Complementary and alternative medicine for the treatment of major depressive disorder

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Abstract

Objective To review the clinical evidence supporting complementary and alternative medicine interventions for treating major depressive disorder.

Quality of evidence PubMed was searched from January 1966 to February 2010 using the term *depressive disorder* in combination with *St John's wort*, *S-adenosylmethionine* (SAM-e), *exercise, acupuncture, omega-3 fatty acids,* and *folate*. Only relevant human trials were selected.

Main message In a large meta-analysis, St John's wort was found to be equivalent to antidepressant drugs with fewer side effects. Exercise reduced depressive scores in 3 meta-analyses. Omega-3 fatty acids reduced depressive scores in a meta-analysis of 16 trials, but publication bias was identified. Oral SAM-e monotherapy reduced depressive scores in 4 of 5 small randomized controlled trials. Folate deficiency is associated with more severe and refractory depression, and supplementation reduced depressive scores in 2 of 3 randomized controlled trials. Acupuncture demonstrated limited efficacy in 1 meta-analysis and 5 other trials.

Conclusion St John's wort and regular exercise appear effective in the treatment of depression. Acupuncture appears ineffective for depression, but it might offer other health benefits. Other promising therapies include SAM-e, omega-3 fatty acid, and folic acid supplementation in selected patients; further study is warranted.

Résumé

Objectif Passer en revue les données cliniques qui indiquent que les interventions de médecine douce sont utiles pour traiter la dépression majeure.

Qualité des preuves On a consulté PubMed entre janvier 1966 et février 2010 à l'aide des rubriques *depressive disorder* en combinaison avec *St John's wort*, *S-adenosylmethionine (SAM-e)*, *exercise*, *acupuncture*, *omega-3 fatty acids* et *folate*. On a retenu uniquement les essais pertinents effectués chez l'humain.

Principal message Une grande méta-analyse a trouvé que le millepertuis était aussi efficace que les antidépresseurs, avec moins d'effets indésirables. Dans 3 méta-analyses, l'exercice physique a réduit les scores de dépression. Les acides gras oméga-3 ont abaissé les scores de dépression dans une méta-analyse couvrant 16 essais, mais des biais de publication ont été identifiés. En monothérapie orale, la SAM-e a réduit les scores de dépression dans 4 petits essais randomisés sur 5. Une carence en folate est associée à des dépressions plus sévères et réfractaires, et l'ajout de suppléments a réduit les scores de dépression dans 2 essais randomisés sur 3. Une efficacité limitée de l'acupuncture a été observée dans une méta-analyse et dans 5 autres essais.

KEY POINTS Regular exercise should be recommended for all patients. There is good evidence that St John's wort is effective as monotherapy, but potential herb-drug interactions should be considered. Physicians should consider screening for and treating folate deficiency, but the benefits of folate supplementation remain unclear. Limited evidence supports the use of omega-3 fatty acids and S-adenosylmethionine, but further research is required. Acupuncture might offer other health benefits to motivated patients, but it appears to have little effect on depression. It is important to ask all patients with depression about their use of CAM therapies.

POINTS DE REPÈRE DU RÉDACTEUR On devrait recommander l'exercice à tous les patients. Il existe de bonnes preuves que le millepertuis (herbe de la St-Jean) est efficace en monothérapie, mais il faut penser à de possibles interactions herbe-médicament. Le médecin devrait penser à dépister et traiter une éventuelle carence en folate, mais il n'est pas certain que les suppléments de folates sont avantageux. L'utilisation d'acides gras oméga-3 et de S-adénosylméthionine est appuyée par certaines données, mais d'autres études seront nécessaires. L'acupuncture pourrait avoir certains avantages pour la santé, mais elle semble avoir peu d'effet sur la dépression. Il est important de questionner les patients déprimés sur l'usage qu'ils font des thérapies complémentaires ou alternatives.

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Conclusion Le millepertuis et l'exercice régulier semblent efficaces pour traiter la dépression. L'acupuncture semble inefficace, mais elle pourrait avoir d'autres avantages pour la santé. Parmi les autres thérapies prometteuses, mentionnons la SAM-e, les acides gras oméga-3 et les suppléments d'acide folique chez certains patients; d'autres études seront toutefois nécessaires.

Major depressive disorder (MDD) is one of the most prevalent and fastest-growing diseases in North America. New-generation antidepressants appear more effective than older drugs, with response rates of up to 50%,[1] but they do not effectively treat all depressed patients. In addition, clinical trials that use numerical rating scales, such as the Hamilton Rating Scale for Depression (Ham-D), might overestimate real-world clinical benefit. Many drugs have side effects that can affect compliance and morbidity. An additional concern is that the efficacy of antidepressant drugs has been overestimated by industry-led publication bias, as was reported by a systematic review that included unpublished studies.[2]

Patients are increasingly using complementary and alternative medicine (CAM) therapies to treat depression. A recent study found that 40% of adults with depression used CAM therapies, and most did not tell their family physicians.[3] It is increasingly important for family physicians to ask their patients about use of CAM therapies and to possess basic knowledge of commonly used therapies. Here we provide a brief evidence-based overview of 6 commonly used CAM therapies for MDD. The evidence for these therapies is outlined in **Table 1**.

Table 1. Summary of complementary and alternative medicine therapies for MDD

INTERVENTION	BODY OF EVIDENCE
St John's wort	Reduction in Ham-D scores in meta-analysis of 29 RCTs as monotherapy
Folate	Small reduction in Ham-D scores in 2 of 3 RCTs as adjunct therapy; folate deficiency related to refractory and severe MDD; other benefits of treating folate deficiency
SAM-e	Reduction in Ham-D scores in 4 of 5 RCTs as oral monotherapy
Acupuncture	No reduction in Ham-D scores in 1 meta-analysis (30 RCTs) and 5 other RCTs as monotherapy or adjunct therapy
Exercise	Reduction in Ham-D scores in 3 meta-analyses (25, 5, and 12 RCTs) as monotherapy or adjunct therapy; other benefits
Omega-3 fatty acids	Small reduction in Ham-D scores in meta-analysis of 16 RCTs as monotherapy; other benefits

Ham-D—Hamilton Rating Scale for Depression, MDD—major depressive disorder, RCT—randomized controlled trial, SAM-e—S-adenosylmethionine.

Quality of evidence

PubMed was searched from January 1966 to February 2010. The MeSH term *depressive disorder* was used, which includes postpartum and peripartum depression, MDD, dysthymic disorder, and seasonal affective disorder. This was combined with *complementary therapies, diet, dietary supplements, vitamins, minerals,* and *exercise* as a preliminary review to find the most commonly researched therapies. Specific CAM therapies were selected based on this review and on our clinical experience. The therapies *hypericum, omega-3 fatty acids, acupuncture therapy, folate, S-adenosylmethionine,* and *exercise* were then combined with *depressive disorder* to develop a definitive list of studies. Search results and references were screened to identify clinical trials, meta-analyses, and reviews.

Main findings

St John's wort. St John's wort (SJW) is an extract of *Hypericum perforatum,* a yellow-flowering perennial herb found in temperate zones worldwide. Its earliest recorded medicinal use was in ancient Greece, and it has been widely used to treat depression since the 1980s, particularly in Germany. Its exact mechanism of action is unclear, although it inhibits serotonin reuptake and alters levels of dopamine, norepinephrine, γ-aminobutyric acid, and other neurotransmitters.[4]

The safety and efficacy of SJW are well established. A recent meta-analysis found 29 double-blind randomized controlled trials (RCTs) that compared SJW with placebo (n = 3064) and antidepressant drugs (n = 2810) for 4 to 12 weeks using Ham-D scores as the primary outcome measure. Doses of SJW varied widely, but most trials used 500 to 1200 mg daily. St John's wort was more effective than placebo, with a response rate of 1.48 (95% confidence interval [CI] 1.23 to 1.77), and as effective as old- and new-generation antidepressants, with a response rate of 1.01 (95% CI 0.93 to 1.09). Side-effects were much less common with SJW, with dropout odds ratios of 0.24 (95% CI 0.13 to 0.46) compared with tricyclic antidepressants (TCAs) and 0.53 (95% CI 0.34 to 0.83) compared with selective serotonin reuptake inhibitors (SSRIs). Most were high-quality studies, but overall bias was noted in country of origin, number of patients, and baseline depression scores.[5] We only identified 1 study that evaluated the long-term efficacy of SJW. In this uncontrolled prospective trial, 440 patients with mild to moderate depression were given 500 mg/d of a standardized extract of SJW for 52 weeks. Depression scores (Ham-D) decreased and there was a lower side effect rate than was seen with antidepressants.[6]

While long-term controlled studies are needed, short-term use of SJW is as effective as antidepressant drugs,

with fewer side effects. We recommend using extracts that are standardized to contain 0.3% hypericin at a starting dose of 600 mg/d, in 3 divided doses, increasing to 1200 mg/d as needed.

St John's wort should not be combined with SSRIs, TCAs, or monoamine oxidase inhibitors, as this might lead to symptoms of serotonin syndrome. It also induces cytochrome P450 enzymes and intestinal P glycoprotein, which affect the metabolism of hundreds of drugs.[7] This need not be a contraindication for SJW use in most cases, but SJW should be avoided in patients taking certain drugs, such as immunosuppressants, antiretrovirals, and chemotherapeutic agents.[8]

Folate. Folate is required for the synthesis of dopamine, norepinephrine, and serotonin.[9] It is also a key component of the methylation cycle, and deficiency of 1 or more components of this cycle leads to accumulation of homocysteine, which is associated with dementia, Parkinson disease, and cerebrovascular disease. People with folate deficiency are more likely to suffer from depression,[10] are more likely to have more severe and longer lasting relapses,[11] and are 6 times less likely to respond to antidepressant drugs.[9]

Folate has been evaluated as adjunctive therapy in depression in 3 small RCTs. The first involved 53 patients with major depression who were taking lithium. After participants took 0.2 mg/d of folic acid or placebo for 1 year, no significant difference was found in Beck Depression Scale scores between folate and placebo groups.[12] The second trial involved 24 patients with depression and folate deficiency (red blood cell folate level <200 µg/L). They were given 15 mg/d of L-methylfolate or placebo for 6 months in addition to their usual antidepressant medication. A small but significant improvement was noted ($P<.05$).[13] Finally, 127 depressed patients taking stable fluoxetine therapy were given 0.5 mg of folic acid daily for 10 weeks. Participants' Ham-D scores declined by 2.6 (95% CI -0.13 to -5.07) points more in the folate group, a small but statistically significant change ($P<.05$).[14] One study evaluated folate monotherapy, but it involved elderly patients with comorbid mild cognitive impairment.[15]

There is insufficient evidence to recommend folate for the treatment of depression. Because folate deficiency is associated with poorer outcomes in depression, as well as mild cognitive impairment, megaloblastic anemia, and neural tube defects, it might be reasonable to screen and treat depressed patients for folate deficiency. It is important to note that folate supplementation at doses greater than 1 mg/d has been associated with increased risk of colorectal cancer. This issue is complicated by a new area of research: folate is methylated by methyltetrahydrofolate reductase (MTHFR) to produce methyltetrahydrofolate, the active form. Polymorphisms of the MTHFR gene increase the risk of depression[11] and cardiovascular disease. Genetic testing for MTHFR gene polymorphisms is now available; possessing these polymorphisms might increase the need for folate, vitamin B12, and other methylating agents. There is still insufficient evidence to guide clinical decisions in this important area of emerging research.

S-adenosylmethionine. S-adenosylmethionine (SAM-e) is a naturally occurring molecule present in all human cells. Like folate and vitamin B12, SAM-e is involved in the methylation cycle; it acts as a methyl donor to membrane phospholipids, myelin, choline, catecholamines, and other molecules important for brain function,[16] affecting receptor function, membrane fluidity, and neurotransmitter production.[17] Depressed patients have low levels of serum and cerebral spinal fluid SAM-e, and supplementation raises levels of SAM-e, dopamine, and other neurotransmitters in the brain.[18,19] Italian researchers first noted its antidepressant effects in the 1970s.[16]

There is some evidence supporting the benefit of SAM-e in treating depression. A recent systematic review reported benefit in 7 of 7 trials using parenteral SAM-e and in 4 of 5 studies using oral SAM-e at doses of 1600 mg/d.[17] Of the 5 studies using oral SAM-e, it was equivalent to TCAs in 3. One study was large (n=281) and reported a 12.5-point reduction in Ham-D scores in both groups after 6 weeks. Drug-related side effects occurred in 5% of SAM-e patients versus 20% of TCA patients.[20] In the remaining 2 trials, it was superior to placebo in 1. The negative trial involved an unstable formulation of SAM-e that has since been withdrawn, as reported by the authors.[21]

There is some evidence to support the use of SAM-e, but this requires confirmation by larger studies. Side effects are uncommon, but occasionally nausea, gastrointestinal upset, and anxiety can occur. The main drawback of SAM-e is cost—treatment at therapeutic doses costs approximately $80 per month, which is similar to newer antidepressants.

Acupuncture. Acupuncture is a part of traditional Chinese medicine that involves inserting fine needles into specific points to restore proper flow of energy in the body.[22] Modern research has documented several physiologic effects of acupuncture, including the release of neurotransmitters,[23] decreased activation of pain-associated limbic areas,[24] and changes in cerebral spinal fluid biochemistry.[24] Some practitioners use modified techniques, attaching electrodes to needles to deliver a pulsed electrical current (electroacupuncture) or using a low-power laser to stimulate acupoints instead of needles (laser acupuncture).

A recent Cochrane review identified 30 RCTs that evaluated manual acupuncture, electroacupuncture, or

laser acupuncture in 2812 patients with MDD. No consistent benefit was noted with any form of acupuncture when compared with wait-list or sham acupuncture controls. Three RCTs (n=94) comparing acupuncture with SSRI or TCA treatment yielded similarly inconclusive results.[22] One methodologic issue that has plagued acupuncture research is the use of sham acupuncture techniques as a placebo, because experienced practitioners insist that these sham techniques have physiologic effects. Another issue has been the use of different acupuncture points for different patients, which is part of traditional Chinese diagnosis and treatment and is considered a positive attribute of acupuncture. We identified 5 RCTs not included in the Cochrane review, but no consistent benefit was noted in these trials.[24-26]

There is moderate evidence that acupuncture is not effective for treatment of depression, with most trials reporting no better outcomes than experienced by wait-list controls. Interestingly, 3 of 3 trials reported it to be as effective as antidepressant drugs, raising further questions about the efficacy of the latter. Adverse events are uncommon, with an event rate of 0.55 per 10 000 patients. The only serious complication is pneumothorax, which is exceedingly rare in experienced hands. There have also been case reports of infection and transient neuropathy.[27] Acupuncture might be considered in patients who are unwilling or unable to use traditional antidepressants, or as adjunctive therapy. Appropriate care must be taken in finding a suitable acupuncturist.

Exercise. Exercise is known to make people feel good, but precisely how this occurs is not clear. Proposed cognitive mechanisms include diversion from negative thinking, social contact, and feelings of control over one's health. Exercise lowers cortisol, alters neurotransmitter function, and even promotes growth of the hippocampus, a phenomenon also seen after prolonged antidepressant use.[28] Exercise is generally classified as aerobic (eg, running or walking), resistance (eg, weight training), or mindfulness-based (eg, yoga or qigong).

A recent Cochrane review identified 25 RCTs that evaluated some form of exercise in 1505 patients diagnosed with MDD.[29] They included a range of intervention and control groups. In the 23 RCTs (N=907) that used inactive control groups, standardized mean difference (SMD) in Ham-D scores was -0.82 (95% CI -1.12 to -0.51), representing a large clinical effect. In the 9 RCTs using active control groups, the efficacy of exercise was equal to cognitive behavioural therapy in 6 RCTs (N=152), equal to antidepressants in 2 RCTs (N=201), and superior to light therapy in 1 small trial. No specific type of exercise was superior, but increased duration improved outcomes in 2 trials. A funnel plot revealed publication bias, and more moderate benefit was seen in the 8 RCTs that used blinded outcome assessors, with SMD in Ham-D scores of -0.39 (95% CI -0.75 to -0.03). One systematic review identified 5 RCTs involving 221 patients with postpartum depression, and positive outcomes were reported in 3 of the 5 trials.[30] Another meta-analysis reported no difference in efficacy between mindfulness-based exercise and traditional forms of exercise in 12 RCTs involving 684 patients. Positive results were reported in 11 of 12 trials. Both reviews reported methodologic concerns similar to those mentioned above.[31]

Large systematic reviews suggest that exercise improves depression. Many physicians are reluctant to recommend lifestyle changes to depressed patients, who might lack motivation. It is worth noting that in 1 trial, 30% of depressed patients continued to exercise for the entire 26-month study period.[32] The magnitude of effect in depression scores might be unclear, but the range of other health benefits of exercise should make it first-line therapy in all patients. We recommend providing patients with a structured exercise prescription based on brief counseling to identify current activity, obstacles, preferred forms of exercise, and other relevant issues.[33]

Omega-3 fatty acids. Docosahexaenoic acid (DHA) and eicosapentenoic acid (EPA) are long-chain polyunsaturated fatty acids, the primary dietary source of which is oily seafood. Alpha-linolenic acid, an omega-3 precursor found in flax, soy, canola, and walnuts, is poorly converted in most humans and thus is not an important source of omega-3 fats.[34] Neurons contain high levels of omega-3 fatty acids, where they influence phospholipid membrane fluidity, receptors, ion channels, and neuroendocrine regulation and inflammation.[35] Depression is less prevalent in societies with high fish consumption, and depressed patients have significantly lower red blood cell omega-3 levels ($P<.05$).[36] It is believed that substantial losses occur during pregnancy to supply the fetal brain, and this might be linked to postpartum depression.[36] Increasing consumption of inflammatory omega-6 fatty acids in the 20th century has made relative omega-3 deficiency more common.[37]

A recently updated systematic review identified 35 RCTs involving 2949 patients. The trials used doses ranging from 0.5 to 9.6 g/d for 4 to 28 weeks. In the 16 RCTs that enrolled only patients diagnosed with MDD, the pooled SMD was 0.41 (95% CI 0.26 to 0.55), which represents a 3- to 4-point change in Ham-D scores. Heterogeneity among the studies was analyzed and revealed publication bias, as well as greater effect in patients with more severe baseline depression. No benefit was seen in trials that enrolled patients without a diagnosis of MDD. No clear dose-response relationship was identified. There was no clear difference in terms of efficacy between EPA and DHA.[38]

Omega-3 fatty acids show promise for the treatment of depression, but further research is needed to better understand sources of heterogeneity. It should be remembered that depression is not a specific disease; it is a syndrome that likely represents a number of different underlying pathophysiologic possibilities. Low levels of omega-3 fatty acids could represent one cause of depression. Diagnostic evaluation of red blood cell omega-3 levels should become increasingly available and might prove useful in this regard. If patients wish to supplement their diets with omega-3 fatty acid fish oil capsules, most clinicians recommend using a total dose (EPA and DHA combined) of at least 1 g/d. The most common side effect is experiencing a fishy taste. There is a theoretical increased risk of bleeding based on antiplatelet effects, but there is good evidence that this does not occur. Several large trials have failed to identify any increased risk of clinically significant bleeding with omega-3 use.[39]

Conclusion

Regular exercise should be recommended for all patients. There is good evidence that SJW is effective as monotherapy, but potential herb-drug interactions should be considered. Physicians should consider screening for and treating folate deficiency, but the benefits of folate supplementation remain unclear. Limited evidence supports the use of omega-3 fatty acids and SAM-e, but further research is required. Acupuncture might offer other health benefits to motivated patients, but it appears to have little effect on depression. It is important to ask all patients with depression about their use of CAM therapies.

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Competing interests
None declared

Contributors
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