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Role of Adjunctive Psychotropic Medications during ECT in the Treatment of Depression, Mania and Schizophrenia

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Abstract

Current guidelines regarding concomitant antidepressants during ECT are inconsistent. Although the American Psychiatric Association Task Force on ECT discouraged combination antidepressant treatment, due to the minimal evidence for enhanced efficacy and concern about increased adverse effects, combination treatment is recommended and considered routine for many practitioners in the US and other parts of the world. Considering the increasing levels of treatment resistance among patients referred for ECT, and the high relapse rate after acute ECT, the role of concomitant antidepressant pharmacotherapy during ECT should be re-evaluated. More research however, is needed to explore the impact of administering specific antidepressants during acute and maintenance ECT, on antidepressant efficacy as well as cognitive side effects. This will require appropriately controlled studies of ECT medication combinations that include attention to a range of cognitive function measures, as well as clinical response. In addition, the role of combination ECT and psychotropic medication in the treatment of mania and schizophrenia continues to receive attention, particularly in those patients who have shown inadequate responses to psychotropic medication alone. While there is insufficient evidence to support the routine addition of antipsychotic medications to ECT during the treatment of acute mania, the literature suggests that it is unnecessary to discontinue antipsychotic medication when ECT is added to the treatment of a manic patient that has been unresponsive to pharmacological treatment. Despite the lack of well controlled studies, the existing literature suggests that combination ECT and antipsychotic treatment is a useful option for patients with schizophrenia who are unresponsive to pharmacological interventions alone, and its side effect profile does not appear different from that seen with ECT alone.

Keywords

pharmacotherapy; electroconvulsive therapy; major depression; mania; schizophrenia

Concurrent antidepressant medication during ECT

Modern pharmacological treatment of major depression utilizes a wide range of antidepressant medications, frequently as monotherapy, but often in combination. The effect of these

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medications during ECT has not been systematically studied. Current guidelines regarding concomitant antidepressants during ECT are inconsistent.¹⁻³ Although the American Psychiatric Association Task Force on ECT discouraged such combination treatment, due to the minimal evidence for enhanced efficacy and concern about increased adverse effects, combination treatment is recommended and considered routine for many practitioners in the US and other parts of the world.

In addition, despite the belief that ECT is the most effective acute treatment for a major depressive episode¹, current remission rates after ECT appear to have substantially declined from approximately 90% noted in earlier reports.⁴⁻⁸ While multiple factors related to the administration of ECT have been considered responsible for this decrease in treatment efficacy, an important patient change is the increasing proportion of patients who are referred for ECT after failing to respond to adequate trials of antidepressant medications. Today, ECT is rarely used as a first-line antidepressant treatment and antidepressant resistance has become its primary indication.¹ Of persistent clinical concern, relapse during the early weeks after ECT remains common despite the increasing use of antidepressants for post-ECT continuation pharmacotherapy.^{8,9} Considering the observed delay in the onset of therapeutic action after initiation of antidepressants, it has been hypothesized that early relapse after ECT may be a consequence of delaying resumption of antidepressant pharmacotherapy until after completion of acute ECT. It has been suggested that concurrent antidepressant pharmacotherapy during the course of acute ECT might decrease the frequency of early post-ECT relapse.¹⁰

This apparent reduction in ECT efficacy, associated with increasing levels of treatment resistance among patients referred for ECT, and the high relapse rate after acute ECT suggest that the role of concomitant antidepressant pharmacotherapy during ECT should be re-evaluated.

Early anecdotal and uncontrolled studies between 1961 and 1990 examined the use of concomitant medication, tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI) with ECT. While some studies suggested benefits of the combination,^{11,12} there were a number of methodological limitations. Studies were retrospective, inadequately powered, lacked adequate comparison groups, or relied on number of ECT treatments as the measure of efficacy.¹³⁻¹⁵ Even randomized placebo-controlled trials of ECT combined with a TCA or MAOI, from this era, failed to demonstrate increased efficacy.¹⁶⁻¹⁸ Unfortunately some studies utilized relatively low doses of antidepressant that may have been subtherapeutic¹⁹ and in the Kay et al. study¹⁶, it is unclear whether amitriptyline enhanced ECT or, by increasing the seizure threshold in the comparison group, diazepam reduced ECT efficacy.

See Table 1 for a summary of these early studies.

Subsequent studies of this question have produced inconsistent results. One study suggested that the addition of imipramine (IMI) to acute ECT resulted in superior efficacy compared with the addition of paroxetine or placebo.²⁰ During continuation treatment however, patients receiving paroxetine had decreased relapse rates compared to IMI or placebo. Another study, that used a novel and clinically relevant design, randomised 30 patients to either continue their antidepressant medication or undergo antidepressant withdrawal with placebo substitution.²¹ This study showed no difference in the rate or degree of improvement between groups and did not demonstrate any advantage for concurrent antidepressant treatment. Most patients however, were treated with TCA during ECT, despite having failed to respond to this treatment and only approximately 50% of patients had received an “adequate antidepressant dose” prior to ECT.

The largest sample appears in a report by Baghai et al.,²² that was drawn from a retrospective review of 455 patients who received 5,482 ECT, although data analysis is restricted to those

patients receiving 1,077 ECT who were unmedicated or received psychotropic monotherapy. The results suggested improved efficacy with concurrent administration of several classes of antidepressant during ECT. The findings of this study are limited by the retrospective design, absence of detailed assessment of mood outcomes, and inclusion of patients with a variety of psychiatric disorders. In addition, an important variable affecting subsequent response to ECT, treatment resistance prior to ECT,²³ was not formally assessed. An unexpected finding from this dataset was a higher incidence of transient cardiovascular and cognitive side effects in patients receiving venlafaxine (VEN), (mean 225mg/day). This finding was also described in a subsequent report that noted adverse cardiac effects, including asystole, associated with the administration of high dose venlafaxine (≥ 300 mg/day) during ECT.²⁴

A recent prospective, randomized, placebo-controlled study tested the hypotheses that compared to placebo, treatment with nortriptyline (NT) or VEN during acute ECT would enhance short-term antidepressant efficacy, without increasing adverse effects, and would reduce the rate of post-ECT relapse.²⁵ In this study, the concurrent administration of NT (given at doses that achieved therapeutic serum levels) was associated with a 15% increase in remission rate, whereas the administration of VEN (mean dose 187 mg/day) resulted in improved outcomes, but of lesser magnitude. The administration of NT or VEN during ECT however, did not decrease the relapse rate during post-ECT follow-up. Neither concurrent administration of NT or VEN during ECT resulted in an increase in serious adverse effects during ECT, although objective measures of retrograde amnesia were reduced by NT and unchanged or worsened by VEN. The observed cognitive protection associated with NT administration during ECT has been hypothesized to result from enhanced noradrenergic transmission. VEN however, does not demonstrate adrenergic properties until higher VEN doses than were achieved during acute ECT and, in the doses used in the study, the pharmacological actions of VEN resembled those of a selective serotonin inhibitor (SSRI). As controlled data on the effect of SSRIs on ECT outcomes is lacking, these findings suggest that effects on cognitive function in particular, warrant further investigation.

Summary and Recommendations

Considering the efficacy of ECT as monotherapy and the limited amount of controlled data on the safety and efficacy of specific antidepressant medications during ECT, it would appear premature to recommend the routine use of adjunctive antidepressant medications to improve efficacy with acute ECT. In patients that do not achieve a sustained remission with ECT alone however, the addition of nortriptyline during the course of ECT may be a useful strategy. High dose venlafaxine, ≥ 300 mg/day, should be avoided during ECT, unless there are unusual clinical reasons to support its use. More research is needed to explore the specific effects of administering each of the antidepressants during ECT, on antidepressant efficacy as well as cognitive side effects. Despite the prediction that reintroducing antidepressants during a course of acute ECT would reduce the risk of relapse post-ECT, evidence to support this is not currently available.

Concurrent pharmacotherapy during ECT for mania

While ECT has been used effectively to treat acute mania since its introduction, the literature on the use of concurrent antimanic medications during ECT is sparse. Current guidelines suggest lithium or anticonvulsants as first-line treatments for mania but there are significant concerns with the use of these medications during ECT.^{1,26-28} Although the literature contains numerous case reports and retrospective reviews suggesting that there are circumstances in which lithium can be beneficially administered during ECT,²⁹ there is no consensus on the safety of this practice. Considering that cognitive side effects are the most widely stated concern associated with ECT, practitioners should be particularly cautious about any practice that might aggravate this side effect. Antipsychotics, however, given alone or in combination with lithium

or anticonvulsants, are commonly used in the treatment of mania and there has been more experience with the use of this class of medications concurrently with ECT. A review of 50 years experience in the use of ECT to treat mania supported its robust effect with remission or marked clinical improvement reported in 80% of patients. This review found some evidence supporting the augmenting effects of adjunctive antipsychotic treatment in patients with mania³⁰ but noted that this combination requires more controlled investigation.³¹ Subsequent case reports however, describing combinations of ECT with clozapine or chlorpromazine in the treatment of mania, suggested that the strategy was therapeutically effective and safe but the absence of controls limits the interpretation of these reports.³²⁻³⁵

A recent study examined the effects of ECT, administered at stimulus intensities just above seizure threshold and 2.5 times seizure threshold, in the treatment of 50 patients with mania who were unresponsive to conventional psychotropic medications.³⁶ All patients were continued on antipsychotic medications, risperidone or olanzapine, and prn IM lorazepam or haloperidol during ECT. Overall 88% of patients achieved remission after 3.6 ± 2.9 ECT over 12 ± 6.1 days, although a mean total of 7.6 ECT were administered during the full course of acute treatment. The authors noted no serious adverse effects in these patients but the lack of controls prevents any conclusions about the efficacy of adjunctive antipsychotics.

Summary and Recommendations

Considering the significant literature supporting the efficacy of ECT in mania, despite its generally uncontrolled nature, ECT remains an appropriate treatment for acute mania, especially those patients who have not responded to conventional antimanic pharmacotherapy. Currently there is insufficient evidence, from appropriately designed studies, to recommend the routine addition of antipsychotic medications to ECT during the treatment of acute mania. Unlike the reported cognitive impairment associated with combination ECT and lithium, the literature does not identify specific hazards associated with the combination of ECT and antipsychotic medication. This suggests that it is unnecessary to discontinue antipsychotic medication when ECT is added to the treatment of a manic patient that has been unresponsive to pharmacological treatment. Conversely however, discontinuation of lithium during ECT would still appear to be the appropriate practice.

Concurrent pharmacotherapy during ECT for schizophrenia

In contrast with the treatment of mania, the literature contains numerous reports addressing the combination of ECT with antipsychotic medications in the treatment of schizophrenia. ECT had been used to treat schizophrenia since its introduction but was less utilized during the 1960s and 1970s after the introduction of effective pharmacological agents. Subsequent identification of a group of patients with schizophrenia, who were either unresponsive to, or unable to tolerate, pharmacological treatment, resulted in a re-examination of the role of ECT in these patients. An early review of the literature from 1959 – 1987³⁷ described many retrospective as well as prospective, controlled studies. While many of the previously mentioned methodological concerns were noted, the author concluded that the combination of antipsychotics, including clozapine, and ECT appears safe and “combined ECT-neuroleptic treatment for patients with schizophrenia may elicit greater rates of response or more rapid improvement than neuroleptics or ECT alone;...” The author also raised a caution that comparison of long term outcome in patients acutely treated with antipsychotic alone or antipsychotic and ECT combination should include a group receiving maintenance ECT. Subsequently Braga and Petrides³⁸ published a comprehensive review of the literature published between 1980 and 2003. They noted that, of the 42 articles identified, only 9 were double-blind randomized controlled studies and the results from these controlled studies did not permit any firm conclusions. Eight studies controlled for ECT effects by including a group of patients who received sham-ECT, many studies limited the number of ECT administered, as well including patients with short duration

of illness that had not failed prior antipsychotic treatment. This latter concern was addressed in a large study of 293 patients, who met published criteria for refractory schizophrenia³⁹ and were treated with flupenthixol and ECT 3 times / week.⁴⁰ The results were encouraging as 54% patients met response criteria although the study did not include a control group receiving antipsychotic alone. The authors did note that responders tended to be younger, have shorter durations of current illness and current episode, less family history of schizophrenia, lower baseline negative symptoms and higher baseline Global Assessment of Functioning.⁴¹ As longer duration of episode has been shown to be predictive of a decreased response to ECT in depressed patients,^{6,42} it is possible that this finding is consistent across diagnoses. As noted in the review “These promising results were corroborated in all other eleven open studies”.

The most recent Cochrane review of electroconvulsive therapy for schizophrenia examined 26 trials with 50 reports.⁴³ The authors concluded that combination ECT and antipsychotic medications can be considered an option for people with schizophrenia when the goal is rapid global improvement and symptomatic reduction, as well as in patients who show a limited response to medication alone. The National Institute for Clinical Excellence (NICE) adopted a more critical view.⁴⁴ They observed that the evidence for the effectiveness of ECT in patients with schizophrenia was inconclusive, that antipsychotic medication may be more effective than ECT alone, but did acknowledge that in selected patients, combination ECT and antipsychotics may be more effective than pharmacotherapy alone. Overall, despite the limitation that the majority of studies in the literature were open or single-blind, there appears to be a signal suggesting that, in patients with antipsychotic-resistant schizophrenia, combination treatment with ECT was more effective than pharmacotherapy alone.

Although the strategy was first proposed in 1990,^{45,46} the literature contains only a small number of subjects treated with the specific combination of ECT and clozapine. One review of 36 patients with various diagnoses treated with this combination reported that 67% patients had marked clinical improvement and the combination was more effective than ECT or clozapine alone.⁴⁷ The concern has been raised that clozapine may lower the seizure threshold and lengthen the seizure duration during ECT⁴⁸, but there is only a single report of a significantly prolonged seizure (6 min) after one ECT.⁴⁹ While more systematic research is needed, these reports suggest that ECT and clozapine is a reasonable treatment option for those patients who have not responded to clozapine alone.

There are only a few reports addressing the combination of ECT with other newer atypical antipsychotics. One study found only a trend for an augmentation effect when ECT was added to the atypical antipsychotics, olanzapine or risperidone.⁵⁰ This study included 30 patients, who had refused to take or failed to respond to clozapine and were offered ECT, while continuing to take either olanzapine or risperidone. Although no serious adverse effects were reported, there were significant methodological limitations that limit the interpretation of this study. The sample size was small, patients who refused ECT were the control population, ECT and control groups differed in duration of illness and hospitalisation, and antipsychotic medication dose was held constant in the ECT group but not the control group. In another report, the use of combination aripiprazole and ECT was well tolerated in 4 patients who did not experience any serious adverse events.

There is a single report of the successful use of ECT and risperidone in the reduction of aggressive behaviours in patients with schizophrenia who were unresponsive to usual pharmacotherapy.⁵¹ This was an open uncontrolled trial of ECT and risperidone in patients with schizophrenia who were demonstrating prominent aggressive behavior. ECT was administered 5 times / week for a total of 5 – 9 ECT and 9 of 10 patients showed complete elimination of aggression within 12 days. This indication must be approached with caution and

it would be crucial to document a relationship between the severity of the aggressive behavior and other symptoms of schizophrenia.

One caution from several of the reviews was the apparent lack of sustained effect after cessation of ECT and the need for systematic follow-up. The use of maintenance ECT (M-ECT) has not been examined with adequately controlled studies but one open study demonstrated superior efficacy of combination ECT and flupenthixol in relapse prevention compared with either alone at 12 month follow up.⁵² Another report described a 3 year retrospective study of 27 treatment resistant patients with chronic schizophrenia who had been unable to tolerate clozapine, failed to respond to, or refused to take clozapine, who were treated with 8 – 14 bitemporal ECT and various antipsychotic medications.⁵³ During 12 month follow up, there were no major adverse events and 37% of patients maintained clinical improvement. Of the 63% patients who relapsed, nearly 50% of these received a second trial of ECT and continued with M-ECT. Five patients resumed self-harm during relapse but this ceased after a second course of ECT.

Summary and Recommendations

Although the literature on combination ECT and antipsychotic treatment of schizophrenia covers over 50 years, there is a general consensus that carefully designed prospective studies are needed to provide solid evidence to support the practice. There are remaining questions about the patient subgroups most likely to benefit from acute treatment with this combination intervention and the role of maintenance ECT in the long-term care of patients with schizophrenia. Despite these gaps in our knowledge, combination ECT and antipsychotic treatment is an option for patients with schizophrenia who are unresponsive to pharmacological interventions alone and its side effect profile does not appear different from that seen with ECT alone. Duration of ECT and the timing of withdrawal of maintenance ECT remains a clinical dilemma with little guidance from the research literature.

Conclusion

The utility of concurrent psychotropic medication during ECT is again receiving attention, but there is a need for more high quality evidence that can lead the discussion about a possible change in standard clinical practice. There is agreement that enhanced efficacy, decreased relapse rates and minimal cognitive side effects are appropriate priorities in ECT practice. The role of combination ECT and psychotropic medication in achieving these goals deserves continued examination, particularly in those patients who have shown inadequate responses to psychotropic medication alone.

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Table 1

Studies of ECT with Antidepressant Augmentation (1961 – 1990)

Authors	Study Design	Subjects	ECT method	Outcome Measures & Results
Muller, 1961 ¹⁹	“Controlled blind” trial: ECT + phenelzine 45 mg ECT + placebo	N=100 depressed	2 ECT / week until clinical response	Improvement rated on “25 point scale” greater with phenelzine (p<0.1) Mean # ECT: phenelzine 7, placebo 8
Seager and Bird, 1962 ¹⁷	Randomised, double-blind: ECT + IMI 150 mg ECT + placebo	N=43 depressed	2 ECT/week until clinical response	All patients responded Mean # ECT: IMI 6.3, placebo 7.0 (ns)
Wilson et al., 1963 ¹³ Error! Bookmark not defined.	Randomised, double-blind: ECT + IMI 150mg ECT + placebo	N=22 depressed	2 ECT/week for 6 ECT Sham ECT control	Mean decrease in HRSD scores: ECT + IMI: 15.6 Sham ECT + IMI 8.4 ECT + placebo: 14.5 Sham ECT + placebo 8.9 “toxic delirium” in 1 patient receiving ECT + IMI
Monaco and Delaplaine, 1964 ¹⁴	Randomised? double-blind, crossover (4 weeks each): ECT + tranylcypamine 20mg ECT + placebo	N=26 depressed		No difference between groups in improvement or side effects
Imlah et al., 1965 ¹⁸	Randomised: ECT + phenelzine 45mg ECT + IMI 75 mg ECT + placebo	N=150 depressed	2 ECT/week until maximal response	Mean # ECT required: ECT + phenelzine 45mg 6.9 ECT + IMI 75 mg 7.2 ECT + placebo 7.9
Kay et al., 1970 ¹⁶	Randomised, double-blind: ECT + AMI 50-150mg ECT + diazepam 4-12 mg	N=132 Affective disorder, schizophrenia, subnormality		Mean improvement in HRSD, Beck, Lubin and 5pt depression scales: HRSD decrease: AMI 72%, diazepam 57% (ns) Beck decrease: AMI 56%, diazepam 30% (p<0.05) 2 patients in AMI group developed mania.
Nelson and Benjamin, 1989 ¹⁵	Retrospective review of 3 groups: ECT alone ECT + low TCA (IMI 50-99 mg) ECT + full TCA	N=84 Elderly depressed	RUL ECT Dosed to achieve seizure of >30 sec	ECT + TCA vs. ECT alone (1 tailed t-test): More improvement with ECT + TCA (p<0.05) # ECT: 8.1 vs. 9.8 (p<0.05) No significant difference in confusion and cardiac effects

Abbreviations: # ECT, number of ECT treatments; ns, not significant; RUL, right unilateral; TCA, tricyclic antidepressant; IMI, imipramine; AMI, amitriptyline; HRSD, Hamilton Rating Scale for Depression.