Welcome to the latest issue of Depression Research Review.

This edition’s focus is on cognition and we start by looking at a large longitudinal cohort study from England that investigates the course of cognitive changes from 18-months of age to 20-years of age in people with psychotic disorders. We also review a study that explored the relationship between cardiometabolic factors, cognitive decline and depression and a French study that looks at the relationship between residual depressive symptoms and cognitive impairment in bipolar patients in the euthymic phase. We report promising clinical results for new depression treatments including adjunct intranasal esketamine for treatment resistant depression; transdermal hormone therapy for menopause-transition depression onset prevention and transcranial direct current stimulation as an add-on therapy for bipolar depression.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

Professor Paul Fitzgerald
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Course of cognitive development from infancy to early adulthood in the psychosis spectrum

Authors: Mollon J et al.

Summary: The Avon Longitudinal Study of Parents and Children (ALSPAC) was a long-term prospective cohort study that aimed to elucidate the course and onset of cognitive deficits and functions in people with psychotic disorders, psychotic experiences and depression. All live births in Avon, England between April 1, 1991, and December 31, 1992 (N= 4322) were enrolled and followed from infancy to early adulthood (20 years of age) and assessed for IQ (full scale, verbal and non-verbal) at 18 months and 4, 8, 15 and 20 years old. A range of cognitive functions (including processing speed, memory, language and attention) were assessed at 8 and 20 years and psychiatric testing was also carried out at 18 years. Compared to controls, individuals with psychiatric disorders showed significant deficits in both full-scale and non-verbal IQ (effect size of change [ESΔ] = −1.09, -0.94, respectively) that increased at each assessed time point. People with psychiatric disorders also exhibited significantly slowed growth between 8 and 20 years of age across several measures of cognitive functioning including processing speed, working memory, attention (ESΔ = −0.68, -0.59, -0.44, respectively) and static deficits in language and visuospatial ability (ES = −0.87, −0.90, respectively).

Comment: This interesting and quite substantive report analysed data from a large longitudinal cohort and investigated the pattern of cognitive changes seen from 18 months of age to 20 years of age in patients with psychotic and mood disorders. Patients with a diagnosis of a psychotic disorder demonstrated a significant decrease in both full-scale IQ and non-verbal IQ from infancy to the age of 20 years. This group also showed decreases in a variety of areas of cognitive function between the ages of eight and 20. In contrast, individuals with a subsequent diagnosis of depression showed a small increasing deficit in non-verbal IQ from infancy to adulthood but no other changes and minimal changes were seen in patients with psychosis and depression. This study certainly supports a neurodevelopmental view of psychosis with progressively worsening cognitive function over time but only provides fairly weak evidence that similar changes may be seen in patients with mood disorder diagnosis.

Reference: JAMA Psychiatry 2018;75(3):270-79

Abstract

Independent commentary by Professor Paul Fitzgerald, Professor of Psychiatry at Epworth Clinic/Epworth Hospital 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 focussed on the conduct of investigative studies of brain function & dysfunction as well as the conduct of a variety of novel clinical trials in Mood, Anxiety, Psychotic and Developmental Disorders. He has published over 350 papers and received grant funding from a range of Australian and international organisations.
A randomized controlled pilot study on mindfulness-based cognitive therapy for unipolar depression in patients with chronic pain

Authors: de Jong M et al.

Summary: This randomised, controlled pilot study aimed to determine the efficacy of mindfulness-based cognitive therapy (MBCT) for the treatment of depression in patients with chronic pain. 40 depressed patients (16-item Quick Inventory of Depressive Symptomatology- Clinician Rated (QIDS-C16) score ≥ 6) with chronic pain (≥ 3 months) were randomised to receive an adapted-MBCT treatment (n=26) or waitlisted (n=14). 19 patients completed the program. Primary outcome measures were changes on the QIDS-C16 and 17-item Hamilton Depression Rating Scale (HDRS-17). The HDRS-17 scores did not differ significantly between groups. Repeated-measures analyses of variance for the per-protocol sample (n=33) revealed a significant treatment × time interaction (F1,14 = 4.67, P = 0.039, ηp² = 0.13) for QIDS-C16 score and the authors concluded that MBCT shows potential as therapy for depression in patients with chronic pain.

Comment: Chronic pain is a common comorbidity with depression but there is little evidence as to the efficacy of many standard depression interventions in patients with this more complex clinical pattern. This current study attempted to explore the use of mindfulness-based cognitive therapy in patients with depression and comorbid chronic pain in a randomised study design. Only 19 of the 26 patients in the active MBCT group completed the program and significant differences between active treatment and the controlled group were not seen on the intention-to-treat analysis. The authors did present per protocol data which should be interpreted fairly tentatively which suggested a greater decrease in depression in the MBCT group compared to the control group on one rating scale (QIDS-C16) but not on the Hamilton depression rating scale. It is likely that the small sample size here undermined the capacity of the study to show meaningful differences between the two groups.

Reference: Journal Clinical Psychiatry 2016;79(1)

Cardiometabolic dysregulation and cognitive decline: potential role of depressive symptoms

Authors: Schnitz N et al.

Summary: These researchers used data from Rotterdam Study, the Netherlands (n = 2940) and the Whitehall II study, UK (n = 4469) to assess the effect of depressive symptoms on the relationship between cardiometabolic factors and cognitive decline. Mediation analysis showed an association between cardiometabolic status and depressive symptoms which then correlated to poorer cognitive function.

Comment: This study, which included data from two large samples, attempted to explore the relationship between cardiometabolic factors, cognitive decline and depression to try and increase our understanding of the causal links between these various issues. The core study results suggested that poorer cardiometabolic status led to greater depressive symptoms which in turn led to a greater degree of cognitive decline over time. In other words, the development of depressive symptoms appears to be in some way an intermediate step between cardiometabolic dysregulation and the development of cognitive problems. This is both theoretically interesting but also potentially of clinical value as screening for the development of depressive symptoms in individuals with cardiometabolic risk factors could be used as a way to identify those at risk of cognitive impairment for early intervention purposes.

Reference: The British Journal of Psychiatry 2018;212(2):96-102

Associations between residual depressive symptoms, cognition, and functioning in patients with euthymic bipolar disorder

Authors: Roux P et al.

Summary: This analysis of the FondaMental Academic Centers of Expertise for Bipolar Disorders (FACE-BD) cohort data studied 241 adults with euthymic bipolar disorder from the French national network of nine bipolar disorder expert centers (Bordeaux, Creteil, Grenoble, Marseille, Monaco, Montpellier, Nancy, Paris, and Versailles) to assess the relationship between residual depression symptoms on cognition and functioning. A mediation analysis was performed using a path analysis to determine the effect of depressive symptoms on 6 domains of cognition and functioning. Poorer functioning was significantly associated with residual depressive symptoms, however, no relationship between residual depressive symptoms and cognition was found.

Comment: Although it is a relatively under researched area, there is considerable value to be gained in the study of patients with mood disorders who are nominally in euthymic stages of illness. We lack a significant understanding of the factors that determine illness relapse or which influence longer term functioning. This current study explored the relationship between residual depressive symptoms and cognitive impairment in bipolar patients in the euthymic phase. The analysis indicated, unsurprisingly, that residual depressive symptoms were associated with poorer functioning and there was also a relationship with specific aspects of verbal and working memory and functioning. Interestingly, the influence of cognitive performance and depressive symptoms on functioning were not related indicating that these are independent determinants of function and therefore potentially require therapeutic consideration separately.


Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression

Authors: Daly E et al.

Summary: This first clinical study of adjunctive intranasal esketamine hydrochloride for treatment resistant depression (TRD) was funded by Janssen Research and Development and conducted in 14 outpatient referral centres (13 in the United States and 1 in Belgium) between 2014 and 2015. 67 adult patients with treatment resistant (defined as inadequate response to ≥ 2 antidepressants) major depressive disorder (MDD) currently on an oral antidepressant regimen were enrolled. The phase 2 study comprised of 2 sequential double-blind, double-randomised, placebo-controlled trials, an open-label section and 8-week post treatment follow-up. In the first trial, participants were randomised to placebo (n=33) or one of 3 esketamine doses; 28 mg (n=11), 56 mg (n=11) or 84 mg (n=12) twice weekly for 1 week. In the second trial, 28 of the previously placebo-treated participants were re-randomised to one of the 4 treatment arms for 1 week. The open-label portion of the trial (n=57) consisted of a primary dose of 56 mg esketamine then subsequent administration at various (28 – 84 mg) doses twice weekly for the first 2 weeks, weekly for the next 3 weeks and then every 2 weeks. Participants all continued their pre-trial antidepressant medication for the duration of the entire trial. Efficacy of treatment was determined by change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to day 8 (each period) and analysed using the analysis of covariance model. All doses of esketamine resulted in a significant improvement in depressive symptoms compared to placebo with increasing doses resulting in increasing positive effects (esketamine 28 mg: −4.2 [2.09], P = .02; 56 mg: −6.3 [2.07], P = .001; 84 mg: −9.0 [2.13], P < .001). Reduced dosing frequency in the open-label phase maintained the improved depressive symptoms. No new safety concerns were noted.

Comment: There has been considerable interest in recent years in the potential use of ketamine or related molecules in the treatment of depression. Previous research has clearly demonstrated the rapid onset of antidepressant effects with intravenous ketamine but translating this into a practically usable longer term therapy has been more difficult. This paper reported the outcomes of a randomised double-blind study of intranasal esketamine in patients with treatment resistant depression. Greater antidepressant effects were seen with three different doses of esketamine compared to placebo with a positive dose-response relationship. Clinical improvements were sustained during an open-label phase when dosing administration was reduced to weekly and then to every two weeks. This study clearly supports the potential clinical value of the use of intranasal esketamine and justifies the conduct of large-scale phase 3 trials.

Reference: JAMA Psychiatry 2018;75(2):139-48
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Enable patients to not only feel better, but to think and function better*2-7

*Brintellix displayed efficacy on depressive symptoms (MADRS, HAM-D24) and improved cognitive symptoms (DSST, RAVLT, UPSA) of major depressive disorder vs. placebo2-7

DSST: Digit Symbol Substitution Test; HAM-D24: 24-item Hamilton Depression Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; RAVLT: Rey Auditory Verbal Learning Test; UPSA: University of San Diego Performance-Based Skills Assessment.
The perimenopausal period is a high risk period for the development of depressive symptoms in women. Researchers from the University of North Carolina at Chapel Hill randomized 172 eudismic women from the community (aged 45-60 years) to 12 months of hormone therapy or placebo. Participants all had mean household incomes of between $50,000 - $79,999. 76% were white and 19% African American. All participants were scored on the Center for Epidemiological Studies–Depression Scale (CES-D) and assessed at baseline and months 1, 2, 4, 6, 8, 10, and 12. 43 women developed depressive symptoms (defined as CES-D ≥ 16). Women who received placebo were more likely to experience depressive symptoms at any point during the study (32.3% vs 17.3% odds ratio [OR], 2.5; 95% CI, 1.1-5.7; P = .03) than those who received TE+IMP treatment. The effect of treatment was moderated by stage of menopause at time of treatment with only women in the early menopause transition benefiting from TE+IMP treatment (β = −4.2; SEM, 1.2; P < .001). Stressful life events in the 6-months preceding treatment also impacted treatment with a positive correlation seen between mean CES-D scores and β, (β = −1.68; SEM, 0.40; P = .003). Other factors such as baseline estradiol levels, history of depression or history of abuse did not have any impact on treatment effects. The authors concluded that 12 months of TE+IMP for peri- or early postmenopausal women was effective in preventing the onset of depression.

Comment: The perimenopausal period is a high risk period for the development of depression with this increased risk presumably at least substantially related to the changes in hormone milieu that women experience at this time. There has been increasing interest in the use of oestrogenic products to treat depression in the perimenopausal period. This report went somewhat further exploring the use of an oestrogen patch to prevent the development of depression in perimenopausal women. The use of a oestradiol patch over a 12-month period was developed depressive symptoms (defined as CES-D ≥ 16). Women who received TE+IMP treatment (β = −1.68; SEM, 0.40; P = .003). Other factors such as baseline estradiol levels, history of depression or history of abuse did not have any impact on treatment effects. The authors concluded that 12 months of TE+IMP for peri- or early postmenopausal women was effective in preventing the onset of depression.

Reference: JAMA Psychiatry 2018;75(2):149-57

Efficacy and safety of transcranial direct current stimulation as an add-on treatment for bipolar depression

Authors: Sampaio-Júnior B et al.

Summary: The Brazilian Bipolar Depression Electrical Treatment Trial (BETTER) assessed the safety and efficacy of transcranial direct current stimulation (tDCS) as an add-on therapy for the treatment of bipolar depression. The randomised, sham-controlled trial was conducted at an outpatient centre and enrolled 59 adults with type I (n = 36) or type II (n = 23) bipolar disorder. All patients were currently undergoing a major depressive episode and were on a stable pharmacologic regimen. Patients were randomised to receive sessions of prefrontal active tDCS or sham (ten daily 30-minute, 2-mA, anodal-left and cathodal-right tDCS on weekdays and then 1 session every fortnight until week 6). 52 patients completed the trial. The primary outcome measure was change in 17-item Hamilton Depression Rating Scale (HDRS$_{17}$) score at week 6. Intention-to-treat analysis, compared to sham, showed tDCS-treated patients had a significant improvement in depressive symptoms ($β_{int} = −1.68$; number needed to treat, 5.8; 95% CI, 3.3-25.8; $P = .01$), and higher cumulative response rates (67.6% vs 30.4%; number needed to treat, 2.69; 95% CI, 1.84-4.99; $P = .01$). Overall, remission rates were lower in the treatment group (37.4% vs 19.1%). The only minor safety concern or adverse effect noted was an increased incidence of localised skin redness in the treatment group (54% vs 19%). The authors concluded that tDCS is a safe and effective add-on therapy for bipolar depression.

Comment: Non-invasive forms of brain stimulation such as transcranial magnetic stimulation (TMS) are increasingly becoming part of the therapeutic armamentarium in psychiatric practice. Transcranial direct current stimulation (tDCS) has been subject to considerably less research than TMS but emerging literature is suggesting that it is likely to have clinically relevant antidepressant properties. In the current report, tDCS was used in the treatment of patients with bipolar depression (type I and type II) in a sham controlled study. Patients who received active tDCS had a numerically greater reduction in depressive symptoms and a significantly higher response rate. The remission rate was not different between the two groups but this may have been an effect of the sample size. tDCS was generally well tolerated. This is a highly promising study but strongly suggests the need for substantive phase III scale investigations, something that took considerable time to emerge for TMS delaying its clinical translation.

Reference: JAMA Psychiatry 2018;75(2):158-66

Abstract: Efficacy and safety of transcranial direct current stimulation as an add-on treatment for bipolar depression

Authors: Gordon J et al.

Summary: To test the effectiveness of hormone therapy (0.1 mg/d transdermal estradiol and oral micronized progesterone [200 mg/d for 12 days every 3 months] - (TE+IMP)) to prevent the onset of perimenopausal and early postmenopausal depressive symptoms, researchers from the University of North Carolina at Chapel Hill randomized 172 eudismic women from the community (aged 45-60 years) to 12 months of therapy or placebo. Participants all had mean household incomes of between $50,000 - $79,999. 76% were white and 19% African American. All participants were scored on the Center for Epidemiological Studies–Depression Scale (CES-D) and assessed at baseline and months 1, 2, 4, 6, 8, 10, and 12. 43 women developed depressive symptoms (defined as CES-D ≥ 16). Women who received placebo were more likely to experience depressive symptoms at any point during the study (32.3% vs 17.3% odds ratio [OR], 2.5; 95% CI, 1.1-5.7; P = .03) than those who received TE+IMP treatment. The effect of treatment was moderated by stage of menopause at time of treatment with only women in the early menopause transition benefiting from TE+IMP treatment (β = −4.2; SEM, 1.2; P < .001). Stressful life events in the 6-months preceding treatment also impacted treatment with a positive correlation seen between mean CES-D scores and β, (β = −1.68; SEM, 0.40; P = .003). Other factors such as baseline estradiol levels, history of depression or history of abuse did not have any impact on treatment effects. The authors concluded that 12 months of TE+IMP for peri- or early postmenopausal women was effective in preventing the onset of depression.

Comment: The perimenopausal period is a high risk period for the development of depression with this increased risk presumably at least substantially related to the changes in hormone milieu that women experience at this time. There has been increasing interest in the use of oestrogenic products to treat depression in the perimenopausal period. This report went somewhat further exploring the use of an oestrogen patch to prevent the development of depression in perimenopausal women. The use of a oestradiol patch over a 12-month period was developed depressive symptoms (defined as CES-D ≥ 16). Women who received TE+IMP treatment (β = −1.68; SEM, 0.40; P = .003). Other factors such as baseline estradiol levels, history of depression or history of abuse did not have any impact on treatment effects. The authors concluded that 12 months of TE+IMP for peri- or early postmenopausal women was effective in preventing the onset of depression.
Switching the antidepressant after nonresponse in adults with major depression

Authors: Bachor T et al.

Summary: This systematic literature search and meta-analysis of controlled trials evaluated the efficacy of continuation of a primary antidepressant compared to switching to a new one in non-responding major depressive disorder patients in acute phase. A search of PubMed, Embase, PsycINFO, and Cochrane Central Register of Controlled Trials (CENTRAL) databases provided 3,234 articles which were screened for those that randomised non-responding, acute phase, monotherapy depressive patients to either continuation of their original treatment or switching to a new antidepressant therapy. These studies were then stratified according to the presence (broad analysis, n=8) or absence (strict analysis, n=4) of dose escalation in the continuation arm. The primary outcome measure of standardised mean difference (SMD) showed no significant superiority of switching antidepressant over continuation of the primary (strict analysis SMD = −0.17, 95% CI, −0.59 to 0.26; P = .45; I² = 77.8%, broad analysis SMD = 0.031, 95% CI, −0.26 to 0.32; P = .836; I² = 85.3%). These results were supported by the secondary outcome analyses of response and remission rates, low risk of bias studies only, leave-one-out analysis and dropouts.

Comment: Unfortunately, only about 40% of patients will respond to an initial course of an antidepressant in the treatment of major depression. Therefore, clinicians are faced every day with decisions in regards to how to manage patients in the face of initial medication and response. However, there is surprisingly limited literature addressing this common clinical dilemma. This paper summarised studies which compared switching to a new antidepressant to continuation of the medication that had been initially unsuccessful. Across a relatively small number of studies there was no difference in outcomes with medications switch or continuation. This finding was consistent across multiple analyses and was seen whether the initial antidepressant was left at its initial dose or increased following randomisation. This study provides really no support for the common clinical practice of switching of antidepressants although there was little analysis of the relative benefits of the types of medications that could be considered in a potential switch. Clearly clinicians need to consider a range of options including adjuvant therapies and non-medication treatments such as psychotherapy and TMS when patients initially present with non-response to first-line medication treatment.

Reference: J Clinical Psychiatry 2018;79(1)

Abstract

Long-term acute-phase treatment with antidepressants, 8 weeks and beyond

Authors: Henssler J et al.

Summary: This systematic review and meta-analysis of randomised, placebo-controlled trials evaluated the efficacy of antidepressant monotherapy for acute depressive disorder treatment at and beyond 8 weeks in adult patients. 104 studies (n= 35,052) were selected from a search of MEDLINE, Embase, PsycINFO, and CENTRAL databases. Guidelines of the Cochrane Collaboration were followed for data extraction and synthesis. The primary outcome measure of standardised mean difference (SMD [95% CI]) between antidepressant and placebo showed active treatment to be significantly superior to placebo after 8, 12, 16, 20 and 24 weeks (SMD = 0.27, 0.34, 0.24, 0.31 and 0.34, respectively). Secondary outcome measures of response, remission and dropouts as well as subgroup and sensitivity analyses all confirmed the efficacy of antidepressant therapy over placebo at and beyond 8 weeks.

Comment: This paper reported a second meta-analysis this month exploring a common element of clinical prescribing in psychiatry in the management of depression. In this case the authors were interested in the degree of antidepressant response seen in the months that follow the initial prescribing of treatment. The meta-analysis included over 35,000 patients from 104 studies that analysed antidepressant – placebo differences in studies that continued beyond the traditional eight-week acute treatment period. The analysis found that there were statistically significantly superior effects of medication compared to placebo up to 24 weeks following medication commencement with no indication of a decrease in effect size the longer patients were followed for. The authors argued that this supports a continued antidepressant effect rather than improvements being seen later due to the occurrence of spontaneous remission associated with the course of the disorder itself.

Reference: J Clinical Psychiatry 2018;79(1)

Abstract

Prediction of electroconvulsive therapy response and remission in major depression

Authors: van Diermen L et al.

Summary: This meta-analysis investigated determinants of a successful remission response to electroconvulsive therapy (ECT) in major depression. 34 articles were included in the analysis that explored response rate by one of the following variables: age, depression severity, psychotic and melancholic features. ECT-induced remission was predicted by the presence of psychotic feature (odds ratio (OR) = 1.47, P = 0.001) and older age (standardised mean difference (SMD) = 0.26). Response rates to ECT treatment showed an inverse correlation with the severity of depression (SMD = 0.19, P = 0.001) but did not predict response.

Comment: ECT is a powerfully effective antidepressant treatment but one with significant side-effects, costs and stigma. In this context, developing ways to predict successful antidepressant treatment response with ECT would be of significant clinical value. This meta-analysis attempted to explore clinical and demographic variables which might be associated with improved ECT response through the conduct of a meta-analysis of data from 34 previous trials. The authors found that the presence of psychotic features, older age and severity of depression were all associated with improved ECT outcomes (some are associated with remission and some with response). Somewhat surprisingly, melancholic symptoms were not associated with ECT outcome. The association between ECT response and the presence of psychotic symptoms, older age and more severe depression were fairly clear but it is unlikely that clinicians would include/exclude patients from ECT treatment based upon these criteria alone. Further research is required to establish biomarkers which may be able to be used in a more substantive way in clinical practice.

Reference: British Journal of Psychiatry 2018;212(2):71-80

Abstract