Received: 31 May 2017 | Revised: 12 September 2017 | Accepted: 20 September 2017

DOI: 10.1002/clc.22822

WILEY CLINICAL CARDIOLOGY

REVIEW

Lithium-induced electrocardiographic changes: A complete review

Nikhil Mehta MD[1] | Robert Vannozzi MD[2]

[1]Department of Internal Medicine, Rochester Regional Health, Rochester, New York

[2]Department of Cardiology, Rochester Regional Health, Rochester, New York

Correspondence
Nikhil Mehta, MD, Department of Internal Medicine, Rochester Regional Health, 1555 Long Pond Road, Rochester, NY 14626
Email: nikhil.mehta@rochesterregional.org

Lithium has been used for the treatment of bipolar disorder for more than 6 decades. Reports of cardiac side effects resulting in both benign electrocardiographic (ECG) changes and near fatal arrhythmias have been reported in the literature. A systematic literature search was conducted on 2 electronic databases—PubMed and Medline—for the time period between January 1970 and March 2016 using the key word "lithium," along with "electrocardiography" or "ECG." All articles and their references were then screened by title for relevance by 2 authors and a librarian. A total of 406 articles were found on literature search, of which 56 met the screening criteria. T wave inversion was the most frequently reported ECG finding. Other findings include sinus node dysfunction, sinoatrial blocks, PR prolongation, QT prolongation/dispersion, and ventricular tachyarrhythmias. Some cases have shown lithium-treated patients experiencing serious cardiac outcomes, such as ST elevation myocardial infarction, heart blocks, and the Brugada pattern. Electrical changes from lithium were found to be dependent on both duration of treatment and the serum lithium level. Although there are no standardized ECG guidelines, frequent monitoring of patients on lithium therapy can ensure the medication's safe use.

KEYWORDS

Arrhythmia, Brugada Pattern, Electrocardiography, Lithium, QT Dispersion, Sinus Node Dysfunction

1 | INTRODUCTION

Lithium has been the drug of choice in treating bipolar disorder ever since its serendipitous discovery 60 years ago.[1] It is a monovalent cation alkali metal (Li^+), minimally protein bound, renally excreted, and nonbiotransformable in the body.[2] Decades of use have helped understand its method of action and many of its side effects. The leading theories suggest a mechanism of dose-dependent inhibition of myocyte voltage-gated sodium channels that decreases intracellular potassium, thereby causing electrical instability in both the atria and ventricles.[3,4] This explains why some of the electrocardiographic (ECG) changes in lithium treated patients resemble hypokalemia (with depressed ST segments, T waves, and at times U waves), while serum potassium levels are normal. Cardiac side effects have resulted in some remarkable ECG changes and occasional near-fatal arrhythmias.

Cardiotoxicity is mainly noticed at serum lithium levels >1.5 mEq/L, but can be precipitated during periods of rapidly changing serum lithium concentration due to progressive equilibration between extracellular and intracellular tissue compartments.[5,6] When treating lithium toxicity, a falling serum lithium concentration reflects both renal clearance and ongoing tissue distribution, and is therefore not a reliable measure of improvement. In this review article, we explore the ECG changes caused by lithium as reported in the literature. It is important to point out that our understanding of the cardiac effects of lithium is based on animal models, human case reports, case series, and a handful of prospective studies. No large-scale randomized clinical trial has been reported to date.

2 | METHODS

A systematic literature search was conducted on 2 electronic databases—PubMed and Medline—between January 1970 and March 2016 using the key word "lithium," along with "electrocardiography" or "ECG." Only articles written in the English language were included. Additional published papers were identified looking at the reference

list of these reviewed articles. Most of the literature was concentrated in the 1970 to 1985 time period. All articles were then screened by title for relevance by 2 authors, with help from the librarian of the Department of Internal Medicine, and then imported into Endnote X7 (Thomas Reuters, San Francisco, CA).

3 | RESULTS

A total of 406 articles were found in the literature search, of which 56 were found to meet the screening criteria. These included 26 case reports, 7 case series, 8 clinical studies (prospective/retrospective), 12 review articles, and 3 animal-based models. The relevance of animal-based models is questionable, as lithium was administered in much larger doses in these studies. The effect of lithium on cardiac conduction and the level of evidence associated with each finding is summarized in Table 1 and further explained below.

3.1 | Rate and rhythm

Sinus node dysfunction characterized by sinus bradycardia is the most common conduction disturbance in patients on lithium therapy, and the second most common ECG finding after T-wave depressions (Figure 1).[7–10] Sinus bradycardia was demonstrated by an average fall in heart rate by 10 beats/minute, with 1 study also reporting a decrease in number of atrial premature contractions.[10,11] There is debate whether this effect involves the thyroid gland, as 1 study showed a positive correlation between sinus node dysfunction and decreased triiodothyronine (T3) levels.[10] A surprise study in the late 20th century looked into lithium-treated bipolar patients performing arithmetic tasks, which under normal physiological circumstances is expected to raise the heart rate.[12] Results showed that lithium suppressed this response, similar to how it calms the excited or manic behavior by its central nervous system effect. Isolated cases of lithium toxicity causing sick sinus syndrome, and cardiac asystole were also reported.[13,14] Some of these circumstances involved patients being on other potential cardiotoxic medications and/or having a pre-existing cardiac history that made it difficult to establish a definitive correlation. Supraventricular tachycardia, however, has not been linked to lithium therapy.

3.2 | P wave, PR interval, and the QRS complex

Sinoatrial block comprising reversible first and second degree (type I Wenckebach and type II) blocks and rare cases of atrial flutter were seen in patients on chronic lithium therapy for years.[15–17] Lithium affects the atrial conduction time between the onset of P waves (indicating atrial depolarization) on surface ECG and corresponding peak A waves on tissue doppler, representing atrial contraction. In a series of 53 patients, lithium was noted to increase both maximum and minimum atrial conduction times (Pmin = 25.10 msec, Pmax = 17.84 msec, $P < .001$) when compared to healthy controls.[18] Several studies have shown prolongation of the PR interval (up to approximately 4–8 msec) following months of lithium therapy.[10,19–21] Roose et al. studied 31 patients on lithium, and identified incomplete atrioventricular blocks in 10 patients (32.3%), right bundle branch block in 2 patients (6.5%), and incomplete intraventricular conduction delay in 2 patients (6.5%).[20] The PR prolongation in these patients depends more on the duration of therapy than the serum lithium level. Cases of left anterior hemiblock, complete left bundle branch block, and its

TABLE 1 Summary of ECG findings in patients on lithium therapy

ECG Component	Findings	Level of Evidence[a]	Study Subjects	References
Rate and rhythm	Sinus node dysfunction and bradycardia	2a	Human/animal	7–10
	Increased atrial conduction time	2b	Human	18
	Atrial flutter	5	Human	16
	Sick sinus syndrome	5	Human	13
	Cardiac asystole	5	Human	14
P and PR	Sinoatrial blocks	4	Human	15–17
	PR prolongation and atrioventricular blocks	3b	Human	10,19–21
QRS	Incomplete bundle branch blocks	4	Human	20
	Right bundle branch block	5	Human	20
	Nonspecific intraventricular conduction delay	5	Human	20
	Left bundle branch block	5	Human	23
ST	Depression	4	Human	24
	Elevation	4	Human	25–27
	Brugada pattern	5	Human	28,29
T and QTc	T wave flattening or inversion	2a	Human	10,32–34
	QTc prolongation	5	Human	36
	Higher QT dispersion ratio	2a	Human	18,35
	Ventricular tachyarrhythmias	4	Animal	36

Abbreviations: ECG, electrocardiogram.

[a] Levels of evidence: 1a = multiple/homogenous RCTs, 1b = individual RCT, 2a = multiple/homogenous prospective cohort studies, 2b = individual cohort study, 3a = multiple/homogenous retrospective studies, 3b = individual retrospective study, 4 = case series or >3 case reports, 5 = isolated case reports or expert opinion.

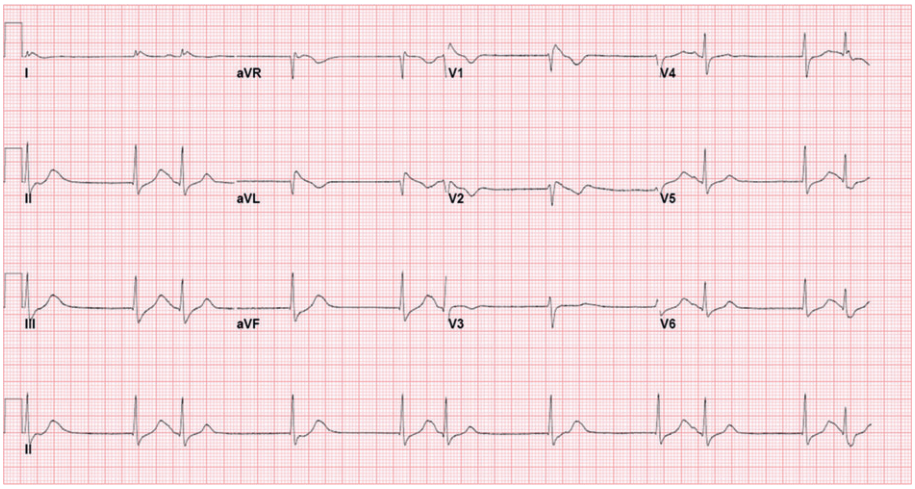

FIGURE 1 Lithium toxicity causing sinus node dysfunction and a classical type 1 Brugada pattern (patient's serum lithium level was 4.3 mEq/L)

progression to complete heart block with junctional escape rhythm have been reported as well.[16,22,23]

3.3 | ST segment and the Brugada pattern

Hansen and Amdisen, in their study covering over 100 patients with lithium toxicity, showed patients developing ST depressions that were reversible, with no persistent deficits after treatment discontinuation.[24] Transient ST elevations have been reported in rare cases of lithium toxicity, when serum lithium levels were anywhere between 4.7 and 14.6 mg/dL.[25–27] The Brugada pattern ECG from lithium treatment, characterized by J point elevation, coved ST segment, and T-wave inversion in anterior precordial leads first surfaced in 2005, and have since been reported on at least 2 occasions.[28,29] Lithium being a sodium channel blocker (similar to tricyclic antidepressants, cocaine, and antihistamines), induces a diagnostic challenge, which unconceals channel defects, resulting in full-blown features of type 1 Brugada (Figure 1). The reported incidence of this is roughly 5 in 1000 (0.5%) and patients are often asymptomatic.[30,31] It is reported that Brugada mutation carriers and other sporadic cases of Brugada syndrome (those without documented family history) often present with normal ECG recordings at first. Whether Brugada pattern results in increased susceptibility to sudden cardiac death, regression from type 1 to type 2 or 3 Brugada pattern, or if this represents an undiagnosed baseline, remains unknown.

3.4 | T wave, QTc, and QT dispersion ratios

T-wave depression is the most widely reported ECG change, with an incidence of 16% to 33% in patients on lithium therapy.[10,32] Depressions, in the form of flattening, rounding, notching, and inversion, can be up to 3.5 mm in limb leads and 5.5 mm in precordial leads.[33] In a study by Demers and Heninger, all patients on lithium therapy had significant T-wave depressions >1 mm at some point during their treatment period.[34] Patients with substantial T-wave changes also developed U waves, resembling that seen in hypokalemia, which further supports the theory of its working mechanism. As with conduction defects, T-wave ECG changes depend on the duration of treatment rather than the serum lithium level, often being reversible on treatment discontinuation.

Multiple case series have showed no significant change in the QTc interval of patients on lithium therapy before and after treatment initiation, lithium levels being in therapeutic range (0.6–1.2 mEq/L).[10,35] However, in patients with lithium toxicity, QT prolongation has been described, which increases the risk of torsades and fatal arrhythmias.[36] An important measure that is affected by lithium toxicity is the QT dispersion ratio (QTdR), which is defined as difference in maximum and minimum QT interval divided by cycle length ([QTmax-QTmin]/rate × 100). This measures heterogeneity in ventricular repolarization and is an important predictive tool in measuring ventricular instability. A recent study by Altinbas et al. not only showed significantly higher QTdRs in lithium-treated patients as compared to healthy controls, but also a prolonged T-peak-to-end interval.[18] This, like QTdR, also indicates heterogeneity and is a measure of ventricular instability, leading to fatal arrhythmias and sudden cardiac death.[5] Many behavioral, antipsychotic, and antidepressant drugs cause changes in the QTc interval; however, lithium has been 1 of the few associated with change in QT dispersion.[35] On the other hand, lithium-based animal models have shown evidence of a ventricular stabilizing effect by raising the threshold for ventricular fibrillation. How this coexists in the setting of prolonged QTdR that typically increases the risk for mortality, as shown by human models, remains unexplored.

4 | DISCUSSION

Decades of lithium use attests to its overall safety, but precarious ECG changes can occur at both therapeutic and toxic levels as described above. At therapeutic levels, T-wave depressions and sinus node dysfunction are most commonly reported. These are, for the most part, benign and asymptomatic, related more to the duration of treatment. Toxic lithium levels (>1.5 mEq/L) can cause sinoatrial block, intraventricular conduction delay, ST depressions/elevations, the Brugada pattern, atrioventricular conduction delays, QTc prolongation, and changes in the QTdR. This may result in ventricular instability, cardiac arrhythmias, and sudden cardiac death. Several drug interactions can increase serum lithium levels, decrease excretion, increase reabsorption, and cause adverse lithium side effects and toxicity.[37–42] These are summarized in Table 2. Because electrical

TABLE 2 Drug interactions causing lithium toxicity

Medication	Effect	Management	References
Cardiac			
Angiotensin-converting enzyme inhibitors	Decrease renal clearance	Dose reduction, consider alternative therapy	40
Angiotensin receptor blockers	Decrease renal clearance	Dose reduction, consider alternative therapy	41
Thiazide diuretics	Increase lithium reabsorption	Dose reduction, consider alternative therapy	41
Potassium sparing diuretics	Increase lithium levels	Monitor closely	41
Noncardiac			
Nonsteroidal anti-inflammatory drugs	Decrease renal clearance	Dose reduction	41
Topiramate	Increase lithium levels	Monitor closely	42
Phenytoin, fosphenytoin	Increase lithium adverse effects	Monitor closely	39
Carbamazepine	Increase lithium adverse effects	Monitor closely	38
Methyldopa	Increase lithium adverse effects	Monitor closely	37
Mifepristone	Increase QTc interval	Monitor closely, consider alternative therapy	Corcept Therapeutics Inc., Menlo Park, CA

changes are dependent on both duration of treatment and the serum lithium level (narrow therapeutic range, 0.6–1.2 mEq/L), it is important to frequently monitor patients to ensure the medication's safe use.

However, there are no standardized approved guidelines for serial ECG monitoring in patients on lithium therapy. One study that looked at ECG monitoring at 0, 4, and 12 months in patients on long-term lithium therapy at therapeutic levels showed only clinically insignificant changes.[10] Therefore, routine monitoring of the ECG seems unnecessary; however, data are limited. The same was not applicable to higher serum lithium levels. Given the possibility of clinically significant ECG changes, such as arrhythmias, QRS, and ST segment changes, obtaining a baseline ECG and repeating it periodically can help identify findings early on. ECGs are relatively inexpensive diagnostic tools, and the benefit of screening outweighs the cost associated with it. This is especially true for patients having labile serum lithium levels, such as those with kidney disease, which can often fluctuate and be supratherapeutic. However, the time to ECG changes based on existing case series varies from weeks to years, and determining an appropriate screening time frame is difficult. Improved human models and prospective studies are needed to substantiate findings of case series and case reports to better outline evidence-based screening guidelines.

Lithium-induced ECG changes have been shown to increase with age, especially in those over 60 years. This is a challenging patient population with high prevalence of ischemic heart disease. The 2 most common lithium-induced ECG changes—T-wave inversions and sinus node dysfunction—are common manifestations of cardiac ischemia. In such cases, the patient's history and physical examination can help delineate the 2. Providers should be cautious when initiating lithium in patients with risk factors for ischemic heart disease, such as hypertension, hyperlipidemia, diabetes, smoking, and a positive family history. Changes in renal function from hypertensive or diabetic nephropathy can further affect lithium clearance and predispose to toxicity. A baseline ECG with routine periodic ECGs and serum lithium levels are necessary, with frequency dependent on the severity of comorbidities. Although there is limited guidance in the literature regarding optimal interval, we would recommend at least once every 6 to 12 months. Determining whether ischemic ECG changes are enhanced by the effect of lithium and distinguishing ischemic from lithium-induced ECG changes are difficult and need further study.

Except in cases of fatal cardiac outcomes (such as cardiac asystole, ST changes, or ventricular arrhythmias), most patients may not need dose adjustment. In most case series, ECG changes such as atrioventricular blocks, bundle branch blocks, and increased QTdRs persisted for years with no clinically adverse outcome. Therefore, it is difficult to conclude on their clinical importance. However, sinoatrial blocks, ST segment changes, and unmasking of the Brugada pattern may need more attention as they increases one's susceptibility to future arrhythmias. These findings warrant either titrating the dose down or discontinuing lithium and switching to an alternative medication. Currently, there are insufficient data to support mortality from lithium-induced ECG changes. Case reports of complete heart block, ventricular arrhythmia, cardiac asystole, and sudden cardiac death have been reported and described earlier. Some ECG changes have been attributed to the genetic susceptibility of patients and the pathogenesis of bipolar disorder in itself. Ion channel gene polymorphisms were shown to be linked to the etiology of bipolar disorder; however, data on this are extremely limited. Often, patients may have baseline ECG changes that go undiagnosed prior to starting lithium and are noticed later on. The latter 2 serve as limitations to the above findings, until more data become available.

5 | CONCLUSION

As lithium continues to be used on a wide scale, better human models and large-scale studies can provide better evidence for lithium-induced ECG findings. At both therapeutic and toxic lithium levels, ECG changes such as T-wave inversions, sinus bradycardia, sinoatrial blocks, PR prolongation, incomplete bundle branch block, QTc prolongation, increased QT dispersion ratio, the Brugada pattern,

and ventricular tachyarrhythmias have been observed. This does not preclude lithium use, but careful cardiac monitoring with a baseline ECG and repeating it at periodic intervals are essential if physicians are to provide early intervention.

ACKNOWLEDGMENTS

The authors thank Dr. Ruth Kouides, who was kind enough to review the article, share her comments, and suggest some structural changes.

Conflicts of interest

The authors declare no potential conflict of interests.

ORCID

Nikhil Mehta http://orcid.org/0000-0001-5971-2158

REFERENCES

1. Cade JF. Lithium salts in the treatment of psychotic excitement. *Med J Aust*. 1949;2:349–352.
2. Ward ME, Musa MN, Bailey L. Clinical pharmacokinetics of lithium. *J Clin Pharmacol*. 1994;34:280–285.
3. Carmeliet EE. Influence of lithium ions on the transmembrane potential and cation content of cardiac cells. *J Gen Physiol*. 1964;47:501–530.
4. Singer I, Rotenberg D. Mechanisms of lithium action. *N Engl J Med*. 1973;289:254–260.
5. Tilkian AG, Schroeder JS, Kao JJ, et al. The cardiovascular effects of lithium in man. A review of the literature. *Am J Med*. 1976;61:665–670.
6. Waring WS. Delayed cardiotoxicity in chronic lithium poisoning: discrepancy between serum lithium concentrations and clinical status. *Basic Clin Pharmacol Toxicol*. 2007;100:353–355.
7. Wellens HJ, Cats VM, Duren DR. Symptomatic sinus node abnormalities following lithium carbonate therapy. *Am J Med*. 1975;59:285–287.
8. Wilson JR, Kraus ES, Bailas MM, et al. Reversible sinus-node abnormalities due to lithium carbonate therapy. *N Engl J Med*. 1976;294:1223–1224.
9. Roose SP, Nurnberger JI, Dunner DL, et al. Cardiac sinus node dysfunction during lithium treatment. *Am J Psychiatry*. 1979;136:804–806.
10. Bucht G, Smigan L, Wahlin A, et al. ECG changes during lithium therapy. A prospective study. *Acta Med Scand*. 1984;216:101–104.
11. Tilkian AG, Schroeder JS, Kao J, et al. Effect of lithium on cardiovascular performance: report on extended ambulatory monitoring and exercise testing before and during lithium therapy. *Am J Cardiol*. 1976;38:701–708.
12. Belmaker RH, Lehrer R, Ebstein RP, et al. A possible cardiovascular effect of lithium. *Am J Psychiatry*. 1979;136:577–579.
13. Rodney WM, Chopivsky P, Hara JH. Lithium-induced dysrhythmias as a marker for sick sinus syndrome. *J Fam Pract*. 1983;16:797–799.
14. Ong AC, Handler CE. Sinus arrest and asystole due to severe lithium intoxication. *Int J Cardiol*. 1991;30:364–366.
15. Eliasen P, Andersen M. Sinoatrial block during lithium treatment. *Eur J Cardiol*. 1975;3:97–98.
16. Mitchell JE, Mackenzie TB. Cardiac effects of lithium therapy in man: a review. *J Clin Psychiatry*. 1982;43:47–51.
17. Goldberger ZD. Sinoatrial block in lithium toxicity. *Am J Psychiatry*. 2007;164:831–832.
18. Altinbas K, Guloksuz S, Caglar IM, et al. Electrocardiography changes in bipolar patients during long-term lithium monotherapy. *Gen Hosp Psychiatry*. 2014;36:694–697.
19. Jaffe CM. First-degree atrioventricular block during lithium carbonate treatment. *Am J Psychiatry*. 1977;134:88–89.
20. Roose SP, Bone S, Haidorfer C, et al. Lithium treatment in older patients. *Am J Psychiatry*. 1979;136:843–844.
21. Martin CA, Piascik MT. First degree A-V block in patients on lithium carbonate. *Can J Psychiatry*. 1985;30:114–116.
22. Tobin JR, Nemickas R, Scanlon PJ, et al. EKG of the month. *IMJ Ill Med J*. 1974;146:396, 403.
23. Azar I, Turndorf H. Paroxysmal left bundle branch block during nitrous oxide anesthesia in a patient on lithium carbonate: a case report. *Anesth Analg*. 1977;56:868–870.
24. Hansen HE, Amdisen A. Lithium intoxication. (Report of 23 cases and review of 100 cases from the literature). *Q J Med*. 1978;47:123–144.
25. Perrier A, Martin PY, Favre H, et al. Very severe self-poisoning lithium carbonate intoxication causing a myocardial infarction. *Chest*. 1991;100:863–865.
26. Puhr J, Hack J, Early J, et al. Lithium overdose with electrocardiogram changes suggesting ischemia. *J Med Toxicol*. 2008;4:170–172.
27. Kayrak M, Ari H, Duman C, et al. Lithium intoxication causing ST segment elevation and wandering atrial rhythms in an elderly patient. *Cardiol J*. 2010;17:404–407.
28. Darbar D, Yang T, Churchwell K, et al. Unmasking of brugada syndrome by lithium. *Circulation*. 2005;112:1527–1531.
29. Wright D, Salehian O. Brugada-type electrocardiographic changes induced by long-term lithium use. *Circulation*. 2010;122:e418–e419.
30. Hermida JS, Jandaud S, Lemoine JL, et al. Prevalence of drug-induced electrocardiographic pattern of the Brugada syndrome in a healthy population. *Am J Cardiol*. 2004;94:230–233.
31. Yap YG, Behr ER, Camm AJ. Drug-induced Brugada syndrome. *Europace*. 2009;11:989–994.
32. Schou M. Electrocardiographic changes during treatment with lithium and with drugs of the imipramine-type. *Acta Psychiatr Scand*. 1963;39(suppl 169):258–259.
33. Wren JC, Dana JB. Electrocardiographic changes during lithium therapy. *J Maine Med Assoc*. 1976;67:185–189.
34. Demers RG, Heninger G. Electrocardiographic changes during lithium treatment. *Dis Nerv Syst*. 1970;31:674–679.
35. Reilly JG, Ayis SA, Ferrier IN, et al. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet*. 2000;355:1048–1052.
36. Jacob AI, Hope RR. Prolongation of the Q-T interval in lithium toxicity. *J Electrocardiol*. 1979;12:117-119.
37. Byrd GJ. Letter: methyldopa and lithium carbonate: suspected interaction. *JAMA*. 1975;233:320.
38. Ghose K. Interaction between lithium and carbamazepine. *Br Med J*. 1980;280:1122.
39. MacCallum WA. Interaction of lithium and phenytoin. *Br Med J*. 1980;280:610–611.
40. DasGupta K, Jefferson JW, Kobak KA, et al. The effect of enalapril on serum lithium levels in healthy men. *J Clin Psychiatry*. 1992;53:398–400.
41. Finley PR, Warner MD, Peabody CA. Clinical relevance of drug interactions with lithium. *Clin Pharmacokinet*. 1995;29:172–191.
42. Abraham G, Owen J. Topiramate can cause lithium toxicity. *J Clin Psychopharmacol*. 2004;24:565–567.

How to cite this article: Mehta N, Vannozzi R. Lithium-induced electrocardiographic changes: A complete review. *Clin Cardiol*. 2017;40:1363–1367. https://doi.org/10.1002/clc.22822