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Viewpoint

May 24, 2019

Evolving Issues in the Treatment of Depression

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JAMA. 2019;321(24):2401-2402. doi:10.1001/jama.2019.4990



Major depressive disorder (MDD) has a lifetime incidence of 10% to 15%.¹ The main treatment options include pharmacological and psychological interventions, with many patients receiving combination treatment. Although randomized clinical trials (RCTs) have established the efficacy of antidepressants,² acute and long-term effectiveness is limited, and one-third of patients develop treatment resistance. New interventions are needed in the field and this Viewpoint examines novel interventions, with a specific focus on exercise, nutrition, and ketamine.

Exercise

Exercise is an attractive option to prevent or treat MDD, given the hypothesis that links exercise, brain-derived neurotrophic factor, and neuroprotection. However, the evidence for efficacy and effectiveness of exercise for MDD is mixed.

A meta-analysis of 33 RCTs (N=1877) showed that resistance exercise training, compared with nonactive control conditions, was associated with a significant reduction in depressive symptoms, with a moderate effect size and a number needed to treat of 4.³ The findings were independent of health status, prescribed volume of training, and improvements in strength. However, 20 RCTs included patients with de-

pressive symptoms and only 4 included patients with a diagnosis of MDD. Furthermore, the reduction in depressive symptoms became significantly smaller when only RCTs with blinded allocation were included. Nevertheless, analyses restricted to patients with mild to moderate MDD indicated a large effect size.

An intriguing study investigated the potential causal association between exercise and MDD via a mendelian randomization approach. Mendelian randomization techniques use gene variants as instrumental variables to investigate possible causal relationships between risk factors (eg, exercise) and health outcomes (eg, depression). Because genes are randomly allocated, mendelian randomization is thought to minimize the risk for confounding and reverse causality. By including data from 611 583 adults, 91 084 of whom had activity measured by accelerometer, Choi and colleagues⁴ found a protective relationship between accelerometer-based activity and MDD by an odds ratio of 0.74 (95% CI, 0.59-0.92). This means that replacing a sedentary lifestyle with 15 minutes of strenuous activity daily or 1 hour of moderate activity was associated with a potential relative reduction in the odds of developing depression by 26%.

Implementing regular exercise is difficult for most people and is even more challenging for those with MDD because of their symptoms of low energy and motivation. Nevertheless, encouraging or prescribing regular exercise can be worthwhile even if just for improved cardiovascular health.

Nutrition

Numerous studies have explored the effect of diet on mood, but the results have been difficult to interpret due to mixed findings and large differences in diets, research designs, and study populations. Observational studies seem to support a positive relationship between mood and a diet consisting of higher contents of plant foods (eg, vegetables, fruits, whole grains) and lean proteins (eg, fish), which has been found across different countries and age groups. However, few studies have specifically investigated the effect of diet in patients with MDD.

The SMILES trial represents one of the first well-performed RCTs and investigated the effect of structured dietary support focusing on a Mediterranean diet.⁵ Among 56 adult patients with moderate to severe MDD, a 12-week individual intervention (7 60-minute sessions) investigated the effect of dietary advice and support by a dietician (ie, motivational interviewing, goal setting, and mindful eating) vs social support. The dietary support group, compared with the social support group, was associated with significantly greater improvement. This finding is consistent with other recent studies among patients with MDD, and some results have indicated an even greater effect among patients with MDD and type 2 diabetes.

Two recent RCTs investigated the effects of dietary interventions on depressive symptoms among obese patients.^{6,7} The RAINBOW trial (N=409; mean age, 51) studied behavioral weight loss treatment and problem-solving therapy⁶ among individuals with a body mass index of 30 or greater and moderate to

severe depressive symptoms. Compared with treatment as usual, the intervention group showed significantly greater decline in mean body mass index (from 36.7 to 35.9 vs 36.6 to 36.6) and in depressive symptoms (from 1.5 to 1.1 vs 1.5 to 1.4) after 12 months.

The MoodFOOD trial (N=1025; mean age, 46.5 years) studied multinutrient supplementation and food-related behavioral activation therapy promoting a Mediterranean-style diet among patients with a body mass index of 25 to 40 without MDD but with at least mild depressive symptoms.⁷ A total of 105 patients (10%) developed MDD within 12 months, with no difference between the 4 intervention groups (9.7% in the placebo-only group, 10.2% in the placebo plus therapy group, 12.5% in the supplement-only group, and 8.6% in the supplement plus therapy group; $P = .48$ for interaction). The findings from the RAINBOW trial indicated significant but only modest effects on weight and depressive symptoms, whereas the MoodFOOD results did not support the use of supplemental nutrients to prevent onset of MDD.

The initial evidence regarding structured dietary support on MDD is promising and seems to favor a Mediterranean diet. A recent Editorial⁸ discussed the previous 2 RCTs and suggested that evidence-based lifestyle interventions (eg, diet, exercise, and smoking cessation) should be used in addition to first-line pharmacological and psychological treatment but not alone to treat depression. Future studies need to include larger study populations and use similar approaches and dietary patterns as previous trials to yield comparable results. In addition, studies with longer follow-up (ie, several years) would be necessary to explore the long-term effects on mood and health status in general.

Ketamine

On March 5, 2019, the Food and Drug Administration approved nasal ketamine (Spravato) as a drug for treatment-resistant depression (TRD). Ketamine has been used as an anesthetic drug since the 1970s and has been investigated for use in MDD for 2 decades.⁹ Ketamine has attracted widespread attention since early trials (with sample sizes ranging from 9 to 73) found large (ie, up to 60%) improvement in depressive symptoms and suicidal ideation among severely depressed and otherwise treatment-resistant patients. The large therapeutic effect was experienced within hours after a slow intravenous administration of a subanesthetic dose (0.5 mg/kg) and these effects were transient, with patients returning to their baseline severity within a few weeks. These initial findings have led to increasing off-label use of ketamine for mood disorders and particularly TRD in the United States.

Regarding potential adverse effects, intravenous administration of ketamine at these doses generally does not significantly affect the respiratory or cardiovascular status of physically healthy individuals with MDD. Because patients may experience sedation, confusion, and dissociation, monitoring is required during and after administration. Potential long-term risks include tolerance, abuse, and misuse.

Clinical trials have established that more than half of the patients with TRD experience antidepressant effect of intranasal or intravenous ketamine in addition to their treatment as usual. However, patients with psychotic features or active substance use disorders have been excluded from RCTs, and long-term safety data are limited. Ketamine represents a promising drug that potentially can help alleviate TRD, but further studies are necessary to identify which patients will receive sustained benefit. Ketamine infusions are costly, and often not covered by insurance, while ketamine intranasal is much less expensive but requires frequent administrations (twice weekly or weekly). Even though the addition of esketamine (the patented s-enantiomer of ketamine that represents 50% of the racemic mix of the generic drug) to the therapeutic armamentarium was anticipated, whether esketamine will become a common treatment for depression is unclear and it will be modulated by availability of specialty centers for administration and insurance coverage.

Another investigational drug with a related mechanism of action through the glutamate system, rapastinel, demonstrated rapid onset of antidepressant effects following intravenous administration in preliminary studies. However, recently reported interim analyses of 3 pivotal clinical trials of rapastinel as treatment for MDD showed no difference, compared with placebo, on the primary outcome and key secondary end points.

Other Approaches

Several other treatments for MDD have attracted increasing attention. Anti-inflammatory drugs have shown promising results, with a recent meta-analysis of 36 RCTs (N=9422) indicating medium to large effect sizes for several anti-inflammatory drugs as add-on to antidepressants.¹⁰ The effect sizes of anti-inflammatory agents added to antidepressants (standardized mean difference=0.64) were larger than the effect sizes of antidepressant drugs alone (SMDs ranging from 0.17 to 0.49).² Another drug with novel mechanisms, brexanolone, an allosteric modulator of the GABA_A receptor, was recently approved by the FDA for postpartum depression, leading the path to the development of similar compounds for MDD. Psilocybin was found to produce significant antidepressant effects in combination with psychological support in a small open-label study (N=20), with effects persisting after 6 months.

In conclusion, several new pharmacological and nonpharmacological potential interventions for MDD have become available or are being evaluated. In particular, the evidence regarding lifestyle modification (ie, exercise and diet) is promising, although the core symptoms of severe depression make implementation challenging. Further research is necessary to determine how to provide the right intervention at the right time for each patient, while considering individual needs and preferences, together with important factors such as somatic and psychiatric comorbidities, severity of depression, previous treatment trials, patient adherence, and the availability of the treatment options.

Article Information

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Published Online: May 24, 2019. doi:[10.1001/jama.2019.4990](https://doi.org/10.1001/jama.2019.4990)

Conflict of Interest Disclosures: Dr Cusin reported being a site principal investigator of a Janssen esketamine study in 2016 and currently being a site principal investigator for a study sponsored by Shenox Pharmaceuticals on development of a ketamine patch. Dr Nierenberg reported receiving personal fees from Alkermes, Assurex Belvior, Clexio, Jazz Pharmaceuticals, Neurocrine, NeuroRx, Neurostar, Otsuka, Sage, Chire, Sunovion, and Supernus and grants and personal fees from Janssen. No other disclosures were reported.

References

1. Pedersen CB, Mors O, Bertelsen A, et al. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry*. 2014;71(5):573-581.

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2. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder. *Lancet*. 2018;391(10128):1357-1366.

[PubMed](#) | [Google Scholar](#) | [Crossref](#)

3. Gordon BR, McDowell CP, Hallgren M, Meyer JD, Lyons M, Herring MP. Association of efficacy of resistance exercise training with depressive symptoms. *JAMA Psychiatry*. 2018;75(6):566-576.

[Article](#)

[Article](#) | [PubMed](#) | [Google Scholar](#) | [Crossref](#)

4. Choi KW, Chen CY, Stein MB, et al; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. Assessment of bidirectional relationships between physical activity and depression among adults: a 2-sample mendelian randomization study [published online January 23, 2019]. *JAMA Psychiatry*. doi:[10.1001/jamapsychiatry.2018.4175](https://doi.org/10.1001/jamapsychiatry.2018.4175)

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5. Jacka FN, O'Neil A, Opie R, et al. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). *BMC Med.* 2017;15(1):23.

[PubMed](#) | [Google Scholar](#) | [Crossref](#)

6. Ma J, Rosas LG, Lv N, et al. Effect of integrated behavioral weight loss treatment and problem-solving therapy on body mass index and depressive symptoms among patients with obesity and depression: the RAINBOW randomized clinical trial. *JAMA.* 2019;321(9):869-879.

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[Article](#) | [PubMed](#) | [Google Scholar](#) | [Crossref](#)

7. Bot M, Brouwer IA, Roca M, et al; MoodFOOD Prevention Trial Investigators. Effect of multivitamin supplementation and food-related behavioral activation therapy on prevention of major depressive disorder among overweight or obese adults with subsyndromal depressive symptoms: the MoodFOOD randomized clinical trial. *JAMA.* 2019;321(9):858-868.

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8. Berk M, Jacka FN. Diet and depression—from confirmation to implementation. *JAMA.* 2019;321(9):842-843.

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9. Sanacora G, Frye MA, McDonald W, et al; American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry.* 2017;74(4):399-405.

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10. Köhler-Forsberg O, N Lydholm C, Hjorthøj C, Nordentoft M, Mors O, Benros ME. Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms. *Acta Psychiatr Scand.* 2019;139(5):404-419.

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May 24, 2019

Missing Pillar of Mental Health - Sleep**Jeffrey Durmer** |

Numerous studies demonstrate the impact of treating common sleep disorders like insomnia and obstructive sleep apnea on mental health, and specifically on mood. Of note, recent large scale online CBTi investigations demonstrate the benefits of treating insomnia (1,2) and obstructive sleep apnea (3) on multiple mental health outcomes. Of course, the "chicken and egg" argument persists regarding cause and effect, however, the same could be said for exercise and nutrition. In addition, since sleep is well known to be impacted by both exercise and nutrition, it may be that the benefits in terms of depression symptoms seen with these approaches ...

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Pathophysiology Understanding is Paramount.**Edoardo Cervoni, M.D.** | Locumdoctor4u Ltd.

Depression may be the leading cause of disability worldwide, but its pathophysiology is poorly understood. Perhaps unsurprisingly, current management strategies remain sub-optimal. We should know far more about brain changes produced by this disorder and its treatment and how the central nervous system produces neuroplasticity to orchestrate adaptive defensive behaviours. My opinion is that different roots to depression may be identified.

CONFLICT OF INTEREST: None Reported

July 5, 2019

What is Major Depressive Disorder?**Ole Thienhaus, MD** | University of Arizona College of Medicine Tucson

The authors competently summarize the support for novel therapies for major depressive disorder (MDD), but neglect to address the critical epistemological conundrum: What is MDD? In 1850, if we had asked for best treatments for dropsy, foxglove preparations would have scored highly on effectiveness if only for less than half the cases. This would have changed only after the syndrome of congestive heart failure would have been introduced as a criterion for assessing treatment response. Today, most treatment studies for MDD indicate some 20 to 30% superiority over placebo -- an efficacy claim that would sink probably any antihypertensive or ...

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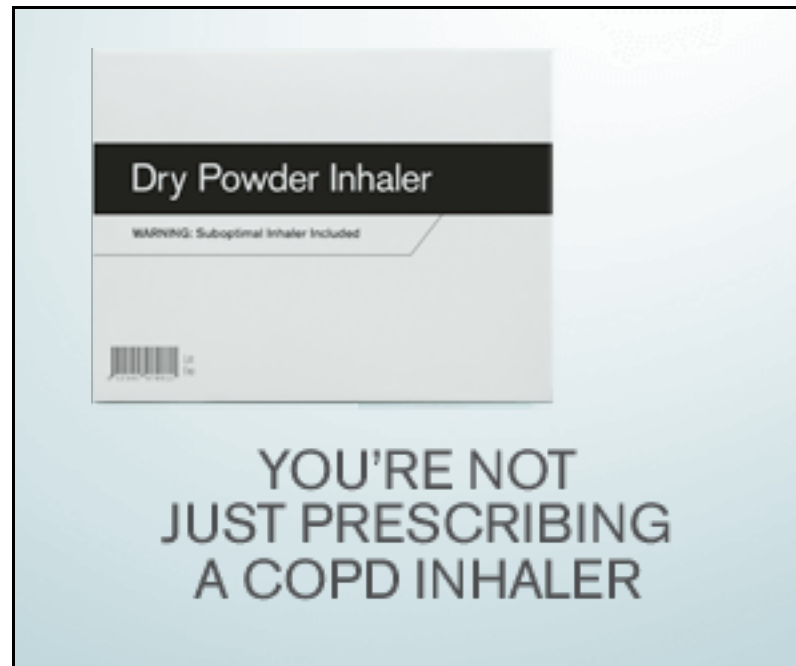
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