Depression Research Review™

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Issue 20 - 2023

In this issue:

Abbreviations used in this issue:

AE = adverse event; **CGI** = Clinical Global Impression scale;
DSM = Diagnostic and Statistical Manual of Mental Disorders;
HAM-D = Hamilton Depression Rating Scale;
ICD = International Classification of Diseases;
IDS = Inventory of Depressive Symptomatology;
MDD = major depressive disorder;
rTMS = repetitive transcranial magnetic stimulation;
SNRI = serotonin–noradrenaline reuptake inhibitor;
SSRI = selective serotonin-reuptake inhibitor.

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Welcome to the latest issue of Depression Research Review.

Specific treatments for depression covered in this issue include esketamine nasal spray, transcranial magnetic stimulation, vortioxetine, vitamin D and omega-3 fatty acid supplementation, zuranolone, and probiotics. Other research covered in this issue deals with maintenance versus discontinuation of adjuvant antidepressant therapy after remission, epidemiology of depression in Europe and Latin America, contribution of genetics to the heterogeneity of depression, and role of neuroinflammation after COVID-19 illness with persistent depressive and cognitive symptoms.

We hope that you enjoy these selections and look forward to receiving your comments and feedback.

Thank you for your readership and feedback.

Kind Regards,

Professor Nagesh Pai
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Esketamine nasal spray versus quetiapine for treatment-resistant depression

Authors: Reif A et al.

Summary: In this multicentre, open-label, single-blind (raters were unaware of group assignments) trial, patients with treatment-resistant depression were randomly assigned (1:1) to receive flexible doses of esketamine nasal spray or extended-release quetiapine, both in combination with an SSRI or SNRI. Esketamine nasal spray plus an SSRI or SNRI was found to be superior to extended-release quetiapine plus an SSRI or SNRI with respect to remission rate at week 8. AEs did not differ from those previously demonstrated with the trial treatments.

Comment: The results of the ESCAPE-TRD trial, a head-to-head comparison of esketamine nasal spray with extended-release quetiapine in the treatment of 676 people with depression whose symptoms had not responded to at least two antidepressants and who were continuing to take either an SSRI or an SNRI such as venlafaxine or duloxetine. The primary end-point was remission at week 8; the key secondary end-point was no relapse at week 32 after remission at week 8. Esketamine nasal spray was more efficacious than extended-release quetiapine (27% of patients vs 18% of patients) and was associated with fewer AEs that led to discontinuation of the trial treatment. The benefit gradually increased over time with both drugs: by week 32, 49% of patients in the esketamine group and 33% in the quetiapine group were in remission and 66% and 47%, respectively, had had a response to treatment. Relapse between week 8 and week 32 was uncommon in both treatment groups. While this was an open trial, there is no perfect solution to the problems of unblinding and expectation bias, which may be substantial in trials of medications with short-term psychoactive effects. Advantages of esketamine include cystitis and cognitive impairment remain theoretical, rather than actual, risks; overuse is prevented because the nasal spray has to be administered in the clinic, and off-label addition of racemic ketamine or other drugs of potential abuse to esketamine nasal spray has not been common. Cost and inconvenience are therefore likely to be decisive factors in its use.

Reference: N Engl J Med. 2023;389(14):1298-1302

Abstract

Duration of adjunctive antidepressant maintenance in bipolar I depression

Authors: Yatham LN et al.

Summary: These investigators conducted a multicentre, randomised, double-blind, placebo-controlled trial of maintenance of treatment with adjunctive escitalopram or bupropion XL compared with discontinuation of antidepressant therapy in patients with bipolar I disorder and a recently remitted depressive episode. Adjunctive treatment with escitalopram or bupropion XL that continued for 52 weeks did not show a significant benefit compared with treatment for 8 weeks in preventing relapse of any mood episode. The frequency of AEs was similar in both groups. Due to slow recruitment and funding difficulties the trial was ended prematurely.

Comment: This trial sought to answer the question of whether continuing adjunctive therapy with antidepressants in patients with bipolar I disorder is effective and safe as a maintenance treatment for depression. The main finding was that continuing adjunctive antidepressant therapy for 52 weeks as compared with discontinuing antidepressants at 8 weeks was not more beneficial with regard to the primary outcome of the occurrence of any mood episode. Limitations of this study include the study was not powered for subgroup analyses and the results are descriptive only. Further, the recruitment was stopped before the planned sample size was reached, the limited generalizability of the results to other countries, and ecitalopram and bupropion XL were the only antidepressants studied.

Reference: N Engl J Med. 2023;389(5):430-440
Abstract

Prevalence and variability of depressive symptoms in Europe: update using representative data from the second and third waves of the European Health Interview Survey (EHIS-2 and EHIS-3)

Authors: Arias-de la Torre J et al.

Summary: The overall results of this population-based study, which was based on large and representative datasets (the second and third waves of the European Health Interview Survey [EHIS-2 and EHIS-3]) and a valid and reliable screening tool for the assessment of depression (8-item version of the Patient Health Questionnaire), indicate that the point prevalence of clinically relevant depressive symptoms in Europe from 2013 to 2020 remains relatively stable but with wide variability between countries.

Comment: This study is one of the largest and most recent studies worldwide that assesses the point prevalence of clinically relevant depressive symptoms. The results provide updated estimations of the point prevalence of clinically relevant depressive symptoms in Europe, showing a marginal increase with respect to EHIS-2 (6.54%, up from 6.38%), with high variability across countries (from 1.58% in Greece to 10.72% in Sweden), and the variability between countries was minimal between the waves. Based on large and representative datasets and on a valid and reliable tool for the assessment of depression, the point prevalence of clinically relevant depressive symptoms in Europe remained relatively stable (approximately 6.5%) between 2013 and 2020, with wide variability between countries. These data could serve as a baseline for further studies on the prevalence of clinically relevant depressive symptoms in Europe and could inform the development of targeted mental health policies and preventive measures.

Reference: Lancet Public Health. 2023;8(11):e889-e898.
Abstract

Prevalence of depressive disorder in the adult population of Latin America: a systematic review and meta-analysis

Authors: Errazuriz A et al.

Summary: These researchers conducted a systematic review and meta-analysis of population-based studies reporting primary data on the prevalence of ICD/DSM depressive disorder in Latin America from 1990 to 2023. Using data from 40 studies, lifetime, 12-month, and current prevalence of ICD/DSM depressive disorder were estimated to be 12.58%, 5.30%, and 3.12%, respectively. There was a high degree of heterogeneity across lifetime, 12-month, and current prevalence, sex, and countries. The results also showed that the country-level development indicators of human development (HDI), income (Gini), and gender inequality (GII) were associated with the 12-month and current prevalence of depressive disorder in the region and that the intentional homicide rate (IHR) was associated with the current prevalence.

Comment: This study has addressed the insufficiently understood epidemiology of depression in Latin America, a region characterised by large income and gender inequalities, and violence. The study has provided systematic, comparable evidence of structural factors related to depression in middle-income countries. It also provides partial evidence of a higher prevalence of depression in the region compared to global estimates, with women consistently showing a higher prevalence across countries and studies. In addition, a strong positive association between Gini and prevalence of ICD/DSM depressive disorder is evident. The study also provides evidence of the adverse association of low HDI, high GII, and IHR with ICD/DSM depressive disorder in the region, over a thirty-year period. The implications of the study include the region's need for better access to high-quality care, particularly for women, the need for the policymakers to understand and more effectively address the mental health needs of their populations, track health progress, improve resource allocation, and contribute to a more comprehensive view of the region's mental health epidemiology.

Reference: Lancet Reg Health Am. 2023:26:100587
Abstract

Zuranolone for the treatment of adults with major depressive disorder: a randomized, placebo-controlled phase 3 trial

Authors: Clayton AH et al.

Summary: This randomised, double-blind, placebo-controlled trial evaluated the efficacy and safety of a 14-day treatment course of zuranolone 50 mg/day in patients with MDD. The key findings in 534 patients (266 in the zuranolone group and 268 in the placebo group) were that treatment with zuranolone resulted in a significantly greater improvement in depressive symptoms at day 15 than placebo, with a rapid onset of effect (day 3). Zuranolone was generally well tolerated and no new safety findings were identified compared with previously studied lower dosages.

Comment: The therapeutic promise of neuroactive steroid gamma-aminobutyric acid type A (GABAA)-receptor positive modulators for treating mood disorders has been supported; brexanolone is the first therapeutic approved specifically for the treatment of postpartum depression. Zuranolone (SAGE-217) is currently under clinical investigation for the treatment of major depressive episodes in MDD, postpartum depression, and bipolar depression. Zuranolone is a novel, synthetic, clinical-stage neuroactive steroid GABAA-receptor positive allosteric modulator designed with the pharmacokinetic properties to support oral daily dosing. This study assessed the efficacy and safety of a 14-day treatment course of once-daily zuranolone 50 mg, for the treatment of MDD. The study demonstrated significantly greater improvements in depressive symptoms at day 15 compared with those receiving placebo, and the observed onset of effect was rapid, with greater improvement in HAM-D and CGI-Severity scores observed for zuranolone compared with placebo at the earliest assessment, on day 3. It is important to note that this was a short-term study designed to assess the outcomes of patients after one 14-day treatment course of zuranolone. The long-term safety and efficacy of zuranolone and the potential need for repeated treatment courses over a 1-year period needs to be addressed. While the patient population was racially and ethnically diverse in both treatment groups, there was a slightly lower proportion of White patients and a higher proportion of African American and Asian patients in the zuranolone group compared with the placebo group, which may limit the generalizability of the results. This study also showed a robust placebo response, and its magnitude was similar to that observed previously for zuranolone or other antidepressant therapies. Even though the study was conducted during the COVID-19 period, the frequent in-person visits in this study may have contributed to alleviating feelings of isolation and predisposed patients to experience improvements in symptoms even if they were receiving placebo.

Reference: Am J Psychiatry. 2023;180(9):676-684
Abstract

Genetic contribution to the heterogeneity of major depressive disorder: evidence from a sibling-based design using Swedish national registers

Authors: Nguyen T-D et al.

Summary: These researchers investigated the genetic characterisation of MDD heterogeneity in 46,255 individuals with specialist-diagnosed MDD that were identified using data from a Swedish patient register. Eighteen subgroups were identified based on nine comparison groups defined by clinical and psychosocial features. Heritability estimates ranged from 30.5% to 58.3% across subgroups, with disabled and youth-onset subgroups showing significantly higher heritability (55.1–58.3%) than the overall MDD sample (45.3%), and the subgroups with single-episode MDD and without psychiatric comorbidity showing significantly lower estimates (30.5–34.4%).

Comment: This study extends evidence for subgroups with greater functional disability and disease burden. Compared with their counterparts, heritability was significantly higher for the MDD subgroups with disability, youth onset, suicide attempt or death by suicide, comorbidity with anxiety disorder or another psychiatric disorder, and recurrence. These results were largely consistent with previous analyses using polygenic risk scores, which showed that subgroups with youth onset, recurrence, and comorbid anxiety disorder had a higher genetic burden of common risk alleles for MDD than the later-onset, single-episode, and non-anxiety MDD subgroups, respectively. This study has produced important insights into the genetic heterogeneity of MDD and a deeper etiological understanding of MDD clinical subgroups. It is important to note that the changes in clinical practice during the study follow-up period constitute a possible limitation of using register data. Changes in practice may have led to differences in MDD diagnoses in individuals across different years. The study lacked sufficient sample sizes to study rare subtypes, such as psychotic MDD (<4% of all MDD cases in the Swedish register), and fine-grained clinical information on symptoms and treatment response to investigate important subtypes such as atypical or treatment-resistant MDD. The results from this study were similar to our previous findings in the UK Biobank, regardless of the differences in birth cohort and follow-up.

Reference: Am J Psychiatry. 2023;180(10):714-722
Abstract

Effectiveness of repetitive transcranial magnetic stimulation in depression, schizophrenia, and obsessive-compulsive disorder: an umbrella meta-analysis

Authors: Patel S et al.

Summary: This umbrella meta-analysis was conducted to assess the safety and efficacy of rTMS for MDD, schizophrenia, and obsessive-compulsive disorder (OCD). A total of 28 meta-analyses were included, 13 of which were on treatment-resistant depression, nine on schizophrenia, and six on OCD. Overall, the results suggest that rTMS exerts its symptom-reducing effects in various psychiatric disorders by altering functional connectivity between brain regions by activating or inhibiting the targeted brain region depending on the frequency of rTMS used.

Comment: The interest in using non-invasive brain stimulation for the treatment of major depression, including treatment-resistant depression, is growing rapidly. In this article the authors reviewed abstracts and full-length articles for meta-analysis studies with data on the safety and efficacy of rTMS and sham and collected them for quantitative analysis. All identified studies were independently screened and full texts were assessed to determine eligibility. Any disagreement was resolved through consensus. In this meta-analysis they demonstrate that rTMS was more effective for treatment-resistant depression, as well as for reducing negative symptoms and auditory hallucinations in schizophrenia and OCD symptoms compared with sham treatment. The interpretation needs to take into consideration, like any meta-analysis, bias from the analysts, overgeneralisations, and overarching statements that lack precision as well as inappropriate conclusions due to summarising large sets of data points. Since different mental illnesses are associated with differences in neuropathology, disease-specific target site and frequency of rTMS are two of the most important parameters related to the efficacy of rTMS in symptom reduction in various psychiatric disorders.

Reference: Prim Care Companion CNS Disord. 2023;25(5):22r03423
Abstract

Effects of vitamin D_3 and marine omega-3 fatty acids supplementation on indicated and selective prevention of depression in older adults: results from the clinical center sub-cohort of the VITamin D and OmegA-3 TriaL (VITAL)

Authors: Vyas CM et al.

Summary: VITAL is a 2×2 factorial trial of vitamin D_3 (2,000 IU/day) and/or omega-3 fatty acids (1 g/day) for cardiovascular disease and cancer prevention. To assess vitamin D_3 and omega-3 fatty acids for late-life depression prevention for indicated (targeting subthreshold depression) and selective (targeting presence of high-risk factors) prevention, this targeted prevention study included 720 clinical sub-cohort participants from VITAL who completed neurobehavioral assessments at baseline and 2 years. The results demonstrated that neither vitamin D_3 nor omega-3 fatty acids were beneficial for indicated and selective prevention of late-life depression.

Comment: Late-life depression has a great public health significance due to both its high prevalence and being the leading cause of disease burden, ranking only under ischaemic heart disease. For both ethical reasons and reasons of cost effectiveness, preventative measures aimed at reducing the incidence of depression should target individuals with high a priori risk through exposure to multiple risk factors. From a public health perspective, prevention should be cost effective and lead to a substantial reduction of total disease burden.

Reference: J Clin Psychiatry. 2023;84(4):22m14629
Abstract

Head-to-head comparison of vortioxetine versus desvenlafaxine in patients with major depressive disorder with partial response to SSRI therapy: results of the VIVRE Study

Authors: McIntyre RS et al.

Summary: In this randomised, double-blind, parallel-group, 8-week study of vortioxetine (n=309) versus the SNRI desvenlafaxine (n=293) in adults with MDD who experienced partial response to SSRI monotherapy, vortioxetine was associated with significantly higher rates of CGI-S remission, better daily and social functioning, and greater treatment satisfaction. Treatment-emergent AEs, which were reported in 46.1% and 39.6% of patients in the vortioxetine and desvenlafaxine groups, respectively, were mostly mild or moderate in intensity.

Comment: Head-to-head studies of antidepressants in patients with MDD are rare, particularly in those experiencing partial or no response to prior therapy. Most adult patients with MDD remain in work despite their disease and the resulting functional impairment. Vortioxetine has demonstrated efficacy across the spectrum of symptoms experienced by patients with MDD, including depressive, cognitive, and physical symptoms, as well as anxiety and functional impairment. The VIVRE study was an international, active-controlled, double-blind phase IV study undertaken to compare the efficacy of vortioxetine versus desvenlafaxine on depressive symptoms, overall functioning, and health-related quality of life in patients with MDD experiencing only partial response to initial SSRI therapy. This study adds to the growing body of evidence supporting significantly greater efficacy of vortioxetine versus SNRIs on clinically relevant outcomes for patients with MDD. Further, vortioxetine-treated patients also reported significantly greater satisfaction with their medication as assessed using the Quality-of-Life Enjoyment and Satisfaction Questionnaire than those who received desvenlafaxine. Non-adherence to antidepressant therapy remains a major challenge in clinical practice, being associated with suboptimal clinical outcomes.

Reference: J Clin Psychiatry. 2023;84(4):23m14780
Abstract

Acceptability, tolerability, and estimates of putative treatment effects of probiotics as adjunctive treatment in patients with depression a randomized clinical trial

Authors: Nikolova VL et al.

Summary: In this single-centre, randomised, double-blind, placebo-controlled pilot trial, 49 patients with MDD who were taking antidepressant medication but having an incomplete response were randomly assigned to receive a multistrain probiotic (n=24) or placebo (n=25) adjunctively every day for 8 weeks. Compared with the placebo group, the probiotic group demonstrated a greater improvement in depressive symptoms assessed using HAMD and IDS, with moderate effect sizes. Those who received the probiotic experienced a reduction of one severity grade on both depression rating scales. The probiotic was well tolerated, with a high adherence rate and no serious AEs observed.

Comment: Recent years have seen a rapid increase in the use of gut microbiota-targeting interventions, such as probiotics, for the treatment of psychiatric disorders. While several studies have demonstrated that probiotics appear to be effective in reducing depressive symptoms when administered adjunctively to antidepressants, they have not provided sufficient safety, efficacy, tolerability data. Compared with the placebo group, the probiotic group exhibited greater improvement in depressive symptoms with moderate effect sizes and greater effects on clinician-rated anxiety. Whether the observed effects are specific to the interaction with SSRIs or generalizable to other treatments is to be determined.

Reference: JAMA Psychiatry. 2023;80(8):842-847
Abstract

Neuroinflammation after COVID-19 with persistent depressive and cognitive symptoms

Authors: Braga J et al.

Summary: Persistent depressive symptoms, often accompanied by cognitive symptoms, can occur after COVID-19 illness, which in this case-control study was referred to as COVID-DC (DC for depressive with/without cognitive symptoms). Conducted at a tertiary care psychiatric hospital during the COVID-19 pandemic, this study compared the translocator protein total distribution volume (TSPO VT, a marker of gliosis) of specific brain regions in 20 individuals with COVID-DC with that in 20 healthy controls. The main finding was that the TSPO VT across the regions of interest was greater in participants with COVID-DC than in healthy control participants, with the difference being most obvious in the ventral striatum and dorsal putamen.

Comment: Depressive symptoms with or without other cognitive symptoms, after an acute episode of mild-to-moderate COVID-19 illness, is a major public health problem. Persons with a history of mild-to-moderate COVID-19 disease would be unlikely to experience certain phenomena seen in severe cases, such as the cytokine storm associated with highly elevated, generalized bodily inflammation with dysregulation of clotting factors and greater risk for vascular lesions or, since supplemental oxygen is not required, hypoxic lesions. This study found generalized differences in TSPO VT between persons with COVID-DC and healthy control participants, most prominent in the ventral striatum and dorsal putamen, and that greater severity of motor slowing correlated with higher dorsal putamen TSPO VT. Aberrant ventral striatum function may lead to anhedonia, and dorsal putamen injury is associated with motor slowing and low motivation or energy, which are also prominent symptoms of COVID-DC. It is important to note that this study does not prove causality of symptoms from gliosis and that the influence of gliosis would ultimately be best determined in humans by the outcome of clinical interventions targeting gliosis. Further, there are heterogenous mechanisms for depressive and cognitive symptoms after COVID-19 illness.

Reference: JAMA Psychiatry. 2023;80(8):787-795
Abstract

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Independent commentary by Professor Nagesh Pai

Professor Nagesh Pai has been a psychiatrist for almost three decades with interests in academic, clinical and research disciplines. He is a member of the World Psychiatric Association Schizophrenia section, Psychiatric Education and sections of Primary care and Lifestyle psychiatry. As an accredited member and NSW Chair of Faculty of Adult Psychiatry (RANZCP) his expertise is in the area of psychopharmacology. He was promoted to full professor in 2001 and has been a Foundation Professor at The University of Wollongong and currently Leader (Clinical) of the Mental Health and the Ageing Brain Research theme at the Illawarra Health Medical Research Institute. He is also the Senior Clinical Academic, at the Older Persons Mental Health Services at the Illawarra Shoalhaven Local health District.

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