Depression Research Review™

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Welcome to the latest issue of Depression Research Review.

This issue features two papers reporting research on alternatives to electroconvulsive therapy. One identifies predictors of non-response to repetitive transcranial magnetic stimulation and the other evaluates continuation magnetic seizure therapy for the prevention of relapse in patients with treatment-resistant depression.

Two other theme-related selections address aspects of the role of systemic inflammation in the pathophysiology of depression: one explores associations between inflammation and a variety of individual symptoms of depression and the other evaluates the efficacy of celecoxib added to vortioxetine for treatment of depression.

Additional papers report on the efficacy of lithium in the prevention of suicide-related behaviours and the impact of the COVID-19 epidemic on the burden of depressive and anxiety disorders.

We hope that you enjoy these selections. Your input is valued; please send us your suggestions and feedback.

Kind Regards,

Associate Professor Steve MacFarlane
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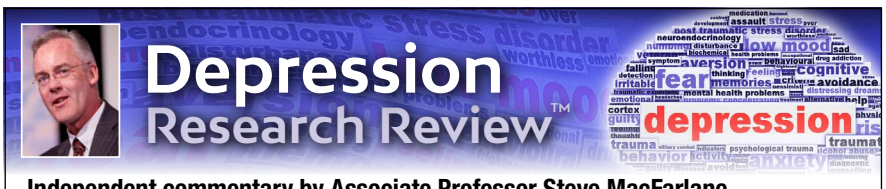
Absence of early mood improvement as a robust predictor of rTMS nonresponse in major depressive disorder

Authors: Mirman AM et al.

Summary: These researchers evaluated early changes in sleep, anxiety, and mood as predictors of non-response to repetitive transcranial magnetic stimulation (rTMS) in 329 patients with non-psychotic major depressive disorder who received a 6-week course of rTMS treatment. Non-response was defined as <50% improvement in compositive depressive symptoms after 6 weeks, which was measured as negative predictive value (NPV; the likelihood that absence of early symptom improvement accurately predicted non-response to treatment). At week 1, patients with severe or very severe baseline depression achieving <20% improvement in mood were correctly predicted as non-responders with NPVs mostly >90%. At 2 weeks, patients with very severe baseline depression in whom there was no improvement in mood were all non-responders. Absence of improvement in sleep at 2 weeks was also a predictor of non-response.

Comment: With ongoing debates about the effectiveness and cost benefit of rTMS, this paper presents some useful findings on predictors of treatment non-response that may help clinicians determine the clinical likelihood of non-response over a six-week course of rTMS. Results suggest that the absence of early improvement in mood symptoms was predictive of non-response (>90% and 100% NPV at 1 and 2 weeks, respectively) in those with severe to very severe depression at baseline. The key predictor of non-response was a failure to demonstrate mood improvement of ≥20% during the first week of treatment.

Reference: Depress Anxiety. 2022;39(2):123–133
Abstract



Independent commentary by Associate Professor Steve MacFarlane

Steve graduated from Monash University in 1991, and became a psychiatrist in 2003, and was appointed Director of Aged Psychiatry at Peninsula Health in 2005. He moved to Alfred Health in 2008 as Associate Professor and Director of Aged Psychiatry, before accepting a position as Head of Clinical Services with Dementia Support Australia in 2016.

Steve is the Chair of the Faculty of Psychiatry of Old Age for the RANZCP, has been running Alzheimer's disease clinical trials for over 20 years, and has clinical interests in frontal lobe disorders and in senile squalor.

REFERENCES: 1. Katona C, *et al. Int Clin Pyschopharmacol* 2012; 27(4):215–223. **2.** Alvarez E, *et al. Int J Neuropsychopharmacol* 2012; 15:589–600. **3.** Brintellix® Australian Approved Product Information. **4.** McIntyre RS, *et al. Int J Neuropsychopharmacol* 2014; 17(10):1557–1567. **5.** Mahableshwarkar AR, *et al. Neuropsychopharmacol* 2015; 40(8):2025–2037. **6.** McIntyre RS, *et al. Int J Neuropsychopharmacol* 2016; 19(10):1–9.

No evidence for clinical efficacy of adjunctive celecoxib with vortioxetine in the treatment of depression: A 6-week double-blind placebo controlled randomized trial

Authors: Baune BT et al.

Summary: In this randomised double-blind trial, patients with major depressive disorder were randomised to receive vortioxetine plus celecoxib or vortioxetine plus placebo for six weeks. There was no evidence of superior efficacy of celecoxib augmentation over placebo on depressive symptom severity, response and remission rates, and cognition and psychosocial functioning. There was also no evidence that pre-treatment inflammation levels (C-reactive protein; CRP) modified the effect of celecoxib augmentation versus placebo.

Comment: There is increasingly robust evidence for the role of inflammation in the development of depression. It logically follows that treatment with anti-inflammatory agents might be beneficial in the treatment of depression. This study used adjunctive celecoxib therapy or placebo in addition to antidepressant treatment over six weeks and found no benefit, admittedly within what was largely a treatment-resistant cohort. Baseline blood CRP levels were taken into account when analysing the results, but negative results were still present when these was accounted for. Celecoxib does not have significant blood-brain barrier penetration, however, with evidence that concentrations achieved in the CNS after oral administration are insufficient for celecoxib to exceed mean inhibitory concentrations for cyclooxygenase-2 following a single 200mg oral dose (Dembo et al. Anaesthesiology. 2005;102(2):409–15).

Reference: Eur Neuropsychopharmacol. 2021;53:34–46
Abstract

Continuation magnetic seizure therapy for treatment-resistant unipolar or bipolar depression

Authors: Tang VM et al.

Summary: In this prospective open-label trial, patients with treatment-resistant depression who met response criteria after acute magnetic seizure therapy (MST) were offered continuation MST. They received 12 continuation MST sessions with decreasing frequency over 6 months, with additional booster sessions if their symptoms started to worsen. Of 30 patients completing ≥1 assessment during continuation MST, 10 (33.3%) relapsed, with no significant differences in survival distributions between unipolar and bipolar groups. Mean (SD) survival time was 18.6 (1.6) weeks. During the continuation phase, 17 patients who achieved resolution of baseline suicidality after acute MST remained free of suicidality. Except for improvement in verbal fluency, neurocognitive test scores remained unchanged during continuation MST.

Comment: Whilst many are becoming familiar with rTMS as a treatment, MST is less well-known in Australia. This treatment still involves the medical induction of a seizure but relies upon using a focussed magnetic field to provide stimulation to discrete brain regions, resulting in less cognitive impairment than is seen with electroconvulsive therapy (ECT). This is the first study to report on the effectiveness of maintenance MST for the prevention of relapse in unipolar or bipolar depression, and as such is worthy of mention. Twelve MST sessions were delivered within a frequency-tapered protocol over 6 months (n=30). Two-thirds of these sustained the improvements they experienced during their initial course, and did not experience declines in cognitive tests during that period. The relapse rate is broadly similar to those seen in studies of maintenance ECT in major depression (Jelovac et al. Neuropsychopharmacology. 2013;38:2467–2474).

Reference: J Clin Psychiatry. 2021;82(6):20m13677
Abstract

Association of hypothyroidism and clinical depression: a systematic review and meta-analysis

Authors: Bode H et al.

Summary: Of the 4,350 articles screened in the systematic literature review, 25 studies (n=348,014) were selected for the meta-analysis. Hypothyroidism and clinical depression were found to be associated (OR 1.30; 95% CI: 1.08–1.57) but the OR for autoimmunity was inconclusive (1.24; 95% CI: 0.89–1.74). Subgroup analyses revealed a stronger association with overt (OR 1.77; 95% CI: 1.13–2.77) than with subclinical (1.13; 95% CI: 1.01–1.28) hypothyroidism. In a post hoc analysis, the association was confirmed in females (OR 1.48; 95% CI: 1.18–1.85) but not in males (OR 0.71; 95% CI: 0.40–1.25).

Comment: Hypothyroidism is a classical biological cause of depression. This systematic review and meta-analysis reveals that the greater the degree of clinical hypothyroidism, the stronger the association with clinical depression. Subclinical hypothyroidism was less strongly associated with depression, whereas any association with broader autoimmune syndromes was inconclusive. Interestingly, no association was seen between hypothyroidism and depression in males, suggesting that other factors may be in play.

Reference: JAMA Psychiatry. 2021;78(12):1375–1383
Abstract

Lithium treatment in the prevention of repeat suicide-related outcomes in veterans with major depression or bipolar disorder: a randomized clinical trial

Authors: Katz IR et al.

Summary: This was a randomised double-blind trial that assessed lithium versus placebo augmentation of usual care in veterans with bipolar disorder or depression who had survived a recent suicide-related event. The trial was stopped for futility after 519 veterans were randomised (255 to lithium and 264 to placebo). Mean lithium concentrations at 3 months were 0.54 mEq/L in patients with bipolar disorder and 0.46 mEq/L in patients with major depressive disorder. There was no overall difference in repeated suicide-related events between treatments (HR 1.10; 95% CI: 0.77–1.55). A total of 127 participants (24.5%) had suicide-related outcomes: 65 in the lithium group and 62 in the placebo group. One death occurred in the lithium group versus three in the placebo group.

Comment: Lithium has long been proposed to be protective against suicide in unipolar and bipolar depression, although the extant data are actually mixed on this point. This study added lithium or placebo to usual care in veterans (n=519, average age 43 years) with suicidal behaviour, with the aim of providing further clarity on this question. Those with significant comorbidities were excluded, along with those who had relative contradictions to lithium. No differences were found in subsequent rates of suicide-related behaviours, and the study was halted following a futility analysis. Given the toxicity of lithium in overdose, this finding has implications for clinical practice and serves to further question the orthodoxy that lithium is protective against suicide.

Reference: JAMA Psychiatry. 2022;79(1):24–32
Abstract

Safety and efficacy of agomelatine in children and adolescents with major depressive disorder receiving psychosocial counselling: a double-blind, randomised, controlled, phase 3 trial in nine countries

Authors: Arango C et al.

Summary: In this randomised, double-blind, parallel-group, multicentre study, children (aged 7–11 years) and adolescents (12–17 years) with major depressive disorder were randomly assigned (1:1:1:1) to treatment with agomelatine 10 mg, agomelatine 25 mg, placebo, or fluoxetine for 12 weeks. The full analysis set of 396 individuals consisted of 247 [62%] girls and 149 [38%] boys (mean age 13.7 years). Agomelatine 25 mg/day (n=94) resulted in a baseline improvement versus placebo (n=101) in Children's Depression Rating Scale-revised (CDRS-R) raw score of 4.22 (95% CI: 0.63–7·82; p=0·040) at 12 weeks, with a similar effect for fluoxetine (n=99). The overall effect was confirmed in adolescents (n=317) but not in children (n=79). Agomelatine treatment was not associated with significant weight gain or an effect on suicidal behaviours.

Comment: This 12-week study recruited children and adolescents (n=396) between 7 and 17 years of age with major depression who had been unresponsive to 12 weeks of psychosocial treatments and randomised them to either agomelatine 10mg or 25mg, fluoxetine 10–20mg or placebo in a double-blind fashion for 12 weeks in addition to standardised psychosocial counselling. The 25mg dose was found to be as effective as fluoxetine treatment in the adolescent subgroup (n=317), but not in children (perhaps unsurprising, given the poor response of this age group to antidepressant treatments in general). The Children's Depression Rating Scale – Revised (based on the adult Hamilton scale) was the main outcome measure, with a mean difference compared to placebo of around 4 points being noted on this scale, on which the total possible score ranges from 17 to 113. On this basis, the clinical significance of the results seems debatable. No safety concerns were noted.

Reference: Lancet Psychiatry. 2022;9(2):113–124
Abstract

Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic

Authors: COVID-19 Mental Disorders Collaborators

Summary: These researchers conducted a systematic review of data reporting the prevalence of major depressive disorder (MDD) and anxiety disorders during the COVID-19 pandemic and published between 1st January 2020 and 29th January 2021. They identified 5,683 unique data sources, of which 48 met inclusion criteria (46 studies met criteria for MDD and 27 for anxiety disorders). Daily SARS-CoV-2 infection rates and reductions in human mobility were associated with increased prevalence of MDD (p=0.0005 for daily SARS-CoV-2 infection and p=0.029 for human mobility) and anxiety disorders (p<0.0001 and p=0.022). Females were affected more by the pandemic than males (p=0.0001 for MDD and p=0.0001 for anxiety disorders) and younger age groups were more affected than older age groups (p=0.0001 for MDD and p=0.0001 for anxiety disorders).

Comment: This study adds to the body of literature on the impact of COVID-19 on global mental health. Mathematical models were used to compare published pre-pandemic prevalence rates of major depressive and anxiety disorders with prevalence rates experienced during the first year of the pandemic in 2020. An estimated increase of 53.2 million cases of major depression (representing a 27.6% increase on pre-pandemic numbers) was reported. Similarly, it was estimated that an additional 76.2 million cases of anxiety disorders arose during this period (an increase of 25.6%). Daily infection numbers and restrictions on mobility (lockdowns) were most strongly associated with the reported increases in prevalence of depression. Being female and of younger age were clear predictors of greater prevalence. These data strengthen the calls for increased mental health resourcing during the ongoing pandemic, in particular targeting vulnerable subgroups.

Reference: Lancet. 2021;398(10312):1700–1712
Abstract

Response to antidepressants among patients with unipolar depression with and without comorbid epilepsy – a nation-wide population-based longitudinal study

Authors: Kessing LV et al.

Summary: These investigators used the Danish nation-wide population-based longitudinal register linkage to evaluate the long-term response to antidepressants in patients with depression with and without comorbid epilepsy. They identified 1,487 patients with depression and comorbid epilepsy and 71,163 patients with depression without comorbid epilepsy during the period of study (1995 to 2017). In patients with depression, the response to antidepressants was decreased with versus without comorbid epilepsy during the ten-year follow-up period. One year after start of antidepressant treatment, the proportion of responders was 12% (CI: 10–14%) lower in patients with versus without comorbid epilepsy in the standardised population. The response to antidepressants was specifically decreased in younger and unemployed patients with depression and comorbid epilepsy.

Comment: Who doesn't love a Scandinavian population-based linkage study?! A national register identified patients with unipolar major depression both with epilepsy (n=1,487) and without (n=71,163). Response to antidepressant treatment across both groups was the outcome of interest ('response' being presumed by a lack of switching to another antidepressant, the addition of an antipsychotic or lithium, or hospitalisation over an extended follow-up period). Those with comorbid epilepsy had a response rate that was 12% lower than in those without epilepsy after one year of treatment. The disparity in response was most apparent in younger and unemployed patients with epilepsy. The results are of interest partly due to the presumption that at least a fair proportion of patients with epilepsy are likely to have been prescribed anticonvulsants that are also approved as mood stabilisers. The findings highlight the need for psychiatrists and neurologists to collaborate in the treatment of this group of patients (Kanner Epilepsy Behav. 2003;4(6)597–601).

Reference: J Affect Disord. 2022;299:1–5
Abstract

Association between systemic inflammation and individual symptoms of depression: A pooled analysis of 15 population-based cohort studies

Authors: Frank P et al.

Summary: This random-effects pooled analysis included 15 population-based cohorts and a total of 56,351 individuals (aged ≥18 years) to explore the associations between systemic inflammation and an array of individual symptoms of depression. Serum or plasma levels of C-reactive protein (CRP) and interleukin-6 (IL-6) were measured at baseline. Using validated self-report measures, 24 depressive symptoms were ascertained in 15 cross-sectional studies, and in seven cohorts they were also assessed at follow-up (mean follow-up period of 3.2 years). The prevalence of depressive symptoms ranged from 1.1% (suicidal ideation) to 21.5% (sleep problems). In cross-sectional analyses, higher CRP levels were strongly associated with higher risk of experiencing four physical symptoms (changes in appetite, felt everything was an effort, loss of energy, and sleep problems) and one cognitive symptom (little interest in doing things). For four symptoms considered exclusively emotional (bothered by things, hopelessness about the future, felt fearful, life had been a failure), the overall evidence against an association with inflammation was robust.

Comment: In an attempt to make sense of the confusing literature around anti-inflammatory drug trials in the treatment of depression, the authors explore the linkages between specific depressive symptoms and peripheral levels of known inflammatory biomarkers (CRP and IL-6). Elevated CRP was associated with experiencing appetite changes, feeling effortful, loss of energy, sleep problems, and loss of interest, with the association remaining after controlling for a number of relevant variables. What a psychiatrist might consider to be more 'core' depressive symptoms (bothered by things, hopelessness, fearfulness, life having been a failure) the evidence was strongly against an association with inflammation. The authors suggest that future anti-inflammatory trials in depression target individuals whose symptom profiles match those where the association with inflammation was noted.

I'm not convinced that the finding is particularly helpful. One might imagine that a person who is symptomatic from an active inflammatory process, whatever the cause, might well report these target symptoms without necessarily being clinically depressed. Even in the presence of depression, these symptoms may well reflect the inflammation, rather than depression. In that case, an improvement in inflammation-mediated physical symptoms may well be appropriately managed by the use of anti-inflammatories, but such a response would say little about the utility of anti-inflammatories in treating major depression.

Reference: Am J Psychiatry. 2021;178(12):1107–1118
Abstract