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REVIEW OPEN ACCESS

The Effect of Natural Therapies in Combination with Usual Care for Depression: A Narrative Review

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Abstract

Introduction: Major depressive disorder (MDD) is the most common and debilitating form of depression with a 12-month prevalence of 4.7% and a lifetime prevalence of 11.2% in Canada. Various classes of antidepressants are commonly used treatments for MDD; however, high failure rates occur due to adverse events and discontinuation of use. Non-drug and alternative interventions are commonly sought by people when drug treatment fails. The purpose of this investigation was to analyze the evidence on the effect of natural therapies in combination with pharmaceutical standard of care for the management of MDD

Methods: The following inclusion criteria were defined before conducting the literature search: 1) population of adults with major depressive disorder, 2) intervention of lavender, folic acid or acupuncture, combined with standard treatment, 3) comparison group of a placebo, standard treatment or natural therapy used alone, 4) changes to Hamilton Depression Rating Scale (HAM-D) as the primary outcome. PubMed, APA PsycARTICLES and Google scholar were used for the research. The articles were limited to randomized clinical trials (RCTs), and systematic reviews with meta-analyses. The different therapies were used as key words in the literature search.

Results: The literature search for 'lavender' yielded 214 studies, of which 3 RCTs met the criteria. 'Folic acid' yielded 680 studies of which 2 RCTs and 1 systematic review with meta-analysis met the criteria. 'Acupuncture' yielded 2240 studies of which 2 RCTs and 2 systematic reviews with meta-analyses met the criteria. Only the RCTs not summarized in the systematic reviews and meta-analyses were summarized in this review.

Discussion: All ten studies using natural interventions showed a statistically significant decrease in the mean score change versus comparison groups, however, the magnitude of the effect varied between the studies. Sample sizes were small and there was significant heterogeneity between studies.

Conclusion: Evidence suggests that natural therapies can be used adjunctively to the pharmaceutical care of MDD, however, the overall research quality is low and substantial heterogeneity exists between studies. Further, additional research using more rigorous methodologies and standardized interventions is needed.

Keywords: depression; major depressive disorder; integrative medicine; lavender; Lavandula; folate; folic acid; acupuncture

Introduction

Depression contributes significantly to the burden of disease throughout the world. It impacts health-related quality of life, functioning, and mortality due to intentional injury and the use of healthcare [1]. Among the types of depression, major depressive disorder (MDD) is the most common and debilitating form of depression [2] with a 12-month prevalence of 4.7% and a lifetime prevalence of 11.2% in Canada [3]. In 2017, MDD was the 11th highest cause of global disability-adjusted life-years (DALYs) which correlates to overwhelming direct and indirect health services expenses [4].

Despite the high prevalence and economic burden, the pathophysiology of depression remains unclear, although several theories based on alteration of stress hormones, various neurotransmitters, neurocircuitry, neurotrophic factors, circadian rhythms [5,6] and altered gut microbiota have been proposed [7]. The risk of MDD is multifactorial with 30-40% contributed to genetic factors [8]. The latter are individual-specific environmental effects comprised mostly of adverse events in childhood and ongoing or recent stress due to interpersonal adversities, including childhood sexual abuse, other lifetime trauma, low social support, marital problems, and divorce [9,10].

There is a broad range of pharmaceutical drugs available for the treatment of MDD. The use of antidepressants is effective in 20%-70% of patients treated for depression [11]. Failure to achieve desired outcomes is associated with adverse events, non-response, and withdrawal from the treatment [2,12]. The addition of effective natural therapies

could facilitate dose reduction of the pharmaceuticals by decreasing their side effects [13] and/or lead to independent objective improvement [2]. The risk of discontinuation of treatment due to adverse events is usually less for natural therapies than for pharmaceuticals [2]. The Canadian Network for Mood and Anxiety Treatments (CANMAT) gives recommendations to the use of some natural therapies based on the availability of published evidence related to efficacy and safety [14]. Natural therapies such as St John's wort, omega 3 fatty acids, and exercise have level 1 evidence as adjunctive treatments in the management of MDD [15,16,17]. The data is well established for the Level 1 category evidence. On the other hand, the data is not fully established for natural therapies such as lavender, folate and acupuncture for use as adjunctive treatments in the treatment of MDD [14].

The purpose of this literature review was to analyze the evidence on the effect of natural therapies in combination with usual care as a treatment for MDD. This research is clinically relevant as clinicians working in different healthcare settings frequently encounter patients with depression. It is usually regarded that pharmacological treatments are better than natural therapies due to a larger evidence base and better-quality evidence for efficacy. However, a lack of data exists regarding interactions between natural therapies and conventional treatments for depression, as well as interactions between different natural therapies. This is of particular concern when patients do not reveal their use of natural therapies to clinicians. The focus of this literature review is to explore the effectiveness of three of these natural therapies; lavender, folic acid and acupuncture used in addition to pharmacological or usual care of MDD. No such review has been done in the literature that includes all three modalities. The three modalities were specifically chosen to describe the current level of evidence, establish their relevance in clinical use based on evidence in the literature and explore additional data related to them. This will guide the clinicians regarding the benefits of the specific therapy, and the specific factors that affect their use. Thus, this will increase the use of these natural therapies for better clinical outcomes.

The genus Lavandula belongs to the family Lamiaceae, which has more than 30 species [18]. *Lavandula angustifolia* (formerly *L. vera* or *L. officinalis),* popularly known as English lavender, has been used medicinally for its antidepressant and sedative properties [19]. The main constituents of lavender include linalyl acetate (30%-55%), linalool (20%-35%), beta-ocimene, cineol, camphor, sesquiterpene, caryophyllene oxide, tannin, rosmarinic acid derivatives, coumarine and flavonoids [20, 21]. Evidence suggests that lavender has an inhibitory effect on the central nervous system by affecting the activity of gamma amino butyric acid (GABA) neurons [22]. It also enhances the downstream effects of serotonin (5-HT1A) receptor activation similar to the effect of antidepressants [23].

Humans do not synthesize folic acid and rely on external sources for physiologic requirements [24]. The natural biologically active form of folic acid, found in sources such as green leafy vegetables, occurs mainly as 5-methyltetrahydrofolate (5-MTHF) [25]. The synthetic form of folic acid occurs as the completely oxidized pteroylmonoglutamic acid that has more stability than the natural form [26]. Folate acts as a cofactor in the pathways associated with the synthesis of various neurotransmitters involved in depression [27] such as dopamine, serotonin, and noradrenaline [28]. It acts as a methyl donor for the conversion of homocysteine to methionine, which leads to the production of S-adenosylmethionine (SAMe) [29]. Elevated homocysteine has been linked to mental health conditions, including depression [29].

Traditional acupuncture consists of the insertion of fine needles into various parts of the body along energy lines described by Traditional Chinese Medicine (TCM) [30]. Manual acupuncture involves the manual insertion of needles by a practitioner while electroacupuncture involves the application of a small amount of electric current through manually inserted acupuncture needles [31]. Neuroplasticity is disrupted in patients with depression stemming from changes induced by stress and other negative stimuli [32]. Acupuncture is involved in the modulation of neuroplasticity in the central nervous system [33] by raising the expression of neurotrophins such as brain-derived neurotrophic factor (BDNF) that increase synaptic transmission [33,34]. Acupuncture upregulates neurotransmitters such as norepinephrine, dopamine, and serotonin [33,35] and facilitates endogenous opioid mechanisms that modulate the pain pathways involved in neuroglial crosstalk and plasticity [36,37]. It reduces associated oxidative stress and apoptosis [36] and the action of inflammatory pathways, especially the toll-like receptor, and tumour necrosis factor (TNF) signaling pathways that activate the nociceptive neurons [37, 38].

Methods

The following inclusion criteria were defined before conducting the literature search: 1) population of adults with MDD, 2) intervention of lavender, folic acid or acupuncture, combined with standard treatment, 3) comparison group of a placebo, standard treatment or natural therapy used alone, 4) changes to Hamilton Depression Rating Scale (HAM-D) as the primary outcome. All published articles from 1970 to April 2020 in English, searched from PubMed, APA PsycARTICLES and Google scholar were used for the research. The articles were limited to randomized clinical trials (RCTs), and systematic reviews with meta-analyses. The selected articles could also not be a part of a selected larger systemic review or meta-analysis used as a standalone reference. The articles were searched with the following keywords that included different treatments: 'depression', 'major depressive disorder', 'unipolar depression', 'lavender', 'lavandula', 'folate', 'folic acid', 'acupuncture'.

Title and abstract screening were done by two reviewers based on the inclusion criteria. Studies that did not meet the inclusion criteria on full text were excluded. There were no disagreements in the selection of the articles.

Results

All ten studies using natural interventions showed a statistically significant decrease in the mean score change versus comparison groups. However, the magnitude of the effect varied between the studies. Sample sizes were small and there was significant heterogeneity between studies. A clinically significant outcome would be a reduction of 11 points in the HAM-D 17 scores and the magnitude of reduction observed in the studies summarized ranged between 4-15 points [39]. The limited number of studies that met the inclusion criteria with supporting evidence were included in the review.

The literature search for lavender yielded 214 studies, of which 3 RCTs met the criteria. Lavender was given in the dose of 3 – 10 g as a decoction or 1:5 tincture in 50% alcohol for 4 – 8 weeks. The HAM-D scores were found to be decreased at different time points in the lavender studies, with a greater reduction in the combined drug and lavender groups than using either alone.

Folic acid yielded 680 studies of which 2 RCTs and 1 systematic review with meta-analysis met the criteria. Folic acid was given as 0.5 mg – 10 mg of folate, 7.5 mg to 15 mg methyl folate or 1 – 5 mg of folic acid for 1 – 3 months. The reduction in the HAM-D score was greater in the combined drug and folic acid groups than using either of them alone. It was directly related to the dose of folic acid, and negatively correlated to the increase of blood folate level.

Acupuncture yielded 2240 studies of which 2 RCTs and 2 systematic reviews with meta-analyses met the criteria. Acupuncture was frequently administered in 30 minutes sessions, 3 times per week for 3 – 8 weeks in the studies. The combination of acupuncture and drugs lead to a significant reduction in the HAM-D score than using either of them alone. The effect of electroacupuncture (EA) was greater than manual acupuncture (MA).

Table 1. The study methods and results for lavender, folic acid, and acupuncture studies

Study	Natural intervention	Comparison	Results
Nikfarjam M, Rakhshan R, Ghaderi H, 2017 [40] N=120	1.5 g tea bag of *L. officinalis* in a cup of water as a decoction every 12 hours for 6 weeks	1. Placebo and 37.5 mg/day venlafaxine 2. 37.5 mg/day venlafaxine	A significant decrease (p=0.004) in score in the combined group versus using both treatments alone. The depression scores of the groups decreased over time and were significantly different at various points of time(p<0.001).
Nikfarjam M et al., 2013 [41] N=100	2 cups/day decoction of 5 g dried *L. angustifolia* for 8 weeks	20 mg citalopram BID	A significant decrease (p<.01) in score in the combined group as compared to using selective serotonin reuptake inhibitor (SSRI) alone. After 8 weeks, HAM-D was 14.8±4 and 16.8±4.6 respectively in the groups (p< 0.01).
Akhundzada et al., 2003 [42] N=48	60 drops/day *L. angustifolia* tincture for 4 weeks	1. Imipramine 100 mg/day plus placebo drops 2. Lavandula tincture (1:5 in 50% alcohol) 60 drops/day plus placebo tablet	A combination of imipramine and Lavandula tincture was more effective than imipramine alone (F = 20.83, df=1, P < .0001).
Morovati et al., 2020 [43] N=30	1 mg/day folic acid supplement for 90 days	20 mg/day citalopram	A decrease in HAM-D score was inversely correlated to blood folate level. No significant differences were found between the two groups in the reduction of depression scores.
Roberts E, Carter B, Young AH, 2018 [44] 7 RCTs N=966	Folate: .5 mg to 10 mg/day or Methylfolate: 7.5 mg to 15 mg/day for 30-60 days	1. Placebo 2. Folate .5 mg to 10 mg/day 3. Methylfolate 7.5 mg to 15 mg/day	Methylfolate at 15 mg/day and Folate <5 mg/day with SSRIs causes a significant drop (p<.002, p<.001, respectively) in HAM-D score. Methylfolate at 15 mg/d had effect size of -0.74 (95% confidence interval (CI): -1.19, 0.29; p=0.002). Folate at < 5 mg had effect size of -0.57 (95% CI: -0.91, 0.23; p<.001).

Venkatasubramanian et al., 2013 [45] N=42	5 mg/day and 1.5 mg/day folic acid for 6 weeks	20 mg/day fluoxetine	HAM-D scores decreased more in the high folic acid dose group but did not achieve statistical significance (p=.15).
Zhao et al., 2019 [46] N=477	Manual acupuncture or electroacupuncture. The acupuncture treatments were done for 30-minute sessionwith 3 sessions per week for 6 weeks	SSRI alone group	A significant improvement (p=.008) in HAM-D score in the combination group. The effect of electroacupuncture was greater than manual acupuncture.
Smith et al., 2018 [47] 11 RCTs, N=653	Manual or electroacupuncture for 30- minute sessions 3-6 times/week for 6-8 weeks	Drug alone	Manual acupuncture and drug combined were more effective than drug alone (p=.0007) Electroacupuncture and drug more effective than drug alone (p<.00001). The effect of acupuncture in combination with antidepressants was better when compared with medication alone (SMD -1.25, 95% CI -1.83 to -0.67).
Chan et al., 2015 [48] 13 RCTs with N=1046	Manual acupuncture for 30-minute sessions 3-6 times/week for 6-8 weeks	Drug alone	A significant fall (p<.001) in score in combined group vs drug alone, EA>MA. The range of response rates varied between 18.2% to 100% (mean of 50.83%) with combination acupuncture and antidepressant treatment. On the other hand, it ranged from 4.2% to 93.6% (mean of 50.83%) with antidepressants alone.
Wang et al, 2014 [49] N=76	Manual acupuncture 30- minute sessions, 5 days/week for 6 weeks	SSRIs alone	A significant reduction of 17 points (p<.05) after 6 weeks (-1.83, 95% CI -2.07 to -1.58) in HAM-D score in the combined group vs SSRI alone.

Discussion

Lavender

Evidence has shown that lavender can be combined with different antidepressants such as venlafaxine [40], citalopram [41], and imipramine [42] with significant improvement in outcome with possible synergistic or additive effects. Rapid therapeutic effects of Lavender can be accredited to uptake inhibition of noradrenaline, dopamine and serotonin [50]. This is similar to the mechanism of the antidepressant effect of Hypericum [50]. Lavender also produces an improvement in sleep in patients with MDD, possibly due to its inhibition of acetylcholine uptake in the neuromuscular junctions [51]. The combination of lavender and antidepressant use is associated with greater early antidepressant effects and reduces the adverse effects linked to the use of antidepressant medications [40]. However, the use of lavender as decoction and tincture increased the chances of non-compliance in the studies summarized in Table 1, indicating that soft gels or capsules are preferred. Soft gels or capsules are easily available and promote better patient adherence than decoction or tincture. Briefly, the combination of antidepressant and lavender was more effective in the management of depression than the antidepressant alone.

Folic Acid

Folate or methylfolate should not be offered as a monotherapy in patients with depression [44]. Folate at doses < 5 mg/day or methylfolate at a dose of 15 mg/day may be considered as an adjunct therapy to SSRIs in patients with MDD [44]. Doses of 1 mg/day of folic acid produced no significant changes in the HAM-D scores although it raised the serum level of folate in the intervention group significantly [43]. The increase in serum folate was inversely correlated with a decrease in HAM-D score [43]. Earlier studies have also shown an inverse correlation between serum folate levels and symptoms of depression [52]. The relationship between dietary folate and depression severity significantly differs by race and ethnicity [43] and baseline levels of folic acid can affect the outcomes in patients without folic acid deficiency [45]. Gender differences in handling folic acid are another factor that might influence the outcomes as the response to folic acid supplementation is more pronounced in females than men [45]. A smaller response in men might be due to minimal changes in the levels of homocysteine [53]. Men might require increased doses of folic acid to lower homocysteine levels, hence boosting the antidepressant effect in men [53]. In terms of duration, the longer duration of supplementation with folic acid is associated with improved outcomes in patients with MDD [45,19]. Finally, the addition of folic acid to

antidepressants augments the effect of antidepressants in the treatment of MDD. The variation in outcomes due to different factors affecting the levels of folic acid does lead to heterogeneity between the studies.

Acupuncture

The combination of acupuncture and antidepressants showed a reduction in the HAM-D score in the first week of treatment [46,47,48,49]. Additionally, the effects of acupuncture and antidepressant use were independent of each other and additive [48]. The quick onset of action is possibly associated with the rise in endogenous opioid peptide content [54]. Acupuncture in combination with a low dose of antidepressants was better tolerated than sham acupuncture with a high dose of antidepressants [55]. Groups receiving acupuncture in addition to medication showed decreased use of medication and improved aspects of quality of life with fewer side effects compared to the medication alone group [47]. Manual and electroacupuncture had a slightly different effect on the parameters of the HAM-D questionnaire. Electroacupuncture had a greater effect on the anxiety/somatization factor ($p<0.001$) and sleep disturbance factor ($p<0.01$) than manual acupuncture [46]. To sum up, the studies showed that there is a significant benefit in using the combination of antidepressants and acupuncture in the management of depression as compared to using them alone with electroacupuncture having greater effect than manual acupuncture.

Clinical Applications

The evidence of the three interventions summarized suggests that have a significant advantage in lowering the depression scores in combination with pharmaceutical therapy. The magnitude of benefit for each natural therapy varied between the studies as indicated by the reduction in HAM-D scores in the combined drug and natural therapy groups versus those given the drugs alone. This could potentially encourage patient engagement and enhance treatment outcomes for patients with MDD.

Based on the evidence summarized, natural therapies appear to be safe when combined with antidepressant medications. However, there are a few side effects associated with their use. The adverse effects related to lavender include nausea, confusion [41], and headache [42] in patients with MDD. In the case of folic acid, an excess amount can mask the symptoms of anemia due to vitamin B12 deficiency leading to neurological complications [56,57]. Monitoring the level of minerals and vitamins in patients with MDD who receive antidepressants helps to optimize the outcome of supplementation with folic acid [43]. The adverse effects associated with acupuncture are few. Some of the minor reported adverse effects of acupuncture in patients with MDD include pain, bleeding, infection at the insertion site, headache, or pneumothorax in rare cases [47,58,59].

Conclusions

Most of the RCTs are double-blinded, and consistently positive results are seen for all interventions. However, small sample sizes, inconsistent dosing, minimal overlap between the acupuncture points, duration and use of antidepressants being different among studies were some of the limitations in the selected studies. A limited number of studies included in the review with rigorous methodologies are required to address lacunae in our current understanding of the efficacy of natural therapies as an adjunct to pharmacological treatment in patients with MDD.

All three natural therapies reviewed could be used as an adjunct to pharmaceutical care of MDD for a better therapeutic effect. This review can guide the clinicians to promote discussion with the patients for the inclusion of natural therapies in their treatment plan for MDD. It also provides a groundwork for studies for further investigation of the safety and efficacy of natural therapies.

List of Abbreviations Used

MDD: major depressive disorder
DALYs: disability-adjusted life-years
CANMAT: Canadian network for mood and anxiety treatments
GABA: gamma amino butyric acid
5-MTHF: 5-methyltetrahydrofolate
SAMe: S-adenosylmethionine
TCM: traditional Chinese medicine
BDNF: brain-derived neurotrophic factor
TNF: tumour necrosis factor
HAM -D: Hamilton depression rating scale
RCTs: randomized clinical trials
EA: electroacupuncture
MA: manual acupuncture
SSRI: selective serotonin reuptake inhibitor

Conflicts of Interest

The authors declare that they have no conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval and/or Participant Consent

Given the literature review nature of this publication, ethics approval did not need to be obtained.

Authors' Contributions

PKC: developed the research strategy, collected and analyzed the data, drafted the manuscript, and gave final approval of the version to be published.
AG critically reviewed the research strategy and data analysis and gave final approval of the version to be published.

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