Sham Electroconvulsive Therapy Studies in Depressive Illness

A Review of the Literature and Consideration of the Placebo Phenomenon in Electroconvulsive Therapy Practice

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Abstract: The gold standard for the establishment of therapeutic efficacy is the randomized placebo-controlled trial. In the case of electroconvulsive therapy (ECT), there is an older literature of a dozen so-called "sham ECT" trials. When cited, these trials are typically referred to as unequivocally demonstrating the superiority of ECT over sham ECT. However, there is an intriguingly high sham ECT response rate in some of the studies, and there is also some information regarding ECT response of depressive subtypes that informs the modern ECT practitioner. In this report, the sham ECT literature is reviewed in detail, and the author discusses possible mechanisms by which sham-treated patients improved.

Key Words: electroconvulsive therapy, placebo, depression

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The gold standard for the establishment of the therapeutic efficacy of a treatment is the randomized placebo-controlled trial. This applies to medications typically but also to procedures such as electroconvulsive therapy (ECT). Electroconvulsive therapy is commonly believed to be highly efficacious for depression, especially psychotic and melancholic (endogenous) depression.[1] Upon first blush, it may seem difficult if not impossible to design something akin to a placebo or sham control for a procedure like ECT, but in fact, there is a literature. Reviews[1] and meta-analyses[2–5] of the sham ECT literature all conclude that in the aggregate, there is strong evidence that ECT superiority over sham is demonstrated. It is commonly assumed that the severe depressions that are usually treated with ECT are not placebo responsive. As will be seen, sham group responses are often surprisingly high, leading to questions about what the mechanism of the improvement could have been. In this article, the author reviews this literature in detail, focusing on the response rates of sham ECT group, and he discusses mechanisms of placebo phenomena in ECT practice.

REVIEW OF LITERATURE

In this review, included is any study in which a group of depressed patients is described who received, through some sort of randomization procedure, either active ECT (ie, a seizure is induced) or some form of sham ECT. Not included are studies in which the sham-treated patients also received active antidepressant medication because such studies constitute ECT-medication comparisons. Also not included are 2 older studies in which sham versus real ECT is described, but not enough information is provided to infer outcomes in depressed patients.[6,7] This results in 12 studies. Of note, 11 studies involve anesthesia (with or without concomitant muscular paralysis) alone as the sham version of ECT, whereas anesthesia plus subconvulsive electrical current constitutes sham treatment in 1 study.[8] In none of the studies was there an attempt to test whether patients knew to which group they were randomized, nor were power analyses described to determine sample sizes.

Ulett et al[9]

This group of investigators studied a method of seizure induction called photoshock therapy, in which flashing lights were used to augment pharmacotherapy-induced seizures. They compared 4 groups: convulsive photo/pharmacoshock, subconvulsive photo/pharmacoshock, ECT, and barbiturate anesthesia control. We consider the ECT versus anesthesia control as essentially a sham ECT study and will not consider the other treatments.

Twenty-one patients each were randomized to sine wave ECT (unspecified electrode placement) or sham ECT, thrice weekly each for 12 to 15 sessions. Blind evaluation used a rating scale of depressive symptoms with outcome classified as recovered-markedly improved-improved-slightly improved-no change or worse. Diagnosis was made by consensus between 2 clinicians and classified as 1 of 6 categories of psychopathology then felt to be ECT responsive: first attack schizophrenic reaction, catatonic type; involutional psychotic reaction; psychotic depressive reaction; manic depressive reaction, depressed type; schizoaffective reaction; and psychoneurotic depressive reaction. There were no more than a few patients with each diagnosis in each arm of the study. Outcome was not broken down by diagnosis. No mention was made of what patients were told about their treatments or whether any kind of informed consent was obtained. The location was an inpatient psychiatric facility.

Interestingly, posttreatment scores on the depressive rating scale were virtually identical for the 2 groups; the ECT group had higher percentage reductions in scores only because it had a much higher baseline score (probably due to uneven distribution of the various diagnostic groups, which were associated with differing levels of severity of psychopathology). For the 5 categorical outcomes listed above, the distributions of the 21 patients were 7-5-4-1-4 for the ECT group and 2-3-3-1-12 for the sham group, in the order that the categories were listed above. Apparently, these were statistically significantly different, although specifics on this comparison were not given. Thus, in this psychopathologically heterogeneous sample, the ECT group fared better than did the sham ECT group, although the latter had, roughly, a 38% rate of at least "improved."

Brill et al[8]

In an early attempt to tease out the possible influence of various anesthetic factors in ECT outcomes, this group randomly assigned either schizophrenic (results in this group

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not reported here) or depressive patients to 1 of 5 groups: unmodified ECT (8 patients), ECT plus succinylcholine paralysis (10 patients), ECT with thiopental anesthesia (3 patients), thiopental anesthesia with subconvulsive current (5 patients), and anesthesia with nitrous oxide (4 patients). The depressive subtype terminology was similar to that used by Ulett et al[9]: schizoaffective type; psychotic depression; involutional depression; reactive depression; and manic depressive psychosis, depressed type. All patients were male at a veteran's hospital. Blind outcome assessment was with a psychopathological rating scale with outcome dichotomized into "recovered" and "not recovered." The ECT device was sine wave with bitemporal electrode placement. Treatments were thrice weekly for up to 20 sessions.

In the 3 active treatment (ie, seizure induced) groups, there was a 76.2% recovery rate; that for the 2 sham groups (thiopental plus subconvulsive current or nitrous oxide) was 44.4%. Due to very low sample sizes, this was not statistically significant. It is interesting that the sham group improvement rate, albeit in heterogeneous samples using crude outcome categories, was strikingly similar to that of the Ulett et al[9] study. A disconcerting aspect of this study is that not only is there no information provided about informed consent issues, but apparently, some patients in the nonseizure groups were told that they were receiving a "new form of ECT." Thus, some element of deception seems to have been at play in this study.

Sainz[10]

In a small study, 20 patients were randomly assigned to active ECT or anesthesia alone (10 patients each). Sessions were thrice weekly for 4 weeks. Electroconvulsive therapy device, electrode placement, and electrical dosing were not specified. No paralysis was given. No power analysis or even statistical analyses were performed. Outcome assessment was impressionistic and unblinded. Patients did not know they were in a study and were not informed of what type of treatment they were given. Nine of 10 ECT patients were rated as recovered, whereas only 1 of 10 sham-treated patients were so rated. The other 9 of the latter group were either unchanged (6) or worse (3). Depressive subtyping was either "manic depressive depression" or "involutional depression."

Harris and Robin[11]

In this extremely small study, only 4 patients each were randomly assigned to active ECT (technical matters not specified), barbiturate anesthesia, or barbiturate anesthesia plus phenelzine. Only 2 sessions per week for 2 weeks were given. The patients were said to suffer from "depressive reaction"; no details are provided about informed consent if done, and blinding of outcome was not described. In the ECT group, 2 patients had slight improvement and 2 had "great" improvement. In the sham group, it was 1 slight improvement with 3 unchanged. With such a short course of treatments, the low response rates are not surprising.

Wilson et al[12]

In another small study, 6 patients each were randomly assigned to active ECT (technique not specified) or anesthesia alone. Two other groups received ECT plus imipramine or sham plus imipramine but will not be considered further here. Method of diagnosis was not specified, but this is the first sham ECT study in which the Hamilton depression scale was used.[13] Depressive subtypes were manic-depressive depressed, involutional depression, and depressive reaction. Sessions were twice weekly for 5 weeks. All 6 ECT patients experienced reductions in Hamilton ratings by study end to around 10 or below (based on visual inspection of the graphically displayed data). Of the 6 sham-treated patients, 2 had such reductions, whereas 3 showed no change and 1 had an approximately 30% reduction by study end. Interestingly, that means that the sham group had an approximately 33% response rate to ECT, much similar to the studies of Ulett et al[9] and Brill et al[8] described above. As was the case in the study of Brill et al,[8] patients not only did not know they were in a study but apparently were under the impression they were all receiving ECT.

Fahy et al[14]

Seventeen patients each were randomly assigned to receive either active ECT (technique not specified) or anesthesia. There was a third group, treated with imipramine, that will not be considered further. Apparently, all patients thought that they were receiving active treatment, so once again, deceptive practices emerge in an older study. No depressive subtyping terminology was used, and outcomes were assessed by review of hospital notes. Diagnosis was established clinically and not through formal means. Outcome was trichotomized as recovered-improved-no change or worse. There were 2 sessions weekly for 3 weeks. In the ECT group, there were 6 recovered, 6 improved, and 5 no change or worse. In the sham group, it was 2, 6, and 9, respectively. Once again, improvement rates in a sham group seem similar to some of the studies alluded to above.

Lambourn and Gill[15]

In this study, 16 patients each were randomly assigned to sham treatment consisting of anesthesia and muscular paralysis or active ECT consisting of right unilateral Lancaster electrode placement.[16] Electrical dose was low, 10 J. Sessions were given thrice weekly for 2 weeks (thus, 6 treatments) to patients described as having "depressive psychosis." No methods are described for how the diagnosis was made or whether any particular criterion set was used. Blind evaluation of outcome was achieved using the Hamilton scale. Patients provided informed consent, although no details are provided regarding what exact information was provided to the patients. The electrical stimulus was a chopped sine wave.

There was no significant difference in Hamilton scale reductions between the 2 groups: a mean drop of 25 points for the active group versus 23 points for the sham group. Abrams[1] has indicated that the lack of difference is due to low-dose unilateral treatments being ineffective; however, a 23- to 25-point reduction is enough to put the majority of patients into the "remitted" category. What is striking in this study is the dramatic improvement in the sham-treated group of supposedly psychotic patients. It should be noted that, especially in times past, the word "psychosis" was used broadly to describe severely ill patients and not necessarily just for patients with delusions or hallucinations.

Freeman et al[17]

These investigators randomly assigned patients to either a course of twice weekly active ECT treatments or to 2 sham treatments followed by twice weekly active treatments. Thus, the sham group eventually received active ECT, but it was delayed by a week of sham treatments. There were 20 patients per group. Apparently, about half the patients in the trial also received antidepressant medications. Patients were described as depressed without specification of criteria used or of any subtyping. Outcome was assessed blindly with the Hamilton and Beck et al[18] scales. Informed consent was obtained, but details of the information provided to patients are lacking. Sham treatment consisted of anesthesia plus muscular paralysis. The ECT stimulus was a chopped sine wave, and placement was bitemporal. At the end of the first week, the active ECT group

had lower depression scale scores than did the sham group. This has led Abrams[1] to proclaim this as evidence that real ECT is better than sham. However, at the end of the second week, the 2 groups had equal scores, which, in both cases, were lower than at the end of week 1 (ie, it was not that the active treatment group plateaued at 1 week). Thus, it seems from this design that 2 treatments followed by 2 real treatments are equivalent to 4 real treatments—this hardly inspires the confident conclusion that real is unequivocally better than sham.

Johnstone et al[19]

This is the Northwick Park ECT trial. Initial results were published in 1980 with analyses of subtypes of depression as predictors of outcome published 4 years later.[20] Electrode placement was described as "bifrontal." However, a precise description of exactly where the electrodes were placed was not given, and it is likely, based on customary ECT practices at the time, that in modern parlance, the location would be described as bitemporal. Seventy patients were randomly assigned to either sham treatment (anesthesia plus paralysis) or active treatment with chopped sine wave stimulation. Sessions were twice weekly for 4 weeks (ie, 8 sessions). Informed consent was obtained, but details of patient information are not provided. Even though no prower analysis was provided, the sample size is one of the larger ones in this literature. Diagnosis was established with the Present State Exam[21]; all patients met Newcastle criteria for endogenous depression.[22] Patients were subtyped as retarded, agitated, or psychotic. Data for Hamilton scores were only provided graphically, so precise means pretreatment and posttreatment are not available. Based on visual inspection of the graphs, it seems that for the entire patient sample, baseline to posttreatment Hamilton scores went from approximately 55 to approximately 18 for the actively treated patients and approximately 50 to approximately 25 for the sham-treated patients; this difference was statistically different, although the approximately 50% reduction in HamD scores for the sham group would meet modern criteria for "response" in a depressive episode. In breaking down the patients into delusional (ie, psychotic) versus nondelusional, the outcome was only significantly better after real versus sham ECT in the former. Nonpsychotic, endogenously depressed patients in this trial fared no better with active versus sham ECT and responded robustly either way. Data for the "retarded" and "agitated" groups were difficult to interpret due to low sample sizes.

West[23]

In this small, single-authored study, 11 patients each were randomly assigned to anesthesia plus paralysis (sham treatment) versus sine wave, bitemporal ECT. Sessions were twice weekly for 3 weeks. Blind ratings were with the Beck scale. All patients received 50 mg amitriptyline nightly during the trial for sleep. Diagnosis was established with the Feighner Criteria for primary depression.[24] No subtyping was described. Mean pretreatment and posttreatment Beck scale scores went from 26.6 to 10.8 for the active treatment group and 24.1 to 22.2 for the sham-treated group, a difference statistically significant. Informed consent was obtained, but details of patient information were not given. In stark contrast to other sham ECT trials, the sham group in this trial had essentially no response. It might be noted that the amitriptyline dose of 50 mg was probably too small to achieve antidepressant effects.

Brandon et al[25]

This is the Leicestershire trial. Fifty-three patients were randomly assigned to active ECT with a chopped sine wave device and bitemporal electrode placement. Forty-two patients were randomized to sham treatment with anesthesia and muscular paralysis. Sessions were twice weekly for 4 weeks (ie, 8 treatments). Diagnosis was established with the Present State Exam. Depressive subtyping included delusional (26), retarded (56), and neurotic (13). Outcome was assessed blindly with the Hamilton scale. Informed consent was obtained, but details of information provided to patients are not given. Outcomes yielded the following overall pretreatment and posttreatment means: for the active group, scores went from approximately 45 to approximately 12 (based on visual inspection of the graphically displayed results); for the sham group, means went from approximately 40 to approximately 30. This difference was statistically significant. Subgroup analysis revealed that the posttreatment mean differences were only significant for the delusional and retarded depressives but not for the neurotic depressives (who responded well to either active or sham ECT).

Gregory et al[26]

This is the Nottingham trial. Patients were randomized to sham ECT, Lancaster placement right unilateral ECT, or bitemporal ECT. Sham treatment consisted of anesthesia plus paralysis. Informed consent was obtained, but the details of it were not provided. There were 23 patients per group randomized. Diagnosis was based on International Classification of Disease, 9th edition and Medical Research Council criteria for depression. No subtyping was used. Outcome was blindly assessed with the Montgomery Asberg Depression Rating Scale[27] and the Hamilton scale. The ECT device used a chopped sine wave stimulus. No information was given on electrical dosing. There were 6 sessions for each group—twice weekly for 3 weeks. There was no difference in response between unilateral and bitemporal electrode placement in this study. Both of those groups went from baseline mean Montgomery Asberg Depression Rating Scale scores of approximately 33 to 35 to approximately less than 10 (this is based on visual inspection of the graphically displayed data). Those in the sham group went from a baseline score of approximately 33 to posttreatment scores of approximately 24, which was highly significantly different from the scores of the 2 actively treated groups.

HOW EFFECTIVE IS SHAM ECT?

The table displays the results of sham ECT treatment assignment in each of the studies. In the first 6 studies, outcomes were categorical. In crude terms, rates of recovery or at least improvement seem to be about one third to one half in the sham groups, excepting the extremely small Harris and Robin[11] study. In the 6 later studies in Table 1, outcomes were quantified as reductions in rating scale scores. Interestingly, sham outcomes are typically 25% to 50% reductions. The exception is the Lambourn and Gill[15] study, in which the average sham patient had essentially remission (ie, 23-point reduction in Hamilton score). Thus, this study does not point to low unilateral efficacy, as Abrams[1] has expressed, but rather to high sham *and* unilateral ECT efficacy. The patients were described as having "depressive psychosis," so one might assume that severely ill patients were included in the trial.

In the trial of Johnstone et al, [19,20] the mean reduction in Hamilton scores among the sham ECT patients was approximately 25 points or 50% (based on visual inspection of the figure). Only the psychotically depressed patients had reductions statistically significantly greater for the real versus sham group. Meeting research criteria for endogeneity was an inclusion criterion for the trial, so again, one may assume that "neurotic"

TABLE 1. Sham Treatment Response

Study	Sham Group Outcome	Comment
Ulett et al[9]	38% at least "improved"	Heterogeneous sample; outmoded nosology
Brill et al[8]	44.4% "recovered"	Heterogeneous sample; outmoded nosology
Sainz[10]	10% "recovered"	Nonblind, impressionistic outcome; small sample
Harris and Robin[11]	1 slightly improved; 3 unchanged	Extremely small sample
Wilson et al[12]	2/6→remission 3/6→no change 1/6→30% improved	Not well defined diagnostically
Fahy et al[14]	2/17→recovered 6/17→improved 9/17 →no change or worse	No standardization of outcome
Lambourn and Gill[15]	Mean 23-point reduction in HamD scores	"Depressive psychosis" diagnosis not defined
Freeman et al[17]	Essentially no change in HamD scores with 1 wk of sham	Only 2 sham treatments are a weak arm of a study
Johnstone et al[19]	Approximately 50% reduction in HamD scores	Meets modern criteria for "response" in a depressive episode
West[23]	Mean BDI from 24 to 22	Poorest showing for sham in all the studies
Brandon et al[25]	Approximately 25% reduction in HamD scores	Approximately equal results to modern low-dose RUL studies
Gregory et al[26]	Approximately 39% reduction in MADRS scores	Good study

depressives (who presumably have high placebo response rates) were excluded. Thus, in 2 well-controlled sham ECT studies using more modern diagnostic methods and outcome measures, substantial proportions of what seemed to be severely ill patients responded to sham treatment quite robustly.

An interesting finding occurred in the study of Freeman et al,[17] in which patients were randomly assigned to receive twice weekly active ECT or 2 sham treatments in 1 week, followed by twice weekly active treatments. At the end of 1 week (thus, a comparison of 2 active vs 2 sham treatments), the active ECT patients had lower rating scale scores than the sham-treated patients, the latter having Hamilton scores essentially unchanged from baseline. This is cited as evidence in favor of real versus sham ECT.[1] However, inspection of the graphically displayed Hamilton rating scale scores over time in that trial reveals that at the end of week 2 (thus, 2 sham-two real vs 4 real treatments), the 2 groups have identical depression scores. That is, the initially sham-treated patients had dramatic reductions in Hamilton scores with just 2 real treatments. One might speculate that the sham-treated patients knew they were receiving sham and, once shifted to active ECT, may have had extra enthusiasm now that they knew they were receiving "the real thing." Because the sham group only received 2 such treatments, this trial hardly constitutes evidence for how depressed patients fare with a full course of sham treatments.

A methodological issue regarding sham ECT is the adequacy of anesthesia induction alone as a "believable" placebo condition. A prerequisite for placebo-controlled trials is that each patient must believe there is a chance that he or she is receiving an active treatment. This is easy to achieve in pharmacologic trials, where placebo pills identical to the active drug can be developed. In procedural trials such as ECT, it is more difficult to develop a placebo condition that is sufficiently close to the active treatment, in which patients do not know which one they are receiving. Is the mere induction of anesthesia for a few minutes similar enough to the real ECT experience for patients not to know what treatment they are receiving? In none of the sham ECT trials was there an attempt to determine if patients correctly guessed to which group they had been randomized. Still, as discussed above, sham group outcomes were often surprisingly high.

It is instructive to compare sham ECT response rates with those of low-electrical dose right unilateral ECT, which has been shown in several studies to be an inferior mode of ECT vis-à-vis bilateral placements and higher dose unilateral placement. The modern, well-controlled studies in which one of the treatment groups was treated with low-dose unilateral ECT include 3 from the Columbia consortium showing response rates in the low-dose unilateral group of 28%,[28] 17%,[29] and 35%.[30] Of note, the latest of their studies involved unilateral ECT at 1.5 times threshold, which is low but actually slightly more intense than in their previous 2 studies. Letemendia et al[31] studied low-dose unilateral ECT, verus bifrontal and bitemporal electrode placements, and reported 50% reductions in depression rating scale scores. As can be seen, response rates seem quite comparable with the aggregate of the sham ECT studies. While acknowledging that there are many methodological differences between these 2 groups of studies (different diagnostic conceptualizations, treatment techniques, and outcome measures), still one may speculate as to whether low-dose ECT is nothing more than a placebo. In other words, in the studies where other forms of ECT were superior, was the mechanism of response in those patients who did respond different between low-dose unilateral and the others?

WHAT IS THE MECHANISM OF SHAM ECT RESPONSE?

One might wonder what the mechanism of action is for those patients randomized to sham ECT who do improve. Much has been written about the placebo response in medicine and possible mediating mechanisms.[32] Some have focused on the cultural basis for the meaning the patient ascribes to the doctor-patient encounter and the treatments proposed.[33] Another view is that various aspects of the patient (education, level of knowledge, cultural background) and the doctor (degree of enthusiasm, politeness, willingness to explain things, degree of

authoritativeness," etc) converge to cause the patient to have a set of expectations as to what the outcome of treatment will be.[34] Thus, in the case of sham ECT, one might speculate that if medical staff present themselves and ECT in a certain way, and the patients develop the expectation that it will be quite strong for their depression, then these expectations alone may cause some improvement. If a patient then participates in a sham ECT study and believes he or she might actually be receiving active ECT, response may occur. Still another theory has it that placebo effects constitute conditioned responses to various aspects of the medical setting (hospital or clinic, medical personnel).[32]

Improvement in sham ECT patients may not just be due to placebo (ie, expectational) phenomena. In all the studies cited above, patients were in hospital units, presumably receiving the various modes of care provided on such units (such things as group therapy, daily visits with caring staff, and support and sympathy from friends and family). All these things are probably good for depressed patients, separate from any expectations of improvement they might incur. One might also speculate on the possible biologically mediated effects of the anesthetic medications on depression. This seems to be a doubtful speculation, except perhaps for ketamine, which was not used in any of the studies I reviewed. Finally, one also should not discount the effect of the natural history of depressive episodes. In none of the studies was there an untreated, natural history control group. Patients tend to get better on their own, even without treatment.

DOES THE SHAM ECT LITERATURE TEACH US ANYTHING ABOUT DEPRESSIVE SUBTYPES AND ECT RESPONSIVITY?

It has long been believed that melancholic and psychotic depressions respond better to ECT than do atypical, neurotic, or reactive depressions.[22] On the other hand, it has also been believed that the latter categories are much more responsive to placebo treatments than are melancholic depressions.[35] Thus, if a group of nonmelancholic, nonpsychotic depressives receive a course of ECT, and a high response rate is observed, how does one know if the responses are "real" versus mediated by the placebo phenomenon? I am aware of no controlled trial in the history of the ECT literature that broaches this important research issue.

The trial of Johnstone et al[19,20] clearly demonstrated that for psychotic depression, active ECT results in higher response rates than does sham ECT. Brandon et al[25] also show that delusionally depressed patients have a better response to active versus sham ECT, providing replication of that finding. However, in the Lambourn and Gill[15] report, patients who are described as having "depressive psychosis" respond quite robustly to sham treatment. In that trial, no methods of diagnosis are described; one is left wondering if the patients were actually psychotic by today's definition. In the former trials, diagnosis and diagnostic subtype were determined by methods considered reliable and valid by today's standards.

Regarding the issue of the responsivity of ECT to melancholic (endogenous) depressions, the trial of Johnstone et al[19,20] provides the surprising finding that with rigorously defined endogenous depressives who are not psychotic, sham and active ECT do not separate. This is a very surprising finding, given that melancholic depressions have been felt to be relatively nonplacebo responsive. Perhaps nonplacebo effects were at work in the trial of Johnstone et al[19,20] in terms of inpatient care which were helpful in the sham-treated patients. In the trial of Brandon et al,[25] "retarded" depressives (who were probably endogenously depressed) did have a better response to real versus sham ECT, confirming previous suspicions about this kind of depression. Also in that trial, the "neurotic" depressives responded well to active or sham ECT—this seems to confirm the suspicion raised earlier that these depressed patients respond to ECT but that the mechanism is placebo (or otherwise not related to the inherent neurobiologic effects of electrically induced seizures). In ECT trials, where mixed populations of endogenous, atypical, and other nonendogenous depressives are studied and where active ECT is the only form of ECT given, then a mixture of placebo and nonplacebo phenomena are probably at work. This is an issue deserving further study.

DISCUSSION

In Western medicine, the placebo phenomenon was first studied in earnest around the middle of the 20th century. The expressions "placebo," "placebo response," and "placebo effect" have been used variably by different authors so that a precise, universally agreed-upon definition is problematic.[33] In general though, it is recognized that through a complex set of circumstances related to the meaning a patient ascribes to en counters with health care providers, which are influenced by cultural factors, individual life experiences, education, and the manner in which doctors communicate, expectations develop in the mind of the patient which by themselves can result in measured improvement in the condition at hand.[34]

A positive change in a particular outcome measure associated with a condition, for example, "depressed mood" or "anhedonia" for major depression, may be attributed to some combination of 3 factors: (a) the natural history of the condition irrespective of treatment (ie, some conditions remit on their own); (b) inherent actions of the treatment irrespective of any expectations the patient has, the so-called "verum" response[35]; and (c) the placebo effect. It is striking how rare it is to find untreated control groups in randomized studies—such groups are necessary to control for natural history factors. This is important because if active treatment and placebo groups both improve, and equally, the researcher may prematurely attribute the improvement to the power of the placebo effect when it may have been natural history all along. However, with modern rules governing the ethics of clinical trials in psychiatric disorders, it is almost impossible to have untreated control groups. One attempt to get around this is to examine historical groups of untreated patients, but for a variety of reasons, such data are unsatisfactory for psychiatric populations. Furthermore, even if one were to attempt to have an untreated group, the very act of identifying patients as ill, offering a randomized trial to them, and then informing them of their randomization to "nothing" affects the "natural history" of the condition because it is a violation of cultural norms in Western society to have a disease identified and receive no treatment.[33] Randomization to such a group may result in the so-called "nocebo" phenomenon, whereby expectational factors lead to worsening of a condition. Thus, even though natural history is generally recognized as important in the longitudinal course of mood disorders, the full extent of its impact will probably not be known in modern psychiatric research.

Teasing out placebo from verum mechanisms of improvement in ECT patients is more difficult than it might seem. If a placebo-treated group improves, for example, in depression scores, it might not necessarily be attributable to patients' expectations. There may be "verum" phenomena at play, just not the ones the researchers think are applicable to their active treatment. In the case of depressed patients in the sham ECT studies, patients in all studies seem to have been hospitalized. As discussed, milieu activities that may be quite therapeutic for

depressed patients were undertaken, separate from any expectations patients may have about their utility. A theoretical way to get around this is to enroll only outpatients who are not receiving any type of therapy in addition to the ECT. However, most patients referred for ECT are too ill for such treatment.

In attempting to extrapolate some of these principles to the sham ECT literature, it becomes clear that in some studies, the sham-treated patients had considerable improvement in depression rating scale scores. In the trial of Johnstone et al,[19,20] which was probably the best trial in terms of methodology and psychopathological characterization of patients, rigorously defined endogenously depressed patients did exceptionally well with sham ECT, just as well as with real ECT. This needs explaining because it is "common wisdom" that endogenous (melancholic) depressions are not supposed to be placebo responsive.[35] Perhaps melancholic patients in hospital do obtain considerable relief from milieu approaches. An interesting note of a recently published, multisite transcranial magnetic stimulation active-versus-sham trial in depressed patients can be made.[36] In that trial, in which both groups had up to 6 full weeks of 5 times a week sessions and where the actively treated group had aggressive magnetic stimulation, active treatment was associated with an only 23.9% response rate by Hamilton rating criteria and a 17.4% remission rate. Thus, an aggressive form of transcranial magnetic stimulation was associated with lesser outcomes than some of the sham ECT groups studied.

In summary, some of the studies indicate an unexpectedly high rate of response in the sham groups. It is quite unlikely that attempts at sham-controlled trials will ever be undertaken again in ECT research, so unanswered questions will probably remain so. The modern ECT practitioner should be aware that placebo effects are commonly at play. As psychiatry moves forward with research on new "neurostimulation" technologies, such as transcranial magnetic stimulation, vagal nerve stimulation, and deep brain stimulation, researchers would be well-advised to pay careful attention to placebo phenomena.

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