Clinical and Practical **Psychopharmacology**

Active Placebo, the Parachute Meta-Analysis, the Nobel Prize, and the Efficacy of Electroconvulsive Therapy

Chittaranjan Andrade, MD

Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

Department of Clinical Psychopharmacology and Neurotoxicology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

ABSTRACT

The efficacy of electroconvulsive therapy (ECT) has been recently questioned on the grounds that placebo-controlled (sham ECT) trials are all old and of poor quality; statements have been made that the prescription of ECT should immediately be suspended because its continued use cannot be scientifically justified. These criticisms have come from academicians and have been presented in scientific and news forums with wide readership. A rebuttal is therefore necessary, if only to counter the formation of negative attitudes among patients, health care professionals, and the general public. The quality of sham ECT randomized controlled trials (RCTs) is undoubtedly poor; however, this is so because these RCTs were conducted in an era in which such methodology was par for the field. What critics of ECT have not considered are the large, well-designed, well-conducted, and well-analyzed modern era RCTs that show that bilateral and high dose right unilateral ECT are more effective than low dose right unilateral ECT, or that brief-pulse ECT is more effective than ultrabrief-pulse ECT; in such situations, the inferior form of ECT may be regarded as an active placebo comparison group that represents a scientifically valid substitute for sham ECT. Critics of ECT also do not consider the parachute meta-analysis analogy; just as one does not need a meta-analysis of RCTs to conclude that parachutes work, so too one does not need a meta-analysis of new sham ECT RCTs to conclude that ECT works. ECT is usually recommended to patients who are catatonic, severely ill, or treatment-refractory, and if ECT did not work well in these patients, common sense tells us that it would not continue to be used for such patients more than 80 years after its introduction. Malaria therapy and leucotomy are somatic therapies that were honored with the Nobel Prize, but it is ECT that has survived.

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About 10 years ago, a review[1] on the effectiveness of electroconvulsive therapy (ECT) stated that "placebo controlled studies show minimal support for effectiveness with either depression or 'schizophrenia' during the course of treatment" and that the effectiveness was apparent "only for some patients, on some measures, sometimes perceived only by psychiatrists but not by other raters." The review concluded that "the cost-benefit analysis for ECT is so poor that its use cannot be scientifically justified."[1(p333)]

More recently, an opinion piece[2] stated that "despite this lack of evidence psychiatry remains so adamant ECT works that no studies to establish efficacy have been conducted since 1985." In a very recent article,[3] the authors reviewed the quality of 11 ECT versus sham ECT trials in 5 meta-analyses. They concluded that the quality of these trials "is so poor that the meta-analyses were wrong to conclude anything about efficacy."[3(p64)] They concluded that the use of ECT "should be immediately suspended until a series of well designed, randomized, placebo-controlled studies have investigated whether there really are any significant benefits against which the proven significant risks can be weighed."[3(p64)]

These conclusions and recommendations appear so extreme that to respond to them might give them a legitimacy that they do not deserve. However, the authors are well-known academicians in respected institutions, one of the papers[2] was published in a leading general medical journal, the subject was considered sufficiently important for the medical education website Medscape to join the discussion in July 2020, and the manufactured controversy has even featured in the BBC News.[4]

It is a matter of concern is that such prejudicial views, through print and electronic media, may adversely influence attitudes toward and decisions about ECT among patients, patients' relatives, non-psychiatrist health care professionals, lawmakers, and the general public, none of whom could be expected to have sufficient scientific knowledge in the field to evaluate the evidence independently.

Adverse attitudes toward ECT, created by misinformation, would discourage the acceptance of a valuable treatment and restrict its use, as has already happened in many parts of the world.[5–7] The present article shows that, despite assertions to the contrary, there is actually visible, credible, randomized controlled trial (RCT) evidence that ECT is effective.

Active Placebo

Ketamine has distinct psychophysiological effects even when used in subanesthetic doses to treat depression. So,

an RCT that compares ketamine infusion with a saline placebo infusion will have its internal validity compromised because depressed patients can easily guess the treatment to which they have been assigned by virtue of what they do or do not experience during the infusion. To reduce the risk of such unblinding, many ketamine researchers set midazolam infusion as the control treatment. Midazolam does not have antidepressant properties but does produce psychophysiological effects that, in ketamine RCTs, would make it harder for patients to guess which drug they have received. Therefore, midazolam, in such a context, is an active placebo.[8]

An active placebo is a control treatment that does not have the therapeutic action of the drug that is being studied but does have physiological effects that could mimic nontherapeutic actions of the study drug. Active placebo can thus prevent unblinding in RCTs.[9,10] What might be an active placebo intervention in brain stimulation contexts? With transcranial direct current stimulation (tDCS), for example, the device is switched on when treating sham stimulation patients; current is ramped up, as in the active stimulation group, but is switched off after 30–60 seconds.[11] A 30–60 second duration of stimulation is almost certainly too brief to be therapeutic for whatever indication tDCS is being studied, but it would suffice for patients to have the opportunity to experience mild tingling of the scalp while the current is being ramped up. This would reduce the risk of unblinding in sham-tDCS patients.

With ECT, a classical control group would require sham ECT patients to undergo the entire treatment procedure, including the administration of anesthesia and muscle relaxant, but without the passage of electricity. There are 2 concerns here. One is that ECT is typically recommended to severely ill or suicidal patients and patients who have failed other treatments; so, it would be unethical to treat such patients with sham ECT. The other is that the administration of anesthesia and muscle relaxant, as part of the sham treatment procedure, would be unethical because it is not without risk.

Sham ECT Trials

In their extensive and detailed critique of the quality of the available sham ECT RCTs and of meta-analyses that include these RCTs, Read et al[3] do battle with a straw man. Most if not all of the sham ECT trials were conducted in an era in which RCTs were characterized by small samples, loose diagnoses, limited clinical assessments, simplistic statistical analyses, and other shortcomings. These problems were typical of all medical intervention research at the time, and not of ECT research alone. This means that poor-quality scientific research supports the efficacy of a sizeable proportion of the medical pharmacopeia, including treatments that even today continue to be used without question.

The above notwithstanding, it is true that no sham ECT trials have been conducted in the modern era. This does not mean that there is no evidence for the efficacy of ECT. The evidence does exist, hidden in plain sight.

Active Placebo and ECT

Many high-quality ECT RCTs have been conducted in the modern era on patients with major depression; none of these had a sham ECT control group. In a small (n = 52) but well-designed and well-conducted RCT, Sackeim et al[12] showed that low dose bilateral ECT was associated with a significantly higher response rate than low dose right unilateral ECT (70% vs 28%, respectively). Here, dosing was defined with reference to the seizure threshold. The seizure threshold was identified by careful dose titration during the first ECT session, and low dosing referred to ECT stimulus dosing that was just above the threshold identified.

In a larger (n = 96) RCT, this team of authors[13] randomized depressed patients to receive either threshold or 2.5× threshold ECT with either unilateral or bilateral electrode placement; the response rate was significantly or near-significantly higher with high dose bilateral ECT (63%), low dose bilateral ECT (65%), and high dose right unilateral ECT (43%) than with low dose right unilateral ECT (17%), and regardless of electrode placement, patients receiving high dose ECT responded faster than those receiving low dose ECT.

In a third RCT (n = 80), these authors[14] obtained significantly higher response rates with bilateral ECT dosed at 150% above threshold and right unilateral ECT dosed at 500% above threshold than with right unilateral ECT dosed at 50% and 150% above threshold (response rates, 65% and 65% vs 35% and 30%, respectively).

A consistent finding in these 3 RCTs[12–14] is that bilateral ECT and high dose right unilateral ECT were each associated with higher response rates than low dose right unilateral ECT. Now, if the reader considers low dose right unilateral ECT to be an active placebo, then these 3 RCTs, all published in high-ranking journals, provide consistent, high-quality evidence for the efficacy of bilateral ECT and high dose right unilateral ECT in patients with major depression.

Other high-quality modern era RCTs have also demonstrated the superiority of one form of ECT over another, where the reader may consider the inferior form of treatment to represent active placebo. For example, McCall et al[15] found that the response rate of patients with major depression (n = 72) was significantly higher with right unilateral ECT delivered at the fixed dose of 403 mC than at a dose that was 2.25× threshold (mean dose, 136 mC); the response rates were 67% vs 39%, respectively. Spaans et al[16] found that, among depressed patients (n = 87) who completed the study, the remission rate was significantly higher in patients who received brief-pulse ECT than in those who received ultrabrief-pulse ECT (68% vs 49%, respectively); also noteworthy was that the brief-pulse patients remitted with fewer treatments than the ultrabrief-pulse patients (mean, 7.1 vs 9.2 ECTs, respectively). The advantage of brief-pulse over ultrabrief-pulse ECT was confirmed in a meta-analysis.[17]

If a different somatic treatment for depression is also acceptable as an active placebo, then readers may note that ECT has been found superior to different forms of repetitive

transcranial magnetic stimulation (rTMS).[18,19] This advantage for ECT has been confirmed in meta-analyses. For example, in a systematic review and meta-analysis of 7 head-to-head RCTs (pooled n = 294) that compared high-frequency rTMS and ECT, the remission rates were significantly higher with ECT than with rTMS (52% vs 34%, respectively), and the effect size for reduction in depression ratings was large (Hedges $g = 0.93$).[20]

Readers may particularly note that low dose right unilateral ECT, ultrabrief-pulse ECT, and rTMS are not truly active placebos; they are active treatments. So, for certain forms of ECT to be found superior to comparator active treatments indicates that these forms of ECT have crossed a higher threshold for the declaration of efficacy than might be set by an inactive or active placebo intervention.

The Parachute Meta-Analysis, the Nobel Prize, and ECT

Nearly 20 years ago, the Christmas issue of the *British Medical Journal* featured a tongue-in-cheek systematic review and meta-analysis of RCTs that examined the effectiveness of the parachute in the prevention of death or major trauma related to gravitational challenge.[21] The authors failed in their objective; they were unable to identify even 1 RCT that met their search criteria. Using good judgment, they did not reject the efficacy of parachutes; rather, they recommended that "individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump."[21(p1460)] In other words, there are situations in which one needs to apply common sense.

What is the relevance of the parachute meta-analysis to ECT? ECT is usually reserved for the most severely ill of patients, including those who are catatonic, those who have psychotic symptoms, those who are suicidal, and those who have failed to respond to other treatments. These are situations in which the bar for efficacy is set very high. Had ECT been ineffective in such patients, its inefficacy would have been exposed long decades ago and the treatment would have fallen into disuse. It is also noteworthy that depressed patients who receive ECT respond and even remit in 2–4 weeks[22]; in contrast, in the average depressed patient, who is usually less severely ill and more treatment-responsive than patients referred for ECT, the duration of an adequate antidepressant drug trial is 4–8 weeks.[23]

Malaria therapy for the treatment of dementia paralytica and leucotomy for the treatment of psychosis were somatic treatments that were each honored with the Nobel Prize[24,25]; nevertheless, neither treatment is practiced today. Were ECT (which was not celebrated with a Nobel Prize) to have been similarly poorly effective, risky, and replaceable by more recent and better interventions, it would not have survived from its inception in 1938 to this date. It is not for nothing that textbooks of psychiatry commonly state that ECT is one of the most effective treatments for major mental illness.

Parting Notes

ECT has been criticized for lacking efficacy beyond the treatment period.[1,3] This criticism is strange because it could be leveled against most if not all treatments in neuropsychiatry. For example, if a patient with anxiety, depression, or schizophrenia were to stop medication immediately upon improvement or recovery, relapse is nearly certain to occur. We do not criticize the antianxiety, antidepressant, or antipsychotic medication for failing to produce lasting effect; rather, we recognize the need for continuation and maintenance treatment. It is so after a successful course of ECT, as well; continuation and maintenance therapy with medications, or with ECT, itself, are necessary for patients to maintain treatment gains.

Finally, it is acknowledged that ECT is associated with cognitive adverse effects and that the more effective forms of ECT are associated with a higher cognitive risk[26]; whereas these risks are probably exaggerated by the anti-ECT lobby, concerns about these risks necessitate the recommendation of ECT to only those patients for whom the likelihood of benefit outweighs the likelihood of risk. As already stated, such patients as usually those who are severely ill, catatonic, suicidal, or medication-refractory; these are usually patients for whom few or no other treatment options remain.

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