

Original Research Article

Exploring the role of therapeutic drug monitoring and regular supervision in optimizing quality of life in patients of bipolar affective disorder receiving lithium therapy in a tertiary care teaching hospital: a prospective observational study

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ABSTRACT

Background: Lithium is considered first line drug effective in treating manic and mixed episodes of bipolar affective disorders throughout the globe. But the chronic and heterogenous nature of disease, along with toxicity of lithium often make patients non-adherent to medication as well as diminished health related quality of life. Present study was done to find out the prospect of regular supervision and follow up with therapeutic drug monitoring in optimization of lithium therapy based on health-related quality of life outcomes.

Methods: It was a prospective, non-randomized, observational study of a cohort of subjects who are suffering from bipolar affective disorders and on lithium therapy. Patients were regularly followed up with therapeutic drug monitoring and personalized interview with questionnaires like WHO Quality of Life Score (QOL-Bref), Montgomery-Asberg Depression Scale (MADRS) and Medication Adherence Rating Scale (MARS).

Results: Results revealed there was significant improvement in health-related quality of life of patients who were monitored with therapeutic drug monitoring and prescribed lithium therapy.

Conclusions: Hence to maintain patients' quality of life improved throughout the cycle of bipolar disorder spectrum, regular follow-up visits with monitoring of serum levels of lithium is needed, so that adverse effects would be minimal and adherence to medication become optimal. These optimal dosing resulting in optimal benefit to patients can be achieved with the involvement of clinical pharmacological consultation.

Keywords: Bipolar affective disorder, Health related quality of life, Lithium, Medication Adherence Rating Scale, Medication adherence, Montgomery-Asberg Depression Scale, Therapeutic drug monitoring, WHO Quality Of Life Score

INTRODUCTION

Bipolar disorder is a heterogeneous, recurrent and chronic psychiatric disorder which is quite debilitating for the patients with fluctuations in mood like euthymia, major depression, and mania or hypomania. The estimated lifetime prevalence ranges from 0.6% to 2.4% worldwide.¹ It affects irrespective of nationality, ethnic

origin, or socioeconomic status causing much cognitive and functional impairment with increased suicide rate.² It has been evident that bipolar disorder is responsible for the loss of disability-adjusted life years (DALYs), and the loss is more graver and serious than all forms of cancer or major neurologic conditions like epilepsy and Alzheimer's disease. It is due to chronic course of the disease throughout the life span as well as quite early

onset.³ Mood stabilizers play a pivotal role in the long-term treatment of patients with bipolar affective disorder. Of the mood stabilizers, the most widely and efficaciously used is lithium salt. Lithium is the first and foremost option for the starting of treatment and has been used in all phases of the disease. The goal of lithium treatment is both the prevention of relapses as well as treatment of acute episodes, such as mania and depression. It is important drug for different specific subtypes, such as mood episodes with mixed features or rapid cycling. It has been seen that with regard to lifespan, the efficacy of lithium in bipolar disorders of paediatric, older aged patients, pregnancy and postpartum periods are evident.¹ Maintenance therapy prevents or diminishes the frequency and intensity of subsequent manic episodes in bipolar patients with a history of mania.

While it is known that mood stabilizers effectively treat symptoms of bipolar disorder, the potential for adverse drug events (ADEs) is of particular concern. It is a drug with a narrow therapeutic index; therefore, careful therapeutic drug monitoring is needed to maximize effectiveness and to minimize ADEs and toxicity. Patients using lithium are known to have a high intra- and interpatient variability in dose concentration relationship, and external factors including drug-drug interactions, environmental temperature, and fluid and electrolyte intake may influence lithium serum levels. Toxicity occurs at serum concentrations greater than 1.5-2.0 mmol/L and is characterized by apathy, hyperreflexia, coarse tremor, hypertonia along with other problems like nausea, diarrhea, myoclonus, seizures, acute renal failure, cardiac dysrhythmia and coma. Serum concentrations greater than 3.5 mmol/L are potentially lethal and necessitate hemodialysis. Recommendations regarding optimal lithium serum levels differ among clinical practice guidelines, with the most common range being between 0.6 and 0.8 mmol/L for maintenance treatment.^{4,5} The illness stage may further require a different approach for lithium serum levels. Hence therapeutic drug monitoring should be done for optimal guidance of the therapy. Therapeutic drug monitoring (TDM) is generally defined as the clinical laboratory measurement of a chemical parameter that, with appropriate medical interpretation, will directly influence drug prescribing procedures.⁶

Rates of noncompliance with lithium are high, with the range from various studies being 18-53%.⁷ There is more and more evidence that bipolar disorder is a neuroprogressive disorder, implying longer duration of the disease causing more pronounced changes at the clinical and neuropathological level, thus leading to treatment refractoriness and neuropsychological deficits.⁸ Good quality of life (QoL) encompasses more than just good health. At a basic level, it can represent the sum of a person's physical, emotional, social, occupational and spiritual well-being, the study of which is complicated by the fact that there is no consensus as to what constitutes

QoL. The increasing awareness about the importance of patients' quality of life within treatment setups has led to a substantial increase in research with different concepts about the predictor as well as outcomes of QoL and measuring them on different scales. It becomes increasingly difficult to make one precise definition due to the multidimensional nature of the concept of this quality of life in the context of disease.⁹ The World Health Organization has described QoL as individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.¹⁰

Present study was done to study the drug therapy and demographic parameters in bipolar affective disorder patients with special reference to lithium in the routine psychiatric outpatients care setting of a tertiary care teaching hospital as well as to understand the prospect of regular supervision and follow up with therapeutic drug monitoring in optimization of lithium therapy based on health related quality of life outcomes.

METHODS

All stable, ambulant bipolar affective disorders patients on lithium therapy attending the Psychiatry OPD, Medical College, Kolkata and willing to participate in this study were included. The participants were undergone therapeutic drug monitoring as and when advised by their treating physician.

Inclusion criteria

- Subjects who are suffering from bipolar disorders and on lithium therapy attending the psychiatry OPD at tertiary care medical college and willing to participate
- Patients from all age groups and both the sexes
- Those who understood the purpose of the study and are ready to provide information regarding their health status and those who signed an informed consent document.

Exclusion criteria

- Subjects not willing to participate
- Any condition resulting in severe learning and/or intellectual disability
- Those unable to comprehend for any other reasons were excluded from the study.

Procedure methodology

The study was a prospective, non-randomized, observational study of a cohort of subjects who are suffering from bipolar affective disorders and on lithium therapy attending the Psychiatry OPD in a tertiary care medical college hospital in Kolkata, West Bengal, India. The quality of life outcome of such patients on lithium

therapy optimized with regular therapeutic drug monitoring over a period of time based on study tools was compared with the baseline for statistical significance. The study commenced after obtaining approval from institutional ethics committee and continued for a span of 9 months. Data was analyzed at the end of study.

In this study, we have prospectively observed a patient cohort of bipolar affective disorders and followed the advice of lithium monitoring in accordance with treating psychiatrist. Dosage modifications were done thereafter, if any needed. Therapeutic drug monitoring of lithium was performed when advised and referred to our department by the treating physician and was done at each visit for 3 consecutive visits. The referral indications were noted.

At the baseline Visit 1, the demographic characteristics, laboratory investigations along with co-morbidity and concomitant medications prescribed were noted. Subjects and their accompanying family members were interviewed by pre-structured questionnaire, investigation reports, past prescriptions and case notes, where available, and were reviewed at every visit for 3 visits. Adverse event history, medication history, medication compliance, health related quality of life based on TDM follow-up and questionnaires and scales were done. They were followed up for 9 months study period and on each and every such occasion the drug adherence and treatment outcome were analyzed based on study questionnaires.

Lithium estimation test was done within 7 days of collection of blood sample. If the serum lithium levels were found to be above target therapeutic level the patients or their family members along with their treating physician were intimated.

The compliance and treatment outcome including health related quality of life were scored using validated questionnaires and compared with the baseline data and then were analyzed statistically. The Visit 2 and 3 to our department usually occurred after 1- 3 months intervals or earlier if the physician suspected any toxicity or made lithium dosage modifications.

Quantitative measurement of serum lithium was done by flame photometer. The following study tools were also applied and used to assess the outcome and health related quality of life of the patients on every visit: WHO Quality of Life Score (QOL -Bref), Montgomery-Asberg Depression Scale (MADRS) and Medication Adherence Rating Scale (MARS) after getting due permissions from the appropriate authorities.

The WHOQOL-BREF contains two items from the overall quality of life and general health, and one item from each of the 24 facets included in the WHOQOL-100. By this, four major domains are assessed like physical, psychological, social relationships and environment.¹¹ Montgomery and Asberg Depression Rating Scale (MADRS) is based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity.¹² Medication Adherence Rating Scale (MARS) was devised by incorporating components of Drug Attitude Inventory and Morisky medication adherence questionnaires, where patients are asked to respond to the statements in the questionnaire by circling the answer which best describes their behavior or attitude towards their medication during the past week.¹³

RESULTS

Thirty ambulant stable bipolar affective disorder patients on lithium therapy was enrolled in the study after obtained their informed consent. At Visit 0, the baseline demographic characteristics, laboratory investigations values were noted. Subjects and their accompanying family members were interviewed by pre-structured questionnaire, investigation reports, past prescriptions and case notes and particularly their quality of life was assessed.

They were reviewed at every visit for 3 visits. Therapeutic drug monitoring of lithium when advised and referred to our department by the treating physician was done at each visit for 3 consecutive visits and its indications noted. Optimal target level serum concentration of lithium for long term maintenance in bipolar affective disorder for this study was taken to be as 0.5 to 1.2 meq/L.¹⁴

Table 1: Baseline demographic characteristics of the study participants.

Educational status (n)	Up to class 8	Class 10	12th	Grads.	P.G.
	10	9	6	4	1
Marital Status	Married	Unmarried	Divorced		
	19 (63)	9 (30)	2 (7)		
Occupation (n)	Student	Homemaker	Service	Self employed	Unemployed
	3	13	3	8	3
Age distribution (n)	< 20 years	21- 30 years	31-40 years	41-50 years	51-60 years
	2	9	8	8	3

Of the 30 cases of stable bipolar affective disorders patients on lithium, 15 were males and 15 females, aged from 16 years to 56 years.

The average age of the participants was 35.73 years and the average height was 159 cms and with mean BMI kg m-2 (SD) 26.74 (+4.4). Within them 33% of the patients were vegetarians and 66% non-vegetarians; while 10% of the patients consumed tobacco in various forms and 10% were alcoholic. The demographic profiles are depicted in Table 1 and Figure 1. These depict the patients' socio-economical profile that play a role in modulating their quality of life.

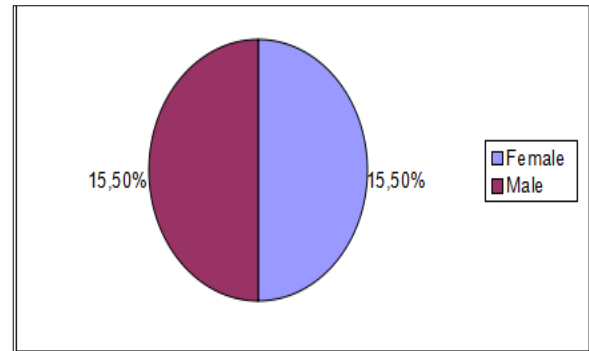


Figure 1: Gender distribution.

Table 2: Distribution of means and standard deviations of transformed quality of life scores obtained from the WHOQOL bref questionnaire.

Domains	WHOQOL bref domains mean Scores (Transformed 0-100)±S.D.			p value (comparison of means)	
	Visit 1	Visit 2	Visit 3	Visit 2 vs.Visit 1	Visit 3 vs.Visit 1
Physical health	40.07±11.26	43.22±13.31	46.76±12.47	0.3265	0.0333*
Psychological health	38.7±12.62	44.3±11.78	47.3±12.83	0.0231*	0.0064*
Social relationship	41.67±10.37	47.8±11.41	49.8 ±13.61	0.0335*	0.0117*
Environmental	47.83±12.23	54.62±14.85	56.79±14.79	0.0581	0.0132*

WHOQOL Bref: World Health Organisation quality of life instrument short form, S.D., Standard Deviation; “*”p-value less than 0.05 is considered as significant

Table 3: Mean depression scores by montgomery-asberg depression rating scale (MADRS).

	Visit 1	Visit 2	Visit 3
Mean MADRS Score	29.6	23.5	21
SD	10.24	8.54	8.34
SEM	1.87	1.56	1.52
p value		equals 0.0150*	equals 0.007*
CI		95% confidence interval From 1.23 to 10.97*	95% confidence interval From 3.77 to 13.43*
N	30	30	30

* versus Visit 1, p-value less than 0.05 is considered as significant

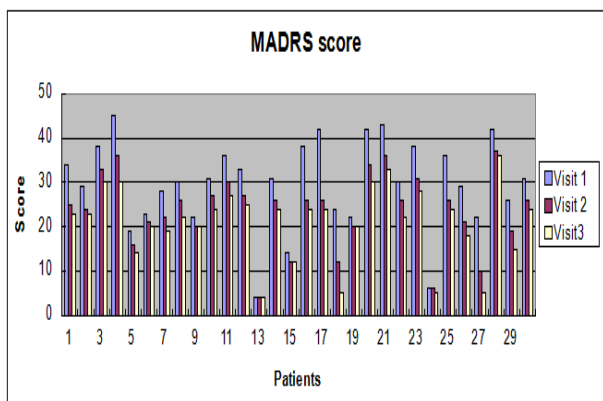


Figure 2: Depressive symptom score of individual bipolar patients during lithium therapy.

Table 4: MARS Score in different visits.

	Visit 1	Visit 2	Visit 3
Mean MARS Score	5.27	7.1	7.5
SD	1.2	0.99	0.82
SEM	0.22	0.18	0.15
p value		<0.001*	<0.001*
N	30	30	30

*versus Visit 1, p-value less than 0.05 is considered as significant

Health related quality of life at baseline and in different visits by WHOQOL- Bref is depicted in Table-2. Mean Depression score by Montgomery-Asberg Depression Rating Scale (MADRS) is depicted for different visits

and for different patients in Table-3 and Figure-2. Measurement of compliance by MARS study tool in different visits and in different patients is expressed in Table 4 and Figure 3.

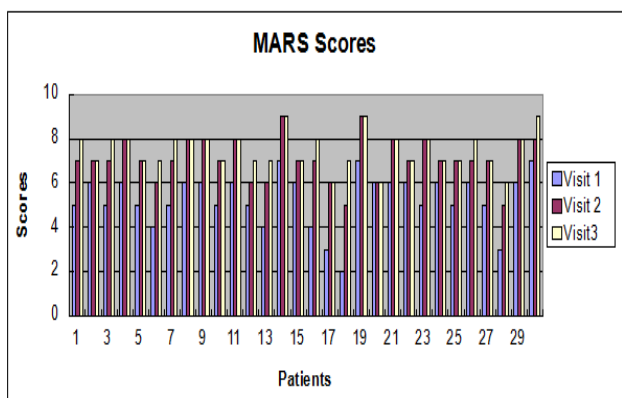


Figure 3: Lithium adherence score i.e. MARS Score of individual bipolar patients during lithium therapy.

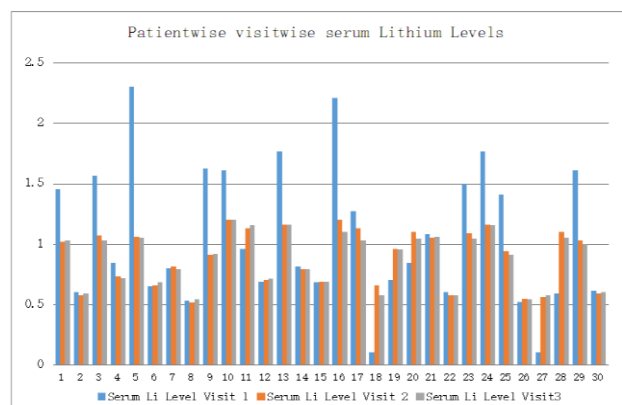


Figure 4: Target lithium serum concentration achievement after 3 visits.

Lastly, target lithium serum achievement concentration by therapeutic drug monitoring after 3 Visits in different patients is shown in Figure 4.

DISCUSSION

Bipolar depression (BD) is the predominant pole in BD type I and type II and responsible for a large number of suicides. The suicide rate is 20-times above that of the general-population, which is considerably larger than that of unipolar depression. Bipolar depression is also associated with a high rate of morbidity and mortality due to comorbid somatic disorders. Many variables have been associated with functional outcome in BD, including demographic, clinical, and neurocognitive factors. Bipolar disorder is episodic, and the lifetime risk of recurrence is approximately 90% in individuals who have had a single manic episode. Hence, long-term treatment is essential for the vast majority of patients.¹⁵ However, medication cannot be effective if patients do not take it. Treatment non-adherence is common in this population

and is associated with an increased risk of relapse.¹⁶ For example Keck et al, found that, among patients hospitalized for acute manic episodes, 64% had been nonadherent with medication in the prior month. Patient factors include demographic characteristics; for example, being of younger age, male, and unmarried are risk factors for nonadherence.¹⁷ The stage or characteristics of the illness can also contribute to nonadherence to treatment. Treatment issues, such as adverse effects, and clinicians' treatment strategies, such as the use of polypharmacy, also may contribute to decreased adherence to medication.^{15,17} A poor therapeutic alliance between the clinician and the patient can adversely affect adherence as well.¹⁵

Although all the patients were stable medically, the health related QoL levels were found to be depressed than the normative values for Indian population. The baseline results at Visit 1 of the WHOQOL- Brèf domains scores were 40.07 (SD =11.26) for the Physical health, 38.7 (12.62) for Psychological health, 41.67 (10.37) for Social relationships and 47.83 (12.23) for the Environment domain. There was significant improvement in WHOQOL-Brèf scores during the Visit 2 and Visit 3 as depicted in the Table 5 above. During the Visit 2 the WHOQOL-Brèf transformed score (0-100) was recorded significantly increased especially for the Psychological health and Social relationships domains. Although in the Physical health and Environment domain the scores increased but were not significant (at p-value <0.05). However, at Visit 3, it was observed that all the four major domain scores were significantly increased to 46.76 (12.47) for the Physical health domain, 47.3 (12.83) for Psychological health, 49.8 (13.61) for Social relationships and 56.79 (14.79) for the Environment domain. Thus, it is clearly evident that the health related QoL levels evaluated with WHOQOL- Brèf revealed significant increase of the Psychological health and Social relationships domains scores early by Visit 2 of the study period itself. All the four major domain scores of WHOQOL- Brèf including the Physical health and Environment domain were increased significantly at the study Visit 3. This indicates an overall improvement of health-related quality of life due to better control of the symptoms and manifestations the disease with treatment.

The MADRS study tool showed mean baseline score at 29.6 (SD =10.24) which during the Visit 2 and Visit 3 were further reduced to 23.5 (SD=8.54) and 21 (SD =8.34) and thus were significant reduced in Visit 2 (p value equals 0.0150 at 95% CI between 1.23 to 10.97) and Visit 3 (p value equals 0.0007, at 95% CI between 3.77 to 13.43) respectively, when compared with the Visit 1 score.

In this study the measurement of compliance by MARS study tool revealed mean baseline score of 5.27 (SD =1.2) and was considered non-adherent. However, the mean scores during the Visit 2 and Visit 3 were significantly improved to acceptable adherence scores of

7.1 (SD =0.99) and 7.5 (SD =0.82) with p value equals 0.001 in both instances, when compared with the Visit 1. This also explains why the lithium TDM levels were in sub-therapeutic range recorded in two patients at Visit 1. These patients become compliant and at Visit 2 and 3 the serum levels were recorded within the optimal therapeutic range. This was possible due to detection by the serum lithium estimation, adherence testing and follow up counseling.

In this study we observed that sometimes the reason for the request of TDM of lithium requested was not mentioned in the OPD prescriptions. This information may highlight the urgency of communicating back the TDM reports like when requested for acute toxicity or non-compliance. The use of properly designed TDM request form, is suggested to overcome these issues.

It is thus evident that psychiatric and medical monitoring as well as monitoring of treatment adherence along with regular TDM is necessary for optimal outcome in patients with bipolar disorder. Treatment adherence can be improved among patients with bipolar disorder through psychoeducation about the nature of their disorder and the vital importance of treatment adherence. Psychoeducation provides patient a practical and theoretical approach to understanding and dealing with the symptoms and consequences of bipolar disorder.¹⁸ Besides, therapeutic drug monitoring of lithium is mandatory to avoid toxicity and to detect non-responders and non-compliance. For these reasons TDM is recommended weekly in the first month of treatment, then monthly for five months and afterwards every three months.¹⁹ Further it was observed in this study that the advice of TDM was not routinely and regularly given to all the patients i.e. at week 1 after starting lithium and then monthly for 3 months and then 6 monthly when the patients has stabilized or even after lithium dose adjustments. Monitoring of these parameters could help in optimizing the outcome of lithium treatment.

It was observed that before administering lithium the patients were not routinely informed in details about the toxic effects of lithium either by the treating physician or the OPD nurse or the pharmacist. They were neither provided in their lithium / Bipolar Medication Patient Information Sheet in their mother language or psycho-education. The routine advice of the following investigations like comprehensive biochemistry panel, renal profile including eGFR, TSH, free T3, calcium, magnesium, phosphorus, urine pregnancy test for women of reproductive age, were also found to be missing in the prescription of many bipolar disorder patients. Also, vital baseline physical and clinical data like vital signs, height, weight, and waist circumference are to be recorded and noted in the prescription or special data sheets. In a medically complex patient and patients above 40 years, we need to consider the medical co-morbid conditions, and appropriate investigations like ECG biochemical investigations etc are needed to be done and specialist

advice to be sought accordingly. Also, even though lithium is contra-indicated in pregnancy, test to rule out pregnancy in women of reproductive age group along with contraceptive advice were not routinely provided. Similar findings were also reported in an audit carried out by National Patient Safety Agency, UK which found that only 42 per cent of patients on initiation of lithium therapy were documented to have been informed of risk factors for toxicity.²⁰ Thus, patients who are being prescribed with lithium, at the start of lithium therapy and throughout their treatment should receive appropriate ongoing verbal and written information and a record book to track lithium blood levels and relevant clinical tests, and since the lithium blood level range may alter with time, that should be amended to reflect the current clinical expectation for safe and effective therapy.²⁰

Adequate monitoring of patients during lithium use is essential for early identification of patients with (potential) ADEs and for optimal dosing. But it is not clear how different health care professionals internationally aim to achieve safe and effective lithium treatment through monitoring. Often, local monitoring guidelines and standard operating procedure of prescribing and monitoring lithium therapy may differ and health care professionals may be confused by different guidelines, institutional or laboratory protocols, scientific literature, and their own personal knowledge and experience.²¹ In the majority of cases the prescriber of lithium, generally a psychiatrist, was responsible for monitoring. Continuity of monitoring is of prime importance and health care system should be organized in a way so that it can be possible.²¹ In the Dutch guideline, the prescriber is appointed to be responsible for monitoring, but another health care professional can have a coordinating function.²²

There are other reasons for the lack of effectiveness in bipolar disorder therapy with lithium like uncertainty about how best to define and determine therapeutic response, the lack of validated animal models, and neglect in research funding compared to that for other more pronounced psychotic disorders like schizophrenia. Study of bipolar disorder poses additional problems because of the episodic nature of the condition, which requires long-term studies to demonstrate prophylactic efficacy, as well as treatment trials for manic and depressive episodes.²³ Thus regular monitoring is a necessity, which our study rediscovered. Besides, quality of life of patients was also improved significantly in different domains in our study with this monitoring intervention.

CONCLUSION

In spite of drawbacks like adverse effects from hand tremors to renal toxicity, as well as often lack of monitoring, even today, almost seventy years after its discovery of effectiveness, lithium salts are the first-choice treatment for the manic phases of bipolar affective

disorders, as well as it is indispensable prophylactic drug in the prevention of cyclic episodes of bipolar disorder. With regular therapeutic monitoring, optimal target serum lithium levels can be achieved with dosage modifications thereby reducing the risk of toxicity and thus improving drug compliance. It also leads to overall significant improvement of health-related quality of life in bipolar patients and disease efficacy outcomes and thereby significantly improves therapeutic success during the study period. Clinical pharmacologists with the involvement in therapeutic drug monitoring as well as regular supervision of the patients can be an important stakeholder in optimizing patients' therapeutic approach and health related quality of life.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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