controlling for this using propensity score matching. The first, a Canadian cohort study of >10,000 admissions, found reduced suicide rates and no clinically significant increase in medical adverse events post-ECT (Kaster et al., 2021). The second study (a cohort of >8,000 people receiving ECT) found no increase in morbidity in the ECT group (Watts et al., 2021).

In conclusion, Read and Moncrieff provide an inaccurate and misleading account of the evidence for ECT. Methodological mishaps include: mis-citing of studies and arguments from before ECT was even invented; a lack of identifiable data-driven hypotheses - where their hypotheses have been tested they have been shown to be incorrect (e.g. expectation effects); ignoring relevant systematic reviews and

meta-analyses that oppose their argument; repeated illogical backward inferencing of brain damage from both neuropsychological test performance and functional brain imaging; and simple factual errors that pervade their narrative. As we have previously noted (Meechan et al 2021), our collective efforts would better serve our patients by using rigorous evidence-based methods to understand and optimise ECT, one of the most effective treatments in Psychiatry.

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Declaration of Interest

CM and KL report no COI.

DM has received speaker's honoraria from Mecta, Otsuka and Jannsen and an honorarium from Janssen for participating in an esketamine advisory board meeting.

AHY employed by King's College London; Honorary Consultant SLaM (NHS UK)

Deputy Editor, BJPsych Open

Paid lectures and advisory boards for the following companies with drugs used in affective and related disorders: Astrazenaca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma, COMPASS, Sage, Novartis

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Consultant to Livanova

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Principal Investigator on "The Effects of Psilocybin on Cognitive Function in Healthy Participants"

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