Graylands Hospital
Drug Bulletin

Complementary Medications in Psychiatry

North Metropolitan Area Health Service - Mental Health August 2010 Vol 17 No.1 ISSN 1323-1251

Introduction

Complementary medicines include herbal remedies, food supplements, vitamin preparations and other organic and inorganic substances.[1] The use of complementary medicines among individuals with a mental illness has been increasing, yet there is still limited evidence for their benefits.[2]

Complementary medicines are used either as an alternative treatment or in addition to conventional medicine.[1] They have been gaining popularity over recent years as patients can choose their own treatment,[3] and many of the treatments have a favourable side effect profile.[4] These medications are often readily available negating the need for consulting a health professional before purchase, yet these therapies could be a source of drug interactions and adverse effects.[5]

This bulletin looks at some of the complementary medicines used in psychiatry and the evidence supporting their use.

St John's Wort

St John's Wort (SJW), or *Hypericum perforatum*, has been widely studied in the treatment of depression.[6] Studies suggest that SJW works by inhibiting the reuptake of serotonin, dopamine and noradrenaline and activating gamma-amino-butyrate and glutamate receptors.[6]

Studies have found SJW to be superior to placebo in the treatment of mild to moderate depression,[6, 7] but there are conflicting results for its efficacy in major or severe depression.[6] SJW has also shown to be as effective as some standard antidepressants, including amitriptyline and fluoxetine.[6, 7]

In clinical trials SJW was generally well tolerated.[6] The most common adverse effects include gastrointestinal upset, increased anxiety and photosensitivity.[6]

The use of SJW is limited however, due to a number of significant drug interactions, some of which are listed in Table 1. SJW contributes to serotonin toxicity, especially when taken in conjunction with other serotonergic agents.[6, 8] When these medications are combined, there is an increased risk the patient will develop serotonin syndrome. SJW should also be used with caution in bipolar disorder as it may induce mania.

SJW induces the enzyme cytochrome P450 3A4, which can reduce the effectiveness of other pharmaceutical agents metabolised by this enzyme. Examples of medications affected include the combined oral contraceptive pill, digoxin and simvastatin.[6]

SJW can be an effective treatment for mild to moderate depression if taken according to the recommended doses. It is not recommended for major depression due to inconsistent evidence in clinical trials.[6] It is generally well tolerated, however clinically significant drug interactions may limit its use.

Omega-3 (Fish Oil)

Fish oils contain the omega-3 polyunsaturated fatty acids eicosapentanoic acid (EPA) and docosahexanoic acid (DHA).[5] These compounds are thought to be involved in maintaining neuronal membrane structure, the modulation of membrane proteins and in the production of prostaglandins and leukotrienes.[5]

Psychosis

The evidence supporting the use of omega-3 fatty acids in the treatment of psychosis is growing, though evidence remains inconclusive. A Cochrane review in 2005 assessed 5 randomised controlled trials including 313 patients.[9] One study found fish oils to have some antipsychotic effect compared with placebo, and in another trial those on the combination of antipsychotic and fish oil had a greater improvement in mental state compared to those on antipsychotic plus placebo.[9]

Peet and colleagues found EPA to be significantly more effective than DHA and placebo in a randomised controlled trial.[10] In a second placebo-controlled trial, EPA was more effective than placebo, though the use of an antipsychotic was still permitted if clinically imperative.[10]

Table 1: Drugs that interact with St John's Wort [6, 8]

Medication	Effects of interaction with St John's Wort
Combined oral contraceptive pill	Increased metabolism and reduced efficacy of oral contraceptive. Avoid combination; use barrier methods for contraception
Digoxin	Reduced digoxin concentration and clinical effect
Atorvastatin, simvastatin	Reduced concentration of statin
Warfarin	Increased metabolism of warfarin decreasing its anticoagulant effect.
Methadone	Reduced concentration and activity of methadone
Omeprazole	Increased metabolism and decreased concentration of omeprazole. Avoid combination or monitor clinical effect and increase omeprazole dose if necessary
Serotonergic drugs, e.g. selective serotonin reuptake inhibitors, tricyclic antidepressants, lithium, tramadol	Increased risk of serotonin toxicity

Prevention of psychosis

A recent study by Amminger et al focussed on the use of omega-3 fatty acids as preventative for psychotic disorders in young people at ultra-high risk of psychosis.[11] This trial looked at whether a first episode of psychotic disorder could be prevented by taking fish oil and whether reduced psychiatric symptoms and improved functioning would result in individuals with subthreshold manifestations of psychosis.[11]

A 12-week intervention phase, where patients were given 700mg of EPA, 480mg of DHA and 7.5mg of vitamin E, reduced the transition rate to psychosis and led to significant symptomatic and functional improvements during the 12-month follow-up period.[11]

This trial supported the use of omega-3 fatty acids for the prevention of psychosis, but further investigations are required as this was the first trial involving omega-3 fatty acids in a preventive role.[11]

Depression

Omega-3 fatty acids may play a role in the prevention and treatment of mood disorders, particularly depressive disorders, though more information and studies are needed.[12]

The studies of omega-3 in major depressive disorder that demonstrated a positive antidepressant effect for omega-3 compared to placebo used either EPA, or EPA and DHA with EPA in a higher dose.[12] Some studies showed no benefit compared to placebo.[12] Due to the heterogeneous nature of the trials, more research is needed before omega-3 fatty acids can be recommended in the treatment of depression.[12]

Omega-3 fatty acids have also been evaluated for the treatment of bipolar depression.[12] Two out of the three trials found a benefit for omega-3 compared to placebo, but study designs were variable and more research is required.[12]

Fish oil supplements are generally well tolerated, with gastrointestinal effects such as diarrhoea the most commonly experienced adverse effect. Along with the possible benefits to mental health, fish oil also benefits an individual's general health.[13] This is relevant to individuals with mental health disorders due to the high rates of co-morbid cardiovascular disease.[12]

Evening Primrose Oil

There are various placebo-controlled and open trials focussing on the efficacy of evening primrose oil in schizophrenia.[14] The trials have generally been small with mixed results and no clear benefit has been shown.[14]

Vitamin E

Vitamin E has been used in psychiatry to treat tardive dyskinesia that has resulted from antipsychotic use.[1, 5] There have been numerous studies looking at the efficacy of vitamin E, but it

is yet to be conclusively established whether it improves tardive dyskinesia.[5] However, in a small number of trials, patients not on vitamin E supplementation showed more deterioration of their symptoms of tardive dyskinesia compared to those taking vitamin E.[15] The dose range used in trials range from 400-1600 IU daily.[5]

The use of vitamin E is based on the assumption that tardive dyskinesia not only results from dopamine receptor supersensitivity, but that it is also related to the oxidative tissue damage of antipsychotic drugs.[1]

Ginkgo Biloba

There are two trials that indicate ginkgo biloba may improve the efficacy of haloperidol when used in combination in patients with treatment-resistant schizophrenia.[16, 17] It is hypothesized that the efficacy is due to the antioxidant action of ginkgo biloba and free radical scavenging may be helpful in alleviating symptoms of schizophrenia.[17] It is not expected that this combination will give rise to additional adverse effects.[5]

More clinical trials are needed to determine any long-term benefits of using ginkgo biloba in patients with schizophrenia.[17] Studies looking at combinations with other, newer antipsychotics, would also be beneficial due to their favourable side effect profiles.[17]

Valerian

Extracts of the roots of valerian, *Valeriana officinalis*, are used for inducing sleep and improving sleep quality.[18] It is generally well tolerated and no serious adverse effects have been reported.[19] Adverse effects that have been reported with valerian include a morning "hang-over" effect, drowsiness, diarrhoea, nausea and irritability.[19] Valerian tends to produce fewer adverse effects than benzodiazepines.[19]

Several studies have reported improved sleep from taking valerian, however the clinical efficacy of this preparation has not been supported in randomised clinical trials.[19] Although sleep outcomes did improve in some studies, placebo-effects in many of these trials cannot be ruled out.[19] No standard dose was used and the studies varied in regards to the sample size, reporting and methodology.[18]

Valerian may be useful in the treatment of mild sleep disturbance, but current evidence does not support its use.[19] Further research is needed to determine which products might be efficacious and at what recommended doses.[19]

SAMe

S-adenosylmethionine (SAMe) is derived from the essential amino acid L-methionine and has been used for the treatment of depression.[20] Vitamin B12 and folate are also required in the SAMe synthesis pathway, and deficiencies in these have also been associated with depression.[20]

The mechanism of antidepressant effect of SAMe is still uncertain.[20] While oral and parenteral SAMe appear to be effective in the treatment of depression, further studies focusing on independent and adjunctive therapy are required.[20] Current results are based on a small number of short term trials, which makes translation into the clinical setting difficult.[20]

Folate

There are reports that low levels of folate could cause a decreased response to antidepressants in some patients.[21] These reports recommend that clinicians consider a possible folate deficiency when evaluating patients with depression who do not respond to antidepressant treatment.[21]

The exact dose of folic acid supplementation is unknown, however it is suggested that folic acid 0.5-5mg per day may be suitable.[21]

Interactions of Complementary Medicines

With the increasing use of complementary medicines in the community, there is also an increased risk of interactions between these, prescription medicines and over-the-counter medicines a patient is taking.[22] Although many complementary medicine-drug interactions may be minor or theoretical, some are also serious and can be life-threatening.[23]

Complementary medicine-drug interactions also appear to be grossly under-reported, possibly due to the perception complementary medicines are 'safe' and are not actually drugs.[23] Although many complementary medicines have good safety profiles, these supplements are intended to be taken over an extended period which provides the opportunity for enzyme induction and other mechanisms of interaction to take effect.[23]

There is still very limited published information on complementary medicine-drug interactions despite the use of these medicines progressively growing world-wide.[24]

Table 2 lists some interactions that may be experienced with psychotropic medicines.

Table 2: Complementary Drug Interactions [8, 14, 16, 19, 23, 24]

Complimentary medicine	*Interacting Drugs*	*Effect*
Ginseng	Phenelzine	Possible manic symptoms
	Hypoglycaemics	May reduce blood glucose level
	Lithium, clomipramine	Manic episode (one case report for each)
Gingko biloba	Sodium valproate	Loss of seizure control
	Haloperidol	May enhance efficacy of haloperidol and reduce side effects
	Aspirin, Warfarin	Increased risk of bleeding
Green tea (caffeine)	Lithium	Abrupt caffeine withdrawal can increase serum lithium levels
Grapefruit	Significantly affected: buspirone, carbamazepine, diazepam, midazolam, triazolam, methadone Minor effect: alprazolam, clonazepam, clomipramine, haloperidol, sertraline, zolpidem,	Inhibits CYP 3A4 in the small intestine wall, resulting in increased bioavailability and plasma concentrations of some medications
Valerian	Benzodiazepines, central nervous system (CNS) depressants, alcohol	Increased CNS depression Valerian may also relieve the anxiogenic effects of diazepam withdrawal, which may prove a useful therapeutic effect
Fish oil, evening primrose oil	Orlistat (Xenical®)	Theoretical risk orlistat may reduce absorption of fish oil and evening primrose oil
Evening primrose oil	Phenothiazine antipsychotics (e.g. chlorpromazine, trifluoperazine)	Small number of case reports outlining increased risk of seizures. Monitor for risk of seizures if combination is used. Gamolenic acid in evening primrose oil reportedly lowers the seizure threshold.
Kava	Benzodiazepines, CNS depressants	Increased CNS depression, avoid combination
Kelp	Thyroxine	Increased risk of hyperthyroidism as kelp preparations contain iodine

Conclusion

The evidence base for the use of complementary medicines to treat mental illness is growing, but is currently still limited.[1] The best evidence available is for SJW, though trials with improved definition of inclusion criteria are still required.[1] Well-controlled studies comparing complementary and conventional medicines are lacking and therefore it is premature for psychiatrists to recommend complementary medicines over conventional treatments.[4]

It is important for clinicians to be aware of what complementary medicines patients are taking, their side effects and interactions with other treatments.[1] Patients should be encouraged to disclose information about any complementary medicines they are taking to all healthcare professionals.[1]

Due to the perception that complementary medicines are safe and natural, acceptance and adherence may be higher with these than conventional medicines. This may make it important to be prepared and willing to work in partnership with patients' beliefs and preferences as it may lead to greater adherence with conventional treatment regimens. [1]

This Drug Bulletin was written by Katie Walker and was reviewed by the Graylands Pharmacy Department and Dr Leighton Chadwick

References available on request

Comments are welcome at the email address: DrugInformation.Graylands@health.wa.gov.au