Lithium Beyond Bipolar Mood Disorders:
A Hope or Hype?

Ahmed Naguy, MBBch, MSc,[a,*] and Bibi Alamiri, MD, ABPN, ScD[a]

Lithium remains the only agent with double-blind evidence of efficacy in all 4 phases of bipolar mood disorder—an epitome of a "mood stabilizer" in the strictest sense. By virtue of its composite mode of action (Table 1), lithium might be the only disease-modifying psychotropic agent. It has been shown to prolong lives by preventing completed suicide in bipolar mood disorder by 6-fold (and possibly recurrent unipolar depression as well by 5-fold) and decreasing cardiovascular mortality.[1] It is US Food and Drug Administration approved in patients as young as age 7 years and is available in different salt formulations (carbonate, citrate, and orotate).

Lithium antisuicidality might be related to its thymoleptic actions and true prophylaxis of mood episodes but also to anti-impulsive and antiaggressive actions, procognitive actions and improved decision-making performance, increased glutamine synthetase expression, and, conceivably, increased access to clinical care for mandatory serum monitoring.[1]

Lithium, especially in geriatric bipolar mood disorder, transcends efficacy data on neuroprotection and reduction in risk of dementia and strokes by virtue of its demonstrated anti-inflammatory, antioxidant, and endothelial actions.[2]

Recently, data from neuroscience have confirmed lithium's procognitive actions.[3] These actions include inter alia; increased gray matter volume; promotion of hippocampal neurogenesis; increased *N*-acetylaspartate, which is a putative marker of neuronal viability; increased brain-derived neurotropic factor and vascular endothelial growth factor; increased antiapoptotic Bcl-2; inhibition of proapoptotic protein P53 and β-catenin; inhibition of GSK-3β; inhibition of caspase-3 pathway; boosted cholinergic tone in the cortex; and better white matter integrity.

Moreover, lithium's demonstrated neuroprotectant actions can be in part related to modulating γ-aminobutyric acid–mediated calcium influx, which is a relevant mechanism to neurodegenerative disorders. Research suggests a positive influence of lithium on the deposit of α-synuclein and β-amyloid proteins—hallmarks of Parkinson's and Alzheimer's diseases, respectively.[3] Due to the diversity of lithium's pharmacologic portfolio, it is obvious that lithium might be a promising therapeutic option in numerous disorders, although solid scientific evidence is lacking for most of these potential albeit off-label indications to date.

Table 1. Lithium's Composite Mode of Action

- Slowing of biologic rhythms
- Decreasing of dopamine turnover
- Decreasing of prostaglandin E1 synthesis
- Reducing neuronal calcium^{++} mobilization
- Hyperpolarization of neuronal membranes
- Blocking β-adrenergic–stimulated adenylate cyclase via activation of membrane phosphoinositide signaling system
- Increasing of tryptophan uptake, ergo stabilizing 5-HT synaptic dynamics
- Increasing presynaptic deamination of norepinephrine, ergo decreasing its release
- Affecting G-protein–coupled second messenger systems
- Alters sodium transport
- Modest but significant proserotonergic effect with cornu ammonis 3 hippocampal postsynaptic neuron sensitization
- Increasing acetylcholine synthesis and tone in cortex
- Altered γ-aminobutyric acid metabolism

Clinical uses of lithium in psychiatry are protean apart from bipolar mood disorders. These clinical uses include anti-impulsivity, antisuicidality, antiaggressivity, dual diagnoses, schizoaffective disorder, augmentation in unipolar depression, cyclothymia, cycloid psychosis, Klein-Levine syndrome, borderline personality disorder, clozapine-induced neutropenia (it increases colony-stimulating factors, stimulates proliferation of pluripotent stem cells and granulopoiesis/megakaryocytopoiesis), augmentation in schizophrenia, and psychogenic polydipsia, just to name few.[4]

Even beyond psychiatric indications, lithium has been trialed successfully in many medical conditions including cluster/hypnic headaches, Felty syndrome, gout, Huntington's disease, thyrotoxicosis, seborrheic dermatitis (topical), Herpes simplex, syndrome of inappropriate antidiuretic hormone secretion, Canavan disease, cyclic vomiting, and asthma.[5,6] Nonetheless, use in some of these indications remains largely of historical interest.

Of note, typical dosing, serum level of lithium, and duration to obtain targeted response in these diverse indications, beyond bipolar mood disorders (wherein serum lithium concentration of 0.8–1.2 mmol/L is generally optimal), are largely unknown. Some authors[7] suggest a low

[a]Al-Manara CAP Centre, Kuwait Centre for Mental Health, Shuwaikh, Kuwait

*Corresponding author: Ahmed Naguy, MBBch, MSc, Al-Manara CAP Centre, Kuwait Centre for Mental Health, Jamal Abdul-Nassir St, Shuwaikh, Sulibikhat 21315, Kuwait (ahmednagy@hotmail.co.uk).

Prim Care Companion CNS Disord 2022;24(5):21br03109

To cite: Naguy A, Alamiri B. Lithium beyond bipolar mood disorders: a hope or hype? *Prim Care Companion CNS Disord.* 2022;24(5):21br03109.

To share: https://doi.org/10.4088/PCC.21br03109

lithium dose of 150–300 mg/d (corresponding to 0.1–0.4 mmol/L) for suicide prevention and neuroprotection in dementia.

That said, lithium is globally underutilized given its narrow therapeutic index, mandatory monitoring, concerns about long-term end-organ effects (eg, hypothyroidism, nephrogenic diabetes insipidus, hyperparathyroidism, weight gain, teratogenicity), and comedications that have potentially hazardous interactions (eg, nonsteroidal anti-inflammatories, angiotensin converting enzyme/angiotensin receptor blockers, diuretics, metronidazole).[8–11] It is incumbent on prescribers to renounce aversive attitudes regarding lithium in the best interest of our patients.

Submitted: August 21, 2021; accepted November 4, 2021.
Published online: September 8, 2022.
Relevant financial relationships: None.
Funding/support: None.

REFERENCES

1. Naguy A. Lithium antisuicidality: is it all about thymoleptic actions? *Prim Care Companion CNS Disord*. 2020;22(6):19br02588.
2. Naguy A, Shoukry TM. Lithium for geriatric bipolar mood disorder - gold standard or faux bijoux? *Australas Psychiatry*. 2019;27(1):93–94.
3. Liu M, Qian T, Zhou W, et al. Beneficial effects of low-dose lithium on cognitive ability and pathological alteration of Alzheimer's disease transgenic mice model. *Neuroreport*. 2020;31(13):943–951.
4. Barroilhet SA, Ghaemi SN. When and how to use lithium. *Acta Psychiatr Scand*. 2020;142(3):161–172.
5. Freeman MP, Freeman SA. Lithium: clinical considerations in internal medicine. *Am J Med*. 2006;119(6):478–481.
6. Yung CY. A review of clinical trials of lithium in medicine. *Pharmacol Biochem Behav*. 1984;21(suppl 1):51–55.
7. Baethge C. Low-dose lithium against dementia. *Int J Bipolar Disord*. 2020;8(1):25.
8. Naguy A. Lithium is clearly underutilized in child psychiatry. *Chin Med J (Engl)*. 2016;129(3):376.
9. Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. *Int J Bipolar Disord*. 2016;4(1):27.
10. Naguy A, Naguy C, Alkhadhari S. Probable lithium-related paroxysmal perceptual alterations in an adolescent with bipolar mood disorder. *Am J Ther*. 2020;28(6):e730–e731.
11. Naguy A, Moodliar-Rensburg S, AlKhadhari S. Lithium-induced Ekbom syndrome in a case of juvenile bipolar mood disorder. *Am J Ther*. 2022;29(3):e361–e362.