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Combination of lithium and electroconvulsive therapy (ECT) is associated with higher odds of delirium and cognitive problems in a large national sample across the United States

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ABSTRACT

Background: Lithium is a helpful adjunct to patients undergoing ECT. However, only case reports and limited data suggest increase risk of delirium. Thus, this continues to be a controversial issue.
Objective: In this study, we examine 1) The association and odds of delirium and cognitive problems with ECT and lithium (ECT + Li) combination compared to ECT alone, 2) If positively associated, would this association vary by both type of mood episode and type of disorder?
Methods: A national sample of 64,728 adult psychiatric inpatients across the US (identified from a total data of about 70 million total discharges annually) was analyzed using linear-by-linear association and logistic regression to assess the odds ratio (OR) for delirium and cognitive impairment for those treated with lithium (N = 158), ECT (N = 64148), or ECT + Li (N = 422) after adjusting for demographics and psychiatric diagnoses.
Results: The prevalence of delirium was higher in the ECT + Lithium group (5.7%) vs. ECT only (0.6%) or lithium only groups (0%). Patients managed with ECT + Lithium have 11.7-fold higher odds (95% CI 7.55 −17.99, $P < 0.001$) of delirium compared to ECT alone. In the ECT + Li group, delirium prevalence was 7.8% in unipolar depression, 3.4% in bipolar depressed, 0% in bipolar mania.
Conclusion: These results are surprising given the fading concern about delirium association with ECT + lithium combination. The high odds in the combination group warrant clinical caution, use of lower lithium doses (if combinations cannot be avoided), and vigilance regarding early signs of delirium. These results warrant replication in future studies.

Introduction

Lithium is a cornerstone treatment option for bipolar disorders (BD) as well as treatment-resistant major depressive disorder (MDD), as supported by many studies and guidelines [1,2]. Electroconvulsive therapy (ECT) is also the most effective treatment modality for BD and treatment-resistant MDD (TRD) [3]. However, in TRD cases of both BD and MDD, a combination of both lithium and ECT is sometimes needed to improve effectiveness [4,5]. Combinations seem to work better than either ECT or lithium alone for acute treatment, as well as for relapse prevention [4,5].

However, there are conflicting opinions related to lithium use with ECT [6]. There are limited data concerning the combination treatment of lithium and ECT that indicates that this combination may increase the risk of delirium [7–10] and cognitive side effects [11,12]. Literature on lithium–ECT combination (Li + ECT) consists of case reports [7,9,10,12–14] and observational studies [11,15–17]. The American Psychiatric Association (APA) task force recommends withholding lithium for 24 h before starting ECT, then measuring lithium levels before ECT, in order to reduce post-ECT neurocognitive effects [8]. The guidelines regarding Li-ECT combination

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have been unclear due to ongoing debate about its safety, especially given that the literature about delirium is limited.

In some circumstances (including if patients are not responsive to either treatment alone), psychiatrists may want to continue lithium after the acute course to avoid relapse which is a different issue [18,19]. Given that former issue, of using lithium during the acute course of ECT, is still relatively controversial according to many, and different practitioners have different views and practices, we address this issue in this study by examining the following:

1) The association and odds of delirium and cognitive problems with the combination of Li + ECT compared to either treatment alone using a large database from hospitals across the US.
2) If positively associated, would this association vary by both type of mood episode and type of disorder?

Materials and methods

Study sample

Our study included adult inpatients (age 18 years or above) with discharges in January 2010 to December 2014 from the Nationwide Inpatient Sample (NIS) data and previously described in reference [20]. The NIS is the largest inpatient data in the US and includes about 20% of discharges from nonfederal, acute care hospitals [21]. This data consists of about 70 million total discharge patient records annually, and we identified the psychiatric hospitalizations based on the primary discharge diagnosis (DX1) field on patient records. The data is based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes as the Healthcare Cost and Utilization Project (HCUP) data processing included ICD-10 diagnosis codes only after 2014. All patients with a primary discharge diagnosis (DX1) [22] of bipolar depression, bipolar mania, or major depressive disorder (MDD) based on the ICD-9-CM diagnosis codes, and major or extreme severity of illness based on APRDRG_Severity variable of the NIS [22] were included in this study. A total of 64,728 patients were included in this study and were further grouped by the procedures (ICD-9-CM procedure code) received during inpatient management. Thus, patients were divided into lithium (N = 158, ICD-9-CM code: 94.22), ECT (N = 64148, ICD-9-CM code: 94.27) and ECT + Li (N = 422) groups.

Variables

Sociodemographic variables including age, sex, race, and primary payer were evaluated [22]. ICD-9-CM diagnosis codes were used to detect acute complications, namely acute delirium (ICD-9-CM codes: 293.0, 293.1) and mild cognitive impairment (ICD-9-CM code: 331.83) in other diagnoses fields (DX2 to DX25 variables) [22].

Statistical analysis

All statistical analyses were done using SPSS version 25 (IBM Corp., Armonk, NY) and discharge-level sampling weights provided by the NIS dataset were utilized to report national estimates from all US community hospitals. We compared the distributions of sociodemographic characteristics and acute complications between hospitalizations with lithium vs. ECT vs. ECT + Li groups by performing linear-by-linear association and descriptive statistics. Acute complications were further distributed based on the primary diagnoses and procedure using descriptive statistics. We calculated the odds ratio (OR) for acute complications in ECT + Li versus ECT only group using binomial logistic regression model with *apriori* confounders including age, sex, race, and median household income, and primary diagnoses. Statistical significance for all analyses was set at a two-sided P value < 0.05.

Ethical approval

The NIS is a publicly available de-identified database that protects the privacy of patients, physicians, and hospitals [21]. So, we were not required to take Institution Review Board permission for this study.

Results

Patients in the ECT (mean age, 52.6) and Li + ECT (mean age, 49.7) groups were older than the Li only group (mean age, 42.9). The percentage of females that was treated with Li was 58.9%, Li + ECT was 56.7%, and with ECT alone was 65.2%. There were higher proportions of Caucasian inpatients with BD (manic/depressed) and MDD. More ECT and Li + ECT were used in Caucasians, yet Li only was used comparatively higher in the Black population (21.4% vs. 2.4–4.8%). In the Li + ECT group, 50% had private insurance (see Table 1). ECT and Li + ECT were utilized in higher proportion in MDD patients, and Li only was utilized in higher proportion in BD (manic/depressed) patients.

Acute delirium was seen in 5.7% of all the patients who had combination of Li + ECT. Of the total sample, more MDD patients (7.8%) treated with Li + ECT had delirium than bipolar depression (3.4%) patients. Cognitive impairment was also seen in higher proportion of the Li + ECT group of 2.4%, versus 0.5% in ECT only group (Table 2). When stratifying cognitive impairment for the Li + ECT group by disorder, 4.1% of patients with MDD, and 0% of patients with bipolar depression had cognitive impairment.

Odds for delirium and cognitive problems in the combined lithium and ECT group compared to ECT only group for the total sample

In the multivariable logistic regression model adjusted for age, sex, race and primary psychiatric diagnoses, patients who were managed by combination treatment of Li + ECT had 11.7-fold higher odds (95% CI 7.55–17.99) of acute delirium and 6.4-fold higher odds (95% CI 3.36–12.29) for cognitive impairment compared to the group who had ECT alone (Table 3).

Discussion

The main finding of this study is that patients managed with ECT and Li during inpatient stay had 11.7-fold higher odds of delirium compared to those treated with ECT alone. Equally important is that cognitive impairment (other than delirium) was also higher in the ECT and Li group compared to those treated with ECT alone.

In our clinical experience, many patients during mania are much less likely to exhibit side effects for many mood stabilizers and antipsychotics than during depressive episodes. Thereby, the same patients start exhibiting side effects during depressive episodes even when continued on the same medications that treated the manic episode. For that reason, we did a sub-analysis to examine the results stratified by diagnoses and episode in which ECT and lithium are used (i.e. MDD, bipolar depression, and bipolar mania). Treated with the combination of ECT and lithium, delirium prevalence was 7.8% in patients with MDD, while it was 3.4% in patients with bipolar depressed, and 0% in bipolar mania. This is in agreement with our *priori* hypothesis. The prevalence of acute delirium was comparatively higher in patients on Li + ECT with MDD than those with bipolar depression. This might be due to that patients

Table 1
Demographic distribution by treatment.

Variable	Lithium	ECT	ECT + lithium	Total	P value
Total inpatients, N	158	64148	422	64728	–
Age at admission, in %					
Mean age (SD), in years	42.9 (13.2)	52.6 (14.9)	49.7 (15.9)	50.5 (16.0)	<0.001
18–40 years	50.0	21.8	25.4	21.9	.060
41–60 years	38.0	46.0	49.3	46.0	
61–80 years	12.0	32.2	25.4	32.2	
Gender, in %					
Male	41.1	34.8	43.3	34.9	.027
Female	58.9	65.2	56.7	65.1	
Race, in %					
White	68.6	87.3	87.4	87.3	.201
Black	21.4	4.8	2.4	4.8	
Hispanic	6.9	3.2	5.7	3.2	
Other	3.1	4.7	4.5	4.7	
Primary payer					
Medicare	24.1	45.5	32.2	45.3	<0.001
Medicaid	48.7	11.8	14.9	11.9	
Private	20.3	38.5	48.3	38.6	
Self-pay or uninsured	7.0	4.2	4.5	4.2	
Primary diagnosis, in %					
BD, depressed	44.3	27.5	35.3	27.6	.032
BD, manic	43.7	6.9	6.9	7.0	
MDD	12.0	65.7	57.8	65.5	

The proportion between total inpatients and patients receiving lithium, ECT and ECT + lithium were obtained using cross tabulation and the linear-by-linear association test; and were significant with P value ≤ 0.05 at 95% Confidence Interval. N: number of inpatients; SD: standard deviation; BD: bipolar disorder; MDD: major depressive disorder.

Table 2
Distribution of the study population by primary diagnoses.

Variable	BD, depressed		BD, manic		MDD		Total	
	ECT	ECT + Li	ECT	ECT + Li	ECT	ECT + Li	ECT	ECT + Li
Mean age (SD), in years	49.8 (14.2)	50.1 (15.8)	49.6 (15.7)	45.2 (18.7)	54.1 (14.8)	51.3 (15.7)	52.6 (14.9)	50.5 (16.0)
Gender, in %								
Male	32	46.3	28.9	16.7	36.7	44.7	43.3	34.9
Female	68	53.7	71.1	83.3	63.3	55.3	56.7	65.1
Complications, in %								
Acute delirium	0.3	3.4	0.9	0	0.7	7.8	0.6	5.7
Cognitive impairment	0.2	0	0.5	0	0.6	4.1	0.5	2.4

The proportion between inpatients and patients receiving ECT and ECT + lithium were obtained using cross tabulation. SD: standard deviation; Li: lithium; BD: bipolar disorder; MDD: major depressive disorder.

with bipolar disorder may have higher metabolism or are more tolerant for some reason to lithium compared to patients with MDD, albeit speculative. Alternatively, it may be due to the fact that patients with bipolar depression usually need fewer ECT sessions due to quicker response. Future studies should be done to evaluate the differences in delirium between patients with MDD vs bipolar depression.

Table 3
Predictors of the complications in inpatients.

Variable	Acute delirium			Mild cognitive impairment		
	OR	95% CI	P value	OR	95% CI	P value
Age, in years (vs. 18–40)						
41–60	2.41	1.56–3.74	<0.001	0.87	0.53–1.43	0.574
61–80	5.99	3.85–9.35	<0.001	5.55	3.51–8.78	<0.001
Sex (vs. male)						
Female	1.12	0.90–1.38	0.317	0.69	0.55–0.89	0.003
Race (vs. White)						
Black	0.88	0.52–1.48	0.624	0.41	0.17–0.99	0.049
Hispanic	0.36	0.15–0.86	0.022	1.03	0.54–1.95	0.931
Other	1.00	0.63–1.59	0.997	0.68	0.36–1.27	0.225
Primary diagnosis (vs. BD, depressed)						
BD, manic	1.95	1.25–3.04	0.003	1.88	1.09–3.21	0.021
MDD	1.89	1.43–2.51	<0.001	1.88	1.35–2.63	<0.001
Treatment (vs. ECT only)						
ECT + Lithium	11.66	7.55–17.99	<0.001	6.42	3.36–12.29	<0.001

The odds for the patients with co-diagnoses of acute delirium and mild cognitive impairment were obtained using logistic regression model; and were significant with P value ≤ 0.05 at 95% Confidence Interval. The variable in parentheses is the reference category. OR: odds ratio; CI: confidence interval; Li: lithium; BD: bipolar disorder; MDD: major depressive disorder.

These results are surprising given the fading concern within the field (including our own) about the association of delirium with the combined use of ECT and lithium. It is possible that ECT electrode placement could play a role, and this would be worth examining in future studies. However, this cannot be examined using the current study. Among other explanations are that the development of delirium could be a function of the lithium dose, indication (diagnosis), or even the mood episode.

We believe that, in some well-selected cases, the combination of ECT and lithium is necessary for effectiveness reasons and can even be lifesaving. *However the practice of combination of Li + ECT, whether necessary or not, may need to be reexamined in the light of the findings of this study.*

A systematic review by our group supports the notion that combined ECT with pharmacotherapy (including lithium) can be more effective in some and would increase percentage of patients that stay in remission after an acute course of ECT [4]. This has also been supported by a recent large randomized clinical trial: the Prolonging Remission in Depressed Elderly (PRIDE) [5]. In the PRIDE study, an average of seven right unilateral ultrabrief pulse ECT sessions were effective in depressed older patients in phase I,

with remission seen in 61.7% [23]. In phase 2 of the PRIDE study for relapse prevention, ECT with medications (venlafaxine + Li, at 24 weeks) had statistically significantly lower Hamilton Depression Rating (HAM-D) scores than the medication only group (effect size = 4.2 points, 95% CI 1.6–6.9) [5]. So, ECT with venlafaxine + Li is effective in maintaining remission from depressive symptoms for six months post-remission [5]. It should be noted, however, that our study examined combination of acute course of ECT with lithium treatment, but the above systematic review and the Phase II of the PRIDE study both examined this combination during the continuation phase of ECT (with a much less frequent ECT administration) to prevent relapse, rather than treat the acute episode.

The association of much higher odds of delirium during acute ECT course in the combination group compared to ECT alone, however, warrants clinical caution when deciding to use this combination. Perhaps a lower lithium doses (if combinations cannot be avoided) may reduce the odds for delirium. Also, holding lithium the evening before/day before ECT might be beneficial (as was done in the PRIDE study) and is commonly practiced clinically. It should be noted that our sample contains real life clinical practice in a nationalistic fashion and none of the variables or practices have been manipulated for the purpose of research. Thus, the higher odds of delirium may still be a concern even for many clinicians utilizing this strategy of holding lithium prior to the ECT session, but we cannot conclude as per our study due to lack of information on dosing of lithium pre and post-ECT.

The findings of our study advise us, ECT psychiatrists, and other clinicians referring patients for acute ECT course to exercise extra caution and to be vigilant to early signs of delirium with this combination and, if possible, be ready to discontinue lithium before or during the ECT course if the episode can be managed with ECT alone [6].

There is limited prior data that includes case reports and retrospective case reviews that state that co-administration of Li with ECT lead to adverse events [14] including delirium with rates ranging from 5% to 10% [15,16]. Generally speaking, the likelihood for acute delirium increases with age. Similarly, in our study, older patients who were above 60 years have six-fold higher odds (OR = 6) of delirium compared to the younger age group. Also, there were higher odds of cognitive impairment in the older (OR = 3.5) than the younger (see Table 3).

This could be due to only age-related changes [14,24]. When comparing ECT only group versus Li + ECT group in BD patients (both depressive and manic episodes), there was no statistically significant mean age difference. Although in patients with MDD, the Li + ECT group was younger (51 vs. 54 years, P = 0.003). Yet, a higher proportion of MDD patients on the combination of Li + ECT had delirium (7.8%) and mild cognitive impairment (4.1%).

A study by Thirthalli et al. [17] found that the duration of recovery after ECT session is directly correlated with serum Li levels. Low Li dose and maintaining low serum Li levels can reduce the chances of delirium in such patients [9]. Li + ECT may be associated with complications, but it does not impact a patient's length of hospitalization unless Li is administered in close sequential association with ECT [25].

A case report suggested that patients with significant head injury may be more susceptible to developing delirium with Li + ECT combination [9]. In patients with high vulnerability for delirium and cognitive side effects, it may be safer to withhold Li during the ECT [9,26].

Cognitive impairment side effects

In our study, patients on Li + ECT combination had 542% higher likelihood for cognitive impairment compared to ECT only group. Cognitive impairment is higher in the older age group of 61–80 years (increased by 5.5 times the odds). This was only found in MDD patients on Li + ECT. Also, in a study by Milstein and Small, patients on Li + ECT reported some memory problems, but they tested negative for cognitive impairment in neuropsychological testing [27].

Collectively, the data above highlights the importance of assessing cost-benefit ratio between effectiveness and the risk of delirium and cognitive issues. The combination of Li + ECT [28] can be appropriate [29] when there is a high benefits to risk ratio. When used, we suggest caution and use of a low dose of Li (lower than the common standard of care, if possible). If used together, Li would be better withheld for a day before each ECT session (as was done in the PRIDE study) [23]. Alternatively, Li can also be started after index ECT is completed [30].

Limitations

This study has some limitations due to the characteristics of the administrative database. For example, information on several patient related variables was not available. Also, no information was provided about the quality of inpatient ECT technique or the specifics of electric stimulus parameters, or electrode placements. The data does not include information about other concomitant medications administered to the patients (which may indicate disease severity or might be associated with delirium (e.g. benzodiazepines) if over-distributed in one group than the other), and comorbid risk factors of delirium or any cognitive measures are not available. Acute delirium and mild cognitive impairment were identified using the ICD-9 diagnostic codes and not rating scales. The diagnosis of cognitive impairment clinically using ICD codes is usually has much higher threshold than diagnosing delirium, especially if cognitive rating scales (such as Time to Reorientation and Autobiographic Memory Inventory) are not used. In addition, the study population was limited to non-federal general hospitals. Moreover, there are clearly far less inpatients who receive lithium in the database (with or without ECT) versus ECT alone. This limitation of the database may be due to underreporting of lithium administration as the ICD code for lithium is less frequently used compared to ECT (as it is not associated with billing). Thus, selection and information bias could not be ruled out. However, it is hard to collect such sample size from a prospective study such as clinical trials, so such a database can contribute some towards answering the proposed questions, until further replications in prospective study with larger numbers are achieved. Another limitation is that information about Li dosages or the timing of starting Li during the hospitalization was not available. However, this represents an area with little data in the literature, and the study provides valuable information to the field, especially in an area not only with limited data, but also with contradictory practices. The study also represents both the largest study in the literature to examine the effect of combing ECT with lithium on delirium and cognitive side effects. Given the large sample size of this study, small signals can also be detected. Lastly, it represents a real-world sample representative of the clinical population as practiced across the United States. Thus, the findings of this study can directly impact clinical decision-making.

Conclusion

The findings highlight the field's uncertainty and varying practices and concern about the combination of Li with acute ECT course, as well as the potential association with delirium and even cognitive side effects. Given that prior support for the associated side effects came from case reports and small retrospective reports,

the clinical significance or magnitude of this association is unclear. The main message from this study is that although combining ECT and Li may be necessary in some cases due to improved efficacy that cannot be achieved by either alone, this combination should be balanced due to increasing odds of delirium and cognitive side effects. Thus, we suggest caution, especially with higher doses of Li. The benefits must substantially outweigh the risks, such as serious suicidality or lack of significant clinical progress in effectiveness. When doing so, the clinician should be extra vigilant to early signs of delirium or cognitive side effects. These results warrant replication in future studies.

Conflict/declaration of interest

Dr. Patel and Dr. Bachu report no conflicts of interest. Dr. Youssef discloses that he receives research support (but not salary support) from Merck & Co., MECTA Corporation, the U.S. Department of Veterans Affairs, and August Biomedical Research Corporation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.08.012.

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