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Editorial

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Electroconvulsive therapy: still the gold standard for highly treatment-resistant mood disorders

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As novel forms of neuromodulation (such as vagal nerve stimulation [VNS], transcranial magnetic stimulation [TMS], and deep brain stimulation [DBS]) gain increasing interest from a growing clinical trials database, the editorial in this issue by Cattaneo and colleagues[1] reminds us that in some parts of the world there remains negative bias toward, and surprisingly limited use of, electroconvulsive therapy (ECT). As the progenitor of newer modalities of brain stimulation, ECT is neither experimental nor innovative. It has long been regarded as an established gold standard treatment for severe and/or treatment-resistant mood and psychotic disorders. In major depression, ECT exerts a large effect size (0.91) and superiority to pharmacotherapy (effect size ~0.80).[2] It is demonstrably more effective than antidepressant pharmacotherapy for reducing suicide attempts or completions.[3] And despite transient retrograde amnestic effects, ECT improves verbal memory[4] and other elements of cognitive dysfunction associated with treatment-resistant depression.[5] Nevertheless, a recent meta-analysis by Read et al[6] disputes the quality of evidence for ECT's safety and efficacy. Cattaneo et al[1] rebuke that meta-analysis and its critique of ECT study methodologies, noting that after decades of clinical experience with literally millions of treated patients, Read et al's [6] call for a moratorium on ECT pending new randomized controlled trials (RCTs) is unfounded, hazardous, and potentially life-threatening.

Cattaneo et al[1] draw from the cardiovascular literature in noting that heroic interventions for high lethality conditions are often ethically and scientifically better suited to observational than RCT study paradigms. The latter methodology tends to be more relevant for new and untested treatments, or when comparing the superiority (or noninferiority) of one therapy relative to another (as noted by Yeh et al[7] no RCT has ever demonstrated that parachutes prevent death when jumping from an airplane, yet their widespread use continues). RCTs serve to establish the internal validity of a proposed intervention while controlling for allocation bias across comparative samples—that is, possible confounding factors that could unfairly advantage or disadvantage inferences attributed to the effects of one treatment vs another. But in severe conditions of high morbidity and mortality, it becomes both impractical and ethically tenuous to justify RCTs when few viable options exist, particularly when there is already a large observational database showing favorable outcomes in populations unhelped by more standard therapies.

In major depression, ECT has become niched as a life-saving and unparalleled intervention in the context of grave impairment or disability, high severity, suicidality, psychosis, persistent symptoms, or poor response to multiple medications. "Moderators" (or predictors) of treatment outcome such as these often guide decision-making for next-step therapeutic options in severe depression, particularly when there exist few known alternative options after many previous therapeutic failures. Urgently implementing high-potency therapies without delay minimizes morbidity and mortality—a preferable stance to relegating such interventions to merely a last resort. Prolonged duration of illness and delayed time until an effective intervention for major depressive disorder (MDD) worsen prognosis and disability[8] and eventual pharmacotherapy outcome.[9] In the case of ECT, unlike most pharmacotherapies for depression, the presence of psychosis and severity of illness do not routinely predict poorer response.[10]

Rather than propagate antiquated misperceptions of ECT as anything other than a heroic intervention for a lethal and hard-to-treat condition, consider instead the ethics of subjecting patients with *highly*/multi-drug-resistant major depression to the limitless pursuit of iterative monoaminergic antidepressant trials, beyond the point of likely benefit, with little or no disclosure about the diminishing chances for improvement. Eventual remission from depression eluded fully one-third of patients after four successive interventions in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, and the probability for remission after three prior failed treatments was less than 10%.[11] More chilling was a Massachusetts General Hospital-based study showing that the probability of remission from major depression after five adequate antidepressant trials was *zero*.[12] Should clinicians withhold that information from patients when discussing higher-potency alternative options such as ECT? Particularly given that the known effect sizes of monoaminergic antidepressants relative to placebo are of only small-to-medium magnitude?[13]

While Read et al[6] bemoan the need for additional, more modern ECT trials, there remains a stark dearth of studies involving any biological intervention for *highly*-drug resistant major

depression patients—that is, those failing to respond to >5 pharmacotherapies. FDA registration trials of intranasal esketamine for non-elderly treatment resistant depression (TRD) were restricted to MDD patients unresponsive to *no more than* five antidepressant trials in the preceding 2 years; vagal nerve stimulation (VNS) is a chronic (not acute) treatment for major depression that carries FDA approval for patients unresponsive to *at least* four prior antidepressant trials; a recent large (n = 795) 5-year multi-site observational VNS study enrolled TRD subjects for whom the mean number of failed pharmacotherapy trials was 8,[14] although many appear to have failed a dozen or more medications (Scott Aaronson, personal communication, December 20, 2020). TMS received FDA approval for MDD unresponsive to *at least two* antidepressant trials, with meta-analyses revealing only a 15% remission rate.[15] Subcallosal cingulate deep brain stimulation (DBS), a highly invasive strategy for highly treatment-refractory depression, failed to demonstrate efficacy in a recent 6-month sham-controlled trial.[16]

The observational trials literature on ECT routinely includes MDD patients unresponsive to an average of 5 or more unsuccessful prior pharmacotherapies, with some studies showing robust efficacy regardless of the number of failed previous medications.[17] Perhaps instead of reimplementing basic studies comparing active vs sham ECT, the field might more usefully and ethically undertake equipoise noninferiority-based trials of ECT in TRD relative solely to alternative brain stimulation modalities or other heroic measures rather than sham placebos.

Most expert psychopharmacologists have favored options in their bag of tricks for TRD, such as high-dose monoamine oxidase inhibitors (sometimes bravely combined with stimulants or tricyclics), clever non-redundant pharmacotherapy options (eg, serotonin norepinephrine reuptake inhibitors combined with mirtazapine, bupropion, second generation antipsychotics, or mood stabilizers), old standbys (eg, nortriptyline plus lithium), new ideas (eg, bupropion with dextromethorphan), or the speculative world of anti-inflammatories, nutraceuticals, or psychedelics. Most of these types of idiosyncratic strategies for ultra-TRD have been borne more from theoretical rationales, clinical experience, or preliminary proof-of-concept studies than from well-executed large RCTs and, as such, would be considered novel and experimental. To what nonexperimental, evidence-based therapy does one refer MDD patients who are unresponsive to five or more monoaminergic antidepressants, plus (es)ketamine, VNS, or TMS—if not ECT?

For practitioners who routinely consult on severe, pan-refractory mood disorders, there is little basis from which to instill hope if one wipes ECT off the slate of viable treatment options. As the field continues to explore newer experimental therapies, current and future efforts will both likely benefit more from retaining existing therapies with known large effects, rather than discarding them simply based on their vintage.

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