Current PSYCHIATRY

SECOND OF 2 PARTS

Nontraditional therapies for treatment-resistant depression

BENJAVISA RUANGVAREE ART/SHUTTERSTOCK

Mehmet E. Dokucu, MD, PhD
Associate Professor
Department of Psychiatry and Behavioral Sciences
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Philip G. Janicak, MD
Adjunct Professor
Department of Psychiatry and Behavioral Sciences
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Options include OTC agents, anti-inflammatory/immune system therapies, and devices

When patients with major depressive disorder (MDD) do not achieve optimal outcomes after FDA-approved first-line treatments and standard adjunctive strategies, clinicians look for additional approaches to alleviate their patients' symptoms. Recent research suggests that several "nontraditional" treatments used primarily as adjuncts to standard antidepressants have promise for treatment-resistant depression.

In Part 1 of this article (Current Psychiatry, September 2021), we examined off-label medications. In Part 2, we will review other nontraditional approaches to treatment-resistant depression, including herbal/nutraceutical agents, anti-inflammatory/immune system therapies, device-based treatments, and other alternative approaches. Importantly, some treatments also demonstrate adverse effects (***Table,***[1-32] ***page 34***). With a careful consideration of the risk/benefit balance, this article reviews some of the better-studied nontraditional treatment options for patients with treatment-resistant depression.

Herbal/nutraceutical agents

This category encompasses a variety of commonly available "natural" options patients often ask about and at times self-prescribe. Examples evaluated in clinical trials include:

- vitamin D

Disclosures
Dr. Dokucu reports no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products. Dr. Janicak is a speaker for Otsuka PsychU program and TMS Health Solutions.

doi: 10.12788/cp.0179

- essential fatty acids (omega-3, omega-6)
- S-adenosyl-L-methionine (SAMe)
- hypericum perforatum (St. John's Wort)
- probiotics.

Vitamin D deficiency has been linked to depression, possibly by lowering serotonin, norepinephrine, and dopamine concentrations.[1-3]

A meta-analysis of 3 prospective, observational studies (N = 8,815) found an elevated risk of affective disorders in patients with low vitamin D levels.[4] In addition, a systematic review and meta-analysis supported a potential role for vitamin D supplementation for patients with treatment-resistant depresssion.[5]

Toxicity can occur at levels >100 ng/mL, and resulting adverse effects may include weakness, fatigue, sleepiness, headache, loss of appetite, dry mouth, metallic taste, nausea, and vomiting. This vitamin can be considered as an adjunct to standard antidepressants, particularly in patients with treatment-resistant depression who have low vitamin D levels, but regular monitoring is necessary to avoid toxicity.

Essential fatty acids. Protein receptors embedded in lipid membranes and their binding affinities are influenced by omega-3 and omega-6 polyunsaturated fatty acids. Thus, essential fatty acids may benefit depression by maintaining membrane integrity and fluidity, as well as via their anti-inflammatory activity.

Although results from controlled trials are mixed, a systematic review and meta-analysis of adjunctive nutraceuticals supported a potential role for essential fatty acids, primarily eicosapentaenoic acid (EPA), by itself or in combination with docosahexaenoic acid (DHA), with total EPA >60%.[5] A second meta-analysis of 26 studies (N = 2,160) that considered only essential fatty acids concluded that EPA ≥60% at ≤1 g/d could benefit depression.[6] Furthermore, omega-3 fatty acids may be helpful as an add-on agent for postpartum depression.[7]

Be aware that a diet rich in omega-6 greatly increases oxidized low-density lipoprotein levels in adipose tissue, potentially posing a cardiac risk factor. Clinicians need to be aware that self-prescribed use of essential fatty acids is common, and to ask about and monitor their patients' use of these agents.

S-adenosyl-L-methionine (SAMe) is an intracellular amino acid and methyl donor. Among other actions, it is involved in the biosynthesis of hormones and neurotransmitters. There is promising but limited preliminary evidence of its efficacy and safety as a monotherapy or for antidepressant augmentation.[8] For example, when compared with placebo for depressive symptoms in 19 randomized controlled trials (RCTs) (N = 878)[8]:

- Five out of 6 earlier controlled studies reported SAMe IV (200 to 400 mg/d) or IM (45 to 50 mg/d) was more effective than placebo
- When the above studies were added to 14 subsequent studies for a meta-analysis, 12 of 19 RCTs reported that parenteral or oral SAMe was significantly more effective than placebo for depression ($P < .05$).

Overall, the safety and tolerability of SAMe are good. Common adverse effects include nausea, mild insomnia, dizziness, irritability, and anxiety. This is another compound widely available without a prescription and at times self-prescribed. It carries an acceptable risk/benefit balance, with decades of experience.

Hypericum perforatum (St. John's Wort) is widely prescribed for depression in China and Europe, typically in doses ranging from 500 to 900 mg/d. Its mechanism of action in depression may relate to inhibition of serotonin, dopamine, and norepinephrine uptake from the synaptic cleft of these interconnecting neurotransmitter systems.

A meta-analysis of 7 clinical trials (N = 3,808) comparing St. John's Wort with various selective serotonin reuptake inhibitors (SSRIs) reported comparable rates of response (pooled relative risk .983, 95% CI .924 to 1.042; $P < .001$) and remission (pooled relative risk 1.013, 95% CI .892 to 1.134; $P < .001$).[9] Further, there were significantly lower discontinuation/dropout rates (pooled odds ratio .587, 95% CI .478 to 0.697; $P < .001$) for St. John's Wort compared with the SSRIs.

Existing evidence on the long-term efficacy and safety is limited (studies ranged

Clinical Point

There is promising but limited evidence supporting SAMe as a monotherapy or adjunctive therapy to antidepressants

Clinical Point

A meta-analysis of 7 trials reported comparable response and remission rates for St. John's Wort and SSRIs

Table

Risk levels and adverse effects of adjunctive therapies for treatment-resistant depression

Treatment	Potential adverse effects
Low risk	
Sleep deprivation (wake therapy)[23]	General fatigue, headaches. Possible switch to mania for patients with bipolar depression ***Rare:*** Seizures; unexpected medical conditions, such as acute coronary syndrome
Exercise/yoga[24-30]	Sprains and strains ***Rare:*** More serious injuries
SAMe[8]	Nausea, mild insomnia, dizziness, irritability, anxiety
Vitamin D[1-5]	Toxicity (uncommon), which may include weakness, fatigue, sleepiness, headache, dry mouth, metallic taste, loss of appetite, nausea, vomiting
Probiotics[10-12]	May trigger allergic reactions or cause mild stomach upset, diarrhea, flatulence, or bloating
Mindfulness-based interventions[31,32]	May negatively affect emotions, sensory perception, social interactions, sense of self
Essential fatty acids[5-7]	Accumulates in adipose tissue. In this context, omega-6 rich diets can increase oxidized low-density lipoprotein levels
Medium risk	
Transcranial direct current stimulation[18-20]	Persistent skin lesions similar to burns; mania/hypomania; 1 reported seizure in a pediatric patient
Ganaxolone[16]	Dizziness, sleepiness, fatigue
Statins[15]	Headaches, myalgias (rarely rhabdomyolysis), dizziness, rash, liver toxicity
St. John's Wort[9]	Drug interactions: • serotonin syndrome when combined with certain antidepressants • may compromise efficacy of benzodiazepines and antidepressants
Zuranolone[17]	Somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, sedation One patient who received zuranolone experienced a serious adverse event (confusional state)
High risk	
Anti-inflammatories/ immune system therapies[13,14]	May block effect of some antidepressants Opportunistic infections Possible increased risk of suicide
Agomelatine[21,22]	Anxiety, nausea/vomiting, abnormal dreams, insomnia, dizziness, increased weight, hepatotoxicity

from 4 to 12 weeks), as is evidence for patients with more severe depression or high suicidality.

Serious drug interactions include the potential for serotonin syndrome when St. John's Wort is combined with certain antidepressants, compromised efficacy of benzodiazepines and standard antidepressants, and severe skin reactions to sun exposure. In addition, St. John's Wort may not be safe to use during pregnancy or while breastfeeding. Because potential drug interactions can be serious and individuals often self-prescribe this agent, it is important to ask patients about their use of St. John's Wort, and to be vigilant for such potential adverse interactions.

Probiotics. These agents produce neuroactive substances that act on the brain/gut axis. Preliminary evidence suggests that these "psychobiotics" confer mental health benefits.[10-12] Relative to other approaches, their low-risk profile make them an attractive option for some patients.

Anti-inflammatory/immune system therapies

Inflammation is linked to various medical and brain disorders. For example, patients with depression often demonstrate increased levels of peripheral blood inflammatory biomarkers (such as C-reactive protein and interleukin-6 and -17) that are known to alter norepinephrine, neuroendocrine (eg, the hypothalamic-pituitary-adrenal axis), and microglia function in addition to neuroplasticity. Thus, targeting inflammation may facilitate the development of novel antidepressants. In addition, these agents may benefit depression associated with comorbid autoimmune disorders, such as psoriasis or rheumatoid arthritis. A systematic review and meta-analysis of 36 RCTs (N = 10,000) found 5 out of 6 anti-inflammatory agents improved depression.[13,14] In general, reported disadvantages of anti-inflammatories/immunosuppressants include the potential to block the antidepressant effect of some agents, the risk of opportunistic infections, and an increased risk of suicide.

Statins

In a meta-analysis of 3 randomized, double-blind trials, 3 statins (lovastatin, atorvastatin, and simvastatin) significantly improved depression scores when used as an adjunctive therapy to fluoxetine and citalopram, compared with adjunctive placebo (N = 165, $P < .001$).[15]

Specific adverse effects of statins include headaches, muscle pain (rarely rhabdomyolysis), dizziness, rash, and liver damage. Statins also have the potential for adverse interactions with other medications. Given the limited efficacy literature on statins for depression and the potential for serious adverse effects, these agents probably should be limited to patients with treatment-resistant depression for whom a statin is indicated for a comorbid medical disorder, such as hypercholesteremia.

Neurosteroids

Brexanolone is FDA-approved for the treatment of postpartum depression. It is an IV formulation of the neuroactive steroid hormone allopregnanolone (a metabolite of progesterone), which acts as a positive allosteric modulator of the GABA-A receptor. Unfortunately, the infusion needs to occur over a 60-hour period.

Ganaxolone is an oral analog formulation of allopregnanolone. In an uncontrolled, open-label pilot study, this medication was administered for 8 weeks as an adjunct to an adequately dosed antidepressant to 10 postmenopausal women with persistent MDD.[16] Of the 9 women who completed the study, 4 (44%) improved significantly ($P < .019$) and the benefit was sustained for 2 additional weeks.[16] Adverse effects of ganaxolone included dizziness in 60% of participants, and sleepiness and fatigue in all of them with twice-daily dosing. If the FDA approves ganaxolone, it would become an easier-to-administer option to brexanolone.

Zuranolone is an investigational agent being studied as a treatment for postpartum depression. In a double-blind RCT that evaluated 151 women with postpartum depression, those who took oral zuranolone, 30 mg daily at bedtime for 2 weeks, experienced significant reductions in Hamilton Depression Rating Scale-17 (HDRS-17) scores compared with placebo ($P < .003$).[17] Improvement in core depression symptom ratings was seen as early as Day 3 and persisted through Day 45.

The most common (≥5%) treatment-emergent adverse effects were somnolence (15%), headache (9%), dizziness (8%), upper respiratory tract infection (8%), diarrhea (6%), and sedation (5%). Two patients experienced a serious adverse event: one who received zuranolone (confusional state) and one who received placebo (pancreatitis). One patient discontinued zuranolone due to adverse effects vs no discontinuations among those who received placebo. The risk of taking zuranolone while breastfeeding is not known.

Device-based strategies

In addition to FDA-cleared approaches (eg, electroconvulsive therapy [ECT], vagus nerve stimulation [VNS], transcranial magnetic stimulation [TMS]), other devices have also demonstrated promising results.

Transcranial direct current stimulation (tDCS) involves delivering weak electrical current

Clinical Point

A systematic review and meta-analysis suggested that anti-inflammatory agents can reduce symptoms of depression

Clinical Point

Results of studies of transcranial direct current stimulation for depression have been promising but mixed

to the cerebral cortex through small scalp electrodes to produce the following effects:

- anodal tDCS enhances cortical excitability
- cathodal tDCS reduces cortical excitability.

A typical protocol consists of delivering 1 to 2 mA over 20 minutes with scalp electrodes placed in different configurations based on the targeted symptom(s).

While tDCS has been evaluated as a treatment for various neuropsychiatric disorders, including bipolar depression, Parkinson's disease, and schizophrenia, most trials have looked at its use for treating depression. Results have been promising but mixed. For example, 1 meta-analysis of 6 RCTs (comprising 96 active and 80 sham tDCS courses) reported that active tDCS was superior to a sham procedure (Hedges' g = 0.743) for symptoms of depression.[18] By contrast, another meta-analysis of 6 RCTs (N = 200) did not find a significant difference between active and sham tDCS for response and remission rates.[19] More recently, a group of experts created an evidence-based guideline using a systematic review of the controlled trial literature. These authors concluded there is "probable efficacy for anodal tDCS of the left dorsolateral prefrontal cortex (DLPFC) (with right orbitofrontal cathode) in major depressive episodes without drug resistance but probable inefficacy for drug-resistant major depressive episodes."[20]

Adverse effects of tDCS are typically mild but may include persistent skin lesions similar to burns; mania or hypomania; and one reported seizure in a pediatric patient.

Because various over-the-counter direct current stimulation devices are available for purchase at modest cost, clinicians should ask patients if they have been self-administering this treatment.

Chronotherapy strategies

Agomelatine combines serotonergic (5-HT2B and 5-HT2C antagonist) and melatonergic (MT1-MT2 agonist in the suprachiasmatic nucleus) actions that contribute to stabilization of circadian rhythms and subsequent improvement in sleep patterns. Agomelatine (n = 1,274) significantly lowered depression symptoms compared with placebo (n = 689) (standardized mean difference −0.26; $P < 3.48\times10^{-11}$), but the clinical relevance was questionable.[21] A recent review of the literature and expert opinion suggest this agent may also have efficacy for anhedonia; however, in placebo-controlled, relapse prevention studies, its long-term efficacy was not consistent.[22]

Common adverse effects include anxiety; nausea, vomiting, and stomach pain; abnormal dreams and insomnia; dizziness; drowsiness and fatigue; and weight gain. Some reviewers have expressed concerns about agomelatine's potential for hepatotoxicity and the need for repeated clinical laboratory tests. Although agomelatine is approved outside of the United States, limited efficacy data and the potential for serious adverse effects have precluded FDA approval of this agent.

Sleep deprivation as a treatment technique for depression has been developed over the past 50 years. With total sleep deprivation (TSD) over 1 cycle, patients stay awake for approximately 36 hours, from daytime until the next day's evening. While 1 to 6 cycles can produce acute antidepressant effects, prompt relapse after sleep recovery is common.

In a systematic review and meta-analysis of 7 studies that included a total of 311 patients with bipolar depression[23]:

- TSD plus medications resulted in a significant decrease in depressive symptoms at 1 week compared with medications alone
- higher response rates were maintained after 3 months with lithium.

Adverse effects commonly include general fatigue and headaches; possible switch into mania with bipolar depression; and rarely, seizures or other unexpected medical conditions (eg, acute coronary syndrome). Presently, this approach is limited to research laboratories with the appropriate sophistication to safely conduct such trials.

Other nontraditional strategies

Cardiovascular exercise, resistance training, mindfulness, and yoga have been shown to decrease severe depressive symptoms when

used as adjuncts for patients with treatment-resistant depression, or as monotherapy to treat patients with milder depression.

Exercise. The significant benefits of exercise in various forms as treatment for mild to moderate depression are well described in the literature, but it is less clear if it is effective for treatment-resistant depression. A 2013 Cochrane report[24] (39 studies with 2,326 participants total) and 2 meta-analyses undertaken in 2015 (Kvam et al[25] included 23 studies with 977 participants, and Schuh et al[26] included 25 trials with 1,487 participants) reported that various types of exercise ameliorate depression of differing subtypes and severity, with effect sizes ranging from small to large. Schuh et al[26] found that publication bias underestimated effect size. Also, not surprisingly, separate analysis of only higher-quality trials decreased effect size.[24-26] A meta-analysis that included tai chi and yoga in addition to aerobic exercise and strength training (25 trials with 2,083 participants) found low to moderate benefit for exercise and yoga.[27] Finally, a meta-analysis by Cramer et al[28] that included 12 RCTs (N = 619) supported the use of yoga plus controlled breathing techniques as an ancillary treatment for depression.

Two small exercise trials specifically evaluated patients with treatment-resistant depression.[29,30] Mota-Pereira et al[29] compared 22 participants who walked for 30 to 45 minutes, 5 days a week for 12 weeks in addition to pharmacotherapy with 11 patients who received pharmacotherapy only. Exercise improved all outcomes, including HDRS score (both compared to baseline and to the control group). Moreover, 26% of the exercise group went into remission. Pilu et al[30] evaluated strength training as an adjunctive treatment. Participants received 1 hour of strength training twice weekly for 8 months (n = 10), or pharmacotherapy only (n = 20). The adjunct strength training group had a statistically significant ($P < .0001$) improvement in HDRS scores at the end of the 8 months, whereas the control group did not ($P < .28$).

Adverse effects of exercise are typically limited to sprains or strains; rarely, participants experience serious injuries.

Mindfulness-based interventions involve purposely paying attention in the present moment to enhance self-understanding and decrease anxiety about the future and regrets about the past, both of which complicate depression. A meta-analysis of 12 RCTs (N = 578) found this approach significantly reduced depression severity when used as an adjunctive therapy.[31] There may be risks if mindfulness-based interventions are practiced incorrectly. For example, some reports have linked mindfulness-based interventions to psychotic episodes, meditation addiction, and antisocial or asocial behavior.[32]

References

1. Pittampalli S, Mekala HM, Upadhyayula, S, et al. Does vitamin D deficiency cause depression? Prim Care Companion CNS Disord. 2018;20(5):17l02263.
2. Parker GB, Brotchie H, Graham RK. Vitamin D and depression. J Affect Disord. 2017;208:56-61.
3. Berridge MJ. Vitamin D and depression: cellular and regulatory mechanisms. Pharmacol Rev. 2017;69(2):80-92.

continued

Related Resources

- Kaur M, Sanches M. Experimental therapeutics in treatment-resistant major depressive disorder. J Exp Pharmacol. 2021;13:181-196.
- Janicak PG. What's new in transcranial magnetic stimulation. Current Psychiatry. 2019;18(3):10-16.

Drug Brand Names

Atorvastatin • Lipitor
Brexanolone • Zulresso
Citalopram • Celexa
Fluoxetine • Prozac
Lithium • Eskalith, Lithobid
Lovastatin • Altoprev, Mevacor
Minocycline • Dynacin, Minocin
Simvastatin • Flolipid, Zocor

Clinical Point

Two small trials of patients with TRD found exercise as an adjunctive treatment to pharmacotherapy improved HDRS scores

Bottom Line

Nonpharmacologic options for patients with treatment-resistant depression include herbal/nutraceuticals, anti-inflammatory/immune system therapies, and devices. While research suggests some of these approaches are promising, clinicians need to carefully consider potential adverse effects, some of which may be serious.

Nontraditional therapies for TRD

Clinical Point

A meta-analysis found mindfulness-based interventions as an adjunctive therapy significantly reduced depression severity

4. Anglin RE, Samaan Z, Walter SD, et al. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br J Psychiatry. 2013;202:100-107.
5. Sarris J, Murphy J, Mischoulon D, et al. Adjunctive nutraceuticals for depression: a systematic review and meta-analyses. Am J Psychiatry 2016;173(6);575-587.
6. Liao Y, Xie B, Zhang H, et al. Efficacy of omega-3 PUFAs in depression: a meta-analysis. Transl Psychiatry. 2019;9(1):190.
7. Mocking RJT, Steijn K, Roos C, et al. Omega-3 fatty acid supplementation for perinatal depression: a meta-analysis. J Clin Psychiatry. 2020;81(5):19r13106.
8. Sharma A, Gerbarg P, Bottiglieri T, et al; Work Group of the American Psychiatric Association Council on Research. S-Adenosylmethionine (SAMe) for neuropsychiatric disorders: a clinician-oriented review of research. J Clin Psychiatry. 2017;78(6):e656-e667.
9. Ng QX, Venkatanarayanan N, Ho CY. Clinical use of hypericum perforatum (St John's wort) in depression: a meta-analysis. J Affect Disord 2017;210:211-221.
10. Huang R, Wang K, Hu J. Effect of probiotics on depression: a systematic review and meta-analysis of randomized controlled trials. Nutrients. 2016;8(8):483.
11. Liu RT, Walsh RFL, Sheehan AE. Prebiotics and probiotics for depression and anxiety: a systematic review and meta-analysis of controlled clinical trials. Neurosci Biobehav Rev. 2019;102:13-23.
12. Wallace CJK, Milev RV. The efficacy, safety, and tolerability of probiotics on depression: clinical results from an open-label pilot study. Front Psychiatry. 2021;12(132):618279.
13. Köhler-Forsberg O, N Lyndholm C, Hjorthøj C, et al. Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. Acta Psychiatr Scand. 2019;139(5):404-419.
14. Jha MK. Anti-inflammatory treatments for major depressive disorder: what's on the horizon? J Clin Psychiatry. 2019;80(6)18ac12630.
15. Salagre E, Fernandes BS, Dodd S, et al. Statins for the treatment of depression: a meta-analysis of randomized, double-blind, placebo-controlled trials. J Affect Disord. 2016;200:235-242.
16. Dichtel LE, Nyer M, Dording C, et al. Effects of open-label, adjunctive ganaxolone on persistent depression despite adequate antidepressant treatment in postmenopausal women: a pilot study. J Clin Psychiatry. 2020;81(4):19m12887.
17. Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. JAMA Psychiatry. 2021;78(9): 951-959.
18. Kalu UG, Sexton CE, Loo CK, et al. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychol Med. 2012;42(9):1791-800.
19. Berlim MT, Van den Eynde F, Daskalakis ZJ. Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. J Psychiatr Res. 2013;47(1):1-7.
20. Lefaucheur JP, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128(1):56-92.
21. Singh SP, Singh V, Kar N. Efficacy of agomelatine in major depressive disorder: meta-analysis and appraisal. Int J Neuropsychopharmacol. 2012;15(3):417-428.
22. Norman TR, Olver JS. Agomelatine for depression: expanding the horizons? Expert Opin Pharmacother. 2019;20(6):647-656.
23. Ramirez-Mahaluf JP, Rozas-Serri E, Ivanovic-Zuvic F, et al. Effectiveness of sleep deprivation in treating acute bipolar depression as augmentation strategy: a systematic review and meta-analysis. Front Psychiatry. 2020;11:70.
24. Cooney GM, Dwan K, Greig CA, et al. Exercise for depression. Cochrane Database Syst Rev. 2013;(9): CD004366.
25. Kvam S, Kleppe CL, Nordhus IH, et al. Exercise as a treatment for depression: a meta-analysis. J Affect Disord. 2016;202:67-86.
26. Schuch FB, Vancampfort D, Richards J, et al. Exercise as a treatment for depression: a meta-analysis adjusting for publication bias. J Psychiatr Res. 2016;77:42-51.
27. Seshadri A, Adaji A, Orth SS, et al. Exercise, yoga, and tai chi for treatment of major depressive disorder in outpatient settings: a systematic review and meta-analysis. Prim Care Companion CNS Disord. 2020;23(1):20r02722.
28. Cramer H, Lauche R, Langhorst J, et al. Yoga for depression: a systematic review and meta-analysis. Depress Anxiety. 2013;30(11):1068-1083.
29. Mota-Pereira J, Silverio J, Carvalho S, et al. Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder. J Psychiatr Res. 2011;45(8):1005-1011.
30. Pilu A, Sorba M, Hardoy MC, et al. Efficacy of physical activity in the adjunctive treatment of major depressive disorders: preliminary results. Clin Pract Epidemiol Ment Health. 2007;3:8.
31. Strauss C, Cavanagh K, Oliver A, et al. Mindfulness-based interventions for people diagnosed with a current episode of an anxiety or depressive disorder: a meta-analysis of randomised controlled trials. PLoS One. 2014;9(4):e96110.
32. Shonin E, Van Gordon W, Griffiths MD. Are there risks associated with using mindfulness for the treatment of psychopathology? Clinical Practice. 2014;11(4):389-392.