Lithium Synergy™ combines lithium orotate, known for its ability to help stabilize mood swings related to depression and other mood disorders, with vitamin B12 (methylcobalamin) and trimethylglycine to support healthy methylation pathways.

It is estimated that 26% of Americans suffer from mental disorders such as depression or bipolar disorder. Approximately 16% of Americans have been diagnosed with depression at some point in their lifetime. Clinically, it was Australian doctor, John Cade, who discovered lithium and its role in controlling bipolar disorder. Lithium orotate was introduced as a supplement by the German physician Dr. Hans Nieper, who used it to improve depression, headaches, migraine, epilepsy, and alcoholism. When salts of lithium are ingested, the lithium ions interact with several neurotransmitters and receptors in the central nervous system, resulting in decreased norepinephrine release and increased serotonin synthesis.

Two studies published in 2009 concluded that even very low but sustained levels of lithium in drinking water may play a role in reducing suicide risk within the general population.1 In one study, Japanese researchers evaluated lithium levels in the tap water of 18 municipalities. The researchers compared this data to the suicide standardized mortality ratio in each municipality from 2002 to 2006. The results of the study showed that as lithium levels increased, the suicide standardized mortality ratio averages decreased.2

**Mechanisms of Action**

Irregularities of intracellular calcium homeostasis have been implicated in the pathophysiology of bipolar disorder. Lithium has been researched for its ability to improve receptor function that allows for better calcium flux in and out of the cell. One of the most studied mechanisms of action is the inositol depletion hypothesis.3,4 This hypothesis suggests that lithium’s mood-stabilizing effects comes from its ability to inhibit IMPase, an enzyme involved in the recycling and synthesis of inositol, a primary component of the phosphoinositol signaling pathway. Depleting inositol concentrations decreases the amount of phosphoinositide 4,5-bisphosphate (PIP2), a cellular membrane phospholipid that is available for signaling cascades that rely on this pathway.

GSK-3, a serine-threonine kinase that functions as an intermediary in numerous intracellular pathways, is currently receiving interest as a regulator of apoptosis and cellular resilience. Evidence suggests an association between mood disorders and impairments of neuroplasticity and cellular resilience. In rodent and cell-based models lithium demonstrates neuroprotective effects at least partly by inhibiting GSK-3. Inhibiting GSK-3 attenuates or prevents neuron apoptosis.

**Lithium is Good for the Brain**

Finally, studies show that lithium in general inhibits the atrophy of the hippocampus. Atrophy of the human hippocampus is seen in a variety of psychiatric and neurological disorders including recurrent depression, schizophrenia, bipolar disorder, post-traumatic stress disorder, epilepsy, and Alzheimer’s disease. In Alzheimer’s disease the hippocampus is one of the first regions of the brain to suffer damage.5 Lithium has also been shown to block the production of key proteins involved in Alzheimer’s disease. When given to mice with Alzheimer’s, lithium blocked the build-up of abnormal proteins called amyloid plaque. Amyloid protein deposits destroy nerve cells by blocking transport of nutrients and oxygen.6
Vitamin B12 and Trimethylglycine (TMG)
Observational studies have found as many as 30% of patients hospitalized for depression are deficient in vitamin B12.\textsuperscript{12} The reasons for the relationship between vitamin B12 deficient and depression may involve s-adenosylmethionine (SAMe). Vitamin B12 is required for the synthesis of SAMe, a methyl group donor essential for methylation reactions and subsequently the metabolism of neurotransmitters. SAMe deficiency has been related to depression. This hypothesis is supported by several studies that have shown supplementation with SAMe improves depressive symptoms.\textsuperscript{13}

The addition of vitamin B12 and TMG helps support healthy methylation pathways.

Lithium Orotate Dosage and Toxicity
Lithium carbonate and lithium citrate have a poor toxicity profile and therefore must be used with caution. They show toxic effects at dosages only a little higher than the medically effective dose because lithium in these forms is poorly absorbed by the cells of the body. Consequently, because of this poor bioavailability, high dosages of pharmaceutical forms of lithium must be taken in order to obtain a satisfactory therapeutic effect. In contrast, the therapeutic dose of lithium orotate is much lower than that of the other lithium salts.

Serum lithium levels should be monitored by a qualified health care practitioner during use.

Cautions: This product should not be used to replace any antidepressant medication, including prescription forms of lithium, unless under the direction of a qualified health care practitioner. Lithium Synergy should not be used by individuals with significant renal or cardiovascular diseases, severe debilitation, dehydration or sodium depletion, or by individuals who are taking diuretics or ACE inhibitors. Caution should be taken with patients on antihypertensive drugs, anti-inflammatory drugs, analgesic drugs or insulin. Lithium should not be used by pregnant women and breast-feeding mothers. Serum lithium levels should be monitored by a qualified health care provider during use.

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