Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 5. Complementary and Alternative Medicine Treatments

Arun V. Ravindran, M.B., Ph.D., Lynda G. Balneaves, Ph.D., Guy Faulkner, Ph.D., Abigail Ortiz, M.D., MS.c., Diane McIntosh, M.D., Rachel L. Morehouse, M.D., Lakshmi Ravindran, M.D., Lakshmi N. Yatham, M.B., M.B.A. (Exec)., Sidney H. Kennedy, M.D., Raymond W. Lam, M.D., Glenda M. MacQueen, M.D., Ph.D., Roumen V. Milev, M.D., Ph.D., Sagar V. Parikh, M.D., and the CANMAT Depression Work Group

Background: The Canadian Network for Mood and Anxiety Treatments (CANMAT) conducted a revision of the 2009 guidelines by updating the evidence and recommendations. The scope of the 2016 guidelines remains the management of major depressive disorder (MDD) in adults, with a target audience of psychiatrists and other mental health professionals.

Methods: Using the question-answer format, we conducted a systematic literature search focusing on systematic reviews and meta-analyses. Evidence was graded using CANMAT-defined criteria for level of evidence. Recommendations for lines of treatment were based on the quality of evidence and clinical expert consensus. "Complementary and Alternative Medicine Treatments" is the fifth of six sections of the 2016 guidelines.

Results: Evidence-informed responses were developed for 12 questions for 2 broad categories of complementary and alternative medicine (CAM) interventions: 1) physical and meditative treatments (light therapy, sleep deprivation, exercise, yoga, and acupuncture) and 2) natural health products (St. John's wort, omega-3 fatty acids; S-adenosyl-L-methionine [SAM-e], dehydroepiandrosterone, folate, *Crocus sativus,* and others). Recommendations were based on available data on efficacy, tolerability, and safety.

Conclusions: For MDD of mild to moderate severity, exercise, light therapy, St. John's wort, omega-3 fatty acids, SAM-e, and yoga are recommended as first- or second-line treatments. Adjunctive exercise and adjunctive St.John's wort are second-line recommendations for moderate to severe MDD. Other physical treatments and natural health products have less evidence but may be considered as third-line treatments. CAM treatments are generally well tolerated. Caveats include methodological limitations of studies and paucity of data on long-term outcomes and drug interactions.

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In 2009, the Canadian Network for Mood and Anxiety Treatments (CANMAT), a not-for-profit scientific and educational organization, published a revision of evidence-based clinical guidelines for the treatment of depressive disorders.[1] CANMAT has updated these guidelines in 2016 to reflect new evidence in the field. This section on complementary and alternative medicine (CAM) treatments is 1 of 6 guidelines articles; other sections expand on principles of care, psychological treatments, pharmacological treatments, neurostimulation treatments, and special populations. As before, the scope of these guidelines remains the management of adults with unipolar major depressive disorder (MDD). These recommendations are presented as guidance for clinicians who should consider them in context of individual patients and not as standards of care.

While definitions of CAM treatments vary widely, they can be broadly defined as "a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine."[2] The popularity of CAM continues to increase across the Western world,[3] in part because of a belief that "natural is better"[3] and a preference for self-directed over practitioner-directed

TABLE 1. Criteria for Level of Evidence and Line of Treatment.

	Criteria
Level of evidence[a]	
1	Meta-analysis with narrow confidence intervals and/or 2 or more RCTs with adequate sample size, preferably placebo controlled
2	Meta-analysis with wide confidence intervals and/or 1 or more RCTs with adequate sample size
3	Small-sample RCTs *or* nonrandomized, controlled prospective studies *or* case series *or* high-quality retrospective studies
4	Expert opinion/consensus
Line of treatment	
First line	Level 1 or level 2 Evidence, plus clinical support[b]
Second line	Level 3 Evidence or higher, plus clinical support[b]
Third line	Level 4 Evidence or higher, plus clinical support[b]

RCT, randomized controlled trial.

[a] Note that Level 1 and 2 Evidence refer specifically to treatment studies in which randomized comparisons are available. Recommendations involving epidemiological or risk factors primarily arise from observational studies, and hence the highest level of evidence is usually Level 3. Higher order recommendations (e.g., principles of care) reflect higher level judgement of the strength of evidence from various data sources and therefore are primarily Level 4 Evidence.

[b] Clinical support refers to application of expert opinion of the CANMAT committees to ensure that evidence-supported interventions are feasible and relevant to clinical practice. Therefore, treatments with higher levels of evidence may be downgraded to lower lines of treatment due to clinical issues such as side effects or safety profile.

therapies[4] and the favourable adverse event profiles, lower costs, and perceived efficacy of CAM treatments. Use by people with mental illness is estimated to range between 16% and 44%,[5,6] and a significant majority of these suffer from depression.[7] Unfortunately, although 10% to 30% of depressed patients are thought to use CAM treatments, there is generally no medical supervision, and these treatments are often used in combination with existing medications without considering possible interactions.[4]

As many as 120 different CAM therapies have been identified,[8] but only a small proportion has sufficient published evidence to warrant evaluation. Thus, this section focuses on 2 forms of CAM treatments: physical and meditative treatments (light therapy, sleep deprivation, exercise, yoga, and acupuncture) and natural health products (St. John's wort, omega-3 fatty acids, S-adenosyl-L-methionine (SAM-e), dehydroepiandrosterone (DHEA), tryptophan, folate preparations, acetyl-L-carnitine, *Crocus sativus, Lavandula,* and *Rhodiola rosea)*. Many other CAM therapies, such as qi gong, aromatherapy, and massage therapy, are not reviewed because of a very limited evidence base.

Methods

The full methods have been previously described,[9] but in summary, relevant English-language publications from January 1, 2009, to December 31, 2015, were identified using computerized searches of electronic databases (PubMed, PsychInfo, Cochrane Register of Clinical Trials), inspection of bibliographies, and review of other guidelines and major reports. Each recommendation is informed by the level of evidence for each graded line of treatment, using specified criteria (Table 1). The level of evidence criteria now reflect the primacy of meta-analysis because of its increasing use in the evaluation of evidence. Supplemental materials and citations, including small-sample randomized controlled trials (RCTs) not described in the text, are available online (Suppl. Tables S1-S10). The question-answer format adopted in the previous CANMAT guidelines has been retained for ease of use.

5.1. What Are General Caveats and Limitations of CAM Treatments? As noted in the 2009 guidelines, the varying quality of RCTs (sample size, design, homogeneity of population) presents a major limitation to the systematic evaluation of CAM treatments.[10] In addition, variations within interventions (e.g., potency, dose, duration) across RCTs and frequent lack of long-term data impede the systematic evaluation of their benefit in practice. Blinding also poses a greater challenge for nonpharmacologic trials than pharmacologic trials.[11] Because of these limitations, as well as the volume of research on CAM therapies, we focused primarily on systematic reviews and meta-analyses, whenever available, to construct a global view of the literature for each CAM treatment. Publication bias must also be considered in evaluations of CAM research, given evidence suggesting bias in favour of CAM therapies as well as against.[12,13]

It is accepted that for most patients with MDD, evidence-based pharmacological treatments and/or psychological treatments should be considered ahead of CAM treatments because of a generally larger evidence base and often better quality evidence for efficacy. As well, it is emphasized that appropriate clinical judgement should be employed in determining the suitability of CAM treatments for individual patients. There remains a dearth of information on interactions between CAM therapies and conventional treatments for depression, as well as interactions between different CAM therapies. Such risk is compounded by the fact that patients often do not disclose self-directed CAM use to clinicians,[4,14] and clinicians may not ask.[15] In the absence of adequate safety information on treatment interactions, it is recommended that clinicians discuss the risks and benefits of CAM treatments with their patients and select and administer these therapies in an individual and tailored manner.

Physical and Meditative Treatments

5.2. What Is Light Therapy? How Effective Is Light Therapy for the Treatment of MDD? Light therapy (LT), or phototherapy, involves daily exposure to bright light and is typically administered at home with a fluorescent light box. Dosing of light may vary in intensity, spectrum (soft white to "blue enhanced" light), exposure duration, and time of administration (morning vs. evening).[7] The standard protocol

TABLE 2. Summary of Recommendations for Physical and Meditative Treatments.

Intervention	Indication	Recommendation	Evidence	Monotherapy or Adjunctive Therapy
Exercise	Mild to moderate MDD	First line	Level 1	Monotherapy
	Moderate to severe MDD	Second line	Level 1	Adjunctive
Light therapy	Seasonal (winter) MDD	First line	Level 1	Monotherapy
	Mild to moderate nonseasonal MDD	Second line	Level 2	Monotherapy and adjunctive
Yoga	Mild to moderate MDD	Second line	Level 2	Adjunctive
Acupuncture	Mild to moderate MDD	Third line	Level 2	Adjunctive
Sleep deprivation	Moderate to severe MDD	Third line	Level 2	Adjunctive

MDD, major depressive disorder.

is 10,000 lux (light intensity) for 30 minutes per day during the early morning for up to 6 weeks, with response usually seen within 1 to 3 weeks.[16,17] Proposed mechanisms of antidepressant action include the alteration of circadian rhythms[7] and modulation of serotonin and catecholamine systems.[18] Light therapy is generally well tolerated,[17] with common side effects being eye strain, headache, agitation, nausea, and sedation.[19]

Since 2009, 2 meta-analyses,[16,20] 4 systematic reviews[17,19,21,22] and 3 RCTs[23-25] have been generally confirmatory of recommendations in the 2009 guidelines (see Suppl. Table S1). While 1 meta-analysis (10 trials, $N = 714$) suggested that the efficacy of LT in seasonal depression has been overstated,[16] the other systematic reviews supported its benefit in seasonal depression. A large RCT also found that cognitive-behavioural therapy (CBT) had similar efficacy to LT as monotherapy or adjunctive in acute treatment of seasonal depression,[25] but a naturalistic follow-up study revealed that CBT was superior after 2 years.[26] Newer studies have expanded the LT evidence base for nonseasonal MDD. A recent meta-analysis (20 trials, $N = 881$) also found evidence to support the efficacy of LT as monotherapy in nonseasonal MDD.[20] In addition, an RCT reported that LT monotherapy and LT combined with fluoxetine were superior to placebo in nonseasonal MDD, with the combined treatment showing the most consistent effects.[23] Similarly, medication paired with chronotherapeutic techniques (LT, sleep deprivation, and sleep time stabilization) led to superior remission rates in nonseasonal MDD compared to medication combined with exercise at both 9-week and 29-week follow-up.[24,27]

In summary, the updated evidence continues to support LT as a first-line monotherapy for seasonal depression and as a second-line monotherapy or adjunctive treatment for mild to moderate nonseasonal MDD (Table 2).

5.3. What Is Sleep Deprivation? How Effective Is Sleep Deprivation for the Treatment of MDD? Sleep deprivation (SD) continues to demonstrate rapid antidepressant effects in recent publications.[28] It involves keeping patients awake for extended periods, with total SD lasting up to 40 hours and partial SD allowing 3 to 4 hours of sleep per night.[29] Sleep deprivation is typically employed 2 to 4 times over the course of 1 week, with total SD often interspersed with partial SD or normal (recovery) sleep.[30,31] Several mechanisms of antidepressant action have been proposed, including increased activity of all neurotransmitter systems, synaptic potentiation, and glial signaling.[28] One systematic review[29] supported the efficacy of SD as augmentation to antidepressants in moderate to severe MDD (see Suppl. Table S2).

A practical limitation for the use of SD is maintaining its use for longer than a few weeks. Relapse after discontinuation is often rapid. However, combined chronotherapeutic techniques offer rapid onset of efficacy, greater clinical utility, and sustained response compared to total SD alone.[32] One such strategy is the combination of SD with sleep-phase advance (SPA), which involves scheduling bedtimes that are earlier than usual and then advancing the times on subsequent nights until a normal bedtime is reached. Several RCTs have demonstrated that an estimated 50% to 75% of SD responders experience continued improvement when SD and SPA are combined.[33] Tripartite interventions (total or partial SD + light therapy + SPA) implemented in small open trials also yielded remission rates of 60% to 75%.[31,34,35]

The most common side effect of SD is daytime sleepiness. Recurrence of panic attacks has been noted during SD,[24] but with no adverse impact on treatment of comorbid depression. The only established contraindication for SD is epilepsy, given the high risk of seizure induction with sleep reduction.[36] The risk of SD-induced mania is estimated to be low, with switch rates similar to or lower than with antidepressants and placebo.[36]

In summary, although there is Level 2 Evidence for SD in MDD, the findings are confounded by the challenges of blinding and sustaining treatment. SD is thus recommended as a third-line adjunctive treatment for more severe and refractory forms of MDD, in combination with other chronotherapeutic techniques (Table 2).

5.4. How Effective Is Exercise for the Treatment of MDD? Exercise is a structured physical activity, often supervised, and undertaken with the aim of maintaining or improving physical fitness or health.[37] Potential mechanisms to explain its benefit in depression include biological factors (e.g., increased turnover of neurotransmitters, endorphins, or neurotrophic factors like brain-derived neurotrophic factor; reduction in cortisol levels; changes in kynurenine metabolism), and

psychological factors (e.g., increased self-efficacy).[37] In general, exercise is well tolerated, with adverse events rarely reported in exercise and depression trials.[37] While both cardiovascular (aerobic) and resistance (anaerobic) exercise have been shown to be effective in reducing depressive symptoms, there is no clear evidence for the superiority of either form.[38] Recommendations for administration vary, but at least 30 minutes of supervised moderate-intensity exercise at least 3 times weekly for a minimum of 9 weeks is considered effective.[39,40] As with all physical activity interventions, however, the physical fitness of the participant must be taken into consideration.

Recent meta-analyses[37,41-44] and systematic reviews[39,45] have evaluated exercise as monotherapy or adjunct to antidepressants or psychotherapy for mild to moderate depression (Suppl. Table S3). Two meta-analyses (39 trials, $N = 2326$[31]; 13 trials, $N = 720$[36]) and 2 systematic reviews[43,45] reported that exercise was as effective as pharmacotherapy or psychotherapy. Other meta-analyses reported that adjunctive exercise was effective in the short term (13 trials, $N = 687$),[41] and superior to no-treatment control conditions (13 trials, $N = 720$)[42] and to control conditions like treatment as usual (10 trials, $N = 758$)[43] For moderate to severe MDD, 1 meta-analysis (20 trials, $N = 1298$) found exercise to be superior to control conditions.[44] Some methodological challenges, including suitability of control conditions, adequacy of blinding and self-selection bias, may limit interpretation of results. For example, when only high-quality trials were considered, the effect size for benefit of exercise became smaller.[37,42,44] There is also some evidence that exercise has better adherence when supervised by qualified practitioners, so feasibility may be an issue.[46]

The evidence for the long-term benefits of exercise in MDD is less clear. Meta-analyses have found only small effects[37] or no effects[41] for exercise in the long term, although a continued exercise regimen may help to maintain early benefits. A systematic review of large population-based, prospective studies suggested that participation in physical activity may also prevent the onset of depression.[47] Further research is therefore needed to assess the long-term benefits of exercise for depression.

In summary, there is Level 1 Evidence for exercise in treating MDD. It is recommended as first-line monotherapy for mild to moderate MDD and as second-line adjunctive treatment for moderate to severe MDD, based on the lack of long-term data and feasibility issues (Table 2).

5.5. What Is Yoga? How Effective Is Yoga for the Treatment of MDD? Practitioners of the ancient Indian practice of yoga seek physical, mental, and spiritual balance. Thus, yoga "asanas" or postures aim to improve flexibility and strength, while controlled breathing exercises or "pranayama" target heightening of body awareness, and "dhyana" or meditation is thought to produce cognitive benefits.[48] The proposed neurobiological mechanisms for its benefit include increased turnover of dopamine and gamma-aminobutyric acid (GABA) levels in specific brain regions, regulation of the hypothalamic-pituitaryadrenal axis,[49] and normalization of heart rate variability.[50] The duration of yoga interventions varies, averaging 2 to 4 sessions a week over a course of 2 to 3 months.[49]

Since 2009, 1 meta-analysis (12 trials, $N = 619$)[49] has reported moderate advantage for yoga compared to usual care but only a modest benefit compared to relaxation and aerobic exercise (Suppl. Table S4). Integrated yoga forms, incorporating breath control and meditation, may produce more benefits than those that focus on postures alone. Limitations of yoga studies include low quality of RCTs, variability in practice parameters and physical/mental health of participants, as well as difficulties with suitable control conditions.[49] Long-term efficacy and safety data are also lacking.

Side effects are rarely reported in studies of yoga, and the participant's level of physical fitness may play a role in the presence or severity of any adverse effects that are experienced.[48] There are case reports of meditation-induced mania or psychosis and of excessive or incorrect yoga practice possibly contributing to serious adverse effects such as artery occlusion or lotus neuropathy.[48]

Yoga continues to be recommended as a second-line adjunctive therapy in mild to moderate MDD with Level 2 Evidence (Table 2). Other treatments involving meditative practices (such as mindfulness-based cognitive therapy) are included in Section 2, Psychological Treatments.[51]

5.6. What Is Acupuncture? How Effective Is Acupuncture for the Treatment of MDD? Acupuncture has been used for centuries in Asia as a treatment for a variety of health conditions, including chronic pain, gastrointestinal conditions, and musculoskeletal disorders. It involves the insertion of fine needles at specific physiological points to modulate the activity of nervous, hormonal, and immune systems. In recent years, electro-acupuncture (transmission of a small, pulsed electrical current to the body through acupuncture needles) and laser acupuncture (use of low-level laser beams at specific acupuncture points) have also been evaluated, with comparable efficacy to manual acupuncture.[52] Acupuncture sessions may involve a variety of acupoints, are typically 20 to 30 minutes in duration, and range from 10 to 30 sessions, decreasing in frequency over time from daily to weekly intervals.[52]

While several RCTs and meta-analyses supported acupuncture as both a beneficial monotherapy[53,54] and as adjunct treatment,[54-56] others did not find evidence of efficacy for acupuncture either alone or as an adjunct therapy[52,57] (Suppl. Table S5).

The inconsistency in findings has been attributed to methodological issues. Sham acupuncture is often used as a control condition; however, there is no robust evidence that any specific acupoints are more relevant to depression than others, and as such, even sham treatment may produce benefits.[57] Small sample sizes, unclear randomization procedures, and heterogeneity of study protocols are other limitations.

Generally, acupuncture is well tolerated when performed by a trained and regulated practitioner. Adverse effects are usually mild and include headache, transient bleeding, bruising

at needle insertion sites, skin irritation, and syncope.[11,52] To avoid infection, sterile, disposable needles and aseptic techniques should be used.

Acupuncture is recommended as a third-line treatment, with Level 2 Evidence in the adjunctive treatment of mild to moderate MDD (Table 2).

Natural Health Products

Natural health products are naturally occurring, nonprescription substances that promote or preserve good health, according to Health Canada. They include vitamins and minerals, herbal remedies, traditional and homeopathic medicines, and probiotics. As the list of available natural health products is extensive, only commonly used products with a reasonable body of published data are reviewed.

5.7. What Is St. John's Wort? How Effective Is St. John's Wort for the Treatment of MDD? St. John's wort (SJW) *(Hypericum perforatum)* is a perennial plant that has been used as a herbal medicine for many centuries, with the total extract (which include hypericin/hyperforin and several other flavonoids) being regarded as active. Suggested mechanisms of antidepressant action include direct effect on serotonin receptors, monoamine oxidase inhibition, and neuroendocrine and ion channel modulation.[58,59] Formulations of SJW have varied widely, as has the dose range (500 to 1800 mg/day), while treatment duration has spanned 4 to 12 weeks.[58,60]

Since 2009, 2 systematic reviews[60,61] have confirmed the comparable efficacy of SJW to antidepressants and superiority to placebo for mild to moderate MDD (Suppl. Table S6). In MDD of greater severity, 1 systematic review[60] found SJW to be of equal efficacy to selective serotonin reuptake inhibitors, with a lower rate of withdrawals due to adverse events, whereas the other[61] reported no difference between SJW and placebo. In 2 subsequent RCTs, one found no significant difference between SJW, sertraline, or placebo monotherapy,[62] while the other found SJW monotherapy superior to placebo, particularly for individuals with moderate levels of atypical depression.[63]

Although SJW is significantly better tolerated than many first-line antidepressants,[64] side effects include gastrointestinal upset, headaches, skin irritation, photosensitivity, and dry mouth.[65] There is concern that higher potency extracts can interfere with the metabolism of various medications.[66] In addition, serotonin syndrome and hypomania have been reported when SJW is used concurrently with antidepressants.[67,68]

SJW is recommended as first-line monotherapy in mild to moderate MDD (Level 1 Evidence) and is recommended as a second-line adjunctive treatment for moderate to severe MDD (Level 2 Evidence) (Table 3).

5.8. What Are Omega-3 Fatty Acids? How Effective Are Omega-3 Fatty Acids for the Treatment of MDD? Omega-3 fatty acids (ω-3 fatty acids) are polyunsaturated fatty acids that are primarily found in oily fish and certain nuts and seeds. Different formulations of ω-3 fatty acids have been studied, the most common being eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The typical dose range is 3 to 9 g/day of ω-3 or 1 to 2 g of EPA plus 1 to 2 g of DHA per day.[69] Duration of treatment ranges from 4 to 16 weeks.[70,71]

Four new meta-analyses[70-73] and 2 systematic reviews[69,74] have provided updates on the efficacy of ω-3 fatty acids in MDD (Suppl. Table S7). One reported no benefits (13 trials, $N = 731$),[70] another meta-analysis (25 trials, $N = 1438$)[72] and 1 review[74] reported equivocal outcomes, 1 meta-analysis (15 trials, $N = 916$) reported a positive outcome as monotherapy,[73] and 1 meta-analysis (11 trials, $N = 418$)[69] and 1 review[71] reported a positive outcome as adjunctive therapy.

Contradictory findings may be due to differences in study populations, methodology, and intervention parameters. The most recent and rigorous meta-analysis (11 trials, $N = 418$),[71] reporting specifically on DSM-defined MDD, found large effect sizes for the efficacy of ω-3 fatty acids. The variability in findings may also be due to differences in the composition and dosage of ω-3 fatty acids used. Two meta-analyses[71,73] found that EPA-dominant formulations were superior to DHA-based options for alleviation of depressive symptoms.

The ω-3 supplements are generally well tolerated with only mild side effects, including diarrhea, nausea, and a fishy aftertaste.[11,75] Patients on anticoagulant and antiplatelet medications may also require additional monitoring.[76] Manic induction has been reported in a few cases, although not in bipolar depressed patients.[77,78]

Thus, ω-3 fatty acids have Level 1 Evidence of efficacy but, because of the inconsistency in the evidence, are recommended as second-line monotherapy for mild to moderate MDD and adjunctive to antidepressants for moderate to severe MDD (Table 3).

5.9. What Is SAM-e? How Effective Is SAM-e for the Treatment of MDD? SAM-e is a natural substrate in the human body, including in the brain, that is thought to function as a methyl donor in various physiological processes.[61] Proposed mechanisms of antidepressant action include modulation of monoaminergic neurotransmission.[79]

SAM-e is prescribed in Europe as an oral or parenteral treatment for several conditions, including MDD.[80] In the United States and Canada, SAM-e is available as an oral over-the-counter dietary supplement, often used in the dose range of 800 to 1600 mg/day given in divided doses with meals over 4 to 12 weeks.[81] Studies have also used intravenous and intramuscular formulations of SAM-e, at doses of 200 to 400 mg/day across 2 to 8 weeks,[61,81] which may be more effective than oral supplements.[69]

Two systematic reviews found SAM-e effective as a monotherapy versus placebo in mild to severe MDD[61] or versus comparator antidepressants in mild to moderate MDD[81] (Suppl. Table S8). There is also evidence to support adjunctive SAM-e with antidepressants in mild to moderate MDD.[69,81] There are concerns, however, about trial methodologies and paucity of data on SAM-e as maintenance therapy.[61]

Overall, SAM-e is relatively well tolerated, with the most common side effects being gastrointestinal upset, insomnia,

TABLE 3. Summary of Recommendations for Natural Health Products.

Intervention	Indication	Recommendation	Evidence	Monotherapy or Adjunctive Therapy
St. John's wort	Mild to moderate MDD	First line	Level 1	Monotherapy
	Moderate to severe MDD	Second line	Level 2	Adjunctive
Omega-3	Mild to moderate MDD	Second line	Level 1	Monotherapy or adjunctive
	Moderate to severe MDD	Second line	Level 2	Adjunctive
SAM-e	Mild to moderate MDD	Second line	Level 1	Adjunctive
	Moderate to severe MDD	Second line	Level 2	Adjunctive
Acetyl-L-carnitine	Mild to moderate MDD	Third line	Level 2	Monotherapy
Crocus sativus (saffron)	Mild to moderate MDD	Third line	Level 2	Monotherapy or adjunctive
DHEA	Mild to moderate MDD	Third line	Level 2	Monotherapy
Folate	Mild to moderate MDD	Third line	Level 2	Adjunctive
Lavandula (lavender)	Mild to moderate MDD	Third line	Level 3	Adjunctive
Inositol	Mild to moderate MDD	Not recommended	Level 2	
Tryptophan	Mild to moderate MDD	Not recommended	Level 2	
Rhodiola rosea (roseroot)	Mild to moderate MDD	Not recommended	Insufficient evidence	

DHEA, dehydroepiandrosterone; MDD, major depressive disorder; SAM-e, S-adenosyl-L-methionine.

sweating, headache, irritability, restlessness, anxiety, tachycardia, and fatigue.[11,81]

In summary, SAM-e is recommended as a second-line adjunctive treatment for use in mild to moderate MDD (Level 1 Evidence) (Table 3).

5.10. What Is DHEA? How Effective Is DHEA for the Treatment of MDD? Dehydroepiandrosterone (DHEA) is a hormone produced by the adrenal cortex, which is subsequently converted to sex hormones in the body.[82] It plays a role in modulating neuroendocrine and immune homeostasis and influences monoaminergic and glutaminergic neurotransmission.[83] Dosage of DHEA commonly used in research ranges from 30 to 450 mg/day, with treatment lasting 6 to 8 weeks.[11] No new clinical trials have been conducted since 2009 that specifically evaluated the efficacy of DHEA in treating MDD, and therefore, there is no new evidence to assess.

Side effects of DHEA include hirsutism, acne, hypertension, liver damage, and manic induction.[84] Higher doses are also associated with more serious adverse effects, such as worsening of prostatitis and increased risk of breast cancer.[84]

DHEA remains recommended as a third-line treatment with Level 2 Evidence as monotherapy and Level 3 Evidence as adjunctive treatment (Table 3).

5.11. What Is Tryptophan? How Effective Is Tryptophan for the Treatment of MDD? Tryptophan is a precursor of serotonin, which cannot be synthesized de novo and must be supplied through diet. It is hypothesized that adjunctive tryptophan may potentiate serotonergic neurotransmission, mediating antidepressant benefits by the process of 'precursor loading'.[85] The recommended dose in clinical practice is 2 to 4 g/day, with a suggested duration of 3 to 4 months.[85,86]

A systematic review[69] and 1 RCT[87] have been published since 2009, with no clear evidence to support an adjunctive role for tryptophan to treat MDD (Suppl. Table S9). Reported side effects of tryptophan are mild and most frequently include sedation, dry mouth, and gastrointestinal distress, but may also include serotonin syndrome and a potential to increase lithium toxicity when used in combination.[88]

Tryptophan is therefore not recommended for the treatment of MDD (Table 3).

5.12. What Other Natural Health Products Have Been Evaluated in the Treatment of MDD? Several other natural health products have been evaluated as potential treatments for depression (Table 3). Only the evidence for relatively better evaluated agents (folate preparations, inositol, acetyl-L-carnitine, *C. sativus* [saffron], *Lavandula* [lavender], and *R. rosea* [roseroot]) was reviewed (Suppl. Table S10).

A meta-analysis (11 trials, $N = 2204$) of folic acid found no evidence to support its efficacy as a short-term adjunctive agent for antidepressants, although many subjects had medical and other psychiatric comorbidities.[89] However, 2 narrative reviews[90,91] and a retrospective analysis[92] support the use of folate preparations (particularly L-methylfolate) as monotherapy[90] or adjunct to antidepressants for MDD,[90-92] although small samples and the lack of double-blind, placebo-controlled trials are notable limitations. Genetic polymorphisms may also play a role in efficacy, and certain folate preparations may be better suited to specific genetic profiles.[90]

There was no evidence from a meta-analysis (9 trials, $N = 242$) to support the efficacy of inositol as monotherapy or adjunctive therapy in MDD.[93]

In contrast, a narrative review found that acetyl-L-carnitine was superior to placebo, and as effective as fluoxetine and amisulpride, as a monotherapy for mild to moderate depression.[94] It is generally well tolerated without significant side effects.[10,94]

The usual dose of *C. sativus* (saffron) is 20 to 30 mg/day over 6 to 8 weeks.[95,96] One new meta-analysis (5 trials, $N = 177$)[97] and 3 systematic reviews[96,98,99] further support its use as a monotherapy with comparable efficacy to antidepressants

in mild to moderate MDD. Reported adverse effects of *C. sativus* are mild and include anxiety/nervousness, increased appetite, nausea, and headache.[96]

Lavandula (lavender) doses are recommended at 2 to 4.5 mL/day (alcoholic tincture 1:2) or 6 to 12 mL/day (alcoholic tincture 1:5).[100] It has only been studied as an acute intervention in the short term (4-8 weeks).[69] In 1 RCT, the combination of *Lavandula* and citalopram was significantly more effective than citalopram alone for moderate to severe depression.[101] Adverse effects of *Lavandula* include nausea, confusion, and mild headaches.[69,101]

Standard dose regimens for *R. rosea* (roseroot) are not available in the literature, with studies reporting a range of 100 to 680 mg/day. It, too, has only been studied in the short term (4-8 weeks).[102] One RCT of *R. rosea* monotherapy and sertraline in mild to moderate MDD found that neither condition was significantly different from placebo.[103] *R. rosea* has mild and infrequent side effects, including nervousness, dizziness, allergy, irritability, insomnia, fatigue, and unpleasant sensations.[102,103] Interactions with concomitant medications, such as theophylline and warfarin, have been reported.[104]

In summary, for mild to moderate MDD, acetyl-L-carnitine (Level 2 Evidence) is recommended as a third-line monotherapy and *C. sativus* as third-line monotherapy or adjunctive treatment (Level 2 Evidence) (Table 3). Folate (Level 2 Evidence) and *Lavandula* (Level 3 Evidence) are recommended as third-line adjunctive treatments. Inositol and *R. rosea* are not recommended for the treatment of MDD.

Conclusions

Overall, there are few substantial changes to the recommendations made in the previous CANMAT CAM treatment guidelines.[9] Across CAM treatments, exercise, St. John's wort, and LT (for seasonal depression) have the most robust evidence. For unipolar mild to moderate MDD, there is sufficient evidence and clinical support to recommend, as first- or second-line treatment, the use of exercise, LT, ω-3 fatty acids and St. John's wort as monotherapies, and exercise, LT, yoga, ω-3 fatty acids, and SAM-e as adjunctive treatments. For moderate to severe MDD, adjunctive use of exercise, St. John's wort, ω-3 fatty acids, SAM-e, and SD can be considered. Other physical and natural health products are not recommended as first- or second-line treatment but may be useful in specific clinical situations.

The evidence presented recognizes the strengths and limitations of various CAM treatments. Pharmacological and psychological treatments remain the first-line interventions for moderate to severe MDD because of a generally larger evidence base for efficacy and safety. However, the growing body of evidence in support of specific CAM treatments indicates that they are efficacious for milder forms of illness and/or when patient preference may affect adherence to other treatments. More physician education is needed on the benefits and application of CAM treatments to increase usage and to enhance evidence-based treatment options for patients.

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The CANMAT guidelines are not officially endorsed by the Canadian Psychiatric Association.

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