Psychiatry Research Review™

Making Education Easy

Issue 38 – 2014

In this issue:

Abbreviations used in this issue

OSA = obstructive sleep apnoea

PTSD = post-traumatic stress disorder

Welcome to the thirty-eighth issue of Psychiatry Research Review.

The wide variety of topics discussed in this issue encompasses investigations into the association of use of antidepressants and suicidality/self-harm, an exploration into the longitudinal relationship between alcohol consumption and mental health symptoms in a general population setting, and research suggesting that enduring symptoms that affect many patients after mild traumatic brain injury may be better described and managed as features of post-traumatic stress disorder.

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

Kind regards,

Dr Chris Tofield
Medical Advisor, Research Review
christofield@researchreview.co.nz

Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study

Authors: Yu CY et al.

Summary: These researchers analysed healthcare claims data (2000–2010) from 11 health plans in the US Mental Health Research Network. The data were grouped into 3 study cohorts: ~1.1 million adolescents (10–17 years), ~1.4 million young adults (18–29 years) and ~5 million adults (30–64 years). The study aimed to determine whether the widely publicised warnings in 2003 from the US Food and Drug Administration about a possible increased risk of suicidality with antidepressant use in young people were linked to changes in rates of antidepressant dispensings, psychotropic drug poisonings (a validated proxy for suicide attempts), and completed suicides among young people. Trends in antidepressant use and poisonings changed abruptly after the warnings. In the second year after the warnings, relative changes in antidepressant use were –31.0% among adolescents, –24.3% among young adults, and –14.5% among adults. These reflected absolute reductions of 696, 1216, and 1621 dispensings per 100,000 people among adolescents, young adults, and adults, respectively. Simultaneously, there were significant, relative increases in psychotropic drug poisonings in adolescents (21.7%) and young adults (33.7%) but not among adults (5.2%). These reflected absolute increases of 2 and 4 poisonings per 100,000 people among adolescents and young adults, respectively (approximately 77 additional poisonings in the combined total of 2.5 million young people). Completed suicides did not change for any group.

Comment (WM): This publication addresses an issue that has been under debate for some time, namely the association of use of antidepressant and suicidality. In America, the FDA released safety warnings stating that the use of antidepressants may increase suicidality in youth (the boxed warning). Other countries, including New Zealand, did have warnings but were not as strong as the FDA; however, the strength of the FDA statements with media enhancement had a worldwide impact.

It has previously been shown that there were substantial reductions in the volume of antidepressant prescription, especially for youth (that is we know the warnings did have the targeted effect of decreasing use). What has not been studied before this work was whether the subsequent reduction in use of antidepressants altered the rates of suicidality and attempts.

The study was a carefully constructed review of the health data held by a number of healthcare organisations across the United States. Their methods of obtaining data, checking its veracity and analysing it appear robust. The numbers of subjects and the demographic spread would suggest the findings have wide applicability.

The main finding was the association of the "warning" and decrease in antidepressant use with an increase in suicide attempts. The paper did not show an actual increase in suicides, but that could be because the numbers studied were not large enough to demonstrate that. The study suggests the outcomes from the FDA warnings were in the reverse direction from that intended. The findings support the concerns expressed by Child Psychiatrists in Australia and New Zealand and add weight to the more cautious approach that we saw in New Zealand.

Reference: BMJ. 2014;348:g3596
Abstract

Antidepressant dose, age, and the risk of deliberate self-harm

Authors: Miller M et al.

Summary: This propensity score-matched cohort study used population-based healthcare utilisation data from 162,625 US residents aged 10–64 years with depression, all of whom had initiated antidepressant therapy with selective serotonin reuptake inhibitors (SSRIs) at modal or at higher-than-modal doses between 1 January 1998 and 31 December 2010. Modal doses for citalopram, sertraline and fluoxetine were 20 mg/day, 50 mg/day and 20 mg/day, respectively. When the researchers examined the risk of deliberate self-harm by antidepressant dose, by age group, they found that the rate of deliberate self-harm among those aged ≤24 years who initiated high-dose therapy was approximately twice as high as among matched patients initiating modal-dose therapy (hazard ratio [HR] 2.2; 95% CI, 1.6 to 3.0), corresponding to approximately 1 additional event for every 150 such patients treated with high-dose (instead of modal-dose) therapy. For those aged ≥25 years, the absolute risk of suicidal behavior was far lower and the effective risk difference null (HR 1.2; 95% CI, 0.8 to 1.9).

Comment (WM): This American-based study seeks to build upon the FDA-reported analysis that found children who were randomised to antidepressants were twice as likely to have suicidal ideation and behaviour than those randomised to placebo. It explores the possible link between dose of antidepressant and risk of suicidal behaviour.

Data for the study was obtained by a retrospective analysis of information aggregated from enrolled patients in over 98 health plans in USA who input to a single claims database. Source data is ICD-coded depression and SSRI antidepressant prescription. Analysis of the antidepressant data was restricted to new initiations of treatment. For the purpose of dose consideration three groups were defined, based on the accumulated range of starting doses, modal dose, higher than modal dose and lower than modal dose. One assumes, though it is not absolutely clear, that this decision to subdivide the groups was made ahead of any analysis of the data. The primary outcome of interest was deliberate self-harm. It appears that the maximum period of review was 360 days, but monitoring stopped if there was such an attempt, if they changed medication (including having something added) or they stopped enrolment in the health plan. There were two age ranges reviewed, 10 to 24 years and 25 to 65 years.

The study has strengths including the large population and the limited exclusion criteria, which enhance the real world nature of the studied group. It has limitations from the inability to adjust for depression severity, the uncertainty of the recording of the deliberate self harm and the inability to know about adherence. Despite these limitations, the robust difference in the rate of self-harm in the 10- to 14-year age group who were prescribed doses above the modal group would argue strongly for an initial "start low go slow" approach to antidepressant prescribing for young people.

Reference: JAMA Intern Med. 2014;174(6):899-909
Abstract

High rates of obstructive sleep apnea symptoms among patients with schizophrenia

Authors: Annamalai A et al.

Summary: Data were analysed from 175 outpatients with schizophrenia or schizoaffective disorder attending a large urban community mental health centre, all of whom were screened for obstructive sleep apnoea (OSA) by the STOP questionnaire, a screening tool for OSA that has been validated in surgical patients. Patients were classified as being at high risk for OSA (STOP ≥2) (57.7%), or low risk for OSA (STOP score <2) (42.3%). Patients with diagnosed OSA (14.9%) had significantly higher STOP scores (mean 2.7 vs 1.6 [t = 6.3; p<0.001]). Only 23.8% of patients in the high-risk group were diagnosed with OSA. Body mass index was significantly higher in the diagnosed group (F[2,169] = 25; p<0.001) as was diabetes ($\chi 2$ [2, N = 175] = 35, p<0.001).

Comment (WM): As health services struggle to address the health disparity that is reflected by much higher mortality rates for people with serious mental illness this is a timely reminder of one possible contributor to that disparity. The paper gives reasonable evidence that OSA is both reasonably common and not well recognised. It is a condition that, as well as contributing to physical factors that can reduce life expectancy, can also contribute to worsened mental health indices, such as depression and cognitive impairment. When OSA is recognised, treatment using continuous positive airway pressure (CPAP) is highly efficacious.

The paper suggests screening instruments that are easily utilised and strongly predictive. Screening tests can be administered by medical and non-medical professionals so would be able to be used in an NGO setting. Positive screening would then give a strong argument for establishing the diagnosis by polysomnography. The article also suggests that people with serious mental illness are likely to need enduring support to use CPAP.

Reference: Psychosomatics. 2014 Mar 2. [Epub ahead of print]
Abstract

Checking the plausibility of psychiatrists' arguments for not prescribing depot medication

Authors: Hamann J et al.

Summary: These researchers sought to describe psychiatrist and patient clinical characteristics that might influence the initiation of depot antipsychotic medications among outpatients with schizophrenia. The study sample involved 213 doctor-inpatient-dyads in German psychiatric hospitals. Thirty percent of patients were prescribed depot at discharge; even more (47%) discussed the possibility of depot treatment with their psychiatrists. Survey responses indicated that 50% of the patients were generally open toward receiving depot antipsychotics. The researchers comment that psychiatrists' arguments against depot medications were often illogical and that therefore many more patients might be suitable for receiving depot treatment. Psychiatrists' hesitation to discuss and implement depot might also be founded in concerns regarding patients' acceptance of depot medication. The study researchers suggest that better communication between physicians and patients may increase implementation rates of depot antipsychotics.

Comment (WM): This paper emerging from work in Germany explores in a novel way decisions about prescribing or considering possible prescription of depot medication. The study involved 22 different clinics and hospitals across Germany, thus it was not limited by city or locality enhancing representativeness and generalisability. The focus was on psychiatrists working in services where schizophrenia was frequently treated. The patient population was drawn from the psychiatrist's case load.

Actual treatment data and information re illness was gathered from case note review then additional sampling of both patient and psychiatrist (independently) looked at decisions made, reasons for and information flow. Given the nature of the information sought and the large number of participant sites the data gathered is impressive.

The findings are another reminder that personal biases and assumptions can influence decisions to offer treatment modalities that might not be in line with evidence and might not align with what a patient or their family might choose if given the opportunity.

Reference: Eur Neuropsychopharmacol. 2014;24(9):1506-10
Abstract

Psychiatry Research Review

Independent commentary by Associate Professor David Menkes, Waikato Clinical School, University of Auckland. **For full bio CLICK HERE.**

Independent commentary by Associate Professor Wayne Miles, Director of the Knowledge Centre at Waitemata District Health Board and Clinical Associate Professor at the Auckland University School of Medicine. **For full bio CLICK HERE.**

Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: Do the cognitive deficits progress over, or after, the onset of psychosis?

Authors: Bora E, Murray RM

Summary: This meta-analysis included data from 25 studies published between January 1987 and February 2013 reporting longitudinal cognitive data for 905 patients who presented with first-episode psychosis (FEP), 560 patients at ultra-high risk (UHR) for psychosis, and 405 healthy controls.

Comment (WM): It is generally accepted that cognitive dysfunction is one of the characteristics of schizophrenia. What is less well established is the time trajectory of the cognitive impairment. One school of thought sees the course as being that of any neurodegenerative disorder with a relentless loss of function over time (best fitting the Kraeplinean "dementia praecox" notion). The alternative position is that the cognitive dysfunction is of a neurodevelopmental type. In this model, cognitive and intellectual deficits are evident early, maybe before the onset of the positive psychotic symptoms, and are largely unrelated to those. There is a model that allows a combination of these two processes, where there is deficit early and this may progress. The literature in this area is mostly from cross-sectional design studies comparing people at different phases of the illness. It generally supports there being a considerable cognitive decline that is evident at or before onset of the illness with a more modest decline during illness progression.

This study sets out to compare the results of longitudinal studies of cognitive function in subjects meeting criteria for Ultra-High Risk of psychosis (UHR) and those with First-Episode Psychosis (FEP). The definitions used in this analysis are very sound and the search methods and rules for inclusion and exclusion appear to enhance the quality of findings without introducing unwanted distortion. There is a careful consideration of the actual measures of cognitive function reported.

The findings reported are more in keeping with the neurodevelopmental model with no demonstration of decline over time. Quite importantly for the treating psychiatrist, there is no evidence that use of antipsychotic medication is associated with decline. The analysis does observe a frequent finding of modest improvements in cognitive function over time in all groups, including healthy volunteers. This difference might be accounted for by the practice effect. The authors attempted to examine possible differences between those with UHR who subsequently develop psychosis and those who do not. There is not any evidence of difference, further strengthening a neurodevelopmental model, but the numbers of studies are small.

This work highlights the significant nature of the cognitive component and should remind us all that strategies to help patients address that deficit are crucial and need to be introduced early.

Reference: Schizophr Bull. 2014;40(4):744-55
Abstract

CLICK HERE
to read previous issues of Psychiatry Research Review

Benefits and harms in clinical trials of duloxetine for treatment of major depressive disorder: comparison of clinical study reports, trial registries, and publications

Authors: Maund E et al.

Summary: These researchers assessed data and reporting of analyses from 9 randomised controlled trials (RCTs) of duloxetine (total 2878 patients) submitted to the European Medicines Agency for marketing approval for major depressive disorder. The analysis aimed to determine whether inconsistencies exist between protocols, clinical study reports, and main publicly available sources (journal articles and trial registries), and within clinical study reports themselves, with respect to benefits and major harms. Clinical study reports fully described the primary efficacy analysis and major harms (deaths – including suicides, suicide attempts, serious adverse events, and discontinuations because of adverse events). There were inconsistencies in the primary efficacy analysis between protocols and clinical study reports and within clinical study reports. Information was contradictory within the reports for 7 serious adverse events and 8 adverse events that led to discontinuation but with no apparent bias. In each trial, a median of 406 and 166 treatment-emergent adverse events in the randomised phase were not reported in journal articles and Lilly trial registry reports, respectively. Publication bias was identified in relation to beneficial effects.

Comment (DM): Recent years have seen unprecedented controversy (and, in many cases, litigation) regarding the provenance and reliability of drug information. Indeed, a host of studies, including a recent NZ analysis, has challenged the 'gold standard' of RCTs because even RCTs are subject to uncontrolled bias, notably arising from commercial sponsorship (Every-Palmer S, Howick J. How evidence-based medicine is failing due to biased trials and selective publication. J Eval Clin Pract. 2014 May 12. [Epub ahead of print]). The present study provides a clear illustration of this problem with respect to a new antidepressant, duloxetine. In this case, the authors demonstrate that clinical study reports are a more reliable (less biased) and complete source of information, particularly regarding adverse effects. Unfortunately, the study also indicates that journal articles may be prone to portraying an unrealistically positive view of new drugs, with regard to both benefits and harms of treatment. As was described in a previous Research Review, this has been a recognised problem with regard to publications about antidepressants generally (Turner EH, et al. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med. 2008;358:252-60).

Reference: BMJ. 2014;348:g3510
Abstract

An exploration of the dynamic longitudinal relationship between mental health and alcohol consumption: a prospective cohort study

Authors: Bell S, Britton A

Summary: This investigation into alcohol consumption and mental health used data from the Whitehall II prospective cohort study, which started with a sample of 10,308 British civil servants (6,895 men and 3,413 women), who were aged 34 to 56 years at entry into the study (1985 to 1988). For this clinical investigation, data were obtained from phases 5 (1997 to 1999; referred to hereafter as 'baseline'), 7 (2002 to 2004), and 9 (2007 to 2009), providing approximately 10 years of follow-up for 6330 participants who had consumed alcohol in the year before baseline (73% men; mean age 55.8 years). Mental health was assessed using the Short Form (SF)-36 mental health component score. Alcohol consumption was defined as the number of UK units of alcohol drunk per week. Four competing theoretical models were compared to determine which best reflected the association between these two factors: 1) a baseline model in which alcohol consumption and mental health trajectories did not influence each other, 2) a model in which alcohol consumption influenced changes in mental health but mental health exerted no effect on changes in drinking and 3) vice versa, and (4) a reciprocal model in which both variables influenced changes in each other. The third model, in which mental health influenced changes in alcohol consumption but not vice versa, was the best fit. In this model, the effect of previous mental health on upcoming change in alcohol consumption was negative ($\gamma = -0.31$; 95% CI −0.52 to −0.10), meaning that those with better mental health tended to make greater reductions (or shallower increases) in their drinking between occasions.

Comment (DM): This novel and carefully conducted UK study addresses a long-standing debate among clinicians about whether alcohol consumption is more a symptom or cause of mental disorder. Based on extensive epidemiological data, the authors come to the (largely statistical) conclusion that the former is more likely. Thus, changes in alcohol consumption would appear to signal or reflect mental disorder more than cause it, allowing for the fact that there may be reciprocal effects in some subpopulations. A common clinical example would be that increased alcohol consumption may follow as well as perpetuate a depressive illness. This study is limited by having relatively few women and ethnic minority participants, making its applicability to New Zealand somewhat uncertain. Another important limitation is that it relies completely on self-reported alcohol consumption.

Reference: BMC Medicine. 2014;12:91
Abstract

Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial

Authors: Tannenbaum C et al.

Summary: The EMPOWER (Eliminating Medications Through Patient Ownership of End Results) study was conducted from 2010 through 2012, involving 303 long-term users of benzodiazepine medication aged 65–95 years, recruited from 30 community pharmacies that were randomly allocated to an educational intervention or usual care (control) arm. The 148 participants in the intervention group received a deprescribing patient empowerment intervention describing the risks of benzodiazepine use and a stepwise tapering protocol; the 155 participants in the control arm received usual care. Of the recipients in the intervention group, 62% initiated conversation about benzodiazepine therapy cessation with a physician and/or pharmacist. Of the 261 participants who completed a 6-month follow-up, 27% of the intervention group had discontinued benzodiazepine therapy compared with 5% of the control group (risk difference, 23% [95% CI, 14% to 32%]; intracluster correlation, 0.008; number needed to treat, 4). Dose reduction occurred in an additional 11%. No significant interaction effects were observed for age >80 years, sex, duration of use, indication for use, dose, previous attempt to taper, and concomitant polypharmacy (≥10 drugs/day) in relation to benzodiazepine therapy discontinuation.

Comment (DM): Despite their undoubted short-term efficacy and usefulness, benzodiazepines can be problematic in the medium and longer term, bedevilled as they are by frequent tolerance and dependence, with abuse and diversion less frequent but still serious problems. As we have seen in previous issues of Research Review, benzodiazepine prescription has recently been associated with additional harms, including worsened depression and increased mortality, particularly in the elderly. Efforts to limit new prescriptions are ongoing but many clinicians 'inherit' patients with existing prescriptions and are faced with the challenge of whether to continue or attempt to stop the medication. How to effectively discontinue benzodiazepine prescription thus represents an important issue addressed by the present innovative study, which is equally relevant to psychiatry and medicine generally. Although it must be considered preliminary given the number of subjects, the present study demonstrates an impressive increase in discontinuation rates following an educational intervention. The methodology would appear to be appropriate for the New Zealand context and, particularly if extended to include Z drugs, could substantially reduce drug-related harm. As we have previously documented, rates of hypnosedative prescribing and associated harms are both increasing year on year in this country (Menkes DB, et al. Hypnosedative access and risk of harm. N Z Med J. 2011;124:69-73).

Reference: JAMA Intern Med. 2014;174(6):890-8
Abstract

Variation in benzodiazepine and antipsychotic use in people aged 65 years and over in New Zealand

Authors: Jackson G et al.

Summary: These researchers analysed data from the New Zealand Pharmaceutical Collection, which contains claim and payment information from community pharmacists for all prescription dispensing of patients living in the community and residential care. The data were used to examine the variation in the dispensing of antipsychotic and benzodiazepine medicines in the elderly (aged ≥65) across New Zealand by age, gender, district health board (DHB) of domicile and aged residential care usage rates over a 4-year period (2008/09 to 2011/12). On average, 24 per 1000 people aged ≥65 years in New Zealand in 2008/09 to 2011/12 were dispensed an antipsychotic in any given quarter. Benzodiazepine dispensing rates were even higher, at 109 per 1000 aged ≥65. Both rates climbed steeply with age, were higher in females, and had a 1.6- to 1.8-fold variation across DHBs. Rates did not vary significantly with rest home and private hospital residential care usage, but antipsychotic rates appeared related to the use of psychogeriatric and dementia beds.

Comment (DM): This study provides an important local example of some of the drug-related harm issues outlined in the previous review. The authors were careful to control for a number of confounding variables, and thus the results are likely to be applicable across New Zealand and beyond. One key implication of the findings would seem to be that the effectiveness and tolerability of medications prescribed to elderly patients require routine and careful review – and withdrawal in the event that clear benefit (relative to any side effects) is not apparent. It remains an open question as to whether other therapeutic modalities, including behavioural, can effectively supplant the widespread and often unhelpful prescription of antipsychotics and benzodiazepines in this population.

Reference: N Z Med J. 2014;127(1396):67-78
Abstract

The Royal New Zealand College of General Practitioners
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.

Association of symptoms following mild traumatic brain injury with posttraumatic stress disorder vs postconcussion syndrome

Authors: Lagarde E et al.

Summary: This prospective cohort study involved 534 patients with head injury and 827 control patients with other nonhead injuries at an adult emergency department in a hospital in France. The study assessed whether persistent symptoms 3 months following head injury are specific to postconcussion syndrome (PCS) or may be better described as part of post-traumatic stress disorder (PTSD). At 3 months following the trauma, 21.2% of head-injured and 16.3% of nonhead-injured patients fulfilled the DSM-IV diagnosis of PCS; 8.8% of head-injured patients fulfilled the diagnostic criteria for PTSD compared with 2.2% of control patients. In multivariate analysis, mild traumatic brain injury was a predictor of PTSD (OR 4.47; 95% CI, 2.38 to 8.40) but not of PCS (OR 1.13; 95% CI, 0.82 to 1.55). Correspondence analysis suggested that symptoms considered part of PCS behave similarly to PTSD symptoms in the hyperarousal dimension. None of these 22 symptoms showed any pattern of clustering, and no clear proximity with head or nonhead injury status was observed.

Comment (DM): This fascinating and careful French study addresses a persisting clinical conundrum regarding the nature of symptoms following mild traumatic brain injury. As the British neuropsychiatrist Lishman pointed out decades ago, largely on the basis of case series and clinical anecdote, there seems to be an inverse relationship between the severity of head injury and the psychological (as opposed to organic) basis of persisting symptoms. Results of the current study are thus strongly supportive of Lishman's view, and provide the strong suggestion that assessment and management of PTSD should be a clinical priority in these patients. In addition, these findings suggest that patients' understanding of their injury and its consequences may need to be explored and, in the event of maladaptive beliefs, reframed by CBT or similar manoeuvres.

Reference: JAMA Psychiatry. 2014;71(9):1032-40
Abstract