Psychiatry Research Review™

Making Education Easy

Issue 50 - 2020

In this issue:

Abbreviations used in this issue:

BMI = body mass index; **CI** = confidence interval; **HR** = hazard ratio; **NNH** = number needed to hard; **NNT** = number needed to treat; **OR** = odds ratio; **PTSD** = post-traumatic stress disorder; **RR** = relative risk; **SMR** = standardised mortality rate.

Claim CPD/CME points Click here for more info.

Like us on Facebook
facebook.com/researchreviewau/

Welcome to issue 50 of Psychiatry Research Review.

We start this issue with a study on the risk of suicide in emergency department patients with deliberate self-harm or suicidal ideation. This is followed by two interesting studies, the first on the risks of lithium exposure during pregnancy and the second on the association between dementia and the presence of aluminium and fluoride in drinking water. We have also included two large meta-analyses conducted on trials for antipsychotic treatments. The first highlights the importance of balancing efficacy with side effects and patient characteristics and preferences. The second shows there are marked differences between antipsychotics in terms of metabolic side effects. A study conducted in Japanese earthquake and tsunami survivors looks at the association between depression, PTSD and mortality, which is of importance given the recent bushfires. Population studies that examine suicide risk factors in India and the incidence of cancer screening in people with mental illness have been included. Finally, we conclude the issue with two interesting studies; the first examines the addition of mirtazapine to substance use counselling to reduce methamphetamine use and some HIV risk behaviours among cisgender men and transgender women who have sex with men. The second explores whether there is a genetic link between psychotic experiences and schizophrenia and other mental illnesses.

We hope you enjoy this issue, and we welcome any comments or feedback you have.

Kind Regards,

Professor Nicholas Keks

nicholas.keks@researchreview.com.au

Association of suicide and other mortality with emergency department presentation

Authors: Goldman-Mellor S et al.

Summary: This retrospective cohort study examined the incidence of suicide and other mortality in 648,646 Californian patients 1-year after presenting to the emergency department with nonfatal deliberate self-harm, suicidal ideation, or any other chief concern. Standardised mortality rates (SMR) measured per 100,000 person-years and adjusted for age, sex, and race/ethnicity were determined for each patient group using state-wide mortality data. For patients presenting with deliberate self-harm, the SMR was 56.8 (95% CI, 52.1-61.4) and for patients with suicidal ideation but not self-harm the SMR was 31.4 (95% CI, 27.5-35.2). The SMR for reference patients was 1.9 (95% CI, 1.6-2.3). The rates of non-suicide external-cause mortality were also increased among patients with self-harm (SMR, 14.2; 95% CI, 12.9-15.5) and patients with suicidal ideation (SMR, 11.8; 95% CI, 10.6-13.0). The SMR for reference patients was 2.2 (95% CI, 2.0-2.3). The rates of suicide mortality were higher among men, people 65 years or older, and non-Hispanic white patients compared to their reference groups.

Comment: It is known that patients presenting with attempted suicide or suicidal ideation to emergency departments have significantly elevated risk of completed suicide within the following 12-month period. Current therapeutic interventions tend to be focused on whether such patients should be admitted to hospital or not, and assessments are often carried out by relatively inexperienced professionals. Comprehensive psychiatric assessment that generates an individual treatment plan based on diagnosis and formulation, as well as concrete arrangements for post discharge follow-up are what is needed. Ensuring that these patients can receive adequate treatment is likely to reduce suicide risk. There is evidence that even low-level interventions (such as a telephone call a few days after a presentation to an emergency department with self-harm) can help. Many such patients currently do not receive any psychiatric follow-up or treatment at present. The case for suicide prevention through improved psychiatric treatment is becoming increasingly persuasive with the accumulation of evidence.

Reference: JAMA Netw Open. 2019;2(12):e1917571.
Abstract

Psychiatry Research Review™

Independent commentary by Professor Nicholas Keks

Nicholas Alexander Keks is Professor of Psychiatry at Monash University, a psychiatrist in private practice at Delmont Private Hospital, Honorary psychiatrist at Monash Health, Executive Director of the Centre of Mental Health Education and Research at Delmont, and Professorial Fellow at the Florey Institute of Neuroscience and Mental Health. He is also a Senior Examiner for the Australian Medical Council, and Honorary Secretary of the Psychiatry Section of the Australian Medical Association Victorian Branch. Prof Keks' qualifications include a Bachelor of Medicine and Bachelor of Surgery from the University of Melbourne, Master of Psychological Medicine from Monash University, Fellow of the Royal Australian and New Zealand College of Psychiatrists, Foundation member of its Faculty of Forensic Psychiatry, and Doctor of Philosophy from Monash University. Prof Keks is the author of over 220 peer-reviewed publications. His major interests are in psycho-pharmacology, mood disorders, anxiety disorders, psychoses and suicide prevention.

Lithium exposure during pregnancy and the postpartum period

Authors: Fornaro M et al.

Summary: This systematic review and meta-analysis examined the safety and efficacy outcomes of lithium use during pregnancy and the post-partum period in women with bipolar disorder. The primary safety outcome was any congenital anomaly and the primary efficacy outcome was mood relapse prevention. The use of lithium during pregnancy was associated with higher odds of any congenital anomaly (N=23,300; odds ratio [OR] 1.81; 95% CI, 1.35-2.41) with a number needed to harm (NNH) of 33. Lithium exposure during the first trimester had a higher risk of spontaneous abortion (N=1,289; OR 3.77; 95% CI, 1.15–12.39) with an NNH of 15. When compared to unexposed pregnancies, there was a significant chance of any malformation for lithium exposure during any pregnancy period or the first trimester and for a cardiac malformation when lithium was used in the first trimester. There was no increased risk of spontaneous abortion when exposure occurred in the first trimester or for cardiac malformation for exposure at during any pregnancy period. Lithium was more effective than no lithium in preventing postpartum relapse (N=48; OR 0.16, 95% CI, 0.03-0.89) with a number needed to treat (NNT) of 3. Qualitative analysis suggests that mothers with serum lithium levels <0.64 mEq/L and dosages <600 mg/day had more reactive newborns without an increased risk of cardiac malformations.

Comment: This is a highly relevant paper for clinicians who see female patients suffering from bipolar disorder and who may become pregnant. A number of recent studies clearly indicate that lithium is the treatment of choice for bipolar disorder (e.g. Hayes J *et al.* Lithium vs. valproate vs. olanzapine vs. quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records. World Psychiatry 2016;15:53-58). However, concern about lithium-related teratogenicity often militates against use of this effective treatment. The findings here confirm the known association of lithium use in the first trimester with cardiac and other malformations but show that the risk is modest, at least in the low therapeutic range. For patients with bipolar illness that have responded well to lithium, the risk-benefit findings of this study support the possibility of remaining on lithium throughout pregnancy.

Reference: Psychiatry 2020;177(1):76-92
Abstract

Aluminium and fluoride in drinking water in relation to later dementia risk

Authors: Russ TC et al.

Summary: This longitudinal study explored the effect of aluminium and fluoride in drinking water on dementia risk. Mean aluminium and fluoride levels in drinking water collected between 2005 and 2012 in Scotland were correlated with dementia in members of the Scottish Mental Survey 1932 cohort. A total of 1972 out of 6,990 individuals developed dementia. Dementia risk increased with increasing mean aluminium levels in women (HR per standard deviation increase 1.09; 95% CI, 1.03-1.15, P<0.001) and men (HR 1.12, 95% CI, 1.03-1.21, P=0.004). There was a dose-response increase in mean fluoride levels and dementia in women (HR 1.34; 95% CI, 1.28-1.41, P<0.001) and men (HR 1.30; 95% CI; 1.22-1.39; P<0.001). There was no statistical interaction between aluminium and fluoride levels in relation to dementia.

Comment: This is the largest longitudinal study to date which was carried out in Scotland with the aim of investigating the effects of aluminium and fluoride in drinking water on the risk of developing dementia. Aluminium appears to influence β-amyloid oligomerization. Fluoride appears to enhance aluminium absorption from drinking water. The findings of this study are rather disturbing, indicating that both aluminium and fluoride levels in the water were correlated with increased dementia risk. The benefits of aluminium and fluoride in drinking water (especially where fluoride is added) need to be balanced against the possible risks of dementia identified here.

Reference: Br J Psychiatry 2020;216(1):29-34
Abstract

Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia

Authors: Huhn M et al.

Summary: This systematic review and network meta-analysis of placebo-controlled and head-to-head randomised controlled trials aimed to compare and rank 32 antipsychotics used in the treatment of adults with acute symptoms of schizophrenia or related disorders. The primary outcome was the change in overall symptoms measured with standardised rating scales. The analysis included 402 studies with data for 53,463 participants. All antipsychotics reduced overall symptoms more than placebo (although not statistically significant for six drugs) with mean differences ranging from -0.89 (95% CI, -1.08 to -0.71) for clozapine to -0.03 (95% CI, -0.59 to 0.52) for levomepromazine. For reduction of positive symptoms, mean differences compared to placebo varied from -0.69 for amisulpride to -0.17 for brexpiprazole. For reduction of negative symptoms mean differences ranged from -0.62 for clozapine to -0.10 flupentixol. For depressive symptoms the mean difference ranged from -0.90 for sulpiride to 0.04 for flupentixol. The differences in side-effects were more marked than differences in efficacy. Differences compared to placebo for weight ranged from -0.16 kg for ziprasidone to 3.21 kg for zotepine, the prolactin elevation difference ranged from -77.05 ng/mL for clozapine to 48.51 ng/mL for paliperidone and QTc prolongation differences ranged from -2.21 ms for lurasidone to 23.90 ms for sertindole.

Comment: Many would be familiar with the landmark paper published in 2013 by Leucht *et al.* (Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 2013;382:951). The 2019 study substantially increases the number of antipsychotics which were examined with respect to efficacy and tolerability, although the general pattern of the findings is similar. Clozapine is clearly the most effective antipsychotic but is then followed by a spectrum of efficacy which suggested antipsychotics are a heterogeneous group of drugs which are not simply divided into typical and atypical or first and second generation. The drugs also differ considerably with respect to tolerability in such aspects as propensity for extrapyramidal side-effects, risk of weight gain, sedation, anticholinergic side effects, prolactin elevation, QTc prolongation and so on. There would appear to be little alternative for clinicians other than to become familiar with the characteristics of available antipsychotics as there are no obvious groupings which link efficacy and tolerability. I strongly recommend having a look at the figures in the paper which compare the antipsychotics best to worst across efficacy and adverse effect dimensions.

Reference: Lancet 2019;394:939–51
Abstract

Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology

Authors: Pillinger T et al.

Summary: This systematic review and network meta-analysis of 100 trials and 25,952 schizophrenia patients, compared and ranked 18 antipsychotics based on metabolic side-effects, identified predictors of antipsychotic-induced metabolic dysregulation, and investigated the impact of antipsychotic treatment with change in psychotic symptoms and metabolic parameters. The median treatment duration was 6 weeks. Mean differences for active treatment compared to placebo ranged from -0.23 kg for weight gain (95% CI, -0.83 to 0.36) for haloperidol to 3.01 kg (95% CI, 1.78 to 4.24) for clozapine, -0.25 kg/m^2 change in BMI (-0.68 to 0.17) for haloperidol to 1.07 kg/m^2 (0.90 to 1.25) for olanzapine, -0.09 mmol/L change in cholesterol (-0.24 to 0.07) for cariprazine to 0.56 mmol/L (0.26-0.86) for clozapine, -0.13 mmol/L change in LDL (-0.21 to -0.05) for cariprazine to 0.20 mmol/L (0.14 to 0.26) for olanzapine, 0.05 mmol/L change in HDL (0.00 to 0.10) for brexpiprazole to -0.10 mmol/L (-0.33 to 0.14) for amisulpride, -0.01 mmol/L change for triglycerides (-0.10 to 0.08) for brexpiprazole to 0.98 mmol/L (0.48 to 1.49) for clozapine, and -0.29 mmol/L change in glucose (-0.55 to -0.03) for lurasidone to 1.05 mmol/L (0.41 to 1.70) for clozapine. Higher glucose increases were predicted by higher baseline weight (P=0.0015) and male sex (P=0.0082). Greater increases in cholesterol were associated with non-white ethnicity (P=0.040). Improvements in symptom severity were associated with increases in weight, BMI, total-cholesterol and LDL cholesterol, and decreases in HDL cholesterol.

Comment: The findings are very much as expected from clinical experience. Metabolic side-effects are worst with olanzapine and clozapine, and best with aripiprazole, brexpiprazole, cariprazine, lurasidone and ziprasidone. Other evidence suggests that haloperidol should also be in the "best" list for suspected metabolic risk. Consideration of metabolic risks with an antipsychotic has to be weighed against factors such as efficacy. Some studies have found that despite its high metabolic risk, clozapine is associated with the greatest reduction in excess mortality in schizophrenia, with benefits for both suicide and physical illness, underlining the importance of utilising the most effective treatment.

Reference: Lancet Psychiatry 2020;7(1):64-77
Abstract

Association of postdisaster depression and posttraumatic stress disorder with mortality among older disaster survivors of the 2011 great East Japan earthquake and tsunami

Authors: Li X et al.

Summary: This study assessed whether post-disaster depression and post-traumatic stress disorder (PTSD) were associated with mortality in older survivors (>65 years) of the 2011 Great East Japan Earthquake and Tsunami. A baseline was established 7 months before the disaster with follow-up surveys to assess post-disaster depression (Geriatric Depression Scale Short Form score ≥5) and PTSD (Screening Questionnaire for Disaster Mental Health PTSD subscale score ≥4) conducted 2.5 years after the disaster. Mortality data was obtained from the national long-term care insurance database. Approximately 59% of 8,567 individuals responded to the baseline survey, and a total of 2,965 individuals participated in the study. The mean age was 73.4 years and the mean follow-up was 3.3 years. Overall, 32.8% of participants reported post-disaster depression and 25.2% reported PTSD. Depression more than doubled the risk of mortality (HR, 2.29; 95% CI, 1.54-3.42). PTSD was not associated with an increased risk of mortality (HR, 1.10; 95% CI, 0.73-1.64).

Comment: This study is interesting as it examines the effects of disaster on older survivors. While PTSD is commonly recognised as a consequence, the study shows that post-disaster depression was actually more common, and more dangerous with respect to increased mortality; in fact, PTSD is not associated with increased risk of mortality. Although the study does not demonstrate that treating post-disaster depression in older individuals would reduce mortality, it would seem entirely reasonable to ensure adequate treatment of depression in such circumstances. There are clear implications for the treatment of major depression in older patients who have gone through the recent emotional trauma of Australian bushfires.

Reference: JAMA Netw Open. 2019;2(12):e1917550.
Abstract

A population-based analysis of suicidality and its correlates: findings from the National Mental Health Survey of India, 2015–16

Authors: Amudhan S et al.

Summary: In this study, the prevalence and sociodemographic characteristics of suicidality in India were identified using data from the National Mental Health Survey of India from 2015-2016. Information on suicidality was collected from a community sample of adults (N=34,748) and categorised as low, moderate, high, and overall (any suicidality). The association between sociodemographic factors and overall suicidality and severity was examined by logistic regression analysis. Approximately 5.1% of participants had some level of suicidality, and 0.3% had at least one suicide attempt in the last month. Suicidality was numerically higher in women (6.0%) than men (5.1%) and was highest in women aged 40-49 years and men aged 60 years or older. For every suicide in India, there were more than 200 people with suicidality and more than 15 suicide attempts. There was an increased risk of suicidality in women versus men (OR 1.54; 95% CI, 1.31-1.81; P<0.0001) and in individuals living in urban metropolitan cities versus rural areas (OR 1.75; 95% CI, 1.30-2.35; P=0.0002). Compared to their counterparts, people in the lowest income group, those with depressive disorders and those with alcohol use disorders had an increased risk for high suicidality.

Comment: There has been considerable controversy concerning suicidality in some settings such as Southeast Asia, particularly in terms of the extent of a relationship with depression. This is the first comprehensive population-based, methodologically sound study to assess suicidality and its correlates in a representative sample in India. Many of the findings from India are similar to what has been found elsewhere, particularly the association of suicidality with depression, alcohol use, previous self-harm, older age, social isolation and socio-economic disadvantage. On the other hand, there were local variations in factors such as suicidality in urban and rural areas. The findings of the study will inform the formulation of a national suicide prevention strategy for India.

Reference: Lancet Psychiatry 2020;7(1):41-51
Abstract

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

Authors: Solmi M et al.

Summary: This comparative meta-analysis in 4,717,839 people (501,559 patients with mental illness, and 4,216,280 controls) assessed whether people with mental illness undergo less cancer screening compared with the general population. The systematic review included 47 published studies on any type of cancer screening in patients with mental illness, studies that reported prevalence of cancer screening in patients, or comparative measures between patients and the general population. The primary outcome was the OR of cancer screening in people with mental illness versus the general population. Compared with the general population, screening occurred significantly less frequently in people with any mental illness (OR 0.76; 95% CI, 0.72-0.79). This was the case for breast cancer screening (OR 0.65; 95% CI, 0.60-0.71), cervical cancer (OR 0.89; 95% CI, 0.84-0.95), and prostate cancer (OR 0.78; 95% CI, 0.70-0.86), but not for colorectal cancer (OR 1.02; 95% CI, 0.90-1.15).

Comment: Patients with mental illness are more likely to die from various cancers. However mentally ill patients, particularly those with schizophrenia, appear to be less likely to be screened for cancer. There is clearly an imperative need to develop protocols for facilitating increased cancer screening in mentally ill populations.

Reference: Lancet Psychiatry 2020;7(1):52-63
Abstract

Effects of mirtazapine for methamphetamine use disorder among cisgender men and transgender women who have sex with men

Authors: Coffin PO et al.

Summary: This placebo-controlled, randomised clinical trial examined the efficacy of mirtazapine for the treatment of methamphetamine use disorder and whether there was a reduction in HIV risk behaviours. Participants (N=120) who were sexually active, cisgender men, transgender men, and transgender women who had sex with men who had methamphetamine use disorder and were actively using methamphetamine were randomised to mirtazapine or placebo for 24 weeks. The primary outcome was positive urine test results for methamphetamine over 12, 24, and 36 weeks. By week 12, the rate of methamphetamine-positive urine test results significantly declined in the mirtazapine group compared to placebo (risk ratio [RR], 0.67; 95% CI, 0.51-0.87). Reductions were also observed in the mirtazapine group compared to placebo at 24 weeks (RR, 0.75; 95% CI, 0.56-1.00) and 36 weeks (RR, 0.73; 95% CI, 0.57-0.96). There was no significant difference in sexual risk behaviours between the groups at 12 weeks, however at 24 weeks the mirtazapine group had fewer sexual partners (RR, 0.52; 95% CI, 0.27-0.97; P=0.04), fewer episodes of condomless anal sex with partners who were serodiscordant (RR, 0.47; 95% CI, 0.23-0.97; P=0.04) and fewer episodes of condomless receptive anal sex with partners who were serodiscordant (RR, 0.37; 95% CI, 0.14-0.93; P=0.04). There were no serious adverse events associated with the study drug.

Comment: There is no established effective pharmacotherapy for methamphetamine dependence. Mirtazapine is a complex antidepressant without abuse potential which acts as a mixed monoamine agonist-antagonist. Noradrenaline, serotonin, and dopamine is released by mirtazapine in mesocorticolimbic parts of the brain relevant for drug reward, craving, and drug seeking. The main side effects of mirtazapine are sedation and weight gain. The authors first suggested in 2011 that mirtazapine reduces methamphetamine use by alleviating methamphetamine craving and withdrawal, and usefulness of mirtazapine in reducing methamphetamine use in a high-risk population is also shown here, even with less than perfect compliance. Neither sedation nor weight gain are likely to be as problematic as they are in the general population in methamphetamine users.

Reference: JAMA Psychiatry 2019;doi:10.1001/jamapsychiatry.2019.3655
Abstract

Association of genetic liability to psychotic experiences with neuropsychotic disorders and traits

Authors: Legge S et al.

Summary: This study examined whether genetic liability to psychotic experiences is shared with schizophrenia and other neuropsychiatric disorders and traits and whether psychotic experiences are associated with certain genetic loci. Genetic correlation, polygenic risk scores, and copy number variation were analysed in UK Biobank participants. Genetic loci identification was performed using genome-wide association studies of psychotic experience phenotypes. There were 11,603 participants in the psychotic experience group and 121,843 individuals in the non-psychotic experience group. Individuals with a psychotic disorder were excluded from all analyses. Psychotic experiences were genetically correlated with major depressive disorder, schizophrenia, autism spectrum disorder, and attention-deficit/hyperactivity disorder and there were associations between psychotic experiences and genetic liability for major depressive disorder, schizophrenia, bipolar disorder, autism spectrum disorder, and attention-deficit/hyperactivity disorder. Four genetic loci were identified, including a locus in the Ankyrin-3 gene and a locus in the cannabinoid receptor 2 gene.

Comment: Patients who present with isolated psychotic experiences but have few or no other symptoms of major psychiatric disorders are not uncommon in the clinic. To date the significance of such isolated hallucinations and delusions has not really been understood by psychiatrists. The findings here that patients who report such isolated psychotic phenomena have a shared genetic liability with schizophrenia, major depressive disorder and bipolar disorder (it appears that schizoaffective disorder was not examined) substantially advances our ability to interpret clinical significance. There would appear to be more solid grounds for consideration such as more intensive follow-up, avoidance of stimulants and psychedelics, psychoeducation concerning early illness characteristics and so on. Research with respect to long-term follow-up of patients with isolated psychotic experiences would now also be justified.

Reference: JAMA Psychiatry 2019;76(12):1256-1265
Abstract

Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.

