

**IE** Narrative Review

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### **CME** Objective

After studying this article, you should be able to:

Increase prevention and early detection of lithium neurotoxicity

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# **Second-Generation Antipsychotics Combined With Lithium:** A Systematic Review

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### ABSTRACT

**Objective:** To study cases of lithium neurotoxicity (LN), both reversible (RLN) and irreversible (ILN), due to second-generation antipsychotics (SGAs) combined with lithium.

Data Sources: A comprehensive search was conducted in MEDLINE, PsycINFO, EMBASE, and the Cochrane Library from their inception to July 31, 2017.

Study Selection: Free terms and MeSH headings were combined as follows: [(lithium) AND (adverse events OR safety OR side effects OR neurotoxicity OR neurologic manifestations OR central nervous system) AND (risperidone OR paliperidone OR olanzapine OR aripiprazole OR clozapine OR quetiapine OR ziprasidone OR amisulpride OR asenapine OR lurasidone OR iloperidone)]. Only English-language articles reporting about LN due to SGAs combined with lithium were selected.

Data Extraction: The age, sex, diagnostic categories, clinical features, lithium doses, serum lithium levels, antipsychotic dosages, causative factors, and preventive measures of 11 cases of LN (8 RLN and 3 ILN) due to the lithium and SGA combination were extracted.

Data Synthesis: Forty-five percent of patients were aged > 60 years. The diagnostic categories were schizoaffective disorders, bipolar disorders, and schizophrenia. Cases of RLN presented as an acute brain syndrome, which recovered completely. Cases of ILN presented as a chronic brain syndrome and only partially recovered. The lithium doses in 9 cases were < 1,200 mg/d. The serum lithium levels in 2 cases in each of the groups were > 1.7 mEq/L. The SGAs implicated were clozapine, risperidone, aripiprazole, and quetiapine. One patient with RLN received 2 different first-generation antipsychotics and 1 patient with ILN received 2 different SGAs with lithium. Both groups had patients with medical comorbidities who were taking prescription medication.

**Conclusion:** LN, both reversible and irreversible, due to SGAs combined with lithium presents with certain causative factors and a clinical profile. Early detection and prompt management will help prevent LN.

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It is illegal to post this copyrighted PDF on any website. such as congestive cardiac failure may also precipitate lithium

## **Clinical Points**

- Treatments for schizophrenia and bipolar disorders are now converging, and current evidence supports combining 2 drugs with 2 different mechanisms of action; however, patients receiving lithium and secondgeneration antipsychotics (SGAs) together can develop lithium neurotoxicity.
- High-risk groups on the lithium and SGA combination are elderly patients, those with medical comorbidities, and those on other prescription medication.
- Clinicians can help potentially prevent lithium neurotoxicity by reducing the dose of lithium and SGA when both are prescribed together along with early detection, prompt management, careful prescribing, and psychoeducation of patients and caregivers.

ithium neurotoxicity (LN) may be of 2 types: reversible (RLN) or irreversible (ILN). Most authors define RLN as a complete recovery 2 months after an episode of lithium toxicity, whereas those patients who recover partially or with permanent neurologic sequelae are classified as having ILN.1-3

Lithium toxicity may be of the following subtypes: acute, acute-on-chronic, or chronic. Lithium has a narrow therapeutic range, and patients vary in their response to therapeutic dosing.<sup>4,5</sup> In lithium-naive patients, acute toxicity caused by accidental or intentional overdose presents with gastrointestinal and cardiac symptoms, and neurologic symptoms develop later.<sup>4,5</sup> Acute-on-chronic toxicity occurs with acute overdose in patients on longterm lithium treatment, and the presentation is a more severe form of acute toxicity.4,5 Chronic toxicity occurs insidiously during long-term lithium treatment when serum lithium levels may be in the therapeutic range. These patients develop mainly neurologic symptoms and sometimes only partially recover.<sup>4,5</sup> The distinction between acute-on-chronic and chronic toxicity is often not so clear and difficult to establish.<sup>4,5</sup> The Amdisen Scale<sup>5-7</sup> is a useful tool for the assessment of the severity of lithium toxicity.

Schou<sup>8</sup> was the pioneering researcher to report LN and its long-lasting neurologic sequelae. Lithium toxicity is common in the elderly, with an annual incidence of 1.5%.9 In 1.3%–4% of these cases, there is also acute kidney damage and renal toxicity, which usually resolve within 12 months, but some renal impairment may be more sustained.9-11

Some of the proposed risk factors for LN are nephrogenic diabetes insipidus, age > 50 years, thyroid dysfunction, and impaired creatinine clearance.12 Dehydration and volume depletion may cause lithium toxicity due to increased sodium and lithium reabsorption.13,14 Medications such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, thiazide diuretics, and nonsteroidal antiinflammatory drugs increase renal sodium reabsorption and raise serum lithium levels.13-15 Cardiovascular disease

toxicity by decreasing lithium delivery to the kidneys, the only site of its excretion.<sup>13</sup>

As the evidence for the use of lithium increases, paradoxically, there is a decrease in its use.<sup>16</sup> As there is a delay in the onset of the therapeutic effects of lithium, especially in agitated patients, lithium is sometimes combined with antipsychotics and anticonvulsants.<sup>17–24</sup> In the past, lithium was combined with first-generation antipsychotics (FGAs).<sup>1-3</sup> However, recently, lithium is more commonly combined with second-generation antipsychotics (SGAs).<sup>23,24</sup> This combination has become an area of caution and concern.

In reviews published on RLN and ILN, most authors<sup>1-3</sup> based their opinions on individual case reports and hospital records. However, to our knowledge, no review describes the clinical presentation of both RLN and ILN due to the combination of lithium and SGAs. Hence, we studied the clinical presentation of cases of LN (reversible and irreversible) due to the SGA and lithium combination. We also studied the causes of and preventive measures to avoid LN. This review has important clinical implications for psychiatric management, training of mental health professionals, and further research for patients receiving a combination of lithium and SGAs.

### **METHODS**

Studies were identified from a comprehensive search of the electronic databases in MEDLINE, PsycINFO, EMBASE, and Cochrane Library from their inception to July 31, 2017. We combined free terms and MeSH headings as follows: [(lithium) AND (adverse events OR safety OR side effects OR neurotoxicity OR neurologic manifestations OR central nervous system) AND (risperidone OR paliperidone OR olanzapine OR aripiprazole OR clozapine OR quetiapine OR ziprasidone OR amisulpride OR asenapine OR lurasidone OR iloperidone)]. The search was limited to English-language human studies. Further studies were collected through manual searches, discussion with experts in the field, and review of references of relevant articles. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis<sup>25</sup> flow diagram indicates the flow of information through search and study selection processes (Figure 1).

Two reviewers (I.N. and V.H.P.) independently searched and extracted the data. Disagreements were resolved through discussion. Only articles reporting on LN due to SGAs combined with lithium were selected. All cases of LN in adults, irrespective of their age, sex, ethnicity, functioning level, and inpatient or outpatient status, were included. Cases of LN due to SGAs combined with lithium with insufficient data and no clear outcome of reversibility or partial recovery from LN and cases reporting minor neurologic side effects of lithium were excluded.

The data from the included studies were extracted according to the following criteria: author, year of publication, age, sex, diagnostic categories, lithium dosages, serum lithium levels, investigations, clinical features (physical and It is illegal to post this copyrighted PDF on any website. Figure 1. PRISMA Flow Diagram Indicating the Flow of Information Through the Search and Study Selection Process



mental), and causes and preventive measures. The results obtained were tabulated.

### RESULTS

A total of 137 studies were retrieved through a systematic search. Nine other studies were selected from the references of those studies. A total of 82 articles remained after removing duplicates, which were also screened. Of the 82 articles, 64 did not meet the eligibility criteria. The remaining 18 articles were assessed for eligibility, but 7 were excluded after scrutinizing the full text of each of the 18 articles. A total of 8 studies<sup>5,26–32</sup> with 11 cases of LN due to the lithium and SGA combination were included in the systematic review.

Of the 11 cases studied, 8 were cases of RLN and 3 were cases of ILN. Of the 8 cases of RLN, there were 4 case reports of individual patients and 1 case series of 4 patients.<sup>26–30</sup> Of the 3 cases of ILN, all were reports of individual cases.<sup>5,31,32</sup> None of the studies reported receiving any grants or financial support.

### Year of Publication

*RLN*. Eight cases were published during the period 1992–2015.<sup>26–30</sup>

*ILN.* Three cases were published during the period 2010–2014<sup>5,31,32</sup> (Tables 1–3).

### Age

*RLN*. The age of patients ranged from 27 to 78 years. Of 8 cases,<sup>28–29</sup> 2 were elderly patients aged 75 and 78 years.

*ILN.* The age of patients ranged from 56 to 69 years.<sup>5,31,32</sup> Of 5 cases, 45.5% were aged  $\geq$  60 years (Tables 1–3).

Natural aging increases the risk for lithium toxicity. Due to decreased estimated glomerular filtration rate, the lithium dose required to achieve a given therapeutic serum level may decrease 3 times between the ages of 40 and 95 years.<sup>11</sup>

### Sex

*RLN.* The RLN group included 3 men and 5 women.<sup>26–30</sup> *ILN.* The ILN group included 1 man and 2 women.

Thus, of a total of 11 cases of LN, 7 were women and 4 were men<sup>5,31,32</sup> (Tables 1–3). Two reviews have also reported a greater number of female cases of LN in the literature.<sup>1,3</sup>

### **Diagnostic Categories**

*RLN*. Of the 8 cases of RLN, 2 had bipolar disorders, 4 had schizoaffective disorder, and 2 had schizophrenia.<sup>26–30</sup>

*ILN*. Of the 3 cases of ILN, 1 had a bipolar disorder and 2 had schizoaffective disorders<sup>5,31,32</sup> (Tables 1–3).

Diagnostic classification was reported in only 1 study,<sup>32</sup> which used the *ICD-10* diagnostic classification. Psychiatric diagnosis does not seem to be a factor related to the development of lithium toxicity.<sup>1-3</sup>

### Netto et al <u>It is illegal to post this copyrighted PDF on any website.</u> Table 1. Characteristics of Study Populations<sup>a</sup>

	RLI	RLN ILN Total		al		
Characteristic	(Cases)	%	(Cases)	%	(Cases)	%
Year of study						
≥1990	(4)	50.0	0		(4)	36.4
≥1995	(1)	12.5	0		(1)	9.1
≥2000	0		0		0	
≥2005	(1)	12.5	0		(1)	9.1
≥2010	(1)	12.5	(2)	66.7	(3)	27.3
≥2015	(1)	12.5	(1)	33.3	(2)	18.2
Age, mean, y <sup>b</sup>						
≥20	(1)	12.5	0		(1)	9.1
≥30	(3)	37.5	0		(3)	27.3
≥40	0		0		0	
≥ 50	(1)	12.5	(1)	33.3	(2)	18.2
≥60	(1)	12.5	(2)	66.7	(3)	27.3
≥70	(2)	25.0	0		(2)	18.2
Sex						
Male	(3)	37.5	(1)	33.3	(4)	36.4
Female	(5)	62.5	(2)	66.7	(7)	63.6
Diagnostic categories						
Bipolar	(2)	25.0	(1)	33.3	(3)	27.3
Schizoaffective	(4)	50.0	(2)	66.7	(6)	54.5
Schizophrenia	(2)	25.0	0		(2)	18.2
Lithium dose, mg/d <sup>c</sup>						
≥ 300	0		(1)	33.3	(1)	9.1
≥600	(2)	25.0	0		(2)	18.2
≥900	(2)	25.0	0		(2)	18.2
≥ 1,200	(3)		(1)	33.3	(4)	36.3
≥ 1,500	0		0		0	
Serum lithium level, mEq/L <sup>a</sup>	(2)	275	0		(2)	20.0
≥0.4	(3)	37.5	0		(3)	30.0
≥0.8 > 1.2	(1)	12.5	0		(1)	10.0
21.2	(Z) (1)	25.0	0		(2)	20.0
21.0	(1)	12.5	0		(1)	10.0
> 2.0	0		(2)	66 7	(2)	20.0
> 2 9	0		(2)	00.7	(2)	20.0
≥ 2.0	0		0		0	
>36	0		0		0	
>4.0	(1)	125	0		(1)	10.0
SGAs in combination with lithium	(1)	12.5	0		(1)	10.0
Clozanine	(5)	62 5	0		(5)	417
Bisperidone	(1)	12.5	(2)	50.0	(3)	25.0
Aripiprazole	(1)	12.5	(1)	25.0	(2)	16.7
Ouetiapine	(1)	12.5	(1)	25.0	(2)	16.7
	(1)	12.5	(1)	25.5	(-/	10.7

<sup>a</sup>The number in parentheses is the number of cases; the percentage represents the percentage or mean percentage for patients within that study. <sup>b</sup>Total cases > 60 years = 45.5%.

<sup>c</sup>Lithium dose not reported in 1 case of RLN and 1 case of ILN.

<sup>d</sup>Serum lithium level not reported in 1 case of ILN.

Abbreviations: ILN = irreversible lithium neurotoxicity, RLN = reversible lithium neurotoxicity, SGA = second-generation antipsychotic.

### **Clinical Features: Physical**

*RLN.* Cases of RLN presented with pyramidal, extrapyramidal, and cerebellar signs, and patients recovered completely.<sup>26–30</sup> One patient developed reversible posterior leukoencephalopathy syndrome (RPLS; Table 2).<sup>30</sup>

*ILN.* Cases of ILN presented with pyramidal signs, extrapyramidal signs, cerebellar signs, choreoathetoid movements, Creutzfeldt-Jakob–like syndrome, neuroleptic malignant–like syndrome, cognitive deficits, ocular signs, and impaired frontal lobe functions, and patients recovered partially<sup>5,31,32</sup> (Table 3).

Cerebellar signs have been reported by some authors in cases of RLN.<sup>1–3</sup> One author<sup>8</sup> maintained that cerebellar signs do not occur in acute lithium toxicity. Cases presenting as a serotoninlike syndrome, neuroleptic malignant syndrome, pseudotumor been reported.33-40

### **Clinical Features: Mental**

*RLN.* Most cases of RLN presented as an acute organic brain syndrome (delirium), and patients later recovered completely.<sup>26-30</sup>

*ILN.* Cases of ILN presented initially as an acute brain syndrome, but patients later developed a chronic brain syndrome and only partially recovered from LN<sup>5,31,32</sup> (Tables 1–3). Similar findings have also been found in other studies.<sup>1–3</sup>

### Investigations

*RLN.* Five cases of RLN showed laboratory investigations within normal limits.<sup>26-30</sup> In 3 cases, no laboratory results were reported (Table 2).<sup>26</sup>

*ILN*. Cases of ILN showed abnormal hemogram, renal function, electrocardiogram, electroencephalogram (EEG), and computed tomography findings.<sup>5,31,32</sup>

One patient's EEG findings showed Creutzfeldt-Jakob-like syndrome,<sup>29</sup> and another showed RPLS on magnetic resonance imaging<sup>30</sup> (Table 3). Abnormal EEG findings are important indicators of early LN according to some authors.<sup>41</sup>

### Lithium Dosage

*RLN.* The doses of lithium ranged from 600-1,200 mg/d (Table 2).<sup>26-30</sup>

*ILN.* The doses of lithium ranged from 300–1,200 mg/d (Table 3).

Most cases had lithium dosages < 1,200 mg/d in both groups.<sup>5,31,32</sup> In 1 case each of RLN and ILN, the dose was not reported.<sup>30,32</sup> Neuroleptic-induced LN is dose dependent and has been highlighted by some authors.<sup>42</sup>

### Serum Lithium Levels

*RLN.* The serum lithium levels ranged from 0.7–4.2 mEq/L. In 6 cases of RLN, serum lithium levels were < 1.5 mEq/L, but in 2 cases they were 1.7 and 4.2 mEq/L (Table 2).<sup>26–30</sup>

*ILN.* The serum lithium levels in 2 cases were 2.5 and 2.6 mEq/L, and in 1 case the level was not reported (Table 3).

Generally, serum lithium levels of 1.0–1.5 mEq/L have been recommended for the treatment of acute manic episodes and levels of 0.8–1.0 mEq/L for the prophylaxis of bipolar mood disorders.<sup>43</sup> Severe intoxication occurs at serum lithium levels > 3 mEq/L, and serum lithium levels > 5 mEq/L can be fatal.<sup>44</sup>

In the age group  $\ge 60$  years, the serum lithium levels were 1.47, 1.7, and 4.2 mEq/L in cases of RLN and 2.5 mEq/L in a case of ILN.<sup>28–31</sup> In 1 case of ILN, the serum lithium level was not reported.<sup>32</sup> Three patients had medical comorbidities and were on prescription medication.<sup>29–31</sup> In the age group < 60 years, in cases of RLN, 3 had a serum lithium level of 0.7 mEq/L<sup>26</sup> and 2 You are prohibited from making this PDF publicly available.

_				_				Lith	nium Neurotoxi	city When Com	pined With SGAs
lt	sten	Jelae	llega	l to		st this	copyrig	hted l	PDF on	any w	ebsite.
	Persi	Segu	Z	N	Z	N	N	N	N	Z	versibl
		Other Medication	None	None	None	None	None	None	Levodopa	Hydrochlorothiazide, valsartan, levothyroxine, glimepiride, pipamperone, chlorprothixene	not reported, RPLS = re
	Medical	Comorbidities	Tardive dyskinesia	None	None	None	None	None	T2DM, parkinsonism, nocturnal myoclonus	Hypertension, hypothyroidism, diabetes mellitus, chronic obstructive airway disease	intoxication. <sup>43</sup> imaging scan, NR = nal limits.
		SGA℃	Clozapine 900 mg/d	Clozapine 900 mg/d	Clozapine 900 mg/d	Clozapine 900 mg/d	Clozapine 200 mg/d	Risperidone 2 mg qhs	Aripiprazole 5 mg/d	Quetiapine	ads to severe tic resonance .= within norm
		Investigation Results	NR	NR	NR	Blood chemistry, MRI, EEG results: WNL	Hematologic and biochemical: WNL	WBC: 20.3 K; creatine kinase: WNL; blood cultures, CT, and CSF: negative	CT: cerebral atrophy; leukocytosis; alkaline phosphatase: 424 mmol/L	Brain CT and MRI: bilateral posterior hypodensities suggestive of RPLS	1.0 mEq/L; > 3 mEq/L le xxicity. M = male, MRI = magne: e blood cell count, WNL
	Features	Mental	Hostile, psychotic, bizarre nihilistic delusions not experienced previously, violence	Disoriented, impaired concentration, memory disturbance	Agitated, confused	Poor short-term memory and immediate recall, subjective distress	No mental change except symptoms of mania (expansive mood, hyperactive, excessive talk, inflated self-esteem, racing thoughts, and decreased need for sleep)	Lethargic, no verbal response, expressionless face	Psychomotor agitation, mutism	Somnolence, disorientation, dysarthria, generalized myoclonus	ipolar mood disorders is 0.8– ing factor for lithium neurotc am, F = female, K = thousand, diabetes mellitus, WBC = whit
oined With Lithium	Clinical I	Physical <sup>b</sup>	Diaphoresis, diarrhea, episodic myoclonic jerks	Involuntary jerking of limbs, facial paralysis, pisa syndrome	Stumbling gait, leaning to the right, jerking of hands and tongue	Tremor of the hands and tongue, twitching, general weakness, falling to the right, gait problems, tics, dysarthric speech	Ataxia, coarse tremor of hands, myoclonus, facial spasm and hyperreflexia	Temperature: 100.2°F (37.8°C), tremor at rest, rigidity, weakness	Cogwheel rigidity, EEG, Creutzfeldt-Jakob–like syndrome	RPLS	and for the prophylaxis of bi 1 the SGA was the precipitati 0, EEG = electroencephalogri titpsychotic, T2DM = type 2 c
SGA Com	Serum Lithium	Level <sup>b</sup>	0.7 mEq/L	0.7 mEq/L	0.7 mEq/L	1.0 mEq/L	1.0 mEq/L	1.47 mEq/L	4.2 mEq/L	1.7 mEq/L	ers. .0–1.5 mEq/L of lithium and nography scal generation ar
ty Due to	Lithium Dose,	mg/d	1,200	1,200	1,200	006	600	006	600	Not reported	the disorde mania is 1 mbination puted ton = second-
im Neurotoxici		Diagnosis <sup>a</sup>	Schizophrenia	Schizoaffective disorder	Schizophrenia	Schizoaffective	Bipolar disorder	Bipolar type I mania with psychotic features	Schizoaffective disorder	Schizoaffective disorder	eported for any of ium level for acute mined that the cor inal fluid, CT = cor thy syndrome, SGA
ithiu		Sex	Σ	ш	ш	Σ	ц	Σ	ш	ш	n not re um lith deter ebrosp alopat
ible I	Age,	- -	33	31	27	34	59	75	78	60	icatior ed sert ysician = cere nceph
e 2. Revers		Study	Blake et al, 1992 <sup>26</sup>	Blake et al, 1992 <sup>26</sup>	Blake et al, 1992 <sup>26</sup>	Blake et al, 1992 <sup>26</sup>	Lee and Yang, 1999 <sup>27</sup>	Boora et al, 2008 <sup>28</sup>	Fernández- Torre et al, 2014 <sup>29</sup>	Loens et al, 2015 <sup>30</sup>	Inostic classif recommende patient's phy eviations: CSF iterior leukoe
Tabl		Case	-	2	m	4	ц.	9	7	œ	<sup>a</sup> Diag <sup>b</sup> The cEach Abbri pos

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lt		ʻsistent Sequela 💋	ermittent tongue ptrusions, ocular provements wements wements	paired frontal e functions	or short-term all, dysarthia, xia	<b>rig</b>
le Lithium Neurotoxicity Due to SGA Combined With Lithium		Other Medication Per	Divalproex, Int clonazepam, pro trazodone cho mc	None Im	Ibuprofen, Po. lisinopril 20 mg/d rec ata	ε
	Medical	Comobidities	Vascular dementia	None	Chronic renal failure, hypertension	vere intoxication. <sup>4</sup>
		SGAc	Aripiprazole 5 mg each moming and 25 mg at bedtime	Risperidone 6 mg/d	Quetiapine 300 mg at bedtime; risperidone 1 mg twice daily	Eq/L leads to sev
		Investigation Results	Sodium: 152 mEq/L, BUN: 75 mg/dL, serum creatinine: 4.0 mg/dL, valproate: 2.9 µg/mL; chest x-ray and blood cultures: negative; CT: moderate to severe white matter disease; ECG: prolonged QTc: 510 ms, T-wave inversion	CK: 953 U/L (normal, < 145 U/L), low sodium levels, EEG: suggestive of diffuse encephalopathy	Serum creatinine: 2.28 mg/L, BUN: 49 mg/dL, leukocytosis, CT: periventricular white matter disease	isorders is 0.8–1.0mEq/L; >3 mi thium neurotoxicity.
	Clinical Features	Mental	Disoriented, lethargic, withdrawn	Cognitive deficits	Confused, disoriented, distractable	ipolar mood di ing factor for lit
		Physical	Temperature: 99.5°F; choreoathetoid movements	Hypomimia, hypersalivation, ataxia, rigors, febrile; EPS: neuroleptic malignant–like syndrome	Worsening tremor, diarrhea, heart rate of 105/min, dysarthria, ataxia, dysmetria	for the prophylaxis of b SGA was the precipitati
	Serum	Lithium Level <sup>b</sup>	2.5 mEq/L	N	2.6 mEq/L	0–1.5 mEq/L and f lithium and the
	Lithium Dose,	mg/d	300	NR; prophylactic treatment with lithium	Lithium carbonate 1,200/ mg/d	cute mania is 1. combination o
		Diagnosis	Schizoaffective disorder bipolar type <sup>a</sup>	Schizoaffective disorder (ICD-10 F25)	Bipolar disorder <sup>a</sup>	: reported. thium level for ac ermined that the
		Sex	ш.	ш.	Σ	on not erum li an dete
ersibl	Age.	n N	69	60	56	sificati ded se hysicié
e 3. Irreve		Study	Lloyd et al, 2010 <sup>31</sup>	Boeker et al, 2011 <sup>32</sup>	lvkovic and Stern, 2014 <sup>5</sup>	gnostic clas: recommen patient's p
Tabl		Case	<del></del>	5	m	<sup>a</sup> Diaç <sup>b</sup> The <sup>c</sup> Each

**PDF** on mEq/L,<sup>26,27</sup> and in a case of ILN, the level was 2.6 mEq/L.<sup>5</sup> One author<sup>11</sup> has recommended monitoring of serum lithium levels at 3-month intervals in the elderly due to the high risk for development of LN. The lithium toxicity occurring at low or therapeutic serum lithium levels has been referred to as paradoxical or pathological LN.<sup>43,45,46</sup>

### **Dosages of SGA Medications**

All patients received oral SGA medication.

**RLN.** Clozapine dosages were 900 mg/d in 4 cases<sup>26</sup> and 200 mg/d in another.<sup>27</sup> In 1 case,<sup>28</sup> the risperidone dose was 2 mg/d. In another case,<sup>29</sup> the aripiprazole dose was 5 mg/d. The dose of quetiapine was not reported in 1 case (Table 2).<sup>30</sup>

*ILN.* One patient received aripiprazole 30 mg/d,<sup>31</sup> 1 patient received risperidone 6 mg/d,<sup>32</sup> and 1 patient received an SGA combination of risperidone 2 mg/d and quetiapine 300 mg/d (Table 3).<sup>5</sup> Some authors<sup>42</sup> have emphasized that the dosage of the antipsychotic, not the serum lithium level or lithium dose, predicts neurotoxicity.

### **Medical Comorbidities**

*RLN.* The RLN group had 3 cases with medical comorbidities. One patient had tardive dyskinesia,<sup>26</sup> 1 had parkinsonism and diabetes,<sup>29</sup> and 1 had hypertension, hypothyroidism, diabetes mellitus, and chronic obstructive airway disease<sup>30</sup> (Table 2).

*ILN.* One patient with ILN had vascular dementia, fever, and dehydration<sup>31</sup> and another had chronic renal failure<sup>5</sup> (Table 3).

It has been cautioned that medical comorbidities such as thyroid dysfunction, diabetes insipidus, dehydration, renal disease, cardiovascular disease, and preexisting central nervous system disease may lead to LN.<sup>5–15</sup>

### **Other Medication**

*RLN.* One patient received levodopa<sup>29</sup> and another hydrochlorothiazide, valsartan, levothyroxine, and glimepiride<sup>30</sup> along with the FGAs pipamperone and chlorprothixene (Table 2).

*ILN.* One patient received divalproex, clonazepam, and trazodone<sup>31</sup> and another received ibuprofen and lisinopril<sup>5</sup> (Table 3).

The risk factors for LN include medications commonly prescribed, such as nonsteroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers, which have been reported in some studies.<sup>12–15</sup>

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Various measures to prevent LN due to the lithium and SGA combination have been suggested in light of clinical findings. When combining lithium with SGAs, a decrease in the dose of the antipsychotic as well as a lower dose of lithium is recommended.<sup>27,32</sup> A special caution in the elderly is advised. In addition to serum lithium level, renal function monitoring has also been recommended in the elderly.<sup>9–12</sup> Some authors<sup>5</sup> have recommended that clear guidelines should be made available regarding the use of renal dialysis and other procedures in the management of LN.

### DISCUSSION

This review is the first to examine the clinical presentation of cases of LN, both reversible and irreversible, due to SGAs combined with lithium. A total of 11 cases of LN due to lithium plus SGA combinations were evaluated. Eight were reversible and 3 irreversible.<sup>5,26–32</sup>

The most important hypotheses for neurotoxicity due to the lithium and SGA combination is increased dopamine receptor blockage. Both FGAs and SGAs cause postsynaptic blockade of brain dopamine D2 receptors with the exception of aripiprazole, which is a D<sub>2</sub> receptor partial agonist.<sup>47</sup> Most SGAs differ from FGAs pharmacologically in that serotonin 5-HT<sub>2</sub> receptor binding exceeds their affinity for dopamine D<sub>2</sub> receptors, whereas in FGAs this is generally not the case.<sup>48</sup> SGAs also have loose D<sub>2</sub> receptor binding, rapid dissociation rates, and preferential binding of drugs to receptors in limbic and cortical brain regions rather than striatal areas.<sup>49,50</sup> The interaction of the serotonergic effects of lithium and SGAs has also been postulated as a potential mechanism for LN.<sup>26</sup> Lithium appears to affect multiple neurotransmitter systems and inhibits postsynaptic dopamine release. Some authors have also highlighted "the two-pronged effect" of lithium and SGAs when combined together, resulting in profound dopamine hypofunctionality as a causative mechanism for LN.32

### Similarities and Differences in Cases of RLN and ILN Due to SGAs

RLN and ILN have no specific association with age or sex distribution. RLN was seen in schizophrenia and bipolar and schizoaffective disorders, whereas ILN was seen only in bipolar and schizoaffective disorders. Patients with RLN developed an acute brain syndrome and recovered completely, and patients with ILN developed a chronic brain syndrome with partial recovery. Cerebellar signs in RLN recovered completely, whereas those of ILN did not recover. One patient with RLN developed Creutzfeldt-Jakob-like syndrome and another RPLS.<sup>29,30</sup> Investigations in cases of RLN were normal, whereas those in ILN showed abnormalities. In both groups, the lithium doses in all cases of LN were less than 1,200 mg/d (lithium dosage was not reported in 2 cases). Serum lithium levels in 2 cases of RLN were 1.7 and 4.2 mEq/L and in 2 cases of ILN were 2.5 and 2.6 mEq/L. One RLN patient received 2 different FGAs along

**It is illegal to post this copyrighted PDF on any website**. With the lithium and SGA combination.<sup>30</sup> One ILN patient had received a combination of 2 different SGAs along with lithium.<sup>5</sup> Both groups had cases with medical comorbidities who were also receiving other prescription medication that was a contributing factor for the development of LN.

### Limitations

The data were secondary and heterogeneous in nature. A few studies did not report certain data such as lithium doses and serum lithium levels. The most significant serum lithium level with a temporal relationship to the onset of lithium toxicity was chosen in some studies that reported different serum lithium levels.

### CONCLUSIONS

The following clinical profile emerges after evaluating 11 cases of LN, of which 8 were cases of RLN and 3 of ILN due to the lithium and SGA combination. Fortyfive percent of cases were aged  $\geq 60$  years. There were more female cases compared to males. The diagnostic categories in both RLN and ILN were schizoaffective disorders and bipolar disorders, but 2 patients with RLN had schizophrenia. None of the cases were of the acute subtype with an acute onset due to an accidental or intentional overdose, but all were acute-on-chronic or chronic subtypes with an insidious or gradual onset. The clinical features in cases of RLN were those of an acute brain syndrome with pyramidal, extrapyramidal, and cerebellar signs that recovered completely. Cases of ILN showed signs of a chronic brain syndrome with choreoathetosis, a Creutzfeldt-Jakob-like syndrome, and a neuroleptic malignant-like syndrome and only partially recovered. The lithium doses in all (except 2 cases for which a lithium dose was not reported) were less than 1,200 mg/d. Serum lithium levels in 2 cases of RLN were 1.7 and 4.2 mEq/L and in 2 cases of ILN were 2.5 and 2.6 mEq/L; the rest (except 1 that did not report the serum lithium level) were 1.5 mEq/L. The SGAs used in combination with lithium and responsible for LN were clozapine, risperidone, aripiprazole, and quetiapine. One patient with RLN received 2 different FGAs in addition to the lithium and SGA combination. One patient with ILN received 2 different SGAs with lithium. One patient with RLN had tardive dyskinesia, a second parkinsonism and diabetes, and a third hypertension, hypothyroidism, diabetes mellitus, and chronic obstructive airway disease. One patient with ILN had vascular dementia, fever, and dehydration and another chronic renal failure. One RLN patient received levodopa and another hydrochlorothiazide, valsartan, levothyroxine, glimepiride, pipamperone, and chlorprothixene. One ILN patient received divalproex, clonazepam, and trazodone, while another received ibuprofen and lisinopril. Diagnostic classifications were not reported in all but 1 case. Lithium doses in 2 cases, serum lithium levels in 1 case, and the SGA dose in 1 case were not reported.

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### Netto et al It is illegal to post this copyrighted PDF on any website. Clinical Implications

This review helps to gain a better understanding of LN, both reversible and irreversible, due to the lithium and SGA combination. A ban on the use of the combination has not been recommended but caution while prescribing lithium and SGAs together is urged. A reduction in the doses of both lithium and SGAs along with close monitoring has been suggested. Potential high-risk groups for developing EN on the lithium and SGA combination such as elderly patients, patients with medical comorbidities, and those on prescription medication should be monitored carefully. This review will help in the prevention of LN through early detection, close monitoring, care in combining other drugs with the lithium and SGA combination, prompt management of LN, and proper psychoeducation of patients and caregivers.

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- A 35-year-old man with a diagnosis of schizoaffective disorder is receiving lithium carbonate 1,200 mg/day and the second-generation antipsychotic (SGA) clozapine 400 mg/day in divided doses. He develops disorientation, rigidity, and involuntary jerky movements of the upper extremities. His serum lithium level is 0.7 mEq/L. His absolute neurotrophil count is within normal limits. Further investigation is indicated for which of the following diagnoses?
  - a. Agranulocytosis due to clozapine
  - b. Bipolar disorder
  - c. Paradoxical lithium neurotoxicity due to lithium + SGA combination
  - d. Neurologic illness
- 2. A 75-year-old woman with a diagnosis of bipolar disorder is taking lithium carbonate 600 mg/day and risperidone 2 mg/day. She is also receiving ibuprofen 200 mg/day and lisinopril 20 mg/day for her medical illness. Her serum lithium level is 2.6 mEq/L. She developed ataxia, coarse tremor, and confusion. Which answer best describes the precipitating factor(s) for her developing lithium neurotoxicity?
  - a. Lithium carbonate
  - b. Lithium carbonate + SGA combination
  - c. Old age, lithium carbonate + SGA combination, and medical comorbidity
  - d. Lithium carbonate + SGA combination and ibuprofen + lisinopril combination
- 3. The severity of lithium neurotoxicity is assessed by which of the following?
  - a. Serum lithium levels
  - b. Amdisen scale