

Lithium and Electroconvulsive Therapy

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Why is lithium important?

- Effective for all stages of bipolar disorder – acute treatment as well as prophylaxis
- Effective as an antidepressant augmenting agent for unipolar depression
- Has been shown to reduce suicidality
- Reduces relapse rates post ECT for depression



The Intersection of ECT and Lithium

1. Is it safe to combine lithium with index ECT?
2. Does lithium prevent relapses after a successful course of ECT?
3. Should lithium be combined with continuation/maintenance ECT?
4. Clinical recommendations and future directions

The relationship of ECT and lithium

- Schou M. **Lithium and electroconvulsive therapy: adversaries, competitors, allies?** Acta Psychiatrica Scandinavica. 1991;84:435-438
- In this commentary, Schou discusses the relative efficacies of lithium and ECT for acute treatment and prophylaxis of depression and mania.
- He discusses the literature on the interaction of the two treatments and concludes that the combination is not an absolute contraindication but should not be routinely used either.

Should lithium be discontinued prior to commencing index ECT?

- It is not uncommon for patients starting a course of ECT to be taking lithium already
- This is usually either as antidepressant augmentation for unipolar depression, acute treatment for a manic episode, or maintenance treatment for bipolar disorder
- Ideally, if lithium has shown some type of efficacy for a patient, or if it is felt to be a good prophylactic after ECT is finished, one would like to keep giving it during ECT
- However, some literature suggests a toxic interaction between lithium and ECT
- We will now review that literature

Jephcott and Kerry, 1974

- A 64 year old woman with prolonged awakening time after an ECT treatment. Lithium level found to be toxic at 3.4 meq/liter.
- With subsequent normal lithium levels, there were no problems with ECT.
- The obvious issue here is the lithium toxicity.

Ray, 1975

- A 37 year old man got 3 ECT treatments along with lithium; level = 0.46 meq/liter.
- Two days after the last ECT treatment, he developed “minor seizures” with EEG showing sharp spikes.
- A week later the symptoms and EEG resolved.

Hagen, 1976

- A patient had an “organic brain syndrome” after 2nd and 3rd treatments which cleared in a few days
- No other information provided

Lebovitz, 1976

- Letter to a journal (Convulsive Therapy Bulletin)
- “We had a number of cases of prolonged confusion following ECT with lithium. The effect was so marked that, as a rule, I now withdraw my patients from lithium before putting them on ECT.”
- No other information provided

Hoening and Chaulk, 1977

- A 32 year old man got one ECT treatment with lithium level = 1.09 meq/liter with severe confusion which cleared in two days.
- No other information

Price et al, 1978

- Two women, one 26 and the other 36, got ECT while on lithium (no levels reported)
- Reported to have improved cognition and increased finger tapping speed after ECT.

Remick, 1978

- A 41 year old woman developed catatonia 3 days after her 4th ECT treatment; lithium level 0.6-1.0 in recent days.
- Lithium was stopped, catatonia resolved.
- ECT done again 6 weeks later without lithium without any problems.

Vlissides et al, 1979

- In 6 patients getting lithium and ECT, lithium levels measured serially after treatments.
- No increase in lithium levels measured 1 to 3 hours post-treatments.
- No mention of whether patients tolerated the combination therapy.

Mandel et al, 1980

- A 55 year old man with prolonged confusion after 3rd ECT treatment; level = 0.98 meq/liter. Lithium was stopped and ECT resumed without problems.
- A 67 year old woman with confusion after 1st and 2nd treatment. Level of lithium = 0.6 meq/liter. Lithium stopped, ECT resumed without problems.

Small et al, 1980

- Case-control series
- 25 ECT/Lithium combination patients compared to an age-matched ECT without lithium group
- The combination group had more confusion and memory impairment by chart progress notes but were not different by EEG or neuropsychological testing.
- One ECT/Lithium patient developed temporal lobe seizures, one developed automatisms, and one developed fever with meningismus

Weiner et al, 1980

- 33 year old female in whom lithium was started the day after her 5th ECT treatment.
- She developed confusion and EEG evidence of seizure activity
- Both cleared over several days.
- Lithium not given along with ECT, just after.

DePaulo et al, 1982

- 59 year old woman who developed delirium when lithium was started after ECT #4.
- ECT two months later without lithium was uncomplicated by confusion

Martin and Kramer, 1982

- 17 combined ECT/Lithium patients
- They focused on time to breathing, reflecting anesthesia literature suggesting lithium prolongs the action of succinylcholine
- No evidence of prolonged time to breathing
- No comment on memory or orientation

Ahmed and Stein, 1987

- A 57 year old woman became ataxic, tremorous, and confused while on lithium alone; level not specified
- Lithium stopped
- ECT started an unspecified time later
- Confusion after 2nd treatment
- Unknown if lithium was still present in her bloodstream when ECT given

Kukopoulas et al, 1987

- A cohort of 256 ECT/Lithium patients retrospectively compared to a non-lithium ECT cohort of 130 patients
- No difference in post-treatment agitation, confusion or EEG findings (but only a few had EEG's)

DeQuardo and Tandon, 1988

- A 42 year old woman, lithium level = 0.89 meq/liter, got 4 ECT treatments without a switch to mania which had happened previously with ECT without lithium

Alexander et al, 1988

- 7 manic patients treated with lithium and ECT
- One patient had prolonged confusion and nystagmus

Pearlman, 1988

- A 40 year old man got ECT and lithium without problems

Penney et al, 1990

- 27 patients given lithium concurrently with ECT compared to 49 patients given lithium either within 24 hours of the first treatment or 48 hours after the last treatment and 100 patients not given lithium around the time of ECT
- More cases of post-ECT confusion (22%) in the concurrent group than no lithium group (6%)

Sackeim et al, 1991

- Mentions in passing that ECT and lithium have been combined in their practice without providing details

Bright-Long and Fink, 1993

- A 58 year old woman with lithium blood levels of about 0.8-1.0 meq/liter had index and maintenance ECT without complications.
- Lithium held the night before each treatment

Lippman and Tao, 1993

- A 40 year old woman given about 70 ECT treatments total, index and maintenance, with lithium levels 0.6-1.2 meq/liter without complications
- Lithium held the night before treatment

O'Brien and Berrios, 1993

- 6 patients given lithium concurrently with ECT
- No mention of outcomes

Jha et al, 1996

- 31 cases of lithium combined with ECT
- Levels 0.2-1.9 meq/liter
- No difference in complications between lithium and non-lithium ECT patients

Gupta et al, 1998

- A 56 year old man who got 3 ECT treatments with a lithium level of 0.77 meq/liter without complications

Kramer, 1999

- A 30 year old man receiving maintenance ECT and lithium without complications
- Lithium held 24 hours prior to each treatment

Mayur et al, 1999

- 29 combined ECT/Lithium patients
- Focused on motor and EEG durations
- Found lower ratio of motor to EEG duration but not longer EEG seizures than control group
- No mention of complications or confusion

Stewart et al, 1999

- A 78 year old man experiencing “some” increase in confusion with combination ECT plus lithium but better prophylaxis against recurrent depression than with prior ECT without lithium

Gagne et al, 2000

- Some maintenance ECT patients given lithium (? How many)
- No mention of safety issues

Conway and Nelson, 2001

- Prolonged seizure at first (and only) ECT session in a 45 year old man taking lithium, venlafaxine, and bupropion
- Did lithium have anything to do with this?

Volpe et al, 2003

- In a description of hospital treatment of acute mania, 72.3% of all patients (102) received ECT plus lithium
- No mention of safety information

Dolenc and Rasmussen, 2005

- 12 combined ECT/Lithium cases in whom no observable complications occurred

Sartorius et al, 2005

- Case 1: Lithium level = 0.32 meq/liter. Tardive seizure at first session. Lithium stopped, no further problems at other sessions of ECT. Was lithium to blame?
- Case 2: Fever, rigidity, delirium developed a few hours after the first ECT session in a 62 year old with a lithium level = 0.38. Lithium stopped, no further problems thereafter with ECT.
- Case 3: 79 year old got an acute series of ECT with no lithium and no problems. Lithium/paroxetine started for continuation and 5 days later a focal seizure occurred. ?did this relate to ECT at all?

Thirthalli et al, 2011

- N=27 patients on lithium during ECT; N=28 not on lithium.
- Time to post-ECT recovery directly correlated with lithium level.
- No difference in seizure thresholds
- No overall difference in time to first breath, though the two patients with the highest lithium levels had long time to first breath
- Authors suggest keeping lithium levels as low as therapeutically possible during ECT

Volpe et al, 2012

- 90 patients got ECT and lithium during treatment for mania.
- No cognitive testing done
- No overt complications noted
- No alteration in number of ECT treatments or length of stay compared to non-lithium ECT patients.

Practice Guidelines

- The ECT Handbook (Royal College of Psychiatrists) recommends keeping the electrical dose low to lower the possibility of excess cognitive effects, though there is no evidence supporting this.
- American Psychiatric Association (Committee on ECT) recommends using the combination cautiously and keeping lithium levels as low as feasible and perhaps skipping lithium for a day or so before each treatment

Clinical recommendations

- If a patient is taking lithium for antidepressant augmentation for unipolar depression, then if they are getting ECT, the augmentation has not worked, so I would discontinue lithium. However, a washout is not necessary but may be feasible and desirable depending on the urgency of ECT
- If a patient is taking lithium for acute mania, then it has not worked if ECT is prescribed, so I would discontinue it as well in this situation. Again, no washout is necessary

What if a patient is taking lithium for maintenance treatment of bipolar disorder, and it has worked for the manic phase?

- This is a more difficult situation, because one would not want to discontinue lithium and put the patient at risk for mania.
- Some would say just keep treating with ECT if the depressed patient becomes manic, but the patient may be disagreeable to ECT in that state.
- One option is to continue lithium but observe for untoward reactions
- Another option is to hold lithium for 24 hours before each treatment.
- Another option is to replace lithium with another anti-manic agent, preferably not an anticonvulsant but an antipsychotic agent.
- I strongly recommend against discontinuing lithium without replacing it with another agent.

Should lithium be started after a course of ECT?

- Lithium is often considered a prophylactic against recurrences of mood episodes
- Thus, it has been used after a course of ECT to prevent relapses of unipolar depressive episodes

Review of post-ECT lithium literature

- Perry and Tsuang, 1979
- Coppen et al, 1981
- Abou-Saleh, 1987
- Shapira et al, 1995
- Sackeim et al, 2001
- Kellner et al, 2006
- Prudic et al, 2013
- Atiku et al, 2015
- Kellner et al, 2016

Perry and Tsuang, 1979

- Randomized post-ECT depressed patients to lithium versus a tricyclic
- Found equal relapse rates, arguing that lithium as monotherapy may be effective at preventing relapses
- There was no combined treatment group, however

Coppen et al, 1981

- Randomized post-ECT depressed patients to lithium versus placebo
- Found greater relapses in the placebo group
- Again argues that lithium monotherapy may be an effective prophylactic agent after ECT, but again no combination antidepressant/lithium group was studied

Abou-Saleh, 1987

- In a letter to the editor, the author re-analyzed data from Coppen et al, 1981 and found that the greatest protective effect of lithium was in the second 6 month period after ECT
- He argues that lithium should be maintained for at least a year after ECT

Shapira et al, 1995

- Followed 24 unipolar depressed patients who remitted with index ECT and found a 65% sustained remission rate over 6 months, again suggesting lithium monotherapy may be effective

Sackeim et al, 2001

- Randomly assigned unipolar depressed ECT remitters to three groups for 6 months with precise relapse criteria specified
- **Placebo** = 89% relapse
- **Nortriptyline** = 69% relapse
- **Nortriptyline plus lithium** = 39% relapse
- Question: how would a lithium-only group have fared?
- Blood levels averaged around 0.5 – would higher levels have resulted in lesser relapse rates?

Kellner et al, 2006

- Using the same entry criteria and outcome assessments as Sackeim et al, 2001
- Randomized unipolar depressed patients who remitted with index ECT to two groups
- **Combined lithium/nortriptyline** = sustained remission rates = 46%
- **Continuation ECT** had the same sustained remission rate

Prudic et al, 2013

- The OPT-ECT trial
- Depressed ECT patients randomly assigned to concomitant venlafaxine, nortriptyline, or placebo
- Remitters followed for six months on lithium (added after ECT finished) plus either antidepressant
- There was no lithium only or non-lithium group
- Thus, this study provides no further information on the specific role of lithium in preventing relapses
- If lithium had been added concomitantly with index ECT, would initial remission rates or sustained remission rates have been enhanced?

Atiku et al, 2015

- Retrospective chart review of relapses after ECT for 6 months
- Antidepressant + lithium = 16% relapse rate
- Antidepressant + non-lithium mood stabilizer = 69%
- Antidepressant only = 60%
- Antidepressant + antipsychotic = 75%
- Thus, lithium appears to be prophylactic
- An educational effort to increase usage of lithium after ECT failed
- This points out that lithium is a difficult medication to prescribe

Kellner et al, 2016

- The PRIDE study (“prolonging remission in the depressed elderly”)
- Elderly depressed patients given unilateral ultrabrief pulse ECT along with venlafaxine
- Remitters all given venlafaxine plus lithium, with half the group getting continuation ECT
- Thus, all patients received lithium, so not terribly informative about how helpful lithium is
- Lithium was held a day or two before each treatment, and average lithium levels were pretty low (less than 0.5)
- This points out the difficulty of combining lithium with continuation ECT – if the lithium doses are to be held a day or two prior to each treatment, then it will take a long time for a stable therapeutic lithium level to be reached, thus lessening lithium’s prophylactic capacity

How to combine lithium with continuation ECT

- The PRIDE study informs this issue
- Lithium was stopped a day or two before each continuation treatment
- That brings difficulties logistically and with fluctuations in lithium levels
- Looking carefully at the data, it is unclear just how much benefit adding C-ECT to lithium/venlafaxine was, raising the question whether more aggressive lithium dosing may have helped

Clinical Recommendations for lithium post-ECT as prophylaxis

- What lithium level should be used?
- How long should it be used for?
- Does lithium have to be combined with an antidepressant? If so, which ones?
- What about bipolar patients?

What lithium level to aim for?

- The studies funded by the National Institute for Mental Health in the USA all used levels about 0.5 or so.
- Would higher levels have provided greater relapse protection?
- Higher levels are usually used for treatment of bipolar disorder

How long should post-ECT lithium be used for?

- Most of the research is for 6 months
- The Coppen/Abou-Saleh data indicate a better protective effect in the second 6 months after ECT, however
- Prudence would dictate at least 6 months but not necessarily longer than that, given the effect of lithium on kidney and thyroid function

Should lithium always be combined with an antidepressant?

- The best data indicate combining lithium with either venlafaxine or nortriptyline
- However, earlier data (Coppin et al, Perry and Tsuang, Shapira et al) indicate lithium monotherapy may be effective in preventing relapses
- Since venlafaxine is a relatively easy medication to use, it is recommended
- If the patient cannot tolerate it or has been refractory to it, and cannot safely take a tricyclic, then combining lithium with another antidepressant is prudent

What about bipolar patients?

- All previous recommendations pertain to unipolar depressed patients remitting with ECT
- In the bipolar depressed patient just remitting with ECT, what role does lithium play in prophylaxis?
- This is relatively unstudied, but one would assume that it would be just as protective as in unipolar patients
- It would probably be continued for a much longer time period than 6 months and at higher levels than 0.5
- Also, one would probably not combine it with an antidepressant for fear of precipitating mania or rapid cycling

Should lithium be initiated with index ECT?

- The field has become so accustomed to stopping lithium before ECT that nobody has done any research specifically combining lithium with index ECT (eg, no randomized trials)
- Theoretically, there might be a synergistic effect between lithium and ECT for acute efficacy or relapse prevention
- Perhaps from a pure efficacy standpoint, lithium may enhance acute remission rates and/or prevent relapses better if given earlier rather than after ECT is finished.
- A randomized study would be nice to see

Summary of Recommendations

1. Lithium should not be started concurrently with ECT, but research on this topic would be welcome to see if it enhances acute remission or helps prevent relapses.
2. For unipolar depressed or manic patients starting ECT who are already taking lithium, which has not been effective, the lithium should be stopped in anticipation of ECT. A “washout” is probably not absolutely necessary. However, if lithium levels are fairly high and starting ECT is not urgent, then waiting a few days for the level to go down is desirable.

Recommendations continued:

3. For bipolar depressed patients starting ECT who are taking lithium which has been effective in controlling the manic phase of the illness, the clinician may cautiously wish to continue lithium during index ECT but withhold the dosing 24 hours prior to each treatment and keep blood levels as low as feasible.
4. Alternatively, lithium may be discontinued and substituted with another antimanic agent, preferably not an anticonvulsant.
5. Lithium should not be discontinued in a bipolar patient starting ECT without being substituted with another antimanic agent (assuming one is not already being given).

Recommendations continued:

6. For post-ECT prophylaxis, in both unipolar and bipolar patients, lithium should be used if it can be used safely.
7. For unipolar depressives given lithium for post-ECT prophylaxis, it should probably be used for 6 months and at blood levels at least 0.5.
8. For bipolar patients given lithium after index ECT, it should probably be used for longer periods of time and perhaps at higher blood levels than 0.5.
9. If continuation ECT is used, lithium can also be used, aiming for blood levels around 0.5 and holding dosing 24 hours prior to each treatment.
10. If lithium is used along with either index or continuation ECT, the clinician should always be on the lookout for excessive confusion and be willing to stop lithium if that occurs.