Psychiatry RESEARCH REVIEW™

Making Education Easy

Issue 49 – 2020

In this issue:

Abbreviations used in this issue
IPS = individual placement and support
NSAID = nonsteroidal anti-inflammatory drug
RCT = randomised controlled trial

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Welcome to issue 49 of Psychiatry Research Review.

This issue begins with a systematic review reporting higher rates of adverse birth outcomes for mothers who had used antidepressant agents during their pregnancy, although the authors caution that the data are insufficient to support a true causal association. In other included research, the differential diagnostic efficiency of DSM criteria for borderline personality disorder to distinguish between true borderline personality disorder and bipolar disorder is evaluated. Researchers from France have reported a notable reduction in suicide attempts associated with the use of brief contact interventions. We conclude this issue with a systematic review with meta-analysis reporting that despite increased cancer-related mortality in individuals with mental illness, they receive less cancer screening compared with the general population.

We hope you find this update in psychiatric research informative, and we look forward to your feedback and suggestions.

Kind regards,

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In utero exposure to antidepressant medication and neonatal and child outcomes

Authors: Fitton CA et al.

Summary: These authors systematically reviewed 16 studies reporting the effects of *in utero* antidepressant exposure on the foetus; an untreated comparison study group was required for inclusion. Compared with untreated depression, *in utero* antidepressant exposure was associated with increased risks of lower gestational age and preterm birth, but not low birthweight or being small for gestational age. There was some evidence of a relationship between antidepressant use and congenital defects, particularly between paroxetine exposure and cardiac defects. Evidence regarding the offsprings' neurodevelopment was conflicting, with some studies reporting higher incidences of autistic spectrum disorders and depression, and others reporting no problems when emotional symptoms, peer problems, conduct problems and hyperactivity-inattention scores were measured.

Comment (WM): The evidential base for recommendations for depressed women who are contemplating pregnancy or are pregnant is not strong. There is rightful concern about possible effects of antidepressant medication on the child while *in utero*, given the possible developmental vulnerability of the CNS. The matter is complicated by the need to compare the outcome for the child when the depressed mother is treated with antidepressants versus when a depressed mother is untreated.

This study intended to perform a meta-analysis of available research looking at possible adverse effects of *in utero* exposure to antidepressants on gestational age, birthweight, neonatal intensive care, incidence of congenital defects and longer-term developmental effects. A very sound search strategy and analytical plan yielded 18 relevant articles. Two of these were excluded as the quality was poor using standard measures. Of note, there were no RCTs of drug studies in pregnant woman. Although the authors say this reflects *"possible ethical issues"*, I would contend it represents a gross ethical failure; these drugs are not tested in pregnant woman but are later marketed and used. The second major disappointment was that a meta-analysis was not possible due to the heterogeneity of the literature: different study groups, different drug groups, different outcomes and varied methodologies. The analysis shows an increased risk of preterm birth, but no apparent effect on birthweight. There are no demonstrated developmental issues at 5 or 7 years of age. Although some studies compared treated and untreated women, none analysed results in terms of satisfactory response to treatment. The largest finding was a strong need for a study that uses direct comparator groups of treated and untreated pregnant women to successfully answer this important question. There should also be, in the design, inclusion of indices of remission.

Reference: Acta Psychiatr Scand 2020;141:21–33
Abstract

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Executive functions and memory in bipolar disorders I and II

Authors: Cotrena C et al.

Summary: Data from 126 studies involving 6424 patients with bipolar disorder type 1, 702 with bipolar disorder type 2 and 8276 controls were meta-analysed in this paper evaluating executive functions and episodic memory in bipolar disorder. An association was detected between bipolar disorder type 1 and moderate-to-large cognitive function impairments, whereas bipolar disorder type 2 was associated with small-to-medium impairments. Bipolar disorder types 1 and 2 differed slightly but significantly for all cognitive functions except inhibition. The tasks that were most sensitive to cognitive impairment in bipolar disorder type 1 were the Trail Making Test (*g [g-test]*=0.74 [95% CI 0.67, 0.80]), the Hayling Test (*g*=0.58 [0.34, 0.81]), Digit Span Total (*g*=0.79 [0.57, 1.01]) and Category Fluency (*g*=0.59 [0.45, 0.72]), and those that were sensitive to cognitive alterations in bipolar disorder type 2 were the Trail Making Test (*g*=0.65 [0.50, 0.80]) and Category Fluency (*g*=0.56 [0.37, 0.75]).

Comment (WM): This systematic review and meta-analysis was designed to investigate executive function and episodic memory in bipolar disorder. It examined possible differences between bipolar types 1 and 2 as well as looking at possible moderators of the association between bipolar and cognitive impairment. The executive function included inhibition, cognitive flexibility, verbal working memory, visuospatial working memory, verbal fluency and planning. Episodic memory tasks included immediate verbal memory, delayed verbal memory, immediate visual memory and delayed visual memory. The search strategy, data gathering and data processing are well described; 126 studies of relevance were found. The article summarises findings across the range of cognitive areas explored. This will be very informative for those with a special interest in the area. For the practising clinician, the review does show widespread cognitive impairments both in those with bipolar type 1 and those with bipolar type 2. The size of deficit was much more pronounced in those with bipolar type 1. The moderator analysis had only two factors of note: severity as measured by the Young Mania Rating Scale and lithium use.

Reference: Acta Psychiatr Scand 2020;141:110–30
Abstract

Differentiating borderline personality disorder (BPD) from bipolar disorder: diagnostic efficiency of DSM BPD criteria

Authors: Bayes AJ & Parker GB

Summary: These researchers clinically assessed and assigned diagnoses based on DSM criteria to their study participants; 53 were diagnosed with borderline personality disorder and 83 with bipolar disorder; comorbid participants were excluded. In the respective borderline personality disorder and bipolar disorder groups, the mean numbers of DSM borderline personality disorder criteria assigned were 6.6 and 1.9. In the borderline personality disorder group, 'affective instability' was the criterion most often assigned (92.5%), and 'inappropriate anger' was the least often assigned (49%). The criterion with the highest specificity was 'abandonment fears', which also had the highest positive predictive value at 0.9, and the criterion with the lowest specificity was 'inappropriate anger'. 'Unstable relationships' had the greatest overall negative predictive value at 0.91. 'Identity disturbance' and 'abandonment fears' criteria had the highest percentage accuracy for classification (both 85%).

Comment (WM): Distinguishing these common presenting disorders from each other is of high relevance, not just for epidemiologists and DSM advocates, but for all adult clinicians who have to determine best intervention strategies to help people who have these conditions. There is a strong evidence base behind the interventions that should be targeted. There is, however, frequent expression of diagnostic difficulty.

This article describes a carefully constructed study that examined each of the DSM borderline personality disorder criteria to determine those items that are most prevalent and which discriminate those with borderline personality disorder from bipolar disorder. Care was taken to ensure diagnostic accuracy using well-structured interviews and well-constructed scales. Subjects were drawn from public and private psychiatric services in New South Wales. The presence of abandonment fears links very highly with a borderline personality disorder diagnosis. Identity disturbance was also integral, being present in 80%. The absence of unstable relationships makes borderline personality disorder a very unlikely disorder. Less useful in distinguishing the conditions is affective instability, since it is common to both bipolar disorder and borderline personality disorder. This article and its linked article (Acta Psychiatr Scand 2016:133:187–95) are very useful for clinicians struggling with the distinction between two worrying conditions.

Reference: Acta Psychiatr Scand 2020;141:142–8
Abstract

The iHOPE-20 study: relationships between and prospective predictors of remission, clinical recovery, personal recovery and resilience 20 years on from a first episode psychosis

Authors: O'Keeffe D et al.

Summary: These authors reported 20-year outcomes on remission, clinical recovery, personal recovery and resilience for 80 evaluable participants with a first episode of psychosis from the prospective iHOPE-20 study. The remission rate was 65%, with 35.2% in full functional recovery and 53.7% with confirmed full recovery according to their personal definition. There was a complex array of relationships among the outcomes. Better outcomes were seen for individuals with a short duration of untreated psychosis, those with greater premorbid social adjustment (between the ages of 5–11 years) and those who were older, not living alone, in full-time employment, given a nonaffective diagnosis or who had a low Global Assessment of Functioning score at bassline.

Comment (WM): Views regarding the effects of psychotic illness and the likelihood of recovery from psychotic disorders have been tainted with the general stigma linked with mental illness and the descriptions such as 'dementia praecox'. The more recent advent of first episode psychosis services and the targeted interventions of biological, social and psychological types are challenging this negative view, showing the possibility of a positive outcome from psychosis.

This article reports a prospective study of the long-term outcomes of people treated in an Irish First Episode Psychosis service. The study looked at clinical recovery, personal recovery and resilience 20 years after entry to the service. The study used well-described and tested tools for measuring the outcomes. Eighty of 171 possible eligible subjects (the FEP cohort from 2014 to 2017) were assessed. Reasons for inability to contact are given. The study shows that full remission of psychotic symptoms and return of personally defined satisfactory lifestyle and function are indeed possible in the long term. The factors that are linked with a positive outcome include shorter duration of untreated psychosis and higher premorbid social adjustment.

Reference: Aust N Z J Psychiatry 2019;53:1080–92
Abstract

Effects of individual placement and support supplemented with cognitive remediation and work-focused social skills training for people with severe mental illness

Authors: Christensen TN et al.

Summary: Individuals with severe mental illness (76.5% with schizophrenia spectrum disorder) from three Danish cities were randomised to IPS (individual placement and support; n=243), IPS with the enhancements of cognitive remediation and work-focused social skills training (n=238) or usual care (n=239) in this trial. Compared with usual care, the IPS and the IPS with enhancements groups spent significantly longer in competitive employment or education during the 18-month follow-up period (primary outcome; 411 and 488.1, respectively, vs. 340.8 hours [respective p values 0.004 and 0.016]). No significant difference was seen between the IPS only and IPS with enhancements groups for any vocational outcome assessed, and there were no significant differences among the three groups for any nonvocational outcome with the exception of greater satisfaction with mental health services reported by the IPS and IPS with enhancement groups compared with usual care (respective success-rate differences, 0.310 [95% CI 0.167, 0.445] and 0.341 [0.187, 0.478]).

Comment (WM): I am sure that those reading this will agree (at least on good days) that work is associated with general wellbeing. We know that people with serious mental illness are over-represented in those who are unemployed. This study looked at the effects of IPS with or without augmentation by cognitive remediation. This Danish study recruited individuals with schizophrenia, schizotypal disorder, delusional disorder, recurrent depression or bipolar disorder. They were aged 18–64 years, involved in community mental health services and had expressed desire for competitive employment. Participants were randomised to either service as usual, IPS or IPS plus support. The primary outcome measure was hours in competitive employment or education. The paper outlines data gathering and analysis, as well as giving an outline of programme fidelity. The study showed that those in the IPS and IPS plus support programmes did better than those in standard vocational rehabilitation. What was a little surprising was that the addition of cognitive support did not add to success in employment. This study points to another area where those who are seeking to recover from serious mental illness can gain good assistance to do so.

Reference: JAMA Psychiatry 2019;76:1232–40
Abstract

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School-based interventions to prevent anxiety and depression in children and young people

Authors: Caldwell DM et al.

Summary: This systematic review and network meta-analysis included 137 studies (n=56,620) evaluating educational setting-based, universal or targeted interventions with the primary aim of preventing anxiety and depression in individuals aged 4–18 years; 20 of the studies were evaluated to be at low risk of bias for both random sequence generation and allocation concealment. Weak evidence suggested that anxiety might be reduced by cognitive behavioural interventions in primary and secondary settings. Compared with usual curriculum, mindfulness and relaxation-based interventions were associated with reductions in anxiety symptoms in universal secondary settings (standardised mean difference, –0.65 [95% credible interval –1.14, –0.19]). Evidence for any specific intervention type to prevent depression in universal or targeted primary or secondary settings was lacking. There was evidence for small-study effects for the universal secondary anxiety analysis. Only narratively reported findings were presented for wellbeing, suicidal ideation and self-harm, as a network meta-analysis was not feasible for these outcomes.

Comment (WM): Epidemiological studies have shown high rates of depression and anxiety globally. There is also a suggestion that incidence rates are increasing. Much of this disorder is evident from mid-adolescence. The amount of depression and anxiety puts a considerable burden on those suffering the problems and those attempting to support them. Given the healthcare burden, there is increasing pressure to explore primary preventative interventions to reduce the incidence. In a number of countries, these initiatives are targeted through schools.

This study sought to examine the evidence for effectiveness of preventive strategies set in educational settings. The authors comment on the limitations of standard meta-analytic methods for assisting decisions like these that draw on comparisons of different interventions. They propose network meta-analysis as a tool to allow ranking of different interventions. The search methodology is well described and seems appropriate to the initial question. The data gathering and processing are also well outlined and comprehensible. The results of the study are disappointing. Overall, there is little evidence that these interventions have significantly changed the rates of depression and anxiety in the populations exposed. The authors caution that the lack of evidence does not mean such strategies should be abandoned as the overall quality of the studies reviewed was low; significant biases were noted. The meta-analysis would argue strongly that those who fund and set up interventions should have robust methods to examine outcomes.

Reference: Lancet Psychiatry 2019;6:1011–20
Abstract

Effectiveness of family intervention for preventing relapse in first-episode psychosis until 24 months of follow-up

Authors: Camacho-Gomez M & Castellvi P

Summary: Fourteen studies met the inclusion criteria for this systematic review, which included a meta-analysis of data from 11 RCTs, which compared family intervention for psychosis with treatment as usual, with or without other psychosocial interventions, for patients presenting after a first episode of psychosis. Compared with treatment as usual (with or without other psychosocial interventions), family interventions reduced the likelihood of relapse (relative risk 0.42 [95% CI 0.29, 0.61]), hospitalisation durations and psychotic symptoms, and increased functionality.

Comment (WM): The effectiveness of family interventions in schizophrenia has been well shown; decreases in relapse and hospitalisation, and increases in function and life satisfaction have been evident since the last millennium. One might initially wonder 'why' this piece of work then. I suspect there are two important justifications: the first that is quoted by the authors is that there is a poverty of evidence around effectiveness in first episode psychosis; the second is that the introduction of family interventions to standard care is patchy at best.

A search strategy that found 47 eligible studies is outlined. When those studies were examined, 33 had to be rejected from analysis for mixed reasons, including not treating first-episode subjects, not properly delivering the family intervention or not properly assessing relapse. The authors found significant decrease in duration of hospitalisation, reductions in psychotic symptoms and increased functionality in the family intervention cohorts. This study should suggest to clinicians that prioritising family interventions for people with psychosis is something they should be strongly advocating. It would be interesting for audits to be performed to see how frequently this evidence-based intervention is being applied and whether the duration of involvement is sufficient, given the long-term nature of the disorders.

Reference: Schizophr Bull 2020;46:98–109
Abstract

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Independent commentary by Associate Professor Wayne Miles

Wayne is a psychiatrist with Waitemata DHB, Clinical Director of Awhina Research and Knowledge, and a Clinical Associate Professor with Auckland University School of Medicine. He has had many roles with the RANZCP including that of President, and has also been involved with NZMA. Wayne has had extensive experience in both the treatment of, and research into schizophrenia. He has conducted sponsored research with, and/or received honoraria for services to Otsuka, Pfizer, Roche, Eli Lilly, Janssen, Amgen, Bristol Myers Squibb and GSK.

Changes in the number of suicide re-attempts in a French region since the inception of VigilanS, a regionwide program combining brief contact interventions (BCI)

Authors: Djembi LF et al.

Summary: These researchers evaluated the impact of VigilanS, a brief contact intervention, on suicide attempts; the intervention combines resource cards, telephone calls and mailouts based on a predefined algorithm. There were 21 centres in France running VigilanS in 2018, representing an average 32% penetrance of the intervention within the geographical region. A significant relationship was identified between penetrance of the intervention and a decrease in suicide attempts (slope, –1.13 [p=0.00003]). It was estimated that 25% penetrance would yield a decrease in suicide attempts of 41%.

Comment (FS): Suicide and suicide attempts are presentations mental health services assess and manage. There is much in the literature on the possible drivers of suicidal behaviour; however, the ideal approach(es) for managing such presentations is unclear. This novel study undertaken in France attempts to combine several key aspects of brief contact interventions through a programme called VigilanS and applied it to a geographical region that ranks close to the top for several statistics for suicide and suicidal acts. The VigilanS programme complements treatment as usual whereby people who had been assessed in hospital following suicidal behaviours opted to participate in the programme rather than via randomisation. The brief interventions in this study included toll-free crisis contact details during working hours (provided on a resource card), follow-up phone calls, postcards (for those not engaging) and appointments with a crisis or planned follow-up clinician. Clinicians such as the individual's GP and psychiatrist also received correspondence via the VigilanS system about the individual's progress. Overall, there was an impressive reduction in suicidal behaviour in the geographical region in the centres that participated in the VigilanS programme over a 5-year timeframe. While there are several subgroup analyses pending and likely in future publications, this study has several important considerations and implications. This study has mapped out a stratified approach; for example, engaging with those who are presenting for the first time versus those who are further along their mental health journey, and considering how to engage these various groups. Also, what was coming through the study was that establishing a meaningful relationship with someone after an episode of self-harm or suicidality is a key aspiration that can sometimes get lost in the buzz of mental health service provision. There is an important consideration of balancing risk assessment/management while establishing a meaningful and ongoing relationship with the person in crisis.

Reference: BMC Psychiatry 2020;20:26
Abstract

Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder

Authors: Bai S et al.

Summary: This systematic review and meta-analysis included 30 RCTs (n=1610) reporting data on the efficacy and safety of anti-inflammatory agents for patients with major depressive disorders. Data pooled from 26 RCTs suggested that, compared with placebo, anti-inflammatory agents reduced depressive symptoms (standardised mean difference, –0.55 [95% CI –0.75, –0.35]), with higher response and remission rates (respective risk ratios 1.52 [95% CI 1.30, 1.79] and 1.79 [1.29, 2.49]). Symptom severity was reduced with both anti-inflammatory monotherapy and adjunctive therapy. Significant antidepressant effects in major depressive disorder were seen with NSAIDs, omega-3 fatty acids, statins and minocycline.

Comment (FS): This study undertook both a systematic review and meta-analysis of the literature with focus on trials in depression that utilised a wide range of anti-inflammatory agents. Such agents included NSAIDs, statins, minocycline, polyunsaturated fatty acids, corticosteroids, modafinil, cytokine inhibitors and many more. The authors narrowed the extant literature to 30 trials that fit their criteria. Trial designs included the use of anti-inflammatory agents as monotherapy/adjunctive therapy. While there was heterogeneity in terms of the rating scales, populations and treatment duration of the various therapies, overall, anti-inflammatory agents whether used as adjuncts or as monotherapy appear to reduce objective measures of depression relative to placebo. There were no major adverse events reported including gastrointestinal side effects. The findings from this study should be cautiously welcomed in the context of short treatment duration in the studies assessed and the need for longer-term trials. Also, the pathways of how anti-inflammatory agents exert their potential beneficial effects require further exploration.

Reference: J Neurol Neurosurg Psychiatry 2020;91:21–32
Abstract

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Disparities in cancer screening in people with mental illness across the world versus the general population

Authors: Solmi M et al.

Summary: This was a comparative meta-analysis of data from 501,559 individuals with mental illness and 4,216,280 controls from 47 studies on any type of cancer screening in patients with mental illness, and studies that reported prevalence of cancer screening in patients, or comparative measures between patients and the general population. Compared with the general population, screening occurred significantly less frequently in individuals with any mental illness (primary outcome; odds ratio 0.76 [95% CI 0.72, 0.79]), including screening for breast cancer (0.65 [0.60, 0.71]), cervical cancer (0.89 [0.84, 0.95]) and prostate cancer (0.78 [0.70, 0.86]), but not colorectal cancer (1.02 [0.90, 1.15]).

Comment (FS): People with mental illness, particularly serious mental illness, are recognised to have reduced lifespans of the order of 10–15 years. This impressively large review (covering a population >4 million people globally with the exception of Africa), assessing a variety of mental health disorders and comorbid cancer types, found that there were disparities generally with a mental health illness diagnosis. Globally, these disparities were apparent regardless of geographical region assessed. However, women with schizophrenia tended to experience the greatest disparity. Paradoxically, countries that had the best screening programmes demonstrated the widest disparity, perhaps highlighting the much better outcomes for those in the general population in relation to those with mental illness. This study highlights a number of concerns for those with mental illness, but also opportunities for better integration/holistic care for those with both physical and mental illnesses and also better co-ordination across mental health, primary-care and specialist physical health services across various healthcare systems globally.

Reference: Lancet Psychiatry 2020;7:52–63
Abstract

Independent commentary by Fred Sundram

Dr Frederick Sundram is a Senior Lecturer at the Department of Psychological Medicine at the University of Auckland and a Consultant Liaison Psychiatrist at North Shore Hospital. He was a research fellow at the Institute of Psychiatry, King's College London and the Royal College of Surgeons in Ireland where he completed his PhD in Neuroimaging. He has also completed a Masters in Healthcare Management and a Masters in Healthcare Informatics. He is vice-chair of the RANZCP National Faculty of Consultation-Liaison Psychiatry.

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