REFERENCE SECTION

Drug–Complementary Medicine Interactions PART 6

How do herbs, nutrients and food supplements interact with antidepressants, anticonvulsants, sedatives and CNS agents? **Lesley Braun** and **Prof Marc Cohen** provide clinical guidance from their updated publication.

Assumptions made when collating the information for this chart

- The clinical significance of many interactions is still unknown as controlled trials are lacking in most cases. In these instances, interactions are based on evidence of pharmacological activity and case reports and have a sound theoretical basis, although remain to be tested.
- All information refers to oral dose forms unless otherwise specified.
- Information is correct at time of writing, however new research in the area is constantly being published.
- The interaction table is provided as a guide only and should not replace the use of professional judgement. It has been developed to assist clinicians when advising patients.
- Information listed here is limited to 120 monographs in *Herbs & Natural Supplements – An Evidence-Based Guide* (© 2nd edn Elsevier, 2006).

Using this guide in practice

- Commonly used prescription and OTC medications are organised by therapeutic class and subclass and are listed alphabetically. Herbal and natural medicines are also listed alphabetically.
- Common names have been used when referring to herbs.
- Refer back to original monograph in *Herbs & Natural Supplements – An Evidence-Based Guide* (© 2nd edn Elsevier, 2006) for more information about a particular substance.

Avoid	There may be insufficient information available to be able to advise using the two substances safely together, so avoid until more is known. The drug may have a narrow therapeutic index (NTI) and there is sufficient evidence to suggest the interaction may be clinically significant. Consider an alternative treatment that is unlikely to produce an undesirable interaction.
Avoid long-term use unless under medical supervision	Harmful effects of potential interaction can be avoided if doses are altered appropriately under medical supervision. Some of these interactions can be manipulated to the advantage of the patient. Changes to dose and regimen may be required for safe combined use.
Caution	The possibility exists of an interaction that may change effects clinically; be aware and monitor. It is prudent to tell patients to be aware and seek advice if they are concerned.
Observe	Interaction may not be clinically significant at the usual recommended doses and theoretical, however the clinician should be alert to the possibility of an interaction.
Beneficial interaction possible	Prescribing the interacting substance may improve clinical outcomes, e.g. reducing drug requirements, complementing drug effects, reducing drug side-effects, counteracting nutritional deficiencies caused by drugs, alleviating drug-withdrawal symptoms, enhancing patient well-being.

Drug	CM	Potential outcome	Recommendation	Evidence/Comments
CENTRAL NERVOUS SYSTEM				
Anticonvulsants				
Anticonvulsants	Carnitine	Reduced side-effects	Beneficial interaction possible	L–carnitine deficiency may cause or potentiate valproic acid toxicity, and supplementation is known to reduce the toxicity of valproate as well as symptoms of fatigue — concurrent use is recommended, as a beneficial interaction is possible
	Folate	Reduced side-effects	Monitor for drug effectiveness Beneficial interaction possible	Requires close supervision to ensure that drug efficacy is not substantially reduced
	Ginkgo	Reduced drug effects	Observe	Based on case reports

Drug	CM	Potential outcome	Recommendation	Evidence/Comments
Anticonvulsants	St John's wort	Reduced drug effects	Avoid unless under medical supervision to alter doses appropriately. When St John's wort is started or ceased, monitor serum levels and alter drug dosage as required	St John's wort may increase drug metabolism, resulting in reduced drug efficacy
Carbamazepine (e.g. Tegretol) NTI: signs of overdose include CNS and respiratory depression, hypotension, vomiting, fluid retention	Milk thistle	Increased drug effects	Caution—monitor drug requirements	May reduce metabolism of drug, resulting in increased serum levels and adverse effects (difficult to evaluate evidence)
	Vitamin B12	Decreased B12 levels	Observe for signs and symptoms of B12 deficiency. Beneficial interaction possible	In studies with children, long-term carbamazepine use led to a decrease in vitamin B12 levels. Increased intake may be required with long-term therapy
Phenobarbitone	Celery	Prolonged action	Caution	Celery juice has been found to prolong the action of phenobarbitone in rats—clinical significance unknown
	Kava kava	Increased sedation	Caution	
	Withania	Increased sedation	Observe although beneficial interaction possible	
Phenobarbitone and phenytoin	Kava kava	Increased sedation	Caution	
	St John's wort	Decreased drug effects (increased drug metabolism)	Avoid—monitor drug requirements. When St John's wort is started or ceased, monitor serum levels and alter drug dosage as required	
	Vitamin B12	Increased serum B12 levels	Observe	One clinical study reported that combined long-term use of phenobarbital and phenytoin resulted in significantly increased serum B12 levels— clinical significance unknown
Phenytoin	Vitamin B6	Reduced drug effects	Caution—monitor for reduced drug effectiveness	B6 in high doses may lower plasma levels and efficacy of drug and decrease seizure control
Phenytoin and valproate	Vitamin D	Reduced drug effects	Beneficial interaction possible	Anticonvulsants induce catabolism of vitamin D through liver induction—prolonged use is associated with increased risk of developing rickets and osteomalacia, therefore increased intake may be useful with long-term therapy
Antidepressants				
Antidepressants including SSRIs, SNRIs, tricyclics and MAOIs	Albizia	Additive effects	Observe	Increased risk of serotonergic syndrome is theoretically possible, as the herb increases serotonin levels, according to *in-vivo* studies — clinical significance unknown
	Ginkgo	Reduced side-effects	Beneficial interaction possible	Reduced sexual dysfunction side-effects reported in a clinical study and may also improve sleep continuity
	St John's wort	Additive effects	Avoid unless under medical supervision	Risk of serotonergic syndrome if combined use is not carefully monitored
	SAMe	Additive effects	Caution	Theoretically may increase risk of serotonergic syndrome, and a case report exists; however, an experimental study found that brain SAMe levels were significantly reduced after chronic treatment with imipramine

Drug	CM	Potential outcome	Recommendation	Evidence/Comments
Antidepressants	Tyrosine	Additive effects	Avoid unless under medical supervision	Tyrosine is a precursor for several neurotransmitters, which theoretically increases risk of serotinin syndrome
MAOIs	Tyrosine	Increased side-effects	Avoid	Some tyrosine may be metabolised to tyramine Concurrent use with MAOIs may lead to hypertensive crisis
Tricyclic antidepressants	Andrographis	Reduced side-effects	Beneficial interaction possible	Andrographis may exert hepatoprotective activity against liver damage induced by tricyclic antidepressants
	Coenzyme Q10	Reduced CoQ10 serum levels	Beneficial interaction possible	Increased CoQ10 intake may be required with long-term therapy
	St John's wort	Additive effects	Avoid unless under medical supervision	Although St John's wort decreases drug plasma levels of tricyclic antidepressants, it may increase available serotonin
	Milk thistle	Reduced side-effects	Beneficial interaction possible	Milk thistle may exert hepatoprotective activity against liver damage induced by tricyclic antidepressants
	Vitamin B2 (riboflavin)	Decreased B2 levels	Monitor for signs and symptoms of B2 deficiency. Beneficial interaction possible	Tricyclic antidepressants may reduce the absorption of riboflavin. Increased B2 intake may be required with long-term therapy
Imipramine	Vitamin B3 (niacin)	Additive effects	Beneficial interaction possible	A combination of imipramine with L–tryptophan 6 g/day and niacinamide 1500 mg/day has been shown to be more effective for people with bipolar disorder than imipramine alone
Antipsychotic agents				
Haloperidol (e.g. Serenace)	Ginkgo	Increased drug effects and reduced side-effects	Observe— beneficial interaction possible under professional supervision	Three clinical trials demonstrate that ginkgo increases drug effectiveness
	Iron	Reduced iron effect	Monitor iron status	May cause decreased blood levels of iron — clinical significance unclear. Increased iron intake may be required with long-term therapy
	Quercetin	Reduced drug side-effects	Beneficial interaction possible	According to *in-vitro* studies, reduced chewing movements and tongue protrusions possible with concurrent use
Phenothiazines (e.g. chlorpromazine, trifluoperazine)	Evening primrose oil	Reduced drug effects	Avoid concomitant use until safety can be established	Several case reports suggest that evening primrose oil may reduce seizure threshold and reduce drug effectiveness in patients with schizophrenia treated with phenothiazines
Chlorpromazine (e.g. Largactil)	Vitamin E	Reduced drug effects	Observe	According to *in-vitro* research, vitamin E inhibits drug uptake in human cultured fibroblasts— clinical significance unknown
CNS agents				
Cholinergic drugs Tacrine (e.g. Cognex)	Brahmi	Additive effects	Observe Beneficial interaction possible	Cholinergic activity has been identified for brahmi, so increased drug activity is theoretically possible
	Ginkgo	Additive effects	Observe Beneficial interaction possible	Cholinergic activity has been identified for ginkgo, so increased drug activity is theoretically possible
	Lemon balm	Additive effects	Observe Beneficial interaction possible	Cholinergic activity has been identified for lemon balm, so increased drug activity is theoretically possible
	Milk thistle	Reduced side-effects	Observe Beneficial interaction possible	Milk thistle may exert hepatoprotective activity against liver damage induced by tacrine
CNS stimulants	Guarana	Additive effects	Caution	Herb has demonstrated CNS-stimulant activity
	Tyrosine	Additive effects	Caution	Tyrosine is a precursor for several neurotransmitters (theoretical concern)

Drug	CM	Potential outcome	Recommendation	Evidence/Comments
Movement disorders				
L–dopa (levodopa)	Calcium	Reduced drug absorption	Separate doses by 2 hours	L–dopa can form an insoluble complex with calcium
	Iron	Reduced drug absorption	Separate doses by 2 hours	L–dopa can form an insoluble complex with calcium
	Kava kava	Reduced drug effects	Avoid unless under medical supervision	Theoretical interaction, as dopamine antagonist effects have been reported for kava kava
	Magnesium	Reduced drug absorption	Separate doses by 2 hours	L–dopa can form an insoluble complex with magnesium
	Tyrosine	Decreased drug and tyrosine effect	Avoid unless under medical supervision	L–dopa competes with tyrosine for uptake, so concurrent use may decrease uptake of both substances, thereby reducing efficacy
	Vitamin B6 pyridoxine)	Reduced drug effects	Observe Monitor for reduced drug effectiveness	Interaction does not occur with combination L-dopa products
	Vitamin C	Reduced side-effects	Beneficial interaction possible	A case report of co-administration with vitamin C suggests this may reduce drug side-effects
	Zinc	Reduced drug absorption	Separate doses by 2 hours	L–dopa can form an insoluble complex with zinc
L–dopa with carbidopa	Iron	Reduced drug effects	Separate doses by at least 2 hours	May reduce bioavailability of carbidopa and L-dopa
Sedatives, hypnotics				
CNS sedatives	Guarana	Reduced drug effects	Observe	Theoretically guarana may reduce the sedative effects of drug via its CNS stimulation effects; however, an *in-vivo* study found no interaction with pentobarbital
	Hops	Additive effects	Caution	
	Kava kava	Additive effects	Caution Beneficial interaction possible under medical supervision	May be useful in benzodiazepine withdrawal
	Lavender oil	Additive effects	Observe	
	Passionflower	Additive effects	Caution Beneficial interaction possible under medical supervision	May be useful in benzodiazepine withdrawal
	Valerian	Additive effects	Caution Beneficial interaction possible under medical supervision	May be useful in benzodiazepine withdrawal
Midazolam (e.g. Hypnovel)	St John's wort	Reduced drug effects	Caution Monitor for signs of reduced drug effectiveness and adjust the dose if necessary	St John's wort may increase drug metabolism and so reduce serum levels of drug
Barbiturates	Albizia	Additive effects	Caution Beneficial interaction possible under medical supervision	Potentiation of phenobarbitone-induced sleeping was observed in vivo—clinical significance unknown
	Andrographis	Additive effects	Observe Beneficial interaction possible under medical supervision	Potentiation effects observed in vivo— clinical significance unknown
	Folate	Reduced drug effects	Caution Monitor for signs of reduced drug effectiveness	Concomitant folic acid use can reduce seizure control
	Kava kava	Additive effects	Caution Beneficial interaction possible under medical supervision—monitor drug dosage	Increased sedation

Drug	CM	Potential outcome	Recommendation	Evidence/Comments
Barbituates	Lemon balm	Additive effects	Observe Beneficial interaction possible under medical supervision	Increased sedation
	Passionflower	Additive effects	Caution Beneficial interaction possible under medical supervision—monitor drug dosage	Increased sedation
	St John's wort	Reduced drug effects	Avoid—monitor drug requirements. When St John's wort is started or ceased, monitor serum levels and alter drug dosage as required	St John's wort induces CYP enzymes and P-glycoprotein, so can reduce drug serum levels
	Valerian	Additive effects	Caution Beneficial interaction possible under medical supervision	Increased sedation
	Vitamin B6	Reduced plasma levels and drug effects	Caution Monitor for drug effectiveness	Concomitant B6 use can reduce seizure control
	Withania	Additive effects	Observe Beneficial interaction possible under medical	Theoretically may increase sedation
Benzodiazepines	Chamomile	Additive effects	Observe Beneficial interaction possible under medical	Theoretically an additive effect can occur with concurrent use
	Kava kava	Additive effects	Caution Beneficial interaction possible under medical supervision—monitor drug dosage	Combination has been used to ease symptoms of benzodiazepine withdrawal under medical supervision
	Passionflower	Additive effects	Caution Beneficial interaction possible under medical supervision—monitor drug dosage	Increased sedation
	Valerian	Additive effects	Observe Beneficial interaction possible under medical supervision	Combination has been used to ease symptoms of benzodiazepine withdrawal under medical supervision
	Withania	Additive effects	Observe Beneficial interaction possible under medical supervision	