Depression Research Review™

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Abbreviations used in this issue:

HAM-D = Hamilton Depression Rating Scale;
MADRS = Montgomery-Åsberg Depression Rating Scale;
MDD = major depressive disorder; **QOL** = quality of life.

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Welcome to the eighth issue of Depression Research Review.

Leading this issue is an important study that evaluates brexanolone as a novel therapeutic agent for post-partum depression. Also featured are studies that assess physical fitness as a modifiable risk factor for depression and cardiovascular death in later life, lurasidone as a viable treatment for patients with depression who are concerned about sexual side effects, and the effects of vagal nerve stimulation on QOL in treatment-resistant depression. Also of interest are two studies of the efficacy of omega-three fatty acids as a monotherapy for depressed teenagers and as an adjuvant to standard treatment in adults with depression. Evaluations of the efficacy of ketamine infusions in patients with unipolar and bipolar depression and mindfulness-based cognitive therapy for patients with chronic treatment-resistant depression are also noteworthy.

We hope that you find this issue of **Depression Research Review** illuminating and we look forward to receiving your feedback.

Kind Regards,

Professor Paul Fitzgerald

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Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials

Authors: Meltzer-Brody S et al.

Summary: This paper reports the results of two double-blind, randomised, placebo-controlled trials that assessed the efficacy and tolerably of single-dose brexanolone given by IV injection in a total of 246 women with post-partum depression who were ≤6 months post-partum at screening. Statistically significant and clinically meaningful reductions in HAM-D total score at 60 hours post-dose versus placebo were observed, with rapid onset of action and durable treatment response.

Comment: Any clinician working with patients with depression is well aware of our desperate need for new and novel antidepressant treatment strategies. Therefore, this report from the Lancet is of considerable interest, not just for clinicians working with patients experiencing post-partum depression. In this study, a novel drug that modulates the GABAa receptor was used in the treatment of patients with post-partum depression of moderate-to-severe intensity. The manuscript describes a dose-finding and a second confirmatory study using brexanolone at doses of 60 or 90 µg/kg administered as an IV infusion. In the first study, both doses demonstrated superiority to placebo; in the second study, which only used the 90µg dose, this was also superior to placebo in reducing symptoms of depression 60 hours post dose. The improvements were of a significant level (15–20 points on the HAM-D scale) and the treatment response was seen quite rapidly. There were limited side effects and only two more serious adverse events (altered state of consciousness and syncope) in the active treatment groups. These results are clearly highly promising as they suggest that medication modulating the GABAa receptor may have meaningful antidepressant activity. It will be fascinating to see whether these antidepressant effects can be demonstrated in broader depressive syndromes as well as in post-partum depression.

Reference: Lancet. 2018;392(10152):1058–1070

Abstract

Association of midlife cardiorespiratory fitness with incident depression and cardiovascular death after depression in later life

Authors: Willis BL et al.

Summary: This retrospective study analysed data from a total of 17,989 middle-aged adults (80.2% of whom were men), representing 117,218 person-years of follow-up, to determine whether physical fitness measured in midlife would be inversely associated with later-life cardiovascular mortality with antecedent depression. A high level of fitness in midlife was associated with a 16% lower risk of depression versus a low level of fitness and also a 61% lower risk of death due to cardiovascular disease without depression versus a low level of fitness. After a diagnosis of depression, a high fitness level was associated with a 56% lower risk of death due to cardiovascular disease versus a low fitness level.

Comment: This study explored the long-term emergence of depression as well as cardiovascular disease in a large group of almost 18,000 men assessed at age 50 and followed for several decades. The overall level of fitness assessed at age 50 was significantly correlated with both mood and cardiovascular outcomes. Men who were judged to be fitter at age 50 had lower rates of depression as well as a substantially lower risk of death due to cardiovascular disease. Individuals who did develop depression were substantially less likely to die due to cardiovascular disease if they were fit compared to those with low fitness levels. This clearly supports a meaningful relationship between overall health and both depression-related and cardiovascular outcomes. General fitness appears to be a meaningfully modifiable risk factor for problems that affect both mortality and substantial aspects of QOL in men as they age.

Reference: JAMA Psychiatry. 2018;75(9):911–917
Abstract

Effect of lurasidone on sexual function in major depressive disorder patients with subthreshold hypomanic symptoms (mixed features): Results from a placebo-controlled trial

Authors: Clayton AH et al.

Summary: In this secondary analysis, patients with MDD and manic symptoms were randomized to receive 6 weeks of double-blind treatment with flexible doses of either lurasidone 20–60 mg/day (n=109) or placebo (n=100). Lurasidone significantly reduced mean MADRS total scores by the end of the study (-20.5 vs -13.0; p<0.001) and was associated with significant endpoint improvement in Sexual Functioning Questionnaire (CSFQ-14) total scores versus placebo (+5.1 vs +3.1; p<0.05). Also at the conclusion of the study, the proportion of patients with a baseline-to-endpoint shift from normal to abnormal sexual function (CSFQ criteria) was smaller for lurasidone versus placebo (1.9% vs 4.3%).

Comment: Sexual dysfunction is a common adverse event resulting from a variety of psychotropic agents commonly used in clinical practice. This current report aimed to explore whether lurasidone, a newer atypical antipsychotic, was associated with impaired sexual function in a group of patients with MDD who were presenting with subthreshold hypomanic symptoms. Data from a randomised controlled trial was analysed comparing sexual dysfunction emerging on lurasidone to that on placebo. The rate of emergent sexual dysfunction during the lurasidone treatment was actually lower than that on placebo suggesting that this is not a meaningful side-effect of this newer antipsychotic agent. Lurasidone can be considered a viable treatment for patients concerned about sexual side-effects.

Reference: J Clin Psychiatry. 2018;79(5):18m12132
Abstract

Chronic vagus nerve stimulation significantly improves quality of life in treatment-resistant major depression

Authors: Conway CR et al.

Summary: This multicentre longitudinal registry analysis compared self-reported QOL change associated with treatment as usual (TAU, any antidepressant treatment; n=271) with adjuvant vagus nerve stimulation treatment (VNS + TAU; n=328) in patients with treatment-resistant depression. VNS + TAU demonstrated a statistically significant QOL advantage compared with TAU that began at 3 months and was sustained through 5 years. This finding was confirmed via a clinical global improvement measure. Patients receiving VNS + TAU demonstrated a clinically-meaningful QOL improvement (34% MADRS decrease) compared with TAU alone. An exploratory post hoc sub-analysis demonstrated that VNS + TAU had a statistically significant advantage in multiple QOL domains versus TAU alone.

Comment: Implanted vagal nerve stimulation has undergone a rather rocky pathway towards clinical use since its initial evaluation over 10 years ago and subsequent approval for use in the US. Data has continued to slowly accumulate on its efficacy and potential clinical utility. This current report examined QOL in 328 patients receiving VNS therapy compared to 271 patients provided with treatment as usual. VNS therapy was associated with comparatively improved QOL after three months of therapy and this improvement was sustained through five years of follow-up. Advantages of VNS over treatment as usual were also reported using the global clinical improvement measure. These improvements were seen despite the average improvement in depressive symptoms only being 34% on the MADRS scale suggesting that functional and QOL changes may emerge in a way that is not captured fully with traditional clinical rating scales.

Reference: J Clin Psychiatry 2018;79(5):18m12178
Abstract

Transdermal nicotine for the treatment of mood and cognitive symptoms in nonsmokers with late-life depression

Authors: Gandelman JA et al.

Summary: In this 12-week, open-label, outpatient study, transdermal nicotine was given to 15 non-smoking older adults (≥60 years of age) with MDD and subjective cognitive improvement. Transdermal nicotine patches were applied daily and titrated in a rigid dose escalation strategy to a maximum dose of 21.0 mg/day, allowing dose reductions for tolerability. Response and remission rates of 86.7% and 53.3%, respectively, were observed as was a significant decrease in MADRS scores over the study (p<0.001), with improvement seen as early as 3 weeks. Improvements in apathy and rumination were also observed. Transdermal nicotine was well tolerated, although six participants were unable to reach the maximum targeted dose.

Comment: This novel but somewhat limited study explored the use of transdermal nicotine in the treatment of elderly patients (non-smokers) with persistent depression. The authors proposed that nicotine might improve both depressive and cognitive symptoms in this patient group. They examined this in an open-label study involving 15 participants. Nicotine therapy was associated with a substantive response and meaningful remission rate in this sample although it is worth emphasising that the study was open label. Interestingly, the participants did not demonstrate improvements in experimentally assessed attention as had been proposed would be an effect of nicotine but did describe subjective improvements in cognition that would be consistent with improvements in mood. This is an interesting report but clearly requires replication in a well-designed double-blind trial.

Reference: J Clin Psychiatry 2018;79(5):18m12137
Abstract

A randomized, placebo-controlled study of the efficacy and safety of fixed-dose brexpiprazole 2 mg/d as adjunctive treatment of adults with major depressive disorder

Authors: Hobart M et al.

Summary: This two-stage study assessed the efficacy and safety of fixed-dose brexpiprazole 2 mg/day as adjunctive therapy compared with placebo in the treatment of outpatients with MDD and inadequate response to antidepressant treatment. The study comprised an 8-week, single-blind, prospective treatment phase followed by a 6-week, double-blind, randomized treatment phase for patients who did not fully respond to prospective treatment. Adjunctive brexpiprazole (n=91) significantly improved MADRS total score (p=0.0074) from baseline to week 6 versus placebo (n=202). The treatment groups were not significantly different for the Sheehan Disability Scale mean score (p=0.33). Adjunctive brexpiprazole also improved MADRS total score versus placebo in the subgroups with minimal response to prospective antidepressant treatment (p=0.026) and anxious distress (p=0.0099). Adjunctive brexpiprazole was well tolerated.

Comment: A variety of atypical antipsychotic drugs have been explored as adjuvant treatments in the management of patients with treatment-resistant depression. This study explored the potential efficacy of brexpiprazole (2 mg a day) compared to placebo over a six-week period of therapy. Promisingly, active therapy was associated with greater reductions in MADRS scores in the total group and in subgroups with poor response to antidepressant therapy. Active treatment was also well-tolerated. This substantive trial further supports the use of atypical antipsychotics, and in this case specifically brexpiprazole, in patients with treatment-resistant depression.

Reference: J Clin Psychiatry 2018;79(4):17m12058
Abstract

A double-blind placebo-controlled trial of omega-3 fatty acids as a monotherapy for adolescent depression

Authors: Gabbay V et al.

Summary: In this double-blind study, adolescents (n=51) with untreated MDD were randomized to receive 10 weeks' treatment with omega-three fatty acids or placebo, which were administered on a fixed-flexible dose titration schedule based on clinical response and side effects. Treatment with omega-three fatty acids was not superior to placebo for any clinical feature of MDD, including depression severity and levels of anhedonia, irritability, and suicidality, with response rates being comparable between treatment groups. Both treatments were associated with statistically significant improvements in depression severity on patient and clinician ratings

Comment: Considerable excitement has previously been generated for the potential use of omega-three fatty acids in the treatment of a variety of mental health as well as physical health conditions. These claims, like any, need to be subject to meaningful clinical trials, which sometimes unfortunately yield disappointing results. In the current report, 51 medication-free adolescents with MDD received either omega-three fatty acids or placebo for 10 weeks. Fatty acid therapy was associated with no benefit over placebo on any clinical variable hence not providing any support for the hypothesis that omega-three fatty acids may prove a useful treatment for depression in younger people.

Reference: J Clin Psychiatry 2018;79(4):17m11596
Abstract

Influence of adjuvant omega-3-polyunsaturated fatty acids on depression, sleep, and emotion regulation among outpatients with major depressive disorders - Results from a double-blind, randomized and placebo-controlled clinical trial

Authors: Jahangard L et al.

Summary: In this double-blind study, 50 adult outpatients with MDD, who were receiving standard treatment with sertraline at therapeutic dosages, were randomly assigned either to omega-three fatty acids or placebo. Patients' and experts' ratings of symptoms of depression decreased over time, but to a greater extent in the omega-three fatty acids treatment group than in the placebo group. Similarly, anxiety sensitivity, intolerance of uncertainty, and sleep disturbances improved, and again more so in the omega-three fatty acids group. Additionally, regulation and control of emotions and perception of other's emotions improved over time for both treatments, with the improvement being greater in the omega-three fatty acids group.

Comment: In contrast to the study exploring the use of omega-three fatty acids in adolescent depression, this study explored the use of omega-three fatty acids in standard adult subjects. All patients were stable on treatment with sertraline and followed for up to 12 weeks. Use of omega-three fatty acids was associated with a greater reduction in depressive symptoms then seen in the placebo group. The greater improvement in depression was mirrored by improvement in a number of other symptom domains including sleep and anxiety. This obviously provides significantly greater hope than the study by Gabbay et al. Two noticeable differences between the studies are the use of an adult participants sample in this group but also the fact that patients in this study, in contrast to the study by Gabbay et al., were also receiving standard antidepressant medication therapy. It is possible that omega-three fatty acids interact with SSRI treatment to produce greater responses than when they are applied alone.

Reference: J Psychiatr Res. 2018;107:48–56
Abstract

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Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and bipolar depression

Authors: Zheng W et al.

Summary: This was a non-comparative Chinese study in which 97 patients with unipolar (n=77) and bipolar (n=20) depression were treated with six repeated ketamine infusions (0.5 mg/kg over 40 min), with continuous vital sign monitoring. Response and remission rates were 68.0% and 50.5%, respectively, after the sixth infusion. Significant reductions in depression, suicidal ideation, and anxiety scale scores were observed within four hours following the first infusion, and the decreases were sustained over the subsequent infusion period. Rapid significant improvement in suicidal ideations throughout the course of treatment were observed in the non-responder subgroup.

Comment: Research into the use of ketamine has been one of the hottest topics in depression pharmacotherapy in recent years. However, there is still a lack of studies exploring repeated drug dosing. In the current study, patients with both unipolar and bipolar depression received six repeated ketamine infusions. This resulted in a response rate of 68% and a remission rate of 50%, respectively. Symptoms improved within four hours following the first injection and were generally sustained over the treatment period. Notably, non-responders to ketamine demonstrated improvements in suicidal ideation throughout the course of treatment even when depressive symptoms in general did not improve. These are impressive response rates but the absence of a control group and the powerful psychomimetic effects of ketamine make drawing conclusions from this form of open-label research quite problematic.

Reference: J Psychiatr Res. 2018;106:61–68
Abstract

Independent commentary by Professor Paul Fitzgerald, Professor of Psychiatry at Epworth Centre for Innovation in Mental Health, Epworth Clinic and Deputy Director at the Monash Alfred Psychiatry Research Centre, a joint research centre of Monash University and the Alfred Hospital in Melbourne, Australia. He runs a research program primarily focused on developing novel treatments for mood and other psychiatric disorders and understanding the neurobiology of these disorders to drive therapeutic implications. He has conducted over 20 clinical trials, published over 400 papers and received grant funding from a range of Australian and international organisations. He is also a founder and director of TMS Clinics Australia (https://tmsaustralia.com.au).

Mindfulness-based cognitive therapy for patients with chronic, treatment-resistant depression: A pragmatic randomized controlled trial

Authors: Cladder-Micus MB et al.

Summary: In this pragmatic, multicentre, randomised trial, chronically-depressed outpatients, who had previously received pharmacotherapy (≥4 weeks) and psychological treatment (≥10 sessions), were assigned to treatment-as-usual (TAU; n=57) or mindfulness-based cognitive therapy (MBCT) + TAU (n=49). Patients in the MBCT + TAU group did not have significantly fewer depressive symptoms than those in the TAU group according to intention-to-treat analysis. However, compared with the TAU group, the MBCT + TAU group had significantly higher remission rates (p=0.04), lower levels of rumination (p=0.04), a higher QOL (p=0.048), more mindfulness skills (p=0.001), and more self-compassion (p=0.001). The percentage of non-completers in the MBCT + TAU group was relatively high (n=12, 24.5%). Per-protocol analyses showed that patients who completed MBCT + TAU had significantly fewer depressive symptoms than patients who completed TAU (p=0.04).

Comment: MBCT is a therapeutic method for which there is considerable support as a mechanism to prevent depressive relapse in patients who have responded to psychological or other therapies. It has been explored in the actual treatment of depression to a much lesser degree. In this report, one hundred and six chronically depressed outpatients were treated with either MBCT + treatment as usual or just treatment as usual. Levels of depression were not reduced in the MBCT group compared to the control group in the intention-to-treat analysis although the intervention group did report higher remission rates and improvements in a number of other domains. It is also noted that there was a fairly high dropout rate in the MBCT group of almost 25%. This study provides limited support for the use of MBCT in chronic depression: clearly many participants struggled to remain engaged in therapy and the improvements were somewhat limited and should be judged somewhat sceptically given the absence of a true control group. Whilst mindfulness-based treatments can clearly be effective in patients who have achieved treatment response, they maybe too difficult for many patients who are actively depressed to engage in and achieve meaningful response from.

Reference: Depress Anxiety. 2018;35(10):914–924
Abstract

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