It is time to investigate integrative approaches to enhance treatment outcomes for depression?

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ABSTRACT

Psychological and pharmacological interventions are the most common treatments for adult depression. While these interventions have robust evidence supporting their efficacy, there remain up to 60 percent of individuals who do not respond to treatment, or only partially respond. Unfortunately, efforts at improving outcome rates from new or modified versions of psychological or pharmacological interventions have been disappointing. It is argued that increased treatment efficacy for depression may be achieved by utilising integrative or adjunctive treatments. As depression is influenced by an array of psychological, biological, social, environmental, dietary, and lifestyle factors, it is hypothesised that treatment outcomes will only be improved when integrative interventions are utilised. The research supporting the potential of several of these factors are reviewed in this article including those associated with diet, exercise, sleep, sunshine/light, nature, herbs and nutraceuticals, social connections, meditation, religion/spirituality, and alcohol and nicotine use. It is argued that increased efforts should be directed at investigating integrative or adjunctive interventions, rather than stand-alone treatments, to enhance outcomes for depression.

Introduction

Depression is commonly treated with psychological and pharmacological interventions. These treatments are provided as stand-alone interventions or in combination. Research suggests that as a monotherapy, second-generation antidepressants (e.g., selective serotonin reuptake inhibitors and serotonin and noradrenaline reuptake inhibitors) and cognitive-behaviour therapy (CBT) are comparable in their efficacy. In a meta-analysis by Amick, et al. [1] it was found that there were non-significant differences in remission rates of 40.7% and 47.9% between CBT and second-generation antidepressants, respectively. Response rates (defined as a 50% or greater reduction in depression scores from baseline) were also similar with rates of 44.2% and 45.5% from CBT and second-generation antidepressants, respectively. Similar conclusions were obtained following a meta-analysis by Cuijpers, et al. [2] indicating non-significant differences between psychotherapy and pharmacotherapy for the treatment of depressive and anxiety disorders. However, pharmacotherapy was significantly more efficacious than psychotherapy for the treatment of dysthymia (effect size = 0.30), and psychotherapy was significantly more efficacious than tricyclic antidepressants (effect size = 0.21). When treatments are combined there is evidence to suggest greater improvements in

treatment outcomes. The overall difference between pharmacotherapy alone and combined treatments was an effect size of 0.43, indicating a moderate effect [3]. However, no additional benefit from combined treatments compared to monotherapy was found in a meta-analysis by Amick et al. [1]. This meta-analysis differed from Cuijpers et al. [3] as it only compared the effects of CBT with second-generation antidepressants, whereas Cuijpers and colleagues examined the effects of all forms of antidepressants and psychotherapies.

To enhance treatment outcomes, efforts have been directed at developing newer psychological therapies and antidepressant medications. However, it seems that efficacy rates are not increasing. For example, outcomes were similar to CBT in depressed patients receiving Schema-Focused therapy [4], Acceptance and Commitment Therapy (ACT) [5], and Interpersonal Psychotherapy [6]. Although the number of studies was limited, a meta-analysis of 'Third-Wave' cognitive and behavioural therapies comprising ACT, compassionate mind training, functional analytic psychotherapy, extended behavioural activation, and metacognitive therapy was equally as effective as standard CBT for the treatment of acute depression [7]. In a comparative analysis of 21 different antidepressant drugs for the treatment of acute, adult depression, moderate efficacy and acceptability differences were found although no stand-out drug was identified [8]. Of concern are studies

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suggesting that 20% of depressed primary-care patients do not fill their prescriptions, and even if they start a course of treatment, they may discontinue before receiving an adequate course [9]. Adverse effects from medication intake is a common reason for non-adherence with more than 60% of patients reporting at least one adverse effect from second-generation antidepressants [10].

These results suggest that while antidepressant medications and/or psychological therapies are effective treatments for depression, there remain a significant portion of individuals who are unresponsive to treatment or obtain only a partial response. These rates are as high as 50 to 60% in depressed individuals and despite our best efforts at enhancing psychological and pharmacological interventions, progress has been disappointing. This is likely because major depressive disorder is a multi-factorial disease influenced by psychological, biological, social, nutritional, lifestyle, and environmental factors. Consequently, to improve treatment outcomes it may be prudent to consider individually-tailored interventions that target respective factors that may be adversely influencing a person's mental and physical wellbeing. In this review, factors potentially influencing depressive symptoms are summarised and interventional studies are described. While the level of evidence supporting the influence of such variables on depression varies significantly, the goal is to present adjunctive, or integrative options that have the potential to enhance treatment outcomes for depression. Many of these options will require further investigation through robust, randomised controlled trials (RCTs).

Diet and nutrition

There is increasing research confirming a relationship between diet and depression. In a meta-analysis of 21 studies from ten countries, a dietary pattern characterised by a high intake of fruits, vegetables, whole grains, fish, olive oil, low-fat dairy products, and antioxidants; and a low intake of animal foods was associated with a decreased risk of depression. However, a dietary pattern characterised by high consumption of red and/or processed meats, refined grains, sweets, high-fat dairy products, butter, potatoes, and high-fat gravy; and a low intake of fruits and vegetables was associated with an increased risk of depression [11]. In another meta-analysis, adherence to a high-quality diet, regardless of type (i.e., healthy/prudent or Mediterranean), was associated with a 22 to 36% lower risk of depressive symptoms over time in a linear, dose-response fashion [12]. In a meta-analysis of observational studies, results from 20 longitudinal and 21 cross-sectional studies demonstrated a 33% reduced risk of incident depression in people adhering to a high versus low Mediterranean diet [13]. Eating an anti-inflammatory diet has also been shown to protect against depression. In a meta-analysis of 11 studies and over 100,000 participants, it was confirmed that compared to people eating an anti-inflammatory diet, there was a 40% increased risk of depression in people eating a pro-inflammatory diet [14]. Finally, data from two cohort studies have demonstrated a significant positive association between dietary glycaemic index and depression [15].

Dietary interventions

Research into the efficacy of dietary interventions on adults with depression is limited, although two recent studies have been completed. In a 12-week, single-blinded, RCT, a dietary intervention based on a Mediterranean diet, delivered as an adjunct to psychotherapy and/or pharmacotherapy, was associated with greater reductions in depressive symptoms compared to a social-support control group. Remission rates were also greater in the dietary intervention compared to the control group (32.3% and 8.0%, respectively) [16]. In another single-blinded RCT on adults with self-reported depression, a 3-month Mediterranean-style diet supplemented with fish oil was associated with greater reductions in depressive symptoms and improvements in quality of life compared to a social group. These improvements were sustained at six-

months follow up [17]. Further evidence for the mental-health benefits of dietary interventions is obtained from studies on non-depressed populations. For example, a six-month RCT on healthy, overweight adults demonstrated worsened mood in people allocated to a high-glycaemic-load diet compared to a low-glycaemic-load diet [18]. This finding was replicated by another randomised, crossover study on healthy weight and overweight adults, where the consumption of a high-glycaemic load diet for two months resulted in a 38% higher depression score, 55% higher total mood disturbance score, and 26% higher fatigue/inertia score compared to a low-glycaemic-load diet [19]. Finally, in an eight-week, randomised, controlled, cross-over trial, eating a Mediterranean diet with three-to-four daily serves of dairy food in adults with high blood pressure and at least two other risk factors for cardiovascular disease, was associated with greater improvements in total mood disturbance, tension, depression, and confusion compared to a low-fat control diet [20].

Conclusions: there is a strong body of evidence confirming inferior diet quality in people with depression. A poorer diet is also associated with an increased risk of developing future depression. However, a correlation does not confirm causation as poor eating could be an artefact of a depressed mood in many people. There is preliminary evidence to suggest dietary interventions (based on a Mediterranean diet) can effectively improve mood in depressed adults. However, this has mostly been conducted as an adjunctive treatment and its efficacy as a stand-alone intervention continues to be uncertain. Motivational issues may pose a barrier to behaviour change in many people with depression so developing realistic goals for change and targeting motivational issues and potential barriers to change will also be important.

Caffeine and coffee consumption

There is emerging evidence that caffeine has antidepressant effects. This has been confirmed by observational studies demonstrating a reduced risk of depression in coffee drinkers. Data from 11 observational studies and over 300,000 participants demonstrated that compared to people with the lowest intake, the relative risk for coffee-depression and caffeine-depression was 0.76 and 0.72, respectively. A dose–response analysis revealed that the risk of depression decreased by 8% for each cup a day increment in coffee intake (up to 4.5 cups a day) [21]. In another meta-analysis of twelve studies and a total of almost 350,000 individuals and 8,146 cases of depression, compared to individuals with lower coffee intake, those with higher intakes had a pooled relative risk of depression of 0.76. A dose–response analysis suggested a J-shaped relationship between coffee consumption and risk of depression with a peak protective effect at 400 mL/day. Significant benefits from caffeine consumption were also identified from prospective studies where a relative risk of 0.84 was identified [22]. One study was identified examining the antidepressant effects of caffeine supplementation in depressed adults. In this study on male, depressed inpatients who were not regular coffee drinkers, four-week supplementary administration of a low-dose morning caffeine beverage (60 mg) in conjunction with the SSRI escitalopram produced faster antidepressant effects from week two compared to a placebo (soymilk powder). However, no benefits were identified in participants provided with a higher 120 mg caffeine dose. Caffeine intake at 60 mg was also associated with improved cognitive performance and did not affect sleep as measured by an overnight polysomnography. Interestingly, the researchers found that chronic caffeine consumption inhibited the activation of the hypothalamic–pituitaryadrenal axis by normalising levels of salivary cortisol induced by the Trier Social Stress Test [23].

Although the mechanisms underlying the antidepressant effects of caffeine are not yet understood there are several plausible explanations. Coffee contains several chemicals (e.g., chlorogenic acid, nicotinic acid, tannic acid, and pyrogallic acid) some of which have anti-inflammatory and antioxidant effects [24–26]. Caffeine is also a nonspecific antagonist of adenosine A1 and A2 receptors which may influence

dopaminergic transmission [27,28].

Conclusions: coffee or increased caffeine intake seems to protect against depression and may improve mood in adults with depression. However, determining optimal doses are important as caffeine can adversely affect sleep and anxiety. Caution is therefore warranted in people with comorbid anxiety and depression. To reduce its impact on sleep, morning caffeine intake is a wiser option.

Nutritional status

In addition to diet quality, there is increasing evidence confirming an association between nutrient intake and status on depression. In a recent systematic review, 12 nutrients were found to be associated with the prevention and treatment of depressive disorders. These included folate, iron, long-chain omega-3 fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)], magnesium, potassium, selenium, thiamine, vitamin A, vitamin B6, vitamin B12, vitamin C, and zinc [29]. A summary of the evidence demonstrating the mood-supporting effects of some of these nutrients is outlined below.

Omega-3 fatty acids

There is strong evidence that levels of omega-3 fatty acids and fish consumption are lower in adults with depression and are associated with an increased risk of depression. In a meta-analysis of 10 prospective cohort studies with over 6,500 cases of depression, the pooled adjusted risk ratio of depression for the highest versus lowest category of fish consumption was 0.89. In addition, the pooled adjusted risk of depression for the highest versus lowest category of omega-3 intake was 0.87. In an analysis of dose–response effects, the pooled adjusted relative risks for an increment of one serving a week of fish consumption and 500 mg a day of omega-3 fatty acid intake were 0.89 and 0.99, respectively [30]. In another meta-analysis of 31 studies including 255,000 individuals and over 20,000 cases of depression, fish consumption was associated with a reduced risk of depression (relative risk = 0.78), with a linear dose–response. A dose–response analysis revealed a J-shaped association with a peak decreased risk at 1.8 g a day intake of omega-3 fatty acids [31].

RCTs investigating the effects of omega-3 supplementation on depression have demonstrated positive results, although the dosage and type of supplementation affect therapeutic outcomes. In a meta-analysis of nine studies, the overall treatment effect of omega-3 supplements in reducing depressive symptoms for older adults was not statistically significant. However, it was found through a meta-regression analysis that interventions with doses of omega-3 supplementation greater than 1.5 g/d had a statistically significant average effect size of −0.43 [32]. Finally, in a meta-analysis of 35 double-blind, RCTs and almost 11,000 participants with depression, EPA-predominant formulations (> 50% EPA) demonstrated clinical benefits compared with a placebo (effect size = 0.61). However, no positive effects were found from DHA-predominant formulations (> 50% DHA) [33]. It also seems that the adjunctive use of omega-3 supplementation may be beneficial for adults with depression. As an adjunctive treatment to antidepressant medication, Sarris et al. [34] found in their meta-analysis that omega-3 supplementation had a moderate-to-strong effect compared to a placebo.

B vitamins

There is evidence of an association between vitamin B status (e.g., vitamins B6, B12, and folate) and depression. In a systematic review of 11 observational studies, low folate levels were associated with an increased risk of depression (odds ratio = 1.55). The data also indicated that folate levels were lower in people with depression [35]. Bender et al. [36] also found a significant small effect size, such that individuals with depression had lower folate levels than those without

depression (effect size = -0.24). In a cohort study spanning three years, women in the highest tertile of vitamin B6 intake from food were 43% less likely to become depressed when adjusting for demographic and health factors (odds ratio = 0.57). Men in the highest tertile of dietary vitamin B12 intake had a reduced risk of depression (odds ratio = 0.42) [37]. Low folate and B12 serum levels also seem to be associated with depression in older-age populations [38]. While association does not confirm causation, in a systematic review and meta-analysis of 11 randomised, placebo-controlled trials of folate and vitamin B12 as an adjunct to antidepressants, it was concluded that their short-term use had no effect on depressive symptoms in adults with major depression although their prolonged intake (several weeks to years) was associated with a reduced risk of relapse and the onset of clinically-significant symptoms in at-risk individuals [39]. As an adjuvant treatment for depression, it was also confirmed in a separate meta-analysis that methylfolate but not folic acid enhanced outcomes compared to antidepressants alone [34].

Vitamin D

In a *meta*-analysis of 11 cross-sectional studies and over 43,000 people and five cohort studies comprising over 12,500 primarily elderly participants, an inverse association between depression and serum vitamin D levels was identified [40]. These findings were confirmed in another meta-analysis comprising one case-control study, 10 cross-sectional studies, and three cohort studies with a total of approximately 31,000 participants. Lower vitamin D levels were found in people with depression compared with controls (standardised mean difference = 0.60) and there was an increased odds ratio of depression for the lowest versus highest vitamin D categories in the cross-sectional studies (odds ratio = 1.31). The cohort studies also showed a significantly increased hazard ratio of depression for the lowest versus highest vitamin D categories (hazard risk = 2.21) [41].

Although findings from interventional studies are not entirely consistent, the bulk of evidence points toward mood-enhancing effects from vitamin D supplementation in individuals with depression. In a meta-analysis of four trials involving 948 participants, the pooled mean effect size for vitamin D supplementation on depressive symptom ratings in adults with major depression was 0.58 [42]. Spedding [43] completed a meta-analysis on RCTs examining the effects of vitamin D supplementation in adults with depression. However, only studies without biological flaws were included (i.e., in adults with low baseline vitamin D levels and where supplementation increased vitamin D levels). Based on the seven eligible studies, vitamin D supplementation significantly reduced depression (effect size = 0.78). In contrast to these positive findings, studies with biological flaws were mainly inconclusive, with the analysis demonstrating a statistically significant worsening in depression by taking vitamin D supplements (effect size = -1.1). As an adjunct to antidepressant medications, Sarris and colleagues [34] concluded in their meta-analysis that there was supportive evidence for vitamin D as an adjuvant agent in adults with depression.

Magnesium

Research into the relationship between magnesium stores and magnesium intake is inconsistent although increasing evidence suggests there may be a relationship, albeit, not a clearly defined one. In a meta-analysis of 11 studies, lower serum magnesium in depressed adults compared to non-depressed controls was identified, although these findings were largely influenced by results from two studies. However, there were no significant differences in magnesium levels in the studies analysing plasma and CSF concentrations [44]. In another meta-analysis of six observational studies (three cohort studies, two cross-sectional studies, and a case-control study) with a total of approximately 19,000 patients, the pooled relative risk of depression in patients with

hypomagnesaemia was 1.34 [45]. A further meta-analysis of 17 epidemiological studies found that when comparing the highest with the lowest magnesium intake, the pooled relative risks of depression were 0.81 for magnesium. A dose–response analysis demonstrated a non-linear relationship between dietary magnesium intake and risk of depression, with the largest risk reductions observed at an intake of 320 mg a day [46]. Finally, in another meta-analysis, adherence to a magnesium-rich diet was negatively associated with depression in cross-sectional (odds ratio = 0.66) but not prospective studies. Interestingly, magnesium levels were higher in depressed patients treated with antidepressants and/or mood stabilisers. No association between magnesium levels and symptom severity was identified, and magnesium supplementation was associated with a decline in depressive symptoms in uncontrolled (effect size = −1.60) but not placebo-controlled trials (effect size = −0.21). However, the number of placebo-controlled studies was limited [47].

Zinc

Studies examining zinc concentration in depressed participants suggest they have low levels. In a meta-analysis of nine studies, a relative risk of 0.68 was identified for the highest versus lowest dietary zinc intake [48]. The association between zinc and depression was also confirmed by another meta-analysis of 17 studies where zinc concentrations were approximately −1.85 μmol/L lower in depressed participants compared to controls. Greater depression severity was also associated with a greater relative zinc deficiency [49]. Despite these low zinc concentrations in depressed populations, there are currently no RCTs examining the therapeutic effects of zinc supplementation on depression adults.

Iron

There is limited evidence supporting a relationship between iron and depression, although a meta-analysis of three studies for dietary iron intake demonstrated that, for the highest versus lowest dietary iron intake, the relative risk for depression was 0.57 [48]. As a treatment for depression, the evidence is limited, although six-weeks of iron supplementation in mothers with post-partum depression commenced one-week after delivery significantly improved depressive symptoms compared to a placebo [50].

Conclusions: there is an increasing body of evidence suggesting low levels of most of the reviewed nutrients are associated with depression in adults. Lower levels have also been associated with an increased risk of developing depression and an increased risk of relapse. However, an association does not confirm causation, as lower nutrient levels may simply be an artefact of a poor diet, increased pharmacological intake, or co-morbid medical conditions. Further research is required to assess the antidepressant effects of restoring low nutrient levels in depressed individuals through robustly-controlled clinical trials. The efficacy and safety of supplementation in people with normal body stores compared to deficient levels also requires investigation. The potential of increasing nutrient status (through diet and/or supplementation) as an adjunctive treatment also requires further research. Currently, the greatest body of supportive evidence as an antidepressant treatment is for omega-3 fatty acids and vitamin D (but only in people with deficient levels).

Treatment Cautions: Nutraceutical supplementation is generally safe and well-tolerated. However, caution is warranted with the following: [1] omega-3 fatty acids have blood thinning effects so medical consultation is recommended in people with a bleeding disorder and/or people taking anticoagulant and antiplatelet medications. Discontinuation is often recommended several days prior to surgical procedures; [2] iron supplementation should only be administered after identification of iron deficiency as iron overload is possible. Hemochromatosis and other iron overload disorders should also be ruled out

prior to administration; [3] magnesium supplementation can lead to diarrhoea and loose stools. A gradual introduction may, therefore, be required, and avoidance of poorly absorbed forms of magnesium (e.g., magnesium oxide) is recommended; [4] folic acid administration should be done cautiously in people with pernicious anaemia who also require vitamin B12 supplementation. Further information on supplementation can be obtained from Braun and Cohen [51].

Herbs and other nutraceuticals

In addition to diet quality and the nutraceuticals already discussed, there is an increasing body of evidence supporting the antidepressant effects of several herbs and other nutraceuticals as stand-alone and/or adjunctive agents. St John's Wort has been extensively investigated in RCTs and the bulk of evidence suggests that it can effectively reduce depressive symptoms in adults with mild-to-moderate depression with comparable efficacy to pharmaceutical antidepressants [52,53]. However, St John's Wort interacts with most pharmaceutical antidepressants and therefore does not present as a viable adjuvant agent for antidepressant users. S-adenosylmethionine has been investigated in several RCTs and may be an effective stand-alone or adjuvant agent for adults with depression [34], although more research was recommended by a recent Cochrane review [54]. Saffron has an increasing body of evidence supporting its antidepressant effects and several meta-analyses have confirmed it is an effective stand-alone option for adults with depression [55–57]. However, no studies have been conducted examining its effects as an adjunctive agent, although one is currently underway by the author. Curcumin, the primary therapeutic compound in the spice turmeric has been investigated in several RCTs and has been shown to effectively reduce depressive symptoms in adults with depression [58,59]. In one study it was also found to be an effective add-on agent to pharmaceutical antidepressants in adults with depression [60]. There is also increasing evidence for the antidepressant benefits of probiotics in depressed populations, although it has only been investigated as a stand-alone agent [61,62]. Finally, n-acetylcysteine was confirmed in a meta-analysis to effectively lower depressive symptoms in adults with depression compared to a placebo [63] but had limited effects as an adjunct to antidepressants [64].

Conclusions: there is an increasing body of evidence suggesting herbals and nutraceuticals can help lower depressive symptoms in adults with depression. However, further research is required to identify optimal doses, active ingredients, timing, interactions, contra-indications, safety, and efficacy associated with their long-term use. The quality of herbal ingredients can also vary significantly, so research on standardised, replicable extracts are important. The efficacy of supplements as an add-on treatment to pharmacotherapy and psychological therapy are also limited and require further investigation.

Treatment Cautions: Herbal and nutraceutical supplementation is generally safe and well-tolerated although caution is warranted for the following: [1] St John's Wort can interact with many medications including pharmaceutical antidepressants and the contraceptive pill. People taking medications should, therefore, consult with their medical practitioner prior to its commencement; [2] S-adenosylmethionine intake has been associated with the induction of manic symptoms. It is therefore important to rule out bipolar disorder prior to administration; [3] most herbal products have not been examined for efficacy and safety during pregnancy and breastfeeding. Therefore, use by pregnant and breastfeeding mothers is not recommended for many of the mentioned herbal supplements. Further information on supplementation can be obtained from Braun and Cohen [51].

Exercise

It has been confirmed through systematic reviews and meta-analyses that adults with depression are more sedentary and exercise less than non-depressed adults. Increased sedentary activity is associated

with a greater risk of developing depression [65,66]. Moreover, results from several meta-analyses have confirmed exercise as an effective treatment for adults with mild-to-moderate depression [67–69]. Schuch, et al., [67] concluded that larger effects were found from interventions utilising moderate-intensity aerobic exercise supervised by an exercise professional. In head-to-head comparisons, exercise has been shown in several studies to be as effective as antidepressant medications and CBT for the treatment of adult depression [70,71].

As an adjunct to pharmacotherapy or CBT, there is evidence to suggest additional benefits from combined treatments. In a meta-analysis comprising four studies (188 participants), the combination of exercise and antidepressants as a treatment for depression compared to antidepressant medication alone yielded a moderate effect size (effect size = −0.50) that trended toward significance in favour of the combined treatment [69]. As an add-on to antidepressant medications in hospitalised patients with major depressive disorder, 10 days of aerobic exercise enhanced treatment outcomes compared to a stretching group and a control group where no adjunctive intervention was offered. Compared to the stretching intervention, aerobic exercise had a large treatment effect [72]. It also seems that exercise as an adjunctive treatment has enduring effects, as a follow up in adults with mild-to-moderate depression revealed lower depression scores at 12-months compared to treatment as usual. However, positive effects were mainly observed in participants allocated to a light exercise intervention compared to participants in moderate and vigorous exercise interventions [73].

There is also preliminary evidence to suggest exercise as an adjunct to CBT may enhance treatment outcomes. In a small-scale, 12-week study on patients with moderate-to-severe depression, greatest reductions in depression scores (although not statistically significant) were observed in the exercise plus CBT group, followed by CBT alone, then exercise alone, and finally usual care. At 12 and 24-weeks follow up, only those in the combined group sustained their lower depression scores [74]. In a 12-week study in mild-to-moderately depressed participants, the addition of exercise three times a week led to greater reductions in suicidal ideation, depression, and increases in activities of daily living compared to the CBT-only group [75]. Exercise combined with antidepressant medication and CBT may also provide additional therapeutic benefits. In a small-scale study, low-active, already medicated patients with major depressive disorder were allocated to an 8-week exercise intervention plus group CBT or group CBT alone. Greater reductions in depression symptoms were observed in the combined group, with 75% of patients obtaining either a therapeutic response or a complete remission of symptoms compared to 25% of patients offered CBT alone. In addition, exercise was associated with greater improvements in sleep quality and cognitive function. The exercise group also had a significant increase in plasma brain-derived neurotrophic factor which was associated with improvements in depression scores and sleep quality [76].

Conclusions: there is a robust body of evidence confirming exercise as an effective stand-alone intervention for adults with depression. There is also increasing evidence to suggest that it may be a useful adjunctive intervention to pharmacotherapy and/or psychological therapy, although more research is required. Further research is also important to identify the type, frequency, duration, timing, and intensity of exercise that is required to achieve optimal antidepressant effects. Motivation can be a barrier to implementing exercise interventions for depressed populations so actively incorporating motivation-enhancing and behaviour-change strategies will be important. Health and fitness levels also need to be considered when developing exercise goals. For many adults, reducing sedentary behaviour or increasing lifestyle-based activities may be an initial treatment goal.

Treatment Cautions: People with a medical condition such as heart disease, some metabolic disorders (e.g., diabetes) and acute or chronic pain conditions should seek assessment and recommendation from their healthcare provider prior to the commencement of an exercise program.

Sleep

It is estimated that up to 90% of individuals with depression complain of problems with their sleep [77,78]. Approximately two-thirds of these complaints are associated with insomnia, while 15% of people report hypersomnia. Experiencing sleep difficulties increases the risk of developing depression. In a longitudinal study over a four-year period comprising approximately 19,000 participants with insomnia, the cohort had over eight times greater risk of developing depression compared to people with undisturbed sleep [79]. Further confirmation of a relationship between sleep problems and depression is provided by a meta-analysis of seven prospective studies which showed that compared to people with normal sleep duration, the pooled relative risk of depression was 1.31 in people experiencing short sleep duration and 1.42 in adults reporting long sleep duration [80]. Increased risk of suicidal ideation is also associated with insomnia. Difficulty maintaining sleep was the most predictive marker of suicidal ideation, followed by difficulty initiating sleep [81]. There is also a strong association between depression and obstructive sleep apnoea (OSA), with approximately 35% of individuals with OSA experiencing depressive symptoms [82]. Research also confirms that suffering from insomnia is associated with treatment-resistant depression [83]. In a study spanning a two-year follow-up, long and short sleep duration, but not insomnia, was associated with persistence of depressive symptoms [84]. Hypersomnia and sleep-onset insomnia were also associated with an increased risk of relapse in adults with remitted depression over a 12-month period [85]. It is important to note that treating insomnia may be a viable treatment option for depression. For example, in people with comorbid depression and insomnia, findings from two meta-analyses confirm that CBT for insomnia effectively reduces comorbid insomnia and depressive symptoms [86,87].

Conclusions: there is strong evidence to suggest that treating sleep difficulties in adults with depression can enhance treatment outcomes and reduce the risk of relapse. In many individuals with comorbid sleep problems and depression, it may be prudent to target sleep problems first as research suggests depressive symptoms can resolve following improvements in sleep quality.

Sunlight

Most of the research on the relationship between sunlight exposure and depression suggests a positive influence of sunlight exposure on mood and depressive symptoms. A systematic review by Veleve et al., [88] confirmed that in six out of the seven identified studies, exposure to ultraviolet radiation (including sunlight) was associated with improvements in mood. However, as most studies utilised a cross-sectional design it is difficult to identify the directional relationship between sunlight exposure and depression. In a prospective study lasting approximately 2.3 years, higher levels of reported sun exposure, and not vitamin D status, were associated with less depressive symptoms and fatigue in participants with multiple sclerosis [89]. Lee et al., [90] found that after controlling for sleep quality, mean daily sunlight exposure between 10:00 and 15:00 significantly predicted greater resilience in college students. In a cross-sectional study, outdoor work for greater than two hours a day during winter protected against mood difficulties but was not associated with improvements in depression [91]. Sunlight may also have positive effects on cognitive function as a study on depressed participants confirmed a dose–response relationship between sunlight exposure and cognitive function, with lower levels of sunlight associated with impaired cognitive status [92]. The effect of sunlight/daylight exposure in hospitalised, depressed patients has also been examined. Using a crossover study design, mildly depressed older-age inpatients were exposed to either two days of conventional room light (standard light) or artificial sunlight for 30 min. Room illumination was implemented with an artificial skylight which perfectly imitated solar indoor illumination. Compared to standard light, exposure

to artificial sunlight had a subjective calming effect over time, decreased heart rate, and increased vagal tone both under cognitive workload and in resting conditions [93]. Moreover, in a retrospective study, median hospital stay was 14 days in a hospital with lower light exposure compared to 11 days in a higher-light hospital [94]. Finally, Gbyl et al., [95] found that in depressed hospitalised patients, the ward receiving the greatest daylight had a substantially-reduced length of hospital stay compared to the ward with lower daylight exposure (29.2 days versus 58.8 days, respectively).

How sunlight impacts on mood is still uncertain although there are several plausible mechanisms. Increasing exposure to sunlight is generally associated with increased outdoor activity. Therefore, improvements in mood may simply be due to increased activity rather than exposure to sunlight. However, this does not account for its positive effects during hospitalisation. Sunlight exposure can also increase vitamin D concentrations which may be associated with mood improvements. Although vitamin D levels did not account for the improvements in mood identified by Knippenberg et al. [89]. Other potential mechanisms for the mood-enhancing effects of sunlight include its effects on HPA axis activity [96], on the serotonergic/melatonergic system [97,98], and on the immune system [99]. Sunlight exposure may also reduce depression via its impact on sleep as studies have demonstrated morning exposure to sunlight and overall daily sunlight exposure are associated with improved sleep quality [100–102]. It is important to note that the timing of sunlight exposure likely influences its impact on mental health. Sunlight/ light exposure can alter circadian hormone patterns so morning and early afternoon exposure may have the greatest therapeutic effects. This is important as there are studies suggesting an increased frequency of mania and suicide during months with the greatest sunlight [103].

Conclusions: increasing sunlight exposure could be a simple adjunctive treatment for adults with depression. However, further research is required to determine optimal timing, duration, and intensity of sunlight exposure to achieve the greatest mood-enhancing effects. Caution around timing is warranted in people with bipolar disorder, and sensible sunlight exposure is important to prevent skin damage and carcinomas.

Bright-light therapy

Bright-light therapy involves daily light exposure using a light therapy lamp of greater than 5000 lx for at least 30 min, most often applied in the morning. Bright-light therapy is often used as a treatment for seasonal affective disorder with generally positive effects [104]. As a treatment for non-seasonal depression, increasing research suggests it may also be a viable option. A meta-analysis of nine trials on adults with non-seasonal depression confirmed a significant reduction in depressive symptoms after bright-light therapy (effect size = −0.62). In particular, bright-light therapy was efficacious when administered for two-to-five weeks (effect size = −0.78) and as monotherapy (effect size = −0.71) [105]. In another meta-analysis consisting of 20 RCTs and 881 participants, bright-light therapy was confirmed as an effective treatment for depression (effect size = −0.41) [106]. Bright-light therapy may also be a viable adjunctive agent in adults with depression. A meta-analysis of 10 studies and 458 patients with non-seasonal depression confirmed bright light therapy as an add-on treatment to antidepressant medications enhanced treatment outcomes compared to stand-alone antidepressant pharmacotherapy with an effect size of 0.5 [107]. Despite these positive findings, caution is warranted as bright light therapy may trigger an episode of mania in patients with bipolar disorder.

Conclusions: there is an increasingly robust body of evidence suggesting bright-therapy may be an effective treatment for depression as a stand-alone or adjunctive treatment. Further research is required to determine the optimal duration, timing, and intensity of light exposure. The enduring effects of bright light exposure also requires further

investigation.

Nature

There is increasing research to suggest positive mental-health effects are derived from nature exposure. A review of epidemiological studies confirmed that exposure to greenness was associated with lower depression and depressive symptoms [108]. This finding was supported by a systematic review of 28 studies demonstrating a positive relationship between surrounding greenness and mental health in adults [109]. Greater availability of green and blue space (i.e., lakes and oceans) within 1 km from one's home was also associated with anxiety and mood disorders, with the largest benefits associated with blue space availability [110]. Despite these positive relationships, an association does not confirm causation. However, further evidence of the mental-health benefits of nature exposure is derived from studies demonstrating greater mental and cognitive benefits in participants exposed to outdoor exercise compared to indoor exercise. A meta-analysis of 10 studies involving over 1200 participants confirmed exercise in the presence of nature improved self-esteem and mood. Dose responses for both intensity and duration showed large benefits from short participation in green exercise, and then diminishing but still positive returns over time. Every study in this review found exercising in a green environment improved both self-esteem and mood, and the presence of water generated even greater effects. Studies on adults with a diagnosed mental illness had the greatest positive effects on self-esteem [111]. Further evidence of the benefits from outdoor exercise is provided by another systematic review of eleven trials and 833 adults. All interventions consisted of a single episode of walking or running indoors with the same activity at a similar level conducted outdoors on a separate occasion. Compared with exercising indoors, exercising in natural environments was associated with greater feelings of revitalisation and positive engagement; decreased tension, confusion, anger, and depression; and increased energy. Participants also reported greater enjoyment and satisfaction with outdoor activity and declared a greater intent to repeat the activity at a later date [112].

In a systematic review of 28 studies comparing a control condition with the antidepressant effects of forest therapy (e.g., walking in a forest environment or experiencing the forest through the five senses; ranging from one day to twelve weeks with a duration from 12 min to three hours), it was concluded that forest therapy was an emerging and effective intervention for adult depression [113]. There is also preliminary evidence suggesting that nature exposure can reduce rumination, which is a common problem in people with depression. In one study on healthy participants, a 90-min walk in a natural setting decreased both self-reported rumination and neural activity in the subgenual prefrontal cortex, whereas a 90-min walk in an urban setting has no such effects [114]. A study on adults with major depressive disorder showed that when participants were asked to think about an unresolved negative autobiographical event to prime rumination, taking a 50-min walk in a natural environment resulted in greater mood improvements compared to walking in an urban setting [115]. While 'real world' nature exposure is likely to have the greatest mental health benefits, it seems that 'virtual' exposure may also be beneficial. In a study on healthy participants, video presentations of 'wild' nature resulted in significantly higher levels of positive affect and lower levels of negative affect compared to a non-nature control. Video exposure to 'urban' nature was also associated with significantly lower levels of negative affect, but not higher levels of positive affect compared to the non-nature control video [116].

Conclusions: spending time in nature could be a simple adjunctive option to reduce depressive symptoms in adults with depression. However, most research has been cross-sectional and there are other variables that could account for the positive association between nature exposure and mood. The efficacy of nature exposure on mood in depressed populations also requires attention as most studies have been

conducted on healthy people. Given the antidepressant benefits of exercise, supporting outdoor exercise may have additional effects on mood. Further investigation into the potential of virtual nature exposure is also warranted.

Music

The effects of music on mood and depressive symptoms has been investigated in several clinical trials. Music therapy can comprise several different formats including passively listening to music, active singing, and/or playing a musical instrument. In a Cochrane systematic review and meta-analysis comprising nine studies and 421 participants, it was concluded that music added to treatment as usual provided short-term benefits for people with depression compared to treatment as usual alone (effect size of −0.98 for clinician-rated instruments and −0.85 for patient-reported instruments) [117]. Music therapy seems to have particular benefits for older adults with depression as a meta-analysis comprising 10 studies and 909 participants demonstrated music therapy plus standard treatment had large treatment effects on depressive symptoms in older adults compared to standard treatment alone (effect size = 1.02). Findings from 3 studies and 440 participants also demonstrated music therapy added to standard care and standard drug treatment was more effective than standard care plus standard drug treatments alone (effect size = 0.90) [118].

Conclusions: there is a solid body of evidence suggesting music can have mood-enhancing effects. This is a simple adjunctive intervention that seems particularly beneficial for older adults. Investigations into the efficacy of different types of music exposure and personality variables associated with music's antidepressant efficacy requires further investigation.

Alcohol and nicotine use

Alcohol use

There is strong evidence confirming high comorbidity between alcohol dependence and depression. In a meta-analysis by Boden and Fergusson [119], it was found that the presence of either depression or alcohol-use disorder doubled the risks of the second disorder. Moreover, it was reported that the most plausible causal association was one in which alcohol use increased the risk of depression, rather than vice versa. Unfortunately, it seems that the presence of alcohol problems reduces the efficacy of depression interventions. In a meta-analysis of 33 studies examining the benefits and risks of antidepressants for the treatment of people with co-occurring depression and alcohol dependence, it was confirmed that there was low-quality evidence supporting the clinical use of antidepressants. While antidepressants had positive effects on certain relevant outcomes related to depression and alcohol use, the clinical relevance was modest [120]. In a meta-analysis of 11 studies, it was found in adults with an alcohol use disorder, symptoms of depression improved rapidly after specific treatments for their depression. However, the effect size was small compared to placebo treatments (effect size = 0.17) [121]. The limited efficacy of antidepressant medications in people with alcohol-related problems is further highlighted by a study that demonstrated that discharging patients with an antidepressant prescription was not associated with a reduction in acute alcohol-related re-admissions (readmission rates of 44.6% and 47.0%, respectively) [122]. Further evidence of the limited efficacy of treatments for depression in people with alcohol dependence is provided by a systematic review on treatments for people with co-occurring alcohol misuse and depression where it was concluded that there was little evidence to suggest greater outcomes from dual-focused treatments (i.e., treatment for both depression and alcohol use) compared to single-focused treatments (targeting alcohol use alone). While some benefits from dual-focused treatments were found, the methodological quality of studies was found to be low [123].

Conclusions: these results suggest that in people with comorbid alcohol dependence and depression, the efficacy of treatments for depression (primarily antidepressant medications) are limited. Moreover, it seems that treatments for alcohol use alone have similar antidepressant effects compared to dual treatments. Therefore, in people with an alcohol use disorder and depression, alcohol-targeted treatment may be an essential first-line treatment. Assessing and working with motivational issues will also be important.

Nicotine use

Consistent with findings on alcohol dependence, there is a higher rate of depression in tobacco smokers. In a meta-analysis of observational studies comprising over 120,000 people, it was confirmed that current smokers had 1.85 times greater odds of depression, 1.71 times greater odds of anxiety, and 1.69 times greater odds of psychological distress than people who never smoked. Former smokers also had greater odds of depression, anxiety and psychological distress than people who never smoked [124]. These results were confirmed by another meta-analysis where current smokers were 1.5 times more likely to be depressed than people who never smoked and 1.76 times more likely than former smokers. In prospective studies, smokers at baseline had a 1.62 greater odds of incident depression at follow-up than people who never smoked [125]. Unfortunately, there is research to suggest depression treatment outcomes are lower in depressed smokers compared to non-smokers. In one study, at six months post-treatment smokers had a 60% greater likelihood of having persistent depressive symptoms compared to non-smokers. They also had lower remission rates (odds ratio = 0.60) and rates of treatment adherence (odds ratio = 0.67) [126]. Reduced mental treatment outcomes have also been identified in smokers with bipolar disorder and schizoaffective disorder [127,128].

It seems that smoking cessation interventions are associated with reduced depressive symptoms. This was confirmed in a meta-analysis on 20 smoking cessation interventions for patients with current depression where smoking abstinence was associated with an improvement in depressive symptoms [129]. In another meta-analysis of 26 longitudinal studies, anxiety, depression, mixed anxiety and depression, and stress significantly decreased between baseline and follow-up in quitters compared with continuing smokers. Follow-up mental health scores were measured between seven weeks and nine years after baseline [130].

Conclusions: rates of depression are higher in smokers and it seems that smoking may be associated with worse mental-health treatment outcomes. However, smoking cessation is associated with mental-health improvements. Targeting nicotine use may potentially be an option to enhance treatment outcomes in depressed smokers. However, assessing and working with motivational issues will also be important.

Meditation, yoga, and mindfulness

Meditation, yoga, and mindfulness-based therapies are increasing in their popularity as treatments for depression. There is accumulating research supporting their antidepressant efficacy in adults with depression. In a meta-analysis comprising 11 RCTs in adults with a current episode of major depressive disorder, mindfulness-based interventions were associated with significantly greater reductions in depressive symptoms compared to control conditions at post-treatment (effect size = −0.59). However, this significance disappeared at post-treatment follow-up. A subgroup analysis revealed that the positive benefits of mindfulness-based therapies occurred when they were included as adjunctive treatments [131]. In another meta-analysis of 12 RCTs and 578 individuals examining the effects of mindfulness-based interventions in participants with a current episode of depression or anxiety disorder, positive effects on severity of depression symptoms were found compared to control conditions (effect size = −0.73) [132]. In a

meta-analysis on 18 studies and 1150 participants, stand-alone mindfulness exercises had a small-to-medium effect on depression compared to control conditions (effect size = 0.41). This finding shows that the simple, regular practice of mindfulness exercises can be beneficial even if it is not used as part of a larger therapeutic intervention [133].

Mindfulness-based cognitive therapy (MBCT) is an intervention that incorporates mindfulness-based techniques as a component of cognitive therapy. It has been found that MBCT compared to usual care produces a significant, moderate-intensity reduction in rumination [134]. It has also been demonstrated from a meta-analysis on 10 RCTs and 1258 depressed patients with recurrent depression in full or partial remission, that MBCT can reduce the risk of depressive relapse within a 60-week follow-up period compared to people who do not receive MBCT (hazard ratio, 0.69). Moreover, comparisons with active treatments suggested a reduced risk of depressive relapse within a 60-week follow-up period (hazard ratio = 0.79) [135].

In relation to other meditative techniques, a meta-analysis on 15 RCTs showed a significant benefit in favour of meditative movement (i.e., Tai Chi, Qigong, and Yoga) on depression severity (effect size = −0.56). Meditative movement interventions also showed significantly improved treatment remission rates (odds ratio = 6.7) and response rates (odds ratio = 5.2) over passive controls [136]. Evidence supporting the antidepressant effects of yoga are also increasing. In a review of seven RCTs and 240 participants with depression, it was concluded that there was evidence for the positive effects of yoga compared to a placebo, and some evidence to suggest similar antidepressant efficacy compared to other evidence-based interventions. However, the strength of the conclusions was hindered by the limited availability of high-quality studies. There was also inconsistent evidence of the efficacy of yoga as an adjunctive intervention [137]. Yoga may also be beneficial for pregnant women in reducing depressive symptoms as the results from a meta-analysis of six RCTs and 375 pregnant women confirmed positive antidepressant effects when compared with comparison groups (e.g., standard prenatal care, standard antenatal exercises, social support, etc.) [138].

Conclusions: there is increasing evidence to support the antidepressant efficacy of meditative and mindfulness-based therapies for the treatment of depression. Moreover, MBCT seems to be effective in reducing relapse rates in adults with depression. Accumulating evidence also suggests yoga may have therapeutic benefits in adults with depression. However, further research is required to identify the types of meditative exercises, the intensity of treatment, and the treatment duration required for optimal antidepressant benefits. The adjunct effects of comprehensive mindfulness-based therapy and/or single mindful-based exercises also require further investigation.

Social connections

The importance of social connections on mental health is generally well acknowledged. There is also strong evidence supporting its importance in the prevention and treatment of depression. In a systematic review of studies conducted in Western countries, it was confirmed that most studies reported a significant association between social support and protection from depression among both males and females. The sources of social support most consistently associated with protection from depression in adults were spousal support, followed by support from family, friends, and children. Moreover, the type of social support most consistently associated with protection from depression in adults was emotional support followed by instrumental support [139]. Similar conclusions were obtained from a systematic review of 51 studies where it was concluded that there were consistent findings of significant protective effects from depression in people perceiving greater levels of emotional support, instrumental support, and large, diverse social networks. However, firm conclusions about the importance of social connectedness and negative interactions could not be made due to limited investigations into these variables [140]. It also seems that a

lack of social support is associated with poorer treatment outcomes in people with depression. In a systematic review comprising 34 studies, it was concluded that there was substantial evidence from prospective studies that people with depression who perceive their social support as poorer have worse outcomes in terms of symptoms, recovery, and social functioning. Loneliness also predicted poorer depression outcomes [141]. Interestingly, in another review it was found that depressive symptoms and the absence of social or marital support were significant risk factors for poor prognosis in cardiac patients [142]. Moreover, following an intervention comprising usual care, CBT, and exercise, participants with greater access to supportive social relationships reported greater improvements in depression compared to those with limited social relationships. Better supportive relationships were also associated with 2.17 times greater treatment response (50% score reduction) compared to participants with low availability of relationships [143].

The importance of social connections in depression is also supported by the efficacy of interpersonal psychotherapy (IPT), a psychological intervention that targets the resolution of interpersonal problems and enhancement of interpersonal relationships. In a meta-analysis, adjunctive IPT was more effective than IPT alone (effect size = 0.24), prevented the onset of major depression in people with subthreshold depression, and reduced relapse rates in depressed adults [144]. Befriending involves developing an emotionally supportive relationship in which one-to-one companionship is provided on a regular basis by a volunteer. In a systematic review of RCTs compared with usual care or no treatment, befriending had a modest but significant effect on depressive symptoms in the short term (effect size = −0.27) and long-term (effect size = −0.18) [145].

Conclusions: to enhance treatment outcomes, attention toward social connections will likely be important. Increasing social networks and social connections that provide emotional and instrumental support; while reducing loneliness and social strain are likely to be important components to enhance treatment outcomes and lower relapse rates in people with depression.

Religious and/or spiritual practices

Spirituality involves a sense of connection to something larger than ourselves and typically involves a search for life purpose or meaning. Spirituality is often associated with religion, although this is not essential. There is consistent research confirming a positive relationship between spirituality and mental health. In a systematic review comprising 74 studies assessing the role of religion on mental health outcomes, it was concluded that most reported a significant positive connection between religious beliefs and practices and mental health [146]. Among 43 publications identified in another systematic review, thirty-one (72.1%) found a positive relationship between the level of religious/spiritual involvement and mental health, eight (18.6%) had mixed results, and two (4.7%) reported worse mental health. All studies on suicide and stress-related disorders identified a positive association, while 79% of studies on depression were positive [147]. Positive effects of spirituality and religiosity on psychological outcomes were also identified in a systematic review on adolescents and emerging adults [148]. It also seems that prayer may have positive mental-health effects as a systematic review of 31 observational clinical studies found that in most studies private prayer (individuals praying for themselves) was associated with a significantly lower prevalence of depression, higher optimism, and lower anxiety [149].

Investigations of interventions comprising spiritual practices also seem to be generally positive. A meta-analysis comprising 23 RCTs showed religious/spiritual interventions had significant beneficial effects on anxiety, and to a lesser extent depressive symptoms [150]. Religious/spiritual interventions were defined as 'messages to health' framed by themes of spiritual relevance. This 'message' could use spiritual or religious themes, such as taking care of the body God has

provided, reflective discussions on moral and ethical values to accept the situation faced, or meditation. Finally, in a meta-analysis comprising 16 studies examining the efficacy of faith-adapted CBT, it was found there were larger treatment effects compared to standard CBT. However, most studies had substantial methodological limitations that may have affected identified outcomes [151].

Conclusions: there is a good body of evidence confirming a positive relationship between spirituality and depression. Although further robust research is required, including a spirituality component to psychological interventions has the possibility of enhancing treatment outcomes. However, this will likely be most effective in people with positive beliefs about religion and/or spirituality. Moreover, the essential components of spirituality associated with its positive mental-health effects are uncertain and require further investigation.

Medical conditions

Research confirms a high co-morbidity between depression and most medical diseases. Having a chronic medical disease increases the risk of depression by 2.6 times [152]. One-year prevalence studies show that 9.3% to 18% of people with a single physical disorder have depression, while 23% of patients with two or more physical conditions have depression [152]. The point prevalence rates of having a chronic pain condition was 49% in people with major depression [153]. In terms of specific diseases, depression was found in 31% of stroke survivors [154], 21.5% of patients with heart failure [155], 16.5% of adults with type 2 diabetes [156], 16.8% of people with rheumatoid arthritis [157], 31% in people with a chronic digestive disease [158], and 23% in adults with obesity [159]. While prevalence rates vary significantly based on factors such as age, gender, country, diagnostic measure, and prevalence measures used (i.e., one-year versus lifetime), findings consistently confirm a high-comorbidity. This association with depression is generally considered bi-directional for most disease states [160–162].

Medical comorbidity with depression has significant clinical implications as it is associated with a reduced quality of life, greater functional impairment, increased number of self-reported symptoms (even after controlling for severity), and increased mortality compared to having a chronic medical condition alone [152]. Having a medical condition may also lower treatment responses from pharmacological treatments for depression, although findings are inconsistent [163,164]. However, higher inflammation, which is commonly associated with many medical diseases has been found to be associated with lower treatment response from antidepressant medications [165] and CBT [166].

Conclusions: identifying and treating depression in people with medical conditions is important as it can have a negative impact on disease morbidity and mortality. In depressed adults with a comorbid medical condition, it seems that pharmacological and psychological treatments for depression are effective, although there is inconsistent evidence about their efficacy compared to healthy depressed populations. However, in most cases it is likely prudent to provide treatments for both depression and the medical condition to enhance treatment outcomes. This recommendation is supported by evidence suggesting inferior treatment outcomes from CBT and pharmaceutical antidepressants in people with higher pre-morbid inflammation. Research into the efficacy of integrative interventions on mental and physical outcomes will be important in the future.

Conclusions

We are increasingly aware that depression is a multifactorial condition that can be influenced by a range of psychological, biological, social, lifestyle, dietary, and environmental factors. It is likely that the multifactorial nature of this condition reduces the gains derived from stand-alone or combined pharmacological and psychological

interventions. While psychological treatments target thoughts, beliefs, and some behaviours associated with depression, there remain several other factors that receive little or no attention. The same applies with pharmacological treatments which target physiological factors associated with depression (most commonly believed to be associated with neurotransmitter disturbances), but neglect other lifestyle, dietary, psychological, and social factors that can influence one's mental health. Combining pharmacological and psychological treatments increase the scope of variables targeted, however, there remain an array of influences that continue to be overlooked. While several factors that are associated with depression have been reviewed in this article, there remain other potential options that could comprise part of an adjunctive or integrative approach. For example, there is research suggesting potential benefits from adjunctive thyroid medications [167], testosterone replacement (particularly for ageing men) [168], acupuncture [169], and hypnosis as an adjunct to CBT [170]. There is also increasing evidence confirming the influence of the gastrointestinal tract on mental and cognitive health, thereby making this a potential target for adjunctive treatment for depression [171].

It is proposed in this review that by considering a greater range of potential causative or contributory factors associated with depression, treatment outcomes may be enhanced. A summary of treatment options covered in this review is detailed in Fig. 1 and steps in developing a personalised integrative intervention are summarised in Fig. 2. A helpful integrative treatment decision tree is also summarised by Sarris [172]. However, integrative approaches for depression require further investigation through robustly-designed RCTs. Investigating the efficacy of integrative treatments can present difficulties as increasing the number of variables targeted in an intervention makes it difficult to decipher the most crucial component(s) associated with change. However, this could be overcome by adding one intervention at a time to determine its impact on treatment outcomes. Unfortunately, a criticism associated with this approach is that greater outcomes may be more likely when the 'whole system' is targeted rather than targeting individual parts in isolation. Some changes advocated in an integrative approach are also minor, so the effects on treatment outcome are likely
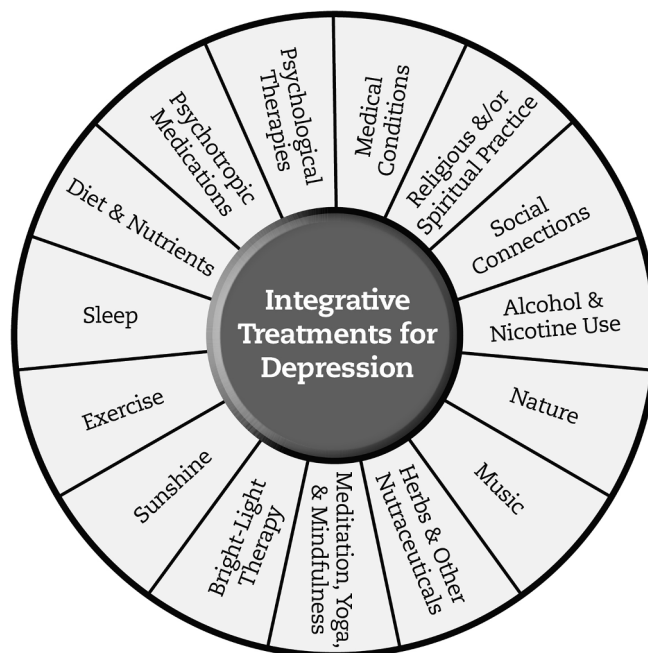

Fig. 1. Integrative Treatment Options for Depression. It is proposed that to enhance treatment outcomes for depression, adjunctive/integrative approaches should be evaluated in future research. Options with evidence supporting their efficacy as stand-alone or adjunctive interventions are included in this figure although the list is not exhaustive.
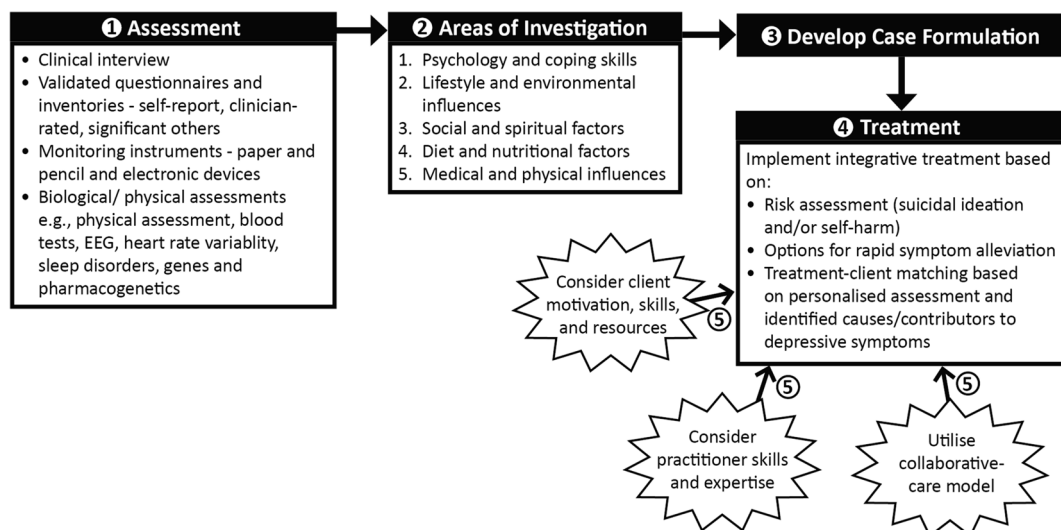
Fig. 2. Steps in Developing Personalised Integrative Interventions. Developing an individually-tailored integrative intervention comprises several steps: (1) the administration of appropriate and validated assessment instruments including a clinical interview, validated questionnaires (e.g., self-report, clinician-rated, and inventories completed by significant others), monitoring tools (e.g., paper and pencil and/or electronic devices such as sleep monitors, physical activity trackers, and smart-phone applications), and biological, medical and physical assessments (e.g., blood tests, physical examination, genetic testing, EEG, and nutritional testing); (2) areas of investigation should include psychological influences and coping skills, lifestyle and environmental factors (e.g., sleep quality, physical activity, current stressors, and sunlight exposure), quality of social connections, spiritual influences and life meaning, diet quality and nutritional status, and medical and physically-related influences (e.g., comorbid medical conditions, hormonal disturbances, and other medication use); (3) based on these assessments a personalised case formulation can be developed that incorporates potential causes and contributors to depression; (4) treatment plans are developed incorporating integrative, evidence-based treatment options; (5) these plans are personalised and are influenced by client motivation, skills and resources, practitioner skills and expertise, multi-disciplinary relationships, and treatment availability from other relevant service providers (e.g., yoga/meditation instructors, exercise physiologists, nutritionists, and naturopathic practitioners). Treatments should also be informed by assessed suicidal risk and interventional options that have the potential to deliver rapid symptomatic improvement.

to be small (e.g., increasing morning sunlight exposure or listening to music). When a small effect size is predicted, large sample sizes are required to detect statistically significant treatment effects. However, utilising a mixed method research design comprising a systematic integration of both quantitative and qualitative data may assist in the identification of multi-factorial causal pathways and efficacy associated with specific integrative components.

Another investigational possibility is to provide a more comprehensive, integrative intervention and then examine its impact on behavioural and physiological changes (i.e., changes in diet, nutrient status, physical activity, sleep, social connections, outdoor activity, etc.). This will facilitate a greater understanding of the relationship (or correlation) between such changes and mood improvements. While a significant correlation does not confirm causation, it will help clarify the potential role each behaviour has on mental-health outcomes. Another possibility is to provide individually-tailored integrative interventions based on assessed areas of need (see Fig. 2). This minimises the potential of treatment redundancy by matching treatments to suitable individuals. For example, dietary interventions may only be offered to depressed individuals eating an unhealthy diet, exercise interventions offered to physically-inactive patients, and vitamin D provided to vitamin D deficient patients. Moreover, the adoption of validated self-report or clinician-rated inventories, physiological biomarkers, and genetic testing present as options to facilitate better patient-treatment matching. For example, higher inflammatory markers such as C-reactive protein, tumour necrosis factor–α, and interleukin-6 are commonly observed in depressed populations [173,174]. This has clinical implications as higher inflammatory markers are associated with increased treatment resistance from cognitive behaviour therapy [166] and antidepressant medications [165,175]. Quantitative electroencephalography (EEG) assessment [176], genetic/pharmacogenetic testing [177,178], and heart rate variability measurements [179] also present as promising options to support patient-treatment matching. Such assessments could be used to facilitate decisions on the need and potential utility of personalised adjunct interventions.

A barrier to the incorporation of complementary and alternative medicine (CAM) treatments into mainstream interventions for depression is their acceptability and awareness by mainstream treatment providers such as psychiatrists, psychologists, and medical practitioners. This will be partly ameliorated through an accumulation of robust evidence supporting their efficacy as either stand-alone or adjunct treatments. However, increasing education and training to mental-health providers on evidence-based CAM therapies and the utility of a collaborative-care model are also essential. This is particularly important as research confirms poor patient-to-practitioner dialogue on CAM use. In a recent study, 42% of patients did not disclose CAM use to their medical practitioner [180]. Reasons for nondisclosure included physicians not asking about CAM, respondents believing that physicians did not need to know about their CAM use and worry of potential discouragement of CAM use by physicians.

Finally, it is important when developing an integrative approach to assess the applicability and acceptability of an approach with depressed populations. Motivation is a common problem in people with depression, so it is important to develop an intervention that will not overwhelm clients. However, this could be achieved by encouraging several small and achievable changes rather than large changes that require intensive effort and resources. As described in this review, many potential areas of change do not necessarily require dramatic changes in behaviour.

In conclusion, while pharmacological and psychological interventions are effective treatments for depression, we are not seeing increases in treatment efficacy over time. By utilising integrative interventions that target factors associated with depression and general mental wellbeing, improved treatment outcomes may be achieved. However, the efficacy, safety, and applicability of such interventions require investigation through robustly-designed RCTs in depressed populations.

Conflict of interest

The author declares no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.03.008.

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