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Nutraceuticals for traumatic brain injury: Should you recommend their use?

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Although commonly used in clinical practice, evidence for their use in TBI is preliminary

Traumatic brain injury (TBI) affects more than 2 million people in the United States each year.[1] TBI can trigger a cascade of secondary injury mechanisms, such as inflammation, hypoxic/ischemic injury, excitotoxicity, and oxidative stress,[2] that could contribute to cognitive and behavioral changes. Although neuropsychiatric symptoms might not be obvious after a TBI, they have a high prevalence in these patients, can last long term, and may be difficult to treat.[3] Despite research advances in understanding the biological basis of TBI and identifying potential therapeutic targets, treatment options for individuals with TBI remain limited.

As a result, clinicians have turned to alternative treatments for TBI, including nutraceuticals. In this article, we will:

- provide an overview of nutraceuticals used in treating TBI, first exploring outcomes soon after TBI, then concentrating on neuropsychiatric outcomes
- evaluate the existing evidence, including recommended dietary allowances (***Table 1***)[4,5] and side effects (***Table 2, page 36***)
- review recommendations for their clinical use.

Pharmacologic approaches are limited

Nutraceuticals have gained attention for managing TBI-associated neuropsychiatric disorders because of the limited evidence supporting current approaches. Existing strategies encompass pharmacologic and non-pharmacologic

Disclosures
The authors report no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

Table 1

Recommended dietary allowances for reviewed nutraceuticals

Nutraceutical	Recommended dietary allowances	
	Male	Female
Zinc	11 mg	8 mg
Vitamin C	90 mg	75 mg
Vitamin D	600 IU (age 19 to 70); 800 IU (age >70)	600 IU (age 19 to 70); 800 IU (age >70)
Vitamin E	15 mg	15 mg
Magnesium	400 mg (age 19 to 30); 420 mg (age >30)	310 mg (age 19 to 30); 320 mg (age >30)
Branched-chain amino acids	Valine, 24 mg/kg/d Isoleucine, 19 mg/kg/d Leucine, 42 mg/kg/d	
Probiotics	Not established	
Glutamine	Not established	
N-acetylcysteine	Not established	
Enzogenol	Not established	
Citicoline	Not established	
Physostigmine	Not established	
Lecithin	Not established	
Cerebrolysin	Not established	

Note: Recommended dietary allowances values applicable for men and non-pregnant women age ≥19

Source: References 4,5

interventions, psychoeducation, supportive and behavioral psychotherapies, and cognitive rehabilitation.[6]

Many pharmacologic options exist for specific neurobehavioral symptoms, but the evidence for their use is based on small studies, case reports, and knowledge extrapolated from their use in idiopathic psychiatric disorders.[7,8] No FDA-approved drugs have been effective for treating neuropsychiatric disturbances after a TBI. Off-label use of antidepressants, anticonvulsants, dopaminergic agents, and cholinesterase inhibitors in TBI has been associated with inadequate clinical response and/or intolerable side effects.[9,10]

What are nutraceuticals?

DeFelice[11] introduced the term "nutraceutical" to refer to "any substance that is a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease." The term has been expanded to include dietary supplements, such as vitamins, minerals, amino acids, herbal or other botanicals, and food products that provide health benefits beyond what they normally provide in food form. The FDA does not regulate the marketing or manufacturing of nutraceuticals; therefore, their bioavailability and metabolism can vary.

Despite their widespread use, the evidence supporting the efficacy of nutraceuticals for patients with TBI is limited. Their effects might vary by population and depend on dose, timing, TBI severity, and whether taken alone or in combination with other nutraceutical or pharmaceutical agents. Fourteen randomized controlled trials (RCTs) have addressed the use of nutraceuticals in TBI (***Table 3, page 38***), but further research is needed to clarify for which conditions they provide maximum benefit.

Nutraceuticals and their potential use in TBI

Zinc is considered essential for optimal CNS functioning. Patients with TBI might be at risk for zinc deficiency, which has been

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Effects of nutraceuticals can vary by population and depend on variables, including dose, timing, and TBI severity

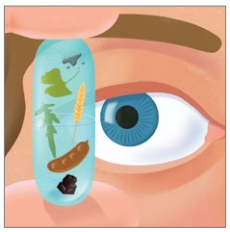

Table 2

Side effects of nutraceuticals

Nutraceutical	Side effects
Zinc	Nausea and diarrhea, interference with healthy antioxidant–pro-oxidant balance in the body. May promote iron overload and rarely causes renal failure in patients with thalassemia or hemochromatosis
Vitamin C	Nausea, vomiting, epigastric pain, lethargy, and fatigue with high intake. Induces copper and iron deficiency symptoms, such as anemia, neutropenia, and impaired immune function
Vitamin D	Anorexia, diarrhea, constipation, nausea, muscle and bone pain, drowsiness, headache, irregular heartbeat, loss of appetite, nocturia, excessive thirst, weakness, anxiety, and kidney stones
Vitamin E	Nausea, abdominal cramps, diarrhea, headache, fatigue, bleeding from inhibition of platelet aggregation, diplopia, muscle weakness, and creatinuria
Magnesium	Diarrhea, abdominal pain, urine retention, lethargy, muscle weakness, and cardiac arrest in individuals with impaired renal function
Branched-chain amino acids	Nausea, pain, and headache
Probiotics	Gas or bloating; infections in immunocompromised patients
Glutamine	Gas, dry mouth, or constipation. Not recommended in patients with renal impairment
N-acetylcysteine	Nausea, vomiting, and diarrhea or constipation. Rarely, increased risk of bruising and bleeding in people with bleeding disorders
Enzogenol	Gastric discomfort, dizziness, nausea, and headache
Citicoline	Gastrointestinal disturbances, transient headache, hypotension, tachycardia, bradycardia, and restlessness
Physostigmine	Nausea, hypersalivation, stomach cramps, diarrhea, loss of appetite and excessive sweating; seizures and hypertension with overdose
Lecithin	Diarrhea, nausea, and abdominal pain
Cerebrolysin	Headache, dizziness, and fatigue. In rare cases, agitation, restlessness, insomnia, and aggression. Not recommended in renal insufficiency or in combination with antidepressants

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Animal studies have shown that zinc supplementation could reduce deficits in spatial learning and depression-like behaviors

associated with increased cell death and behavioral deficits.[12,13] A randomized, prospective, double-blinded controlled trial examined the effects of supplemental zinc administration (12 mg for 15 days) compared with standard zinc therapy (2.5 mg for 15 days) over 1 month in 68 adults with acute severe closed head injury.[14] The supplemental zinc group showed improved visceral protein levels, lower mortality, and more favorable neurologic recovery based on higher adjusted mean Glasgow Coma Scale score on day 28 and mean motor score on days 15 and 21.

Rodent studies have shown that zinc supplementation could reduce deficits in spatial learning and memory and depression-like behaviors and help decrease stress and anxiety,[12] although no human clinical trials have been conducted. Despite the potential neuroprotective effects of zinc supplementation, evidence exists that endogenous zinc release and accumulation following TBI can trigger cellular changes that result in neuronal death.[13]

Vitamins C and E. Oxidative damage is believed to play a significant role in secondary injury in TBI, so research has focused on the role of antioxidants, such as vitamins C and E, to promote post-TBI recovery.[15] One RCT[16] of 100 adults with acute severe head injury reported that vitamin E administration was associated with reduced mortality and lower Glasgow Outcome Scale (GOS) scores, and vitamin C was associated with stabilized or reduced perilesional edema/infarct on CT scan.

Vitamin D. An animal study reported that vitamin D supplementation can help reduce inflammation, oxidative stress, and cell death in TBI, and that vitamin D deficiency has been associated with increased inflammation and behavioral deficits.[17] Further evidence suggests that vitamin D may have a synergistic effect when used in combination with the hormone progesterone. A RCT of 60 patients with severe TBI reported that 60% of those who received progesterone plus vitamin D had GOS scores of 4 (good recovery) or 5 (moderate disability) vs 45% receiving progesterone alone or 25% receiving placebo.[18]

Magnesium, one of the most widely used nutraceuticals, is considered essential for CNS functioning, including the regulation of *N*-methyl-D-aspartate receptors and calcium influx. After a TBI, magnesium deficiency can result in increased oxidative stress and cell death and has been associated with greater neurologic impairment. Animal studies have provided some evidence of the potential neuroprotective effects of magnesium, but human trials have found mixed evidence. One small human study reported a correlation between magnesium balance and oxidative stress in TBI patients.[19]

A RCT evaluated the safety and efficacy of magnesium supplementation in 60 patients with severe closed TBI, with one-half randomized to standard care and the other also receiving magnesium sulfate ($MgSO_4$; initiation dose of 4 g IV and 10 g IM, continuation dose of 5 g IM every 4 hours for 24 hours).[20] After 3 months, more patients in the $MgSO_4$ group had higher GOS scores than controls (73.3% vs 40%), lower 1-month mortality rates (13.3% vs 43.3%), and lower rates of intraoperative brain swelling (29.4% vs 73.3%).

However, a larger RCT of 499 patients with moderate or severe TBI randomized to high-dose (1.25 to 2.5 mmol/L) or low-dose (1.0 to 1.85 mmol/L) IV $MgSO_4$ or placebo provided conflicting results.[21] Participants received $MgSO_4$ 8 hours after injury and continued for 5 days. After 6 months, patients in the high-dose $MgSO_4$ and placebo groups had similar composite primary outcome measures (eg, seizures, neuropsychological measures, functional status measures), although the high-dose group had a higher mortality rate than the placebo group. Patients who received low-dose $MgSO_4$ showed worse outcomes than those assigned to placebo.

Amino acids. Branched-chain amino acids (BCAAs), including valine, isoleucine, and leucine, are essential in protein and neurotransmitter synthesis. Reduced levels of endogenous BCAAs have been reported in patients with mild or severe TBI.[22] Preclinical studies suggest that BCAAs can improve hippocampal-dependent cognitive functioning following TBI.[23]

Two RCTs of BCAAs have been conducted in humans. One study randomized 40 men with severe TBI to IV BCAAs or placebo.[24] After 15 days, the BCAA group showed greater improvement in Disability Rating Scale scores. The study also found that supplementation increased total BCAA levels without negatively affecting plasma levels of neurotransmitter precursors tyrosine and tryptophan. A second study found that 41 patients in a vegetative or minimally conscious state who received BCAA supplementation for 15 days had higher Disability Rating Scale scores than those receiving placebo.[25]

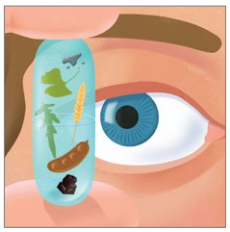
Probiotics and glutamine. Probiotics are non-pathogenic microorganisms that have been shown to modulate the host's immune system.[26] TBI is associated with immunological changes, including a shift from T-helper type 1 (TH1) cells to T-helper type 2 (TH2) cells that increase susceptibility to infection.[27]

A RCT of 52 patients with severe TBI suggested a correlation between probiotic administration-modulated cytokine levels and TH1/TH2 balance.[28] A 3-times daily probiotic mix of *Bifidobacterium longum*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus* for 21 days led to shorter average ICU stays (6.8 vs 10.7 days, $P = .034$) and a decrease in nosocomial infections (34.6% vs 57.7%, $P = .095$) vs placebo, although the latter difference was not statistically significant.[28]

A prospective RCT of 20 patients with brain injury[29] found a similar impact of

Clinical Point

One small study reported a correlation between magnesium balance and oxidative stress in TBI patients



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Clinical Point

Reduced levels of enogenous branched-chain amino acids have been reported in patients with mild or severe TBI

Table 3

Summary of RCTs of nutraceuticals for TBI

Study	Sample	Design	Intervention	Outcome
Young et al, 1996[14]	Severe TBI (n = 68)	1-month RCT	Zinc supplement vs standard zinc therapy	Improved neurological and visceral protein recovery in zinc supplement group
Razmkon et al, 2011[16]	Severe TBI (n = 100)	6-month RCT	Low-dose vitamin C, high-dose vitamin C, vitamin E, or placebo	Improved edema in high-dose vitamin C group; improved mortality and functional outcome in vitamin E group
Aminmansour et al, 2012[18]	Severe TBI (n = 60)	3-month RCT	Progesterone, vitamin D plus progesterone, or placebo	More favorable recovery in vitamin D plus progesterone group vs progesterone and placebo groups
Dhandapani et al, 2008[20]	Severe TBI (n = 60)	3-month RCT	Magnesium plus standard management vs standard management	Greater improvement in functional outcome and intraoperative brain swelling, and lower mortality in magnesium group
Temkin et al, 2007[21]	Moderate to severe TBI (n = 499)	6-month RCT	Magnesium vs placebo	No improvement in outcome and higher mortality compared with placebo
Aquilani et al, 2005[24]	Severe TBI (n = 40)	15-day RCT	BCAA vs placebo	Greater improvement on DRS in BCAA group; improved tyrosine concentration in BCAA group
Aquilani et al, 2008[25]	Severe TBI (n = 41)	15-day RCT	BCAA vs placebo	Improved DRS in BCAA group only
Tan et al, 2011[28]	Severe TBI (n = 52)	21-day RCT	Probiotics vs placebo	Shorter duration in ICU stay and less nosocomial infections in probiotic group
Falcão de Arruda et al, 2004[29]	Moderate to severe TBI (n = 20)	Up to 2-week RCT	Probiotics plus glutamine in standard enteral formula vs standard enteral formula	Shorter duration in ICU stay, less nosocomial infections, and less mechanical ventilation in treatment group
Hoffer et al, 2013[31]	Mild TBI (n = 81)	1-week RCT	NAC vs placebo	Greater symptom resolution and improvement on neuropsychological measures in the NAC group
Theadom et al, 2013[33]	Mild TBI (n = 60)	16-week, phase II RCT	Enzogenol vs placebo	Greater improvement in frequency of self-reported cognitive failures in Enzogenol group
Zafonte et al, 2012[39]	Complicated mild, moderate, and severe TBI (n = 1,213)	90-day, phase III RCT	Citicoline vs placebo	No difference between groups in functional or cognitive status
Levin et al, 1986[41]	Moderate to severe TBI (n = 16)	28-day RCT	Physostigmine plus lecithin vs placebo	Greater improvement in sustained attention in physostigmine plus lecithin group
Chen et al, 2013[45]	Mild TBI (n = 32)	12-week RCT	Cerebrolysin vs placebo	Greater improvement on measures of cognitive function in the Cerebrolysin group

BCAA: branched-chain amino acid; DRS: Disability Rating Scale; NAC: *N*-acetylcysteine; RCT: randomized controlled trial; TBI: traumatic brain injury

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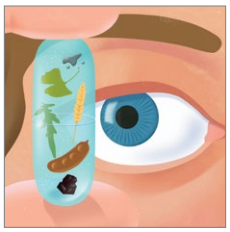

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early enteral nutrition supplemented with *Lactobacillus johnsonii* and glutamine, 30 g, vs a standard enteral nutrition formula. The treatment group experienced fewer nosocomial infections (50% vs 100%, $P = .03$), shorter ICU stays (10 vs 22 days, $P < .01$), and fewer days on mechanical ventilation (7 vs 14, $P = .04$). Despite these studies, evidence for the use of glutamine in patients with TBI is scarce and inconclusive.

***N*-acetylcysteine** (NAC) comes from the amino acid L-cysteine. NAC is an effective scavenger of free radicals and improves cerebral microcirculatory blood flow and tissue oxygenation.[30] A randomized, double-blind, placebo-controlled study of oral NAC supplementation in 81 active duty service members with mild TBI found NAC had a significant effect on outcomes.[31] Oral NAC supplementation led to improved neuropsychological test results, number of mild TBI symptoms, complete symptom resolution by day 7 of treatment compared with placebo, and NAC was well tolerated. Lack of replication studies and generalizability of findings to civilian, moderate, or chronic TBI populations are key limitations of this study.

Proposed mechanisms for the neuroprotective benefit of NAC include its antioxidant and inflammatory activation of cysteine/glutamate exchange, metabotropic glutamate receptor modulation, and glutathione synthesis.[32] NAC has poor blood–brain permeability, but the vascular disruption seen in acute TBI might facilitate its delivery to affected neural sites.[31] As such, the benefits of NAC in subacute or chronic TBI are questionable.

Clinical Point

Enzogenol has antioxidant and anti-inflammatory properties that may counter oxidative damage and neuroinflammation

Neuropsychiatric outcomes of nutraceuticals

Enzogenol. This flavonoid-rich extract from the bark of the Monterey pine tree (*Pinus radiata*), known by the trade name Enzogenol, reportedly has antioxidant and anti-inflammatory properties that may counter oxidative damage and neuroinflammation following TBI. A phase II trial randomized participants to Enzogenol, 1,000 mg/d, or placebo for 6 weeks, then all participants received Enzogenol for 6 weeks followed by placebo for 4 weeks.[33] Enzogenol was well tolerated with few side effects.

Compared with placebo, participants receiving Enzogenol showed no significant change in mood, as measured by the Hospital Anxiety and Depression Scale, and greater improvement in overall cognition as assessed by the Cognitive Failures Questionnaire. However, measures of working memory (digit span, arithmetic, and letter–number sequencing subtests of the Wechsler Adult Intelligence Scale) and episodic memory (California Verbal Learning Test) showed no benefit from Enzogenol.

Citicoline (CDP-choline) is an endogenous compound widely available as a nutraceutical that has been approved for TBI therapy in 59 countries.[34] Animal studies indicate that it could possess neuroprotective properties. Proposed mechanisms for such effects have included stabilizing cell membranes, reducing inflammation, reducing the presence of free radicals, or stimulating production of acetylcholine.[35,36] A study in rats found that CDP-choline was associated with increased levels of acetylcholine in the hippocampus and neocortex, which may help reduce neurobehavioral deficits.[37]

A study of 14 adults with mild to moderate closed head injury[38] found that patients who received CDP-choline showed a greater reduction in post-concussion symptoms and improvement in recognition memory than controls who received placebo. However, the Citicoline Brain Injury Treatment Trial, a large randomized trial of 1,213 adults with complicated mild, moderate, or severe TBI, reported that CDP-choline did not improve functional and cognitive status.[39]

Physostigmine and lecithin. The cholinergic system is a key modulatory neurotransmitter system of the brain that mediates conscious awareness, attention, learning, and working memory.[40] A double-blind, placebo-controlled study of 16 patients with moderate to severe closed head injury provided inconsistent evidence for the efficacy of physostigmine and lecithin in the treatment of memory and attention disturbances.[41] The results showed no differences between the

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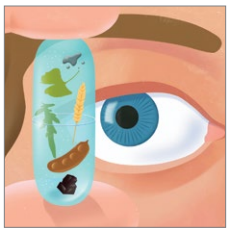

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physostigmine–lecithin combination vs lecithin alone, although sustained attention on the Continuous Performance Test was more efficient with physostigmine than placebo when the drug condition occurred first in the crossover design. The lack of encouraging data and concerns about its cardiovascular and proconvulsant properties in patients with TBI may explain the dearth of studies with physostigmine.

Cerebrolysin. A peptide preparation produced from purified pig brain proteins, known by the trade name Cerebrolysin, is popular in Asia and Europe for its nootropic properties. Cerebrolysin may activate cerebral mechanisms related to attention and memory processes,[42] and some data have shown efficacy in improving cognitive symptoms and daily activities in patients with Alzheimer's disease[43] and TBI.[44]

A blinded 12-week study of 32 participants with acute mild TBI reported that those randomized to Cerebrolysin showed improvement in cognitive functioning vs the placebo group.[45] The authors concluded that Cerebrolysin provides an advantage for patients with mild TBI and brain contusion if treatment starts within 24 hours of mild TBI onset. Cerebrolysin was well tolerated. Major limitations of this study were small sample size, lack of information regarding comorbid neuropsychiatric conditions and treatments, and short treatment duration.

A recent Cochrane review of 6 RCTs with 1,501 participants found no clinical benefit of Cerebrolysin for treating acute ischemic stroke, and found moderate-quality evidence of an increase with non-fatal serious adverse events but not in total serious adverse events.[46] We do not recommend Cerebrolysin use in patients with TBI at this time until additional efficacy and safety data are available.

Clinical Point

The authors do not recommend Cerebrolysin use in patients with TBI until additional efficacy and safety data are available

Nutraceuticals used in other populations

Other nutraceuticals with preclinical evidence of possible benefit in TBI but lacking evidence from human clinical trials include omega-3 fatty acids,[47] curcumin,[48] and resveratrol,[49] providing further proof that results from experimental studies do not necessarily extend to clinical trials.[50]

Studies of nutraceuticals in other neurological and psychiatric populations have yielded some promising results. Significant interest has focused on the association between vitamin D deficiency, dementia, and neurodegenerative conditions such as Alzheimer's disease, multiple sclerosis, and Parkinson's disease.[51] The role of vitamin D in regulation of calcium-mediated neuronal excitotoxicity and oxidative stress and in the induction of synaptic structural proteins, neurotrophic factors, and deficient neurotransmitters makes it an attractive candidate as a neuroprotective agent.[52]

RCTs of nutraceuticals also have reported positive findings for a variety of mood and anxiety disorders, such as St. John's wort, S-adenosylmethionine, omega-3 fatty acids for major depression[53] and bipolar depression,[54] and kava for generalized anxiety disorder.[55] More research, however, is needed in these areas.

The use of nonpharmacologic agents in TBI often relies on similar neuropsychiatric symptom profiles of idiopathic psychiatric disorders. Attention-deficit/hyperactivity disorder (ADHD) closely resembles TBI, but systemic reviews of studies of zinc, magnesium, and polyunsaturated fatty acids supplementation in ADHD provide no evidence of therapeutic benefit.[56-58]

Educate patients in role of nutraceuticals

Despite lack of FDA oversight and limited empirical support, nutraceuticals continue to be widely marketed and used for their putative health benefits[59] and have gained increased attention among clinicians.[60] Because nutritional deficiency may make the brain less able than other organs to recover from injury,[61] supplementation is an option, especially in individuals who could be at greater risk of TBI (eg, athletes and military personnel).

Lacking robust scientific evidence to support the use of nutraceuticals either for enhancing TBI recovery or treating neuropsychiatric disturbances, clinicians must educate patients that these agents are not

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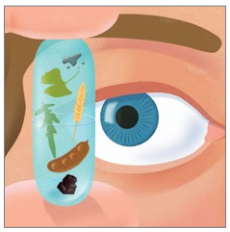

Nutraceuticals for TBI

Related Resources

- National Center for Complementary and Integrative Health. https://nccih.nih.gov.
- National Institutes of Health Office of Dietary Supplements. https://ods.od.nih.gov.

completely benign and can have significant side effects and drug interactions.[62,63] Nutraceuticals may contain multiple ingredients, some of which can be toxic, particularly at higher doses. Many patients may not volunteer information about their nutraceutical use to their health care providers,[64] so we must ask them about that and inform them of the potential for adverse events and drug interactions.

Clinical Point

Use of non-pharmacologic agents in TBI often relies on similar profiles of idiopathic psychiatric disorders, such as ADHD

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Bottom Line

Because evidence regarding the safety and efficacy of nutraceuticals is lacking, health care providers have difficulty drawing clear conclusions about their potential risks and benefits. Additional research evidence, particularly from randomized controlled trials, is needed to better inform medical decision-making for individuals with traumatic brain injury (TBI). Physicians must always monitor patients with TBI who are taking nutraceuticals for side effects and possible drug–drug interactions and use their judgment to determine if these agents really are making a difference.

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Clinical Point

Educate patients that nutraceuticals are not completely benign and can have significant adverse effects and drug interactions