Psychiatry Research Review™

Making Education Easy

Issue 42 – 2017

In this issue:

Abbreviations used in this issue

CBT = cognitive behavioural therapy
HR = hazard ratio
PTSD = post-traumatic stress disorder
RR = relative risk

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Welcome to issue 42 of Psychiatry Research Review.

Apparently, you really are what you eat, according to an Australian investigation, which reports clinical improvements amongst patients with moderate-to-severe depression given tailored dietary advice. Another investigation, based on Danish national registry data from 1995 through 2013, suggests a dose-response association between infections treated with anti-infective agents, particularly those requiring hospitalisations, and subsequent onset of schizophrenia and affective disorders.

Should antipsychotic medications be used in palliative care patients with delirium? An Australian study indicates that such treatment (oral risperidone or haloperidol) might not be helpful. Symptoms of delirium associated with distress worsened among patients treated with age-adjusted titrated antipsychotic doses every 12 hours during this 72-hour study, compared with the placebo group who received individualised treatment and nonpharmacological measures.

We hope you find this issue useful for your daily practice and we welcome any comments or feedback.

Kind regards,

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Off-label indications for antidepressants in primary care: descriptive study of prescriptions from an indication based electronic prescribing system

Authors: Wong J et al.

Summary: This interrogation of records in an indication-based electronic prescribing system from primary care practices in and around two major urban centres in Quebec, Canada, examined the prevalence of off-label indications for antidepressants between 1 January 2003 and 30 September 2015 among patients aged ≥18 years. The 174 study physicians wrote 106,850 antidepressant prescriptions for 20,920 adults. By class, the highest prevalence of off-label indications was seen with tricyclic antidepressants (81.4%), largely due to a high off-label prescribing rate for amitriptyline (93%). Trazodone use for insomnia was the most common off-label use for antidepressants (26.2% of all off-label prescriptions). Strong evidence supported use of the prescribed drug for the respective indication in only 15.9% of all off-label prescriptions. In 39.6% of off-label prescriptions, there was no strong evidence for the prescribed drug but strong evidence supported use of another drug in the same class for the respective indication. For the remaining 44.6% of off-label prescriptions, there was no strong evidence in support of the use of the prescribed drug and all other drugs in the same class for the indication.

Comment (DM): Although this Canadian study is not directly applicable to the New Zealand situation, and includes a number of antidepressants not available here, the results are still worth noting given the extensive sample size and careful data analysis. The tendency for widespread off-label prescribing in both countries (and elsewhere) is understandable, particularly given 1) time constraints in general practice, 2) widespread warnings against the use of benzodiazepines and opioids, and 3) difficulties in accessing evidence-based psychosocial treatments such as CBT and behavioural activation (both summarised recently in Psychiatry Research Review; see also next study of behavioural activation in the elderly). One aspect of the current study's interpretation seemed rather naïve, namely the implied assertion that "other drugs" within a given class could be more "evidence-based" for certain indications, such as anxiety disorders. For SSRIs and SNRIs in particular such an assumption is misleading, given the homogeneity of within-class pharmacology for these 2 groupings.

Reference: BMJ. 2017;356:j603
Abstract

Royal Australian and New Zealand College of Psychiatrists (RANZCP)

Royal Australian and New Zealand College of Psychiatrists (RANZCP) CPD Program participants can claim one credit per hour under 'Category 4 - Self Guided Learning' (minimum 20 credits per year). Research Reviews can be included as 'Self-Guided Learning'

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Effect of collaborative care vs usual care on depressive symptoms in older adults with subthreshold depression: The CASPER randomized clinical trial

Authors: Gilbody S et al.

Summary: This study recruited 32 primary care centres in the UK between May 2011 and November 2014 involving 705 participants aged ≥65 years with subthreshold depression who were randomised to a collaborative care intervention (n=344) or usual primary care (controls; n=361). Collaborative care was co-ordinated by a case manager who assessed functional impairments relating to mood symptoms. Participants were offered behavioural activation and completed an average of 6 weekly sessions. At 4 months' follow-up, the collaborative care group had lower depression scores as measured by the 9-item Patient Health Questionnaire (PHQ-9 score ≥10) compared with the usual care group (mean score 5.36 vs 6.67; p<0.001). Treatment differences persisted at 12 months, with mean PHQ-9 scores of 5.93 for collaborative care and 7.25 for usual care. The proportions of participants meeting criteria for depression at the 4-month follow-up were 17.2% (45/262) vs 23.5% (76/324), respectively (RR 0.83; 95% CI, 0.61 to 1.27; p=0.25) and the 12-month follow-up were 15.7% (37/235) vs 27.8% (79/284) (RR 0.65; 95% CI, 0.46 to 0.91; p=0.01).

Comment (DM): Although beset by a number of methodological challenges, including unequal attrition into the two treatment groups, this innovative American study demonstrates significant and remarkably enduring benefit from collaborative compared to usual care of subthreshold depression. It remains to be established as to what extent the specific ingredient in collaborative care (behavioural activation) is responsible for the effect. If so, these results would complement those arising from other studies in adults (as previously reviewed in Research Review). Given the modest cost and scalability of behavioural activation, investment in this modality in New Zealand would seem overdue.

Reference: JAMA. 2017;317(7):728-37
Abstract

A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial)

Authors: Jacka FN et al.

Summary: In this 12-week trial, 67 patients with moderate-to-severe depression were randomly assigned to either an adjunctive dietary intervention (n=33) comprising 7 individual nutritional consulting sessions delivered by a clinical dietician, or social support protocol to the same visit schedule and length (control condition; n=34). At study entry, 55 patients were utilising some form of therapy: 21 were using psychotherapy and pharmacotherapy combined; 9 were using exclusively psychotherapy; 25 were using only pharmacotherapy. At 12 weeks, complete data were available from 31 patients in the diet support group and 25 in the control group. Montgomery–Åsberg Depression Rating Scale (MADRS) scores were improved from baseline at 12 weeks by a significantly greater amount in the dietary support group compared with those in the social support control group ($t(60.7) = 4.38$; p<0.001; Cohen's $d = -1.16$). Similarly, significantly more patients in the intervention group compared with the control group achieved remission (MADRS score <10); 32.3% vs 8.0%, respectively (χ^2 (1) = 4.84, p=0.028); the number needed to treat (NNT) based on remission scores was 4.1.

Comment (DM): This rigorous Australian study examines a widely held but evidence-poor hypothesis that poor diet may contribute to mood disorders. Although beset by a rather awkward acronym (someone seems to have been trying very hard to come up with "SMILES"), the study carefully evaluates the impact of dietary modification on depressive symptoms. The results, though satisfying, are based on a rather modest *n*, and so require expansion and replication elsewhere. This approach fits with the theory and data around other lifestyle modifications (exercise, smoking cessation), which also have encouraging but not yet compelling evidence for mood improvement in depressive illness. Down the track, it will likely be important to address the challenges of motivation and compliance, often in short supply in this population.

Reference: BMC Med. 2017;15:23
Abstract

Association between prescription of major psychotropic medications and violent reoffending after prison release

Authors: Chang Z et al.

Summary: This investigation included 22,275 released prisoners (mean age, 38 years) in Sweden for the period 1 July 2005 to 31 December 2010 and compared rates of violent reoffending during periods with or without dispensed prescription of psychotropic medications (antipsychotics, antidepressants, psychostimulants, drugs used in addictive disorders, and antiepileptic drugs) after prison release. During a median 4.6-year follow-up, 4031 individuals (18.1%) committed 5653 violent reoffenses. Antipsychotics, psychostimulants, and medications used for addictive disorders were all associated with statistically significant hazard ratios (HRs) of violent reoffending. The within-individual HR for antipsychotics was 0.58 (95% CI, 0.39 to 0.88), based on 100 events in 1596 person-years during medicated periods and 1044 events in 11,026 person-years during nonmedicated periods. The within-individual HR for psychostimulants was 0.62 (95% CI, 0.40 to 0.98), based on 94 events in 1648 person-years during medicated periods and 513 events in 4553 person-years during nonmedicated periods. The within-individual HR associated with dispensed drugs for addictive disorders was 0.48 (95% CI, 0.23 to 0.97), based on 46 events in 1168 person-years during medicated periods and 1103 events in 15,725 person-years during nonmedicated periods. Antidepressants and antiepileptics had no such impact (HRs, 1.09 [95% CI, 0.83 to 1.43] and 1.14 [95% CI, 0.79 to 1.65], respectively).

Comment (DM): This fascinating Swedish study will be of considerable interest to forensic psychiatrists. Some of the results are unsurprising, particularly that antipsychotic prescription is associated with a significantly reduced reoffending risk. It will be important to determine to what extent this effect derives from individuals with diagnosed psychotic disorders compared to others who will have received these medications for another (perhaps off-label) indication. Other results are more surprising, including a reduced rate of violent offending in those receiving psychostimulant prescription. Whether this relates to successful treatment of adult ADHD (known to be elevated in prison populations) or another mechanism deserves further study. Finally, it is notable that antidepressants and antiepileptics were not found to be associated with a change in violent reoffending risk. One possibility is that this risk is redistributed in populations of offenders, such that there are offsetting tendencies for some to get better and others to get very much worse, as suggested in an earlier paper of ours that commented on an earlier Swedish study (Menkes DM, et al. Lancet Psychiatry. 2015;2(6):491-2).

Reference: JAMA. 2016;316(17):1798-807
Abstract

Infections and exposure to anti-infective agents and the risk of severe mental disorders: a nationwide study

Authors: Köhler A et al.

Summary: This analysis involved 1,015,447 individuals born in Denmark between 1985 and 2002 and examined the association between infections treated in primary care with anti-infective agents and the subsequent risk of schizophrenia and affective disorders during 1995 through 2013. In Cox regression analyses adjusted for potential confounders, infections treated with anti-infective agents were associated with increased risks of schizophrenia (hazard rate ratio [HRR] 1.37; 95% CI, 1.20 to 1.57) and affective disorders (HRR 1.64; 95% CI, 1.48 to 1.82). Dose-response associations were observed, with both the total number of these prescriptions and the number of different types of anti-infective prescriptions. The excess risk was primarily driven by infections treated with antibiotics, whereas infections treated with antivirals, antimycotics, and antiparasitic agents were not significant in adjusted analyses. Individuals with infections requiring hospitalisation were at highest risk for schizophrenia (HRR 2.05; 95% CI, 1.77 to 2.38) and affective disorders (HRR 2.59; 95% CI, 2.31 to 2.89). Increased risks persisted after the last recorded anti-infective prescription and generally declined in a time-dependent manner over the study period.

Comment (DM): One of the most intriguing and profound studies I've read in some time, this Danish investigation takes advantage (as we have often seen in Research Review) of another remarkable Scandinavian dataset. The authors have done a particularly thorough job in controlling for potential confounders, which together with the sample size, markedly strengthens the study's conclusion and implications. The results are also plausibly supported by the dose-response relationship (more severe infection, greater risk) and the developing discipline of neuropsychoimmunology, which has provided accumulating evidence on the key role of neuroinflammation and cytokines in the genesis of both psychosis and depression.

Reference: Acta Psychiatr Scand. 2017;135(2):97-105
Abstract

Independent commentary by Associate Professor David Menkes,
an academic psychiatrist with a background in psychology and pharmacology (PhD 1983, Yale). Since completing specialist training in Dunedin (FRANZCP 1989) he has worked as an academic liaison psychiatrist in NZ and the UK. He has a continuing interest in the pharmacology and toxicology of drug treatments in psychiatry, is a member of the Medicines Adverse Reactions Committee (Medsafe), the PTAC Mental Health Subcommittee that advises PHARMAC, www.healthyskepticism.org, and works closely with the International Society of Drug Bulletins (www.isdbweb.org).

RNZCGP Endorsed CPD Activity

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial

Authors: Agar MR et al.

Summary: Outcomes are reported for 247 patients (mean age, 74.9 years) receiving palliative care from inpatient hospice or hospital palliative care services. All participants had life-limiting illness, delirium, and a delirium symptoms score (sum of Nursing Delirium Screening Scale behavioural, communication, and perceptual items) of ≥1. Treatment consisted of age-adjusted titrated doses of oral risperidone (n=82), haloperidol (n=81), or placebo solution (n=84) every 12 hours for 72 hours, based on symptoms of delirium. Patients also received supportive care, individualised treatment of delirium precipitants, and subcutaneous midazolam hydrochloride as required for severe distress or safety. At day 3, delirium symptom scores were significantly higher in the risperidone arm versus the placebo arm (on average 0.48 Units higher; p=0.02), as were scores in the haloperidol arm (on average 0.24 Units higher vs placebo; p=0.009). Compared with placebo, active treatment was associated with more extrapyramidal effects (risperidone, 0.73; 95% CI, 0.09 to 1.37; p=0.03; and haloperidol, 0.79; 95% CI, 0.17 to 1.41; p=0.01). Overall survival was significantly better with placebo than with haloperidol (HR 1.73; 95% CI, 1.20 to 2.50; p=0.003), whereas the between-group difference was not significant for placebo versus risperidone (HR 1.29; 95% CI, 0.91 to 1.84; p=0.14).

Comment (WM): This is a very important paper that has strong relevance to any psychiatrist who treats people with delirium or who gives advice to other doctors who treat delirium. The authors summarise the current situation (where antipsychotics are widely used in delirium) and the evidence for the efficacy of such use (at best equivocal; the few well-performed studies are probably against its use).

The study was conducted across multiple sites in Australia. The study protocol had ethical approval from ethics committees across the States and also from Guardianship Tribunals in Queensland and New South Wales. The approval allowed a proxy who could give written consent for participation. They targeted a particular cohort of people who develop delirium (namely those in palliative care settings) and they used very solid diagnostic criteria for the inclusion.

The design was very good; clear inclusion and exclusion criteria that did not bias results; use of well-validated measures that looked at both symptom severity and impact; sound processes for the randomisation of and blinding of treatment; good safety analysis; transparent analysis with clear expression of primary and secondary outcomes.

The take home message is clear; antipsychotic drugs should not be added to manage specific symptoms of delirium in palliative care. They make symptoms worse and are probably associated with higher mortality. Though the authors are cautious to not over-extend their study, I think it would be very hard to not generalise the findings to any delirium until there is clear evidence that delirium in other settings is actually helped by antipsychotic use.

Reference: JAMA Intern Med. 2017;177(1):34-42
Abstract

Exposure to violence, a risk for suicide in youths and young adults. A meta-analysis of longitudinal studies

Authors: Castellví P et al.

Summary: These researchers evaluated the published literature up until June 2015 for evidence on the association and magnitude of the effect of early exposure to different types of interpersonal violence with suicide attempt and suicide death in youths and young adults (12–26 years of age). For inclusion in this analysis, studies had to (1) assess any type of interpersonal violence as a risk factor of suicide attempt or suicide: (i) child maltreatment (childhood physical, sexual, emotional abuse, neglect), (ii) bullying, (iii) dating violence, and (iv) community violence; (2) comprise population-based case-control or cohort studies. Twenty-nine articles (including 143,730 subjects) met the inclusion criteria and were included in the meta-analysis. The analyses revealed that early exposure to interpersonal violence increased the risks for subsequent suicide attempt (OR 1.99; 95% CI, 1.73 to 2.28), child maltreatment (OR 2.25; 95% CI, 1.85 to 2.73), bullying (OR 2.39; 95% CI, 1.89 to 3.01), dating violence (OR 1.65; 95% CI, 1.40 to 1.94) and community violence (OR 1.48; 95% CI, 1.16 to 1.87). In particular, young victims of interpersonal violence had an OR of suicide death of 10.57 (95% CI, 4.46 to 25.07).

Comment (WM): Given New Zealand's focus on youth suicide and on family violence, this meta-analysis is well timed. Much is written about the association between early exposure to interpersonal violence and later life mental health problems. The authors summarise some of this literature then conclude that there is a lack of sound information about the risk of death by suicide in youth and young adults attributable to exposure to interpersonal violence.

The search strategy, study inclusion rules, assessment of quality and analytic methods are well described and likely to generate reliable results. The authors note the wide range of possible "violences" and separate these as child physical abuse, child sexual abuse, child emotional abuse, neglect, bullying, dating violence and community violence.

As would be anticipated, the findings make for grim reading, with early exposure to any interpersonal violence associated with a 10-fold increased risk of suicide. The results do give us strong ammunition for campaigns to eradicate exposure of children to interpersonal violence and also to find ways to work with those exposed to diminish the risk of suicide.

Reference: Acta Psychiatr Scand. 2016;135(3):195-211
Abstract

Independent commentary by Associate Professor Wayne Miles,

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.

Efficacy of quetiapine monotherapy in posttraumatic stress disorder: a randomized, placebo-controlled trial

Authors: Villarreal G et al.

Summary: In this trial, 80 patients with post-traumatic stress disorder (PTSD) were randomised to receive either quetiapine monotherapy or placebo, for 12 weeks. Quetiapine was initiated at a daily dose of 25 mg and titrated to a maximum of 800 mg; the average was 258 mg. Compared with placebo, quetiapine was associated with significantly greater reductions from baseline in Clinician-Administered PTSD Scale (CAPS) total, re-experiencing, and hyperarousal scores. Quetiapine was also associated with greater improvements versus placebo in scores on the Davidson Trauma Scale, Clinical Global Impressions (CGI) severity and improvement ratings, Positive and Negative Syndrome Scale (PANSS) positive symptom and general psychopathology subscales, and the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). Adverse events were generally mild and as expected. Safety measurements included adverse events, vital signs, the Abnormal Involuntary Movement Scale, the Barnes Akathisia Scale, the Simpson-Angus Scale, and the Arizona Sexual Experiences Scale; no between-group differences were observed for any of these measures.

Comment (WM): This article reports a study emanating from the Veterans Affairs services in the United States. It is examining the efficacy of quetiapine monotherapy compared with placebo. The authors summarise pharmacological reasons why quetiapine might be useful in chronic PTSD then point to a paucity of literature that supports or refutes its efficacy. There is an implication that PTSD in military veterans is more difficult to treat.

They give a clear description of the participant inclusion and exclusion criteria. Though they state the primary outcome is total CAPS score they report at least 13 scales used as secondary measures. A treatment regime summary is given.

Sadly, I found that my reading of their results and their summary of results did not agree. For example, they say they enrolled eighty patients (but fail to say 47 did not complete). They talk of reductions in CAPS (but I struggle to be convinced by their statistical manipulations). PANSS positive symptoms showed "greater improvements.. for quetiapine"; the actual numbers are 12.71 dropping to 11.05.

My recommendation is that you do not take the authors' assertions of efficacy as having been conclusively demonstrated. Perhaps it is significant that the work was actually completed in 2008 but only published now and it was conducted with a grant from AstraZeneca.

Reference: Am J Psychiatry. 2016;173(12):1205-12
Abstract

The prevalence of symptoms of depression and anxiety, and the level of life stress and worry in New Zealand Māori and non-Māori women in late pregnancy

Authors: Signal TL et al.

Summary: This study involved 406 Māori women (mean age,27.6 years) and 738 non-Māori women (mean age,31.6 years), who all completed a questionnaire in late pregnancy recording their prior history of mood disorders; self-reported current depressive symptoms (≥13 on the Edinburgh Postnatal Depression Scale), current anxiety symptoms (≥6 on the anxiety items from the Edinburgh Postnatal Depression Scale), significant life stress (≥2 items on the Life Stress Scale) and dysfunctional worry (>12 on the Brief Measure of Worry Scale). Compared with non-Māori women, Māori women were more likely to report depressive symptoms (15% vs 22%), anxiety symptoms (20% vs 25%), significant life stress (30% vs 55%) and a period of poor mood during the current pregnancy (14% vs 18%). Of those who had experienced ≥2 weeks of poor mood during the current pregnancy, less than half had sought help. Younger age independently predicted depressive symptoms, significant life stress and dysfunctional worry. Women with a prior history of depression were more likely to experience negative affect in pregnancy.

Comment (WM): This report is a segment of data collected in a larger study "E Moe, Māmā: Maternal Sleep and Health in Aoteoroa/New Zealand". This sub-study sought to explore the rates of depression and anxiety in women in late pregnancy and also to see if there were differences between Māori and non-Māori women. The recruitment methods were designed to ensure recruitment of a sufficient number of Māori women. The article does not explain the multiple approach avenues used and the utilisation of Kaupapa Māori principles; if the reader is interested, the paper in the MAI Journal by Paine SJ et al. (2013;2(2):121-32) describes that. The numbers recruited show the strength of their approach. Participants were women aged over 16 years who were 35 to 37 weeks' gestation with a single foetus.

Data gathered regarding anxiety, depression, stress and worry are well described and validated instruments were used. The analytic method seems appropriate to the data and questions asked.

The findings will not surprise people familiar with mental health issues in peri-partum. The size of the unmet need does challenge care systems to better engage and identify the women with anxiety and depression. Women between 16 and 19 years of age are particularly vulnerable and Māori women are less likely to have accessed care and support.

Reference: Aust N Z J Psychiatry. 2017;51(2):168-76
Abstract

Violence and self-harm in severe mental illness: inpatient study of associations with ethnicity, cannabis and alcohol

Authors: Dharmawardene V, Menkes DB

Summary: For this study, data were reviewed from 141 adult psychiatric inpatients in Hamilton, New Zealand. Substance use was assessed using the Alcohol Use Disorders Identification Test (AUDIT) and Cannabis Use Disorders Identification Test, Revised (CUDIT-R). Two-thirds (66%) of the study cohort had a history of violence, over half (54%) had a history of self-harm, and 40% had both; only 20% had neither. Cannabis use was a significant predictor for lifetime history of violence (p=0.02); no such association was seen with other independent variables (gender, age, ethnicity, alcohol use, psychiatric diagnosis). Significant predictors of self-harm included female gender (p<0.001), use of cannabis (p=0.025) and alcohol (p=0.036); age, ethnicity and diagnosis did not reach significance. Less than 10% of the sample had engaged with drug or alcohol services.

Comment (WM): This is the second report emerging from a New Zealand observational study (see Australasian Psychiatry. 2015;23(3):236-40). The observed cohort is people admitted to a general adult acute inpatient service who satisfied a diagnosis of schizophrenia, bipolar disorder, or schizoaffective disorder. Data was gathered both from clinical notes and face-to-face interview. Violence assessment used a wide descriptor (". . . ever committed an act of violence. . .") Substance use was assessed by validated scales (AUDIT for alcohol, CUDIT for cannabis).

Stand-out features found were a high rate of reported violence and self-harm, low recording of alcohol use disorder in clinical notes of people scoring high on AUDIT, and a low rate of engagement of those with cannabis or alcohol abuse in treatments for that. The only feature that was significantly associated with violence history was CUBIT-R score. The largest association with self-harm was female gender; AUDIT score and CUBIT-R score were also predictors.

This piece of work provides a little more information about associations of violence in those with serious mental illness. The study authors give appropriate cautions re over-generalising from the study. It does not, for example, say that people with mental illness are likely to be violent; the study population will be biased to those likely to exhibit violence and indeed the attribution method would contribute. Likewise, it does not say that all cannabis users are likely to be violent; only that if you have a serious mental illness, cannabis abuse makes it more likely you will exhibit violence.

Reference: Australas Psychiatry. 2017;25(1):28-31
Abstract