

Psychiatry Research Review™



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Issue 13 - 2011

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Welcome to the thirteenth edition of **Psychiatry Research Review**, a unique Australian publication bringing you some of the most important research from around the world every month.

Across Australia, smoking is banned by most mental health services. This is an additional stressor to deal with for schizophrenia patients who smoke, when admitted to a smoke-free mental health institution. In our first study, a group of US researchers discusses the impact of nicotine replacement therapy in such patients; strikingly, those treated with nicotine replacement had significantly lower aggression scores compared with those given placebo.

In another study, Canadian researchers suggest that deep brain stimulation is safe and effective for treatment-resistant depression for up to 6 years. This study involved only 20 patients; it would be very interesting to see additional trials with larger samples.

Another interesting study reports a higher margin of efficacy for antidepressants in dysthymia than in major depressive disorder, offering hope of an effective treatment for this insidious and debilitating depressive disorder.

I hope that you enjoy this edition and I welcome your comments and feedback.

Kind regards,

Professor David Castle

david.castle@researchreview.com.au

Effect of nicotine replacement therapy on agitation in smokers with schizophrenia: a double-blind, randomized, placebo-controlled study

Authors: Allen MH et al

Summary: This study involved 40 adult smokers with schizophrenia and at least some agitation who were admitted to a smoke-free psychiatric emergency unit. They were randomised to receive nicotine (21 mg) or placebo patches plus usual care with antipsychotics. Compared with placebo, nicotine was associated with 33% less agitation at 4 hours and 23% less agitation at 24 hours, as determined by the changes from baseline in mean Agitated Behavior Scale scores. The intervention showed a dose-response curve inversely related to the degree of nicotine dependence. The difference in agitation between nicotine replacement and placebo was stronger in patients who smoked less than in those who smoked more.

Comment: Rates of cigarette smoking amongst people with schizophrenia remain very high and contribute to cardiovascular risk profiles and early mortality amongst this vulnerable group. Until relatively recently mental health services have, in many jurisdictions, turned a blind eye to this problem, and tacitly accepted that people with schizophrenia smoke. But this is changing, and most Australian mental health services are now either entirely or in part smoke free. These moves have not been welcomed by all, with consumer groups (and some staff) claiming it is an infringement of human rights to stop people detained against their will in hospital, to engage in what is a legal activity. Another area of concern has been the perception that violent incidents could be exacerbated by restrictions on smoking. That is where this article fits in, investigating whether nicotine patches can ameliorate agitation and aggression in smokers with schizophrenia. This is difficult work to do, as gaining consent for participation in a randomised placebo-controlled trial in agitated individuals is tricky at the best of times, and there are always thus questions about generalisability and so forth. But the findings are nevertheless striking, with significantly lower aggression scores in those patients treated with nicotine replacement, than placebo. This reinforces the importance of screening psychiatric patients upon admission to hospital, to ascertain who are smokers, and to offer nicotine replacement to those who are.

Reference: *Am J Psychiatry* 2011;168(4):395-9.

<http://ajp.psychiatryonline.org/cgi/content/abstract/168/4/395>

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Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years

Authors: Kennedy SH et al

Summary: Long-term follow-up data are presented for 20 patients with treatment-resistant depression who received deep brain stimulation (DBS) to the subcallosal cingulate gyrus region. After an initial 12-month study of DBS, patients were seen annually and at a last follow-up visit (occurring between 3 and 6 years after the procedure) to assess depression severity, functional outcomes, and adverse events. The average response rates 1, 2, and 3 years after DBS implantation were 62.5%, 46.2%, and 75%, respectively. At the last follow-up visit, the average response rate was 64.3%. Functional impairment in the areas of physical health and social functioning progressively improved up to the last follow-up visit. No significant adverse events were reported during follow-up, although two patients died by suicide during depressive relapses.

Comment: Every clinician will have been faced with patients in whom depression simply does not respond adequately to psychological and medication interventions, and even ECT. The evolution of treatments such as magnetic seizure therapy, transcranial magnetic stimulation, vagal nerve stimulation and deep brain stimulation offer alternative therapeutic options for this group of individuals. Deep brain stimulation is being actively explored for this indication in a number of centres around the world, and early outcomes have appeared promising. This paper expands our knowledge base by looking at longer-term outcomes (up to 6 years in some patients). The fact that patients tended not only to maintain earlier gains but indeed to show increased benefit and concomitant increased social functioning is most encouraging. The fact that two of the 20 committed suicide during depressive relapses is tragic and underlines the severity of their illnesses, but should not detract from the overall benefits that accrued in the cohort as a whole. Whilst invasive techniques such as deep brain stimulation will remain of limited applicability in a small group of highly selected patients, it seems to be emerging as a very reasonable therapeutic option in treatment-resistant depression.

Reference: *Am J Psychiatry* 2011;168(5):502-10.
<http://ajp.psychiatryonline.org/cgi/content/abstract/168/5/502>

A post hoc analysis of the effect of nightly administration of eszopiclone and a selective serotonin reuptake inhibitor in patients with insomnia and anxious depression

Authors: Fava M et al

Summary: This analysis pooled data from two randomised, double-blind, 8-week trials, one of which involved patients with insomnia and comorbid major depressive disorder (MDD) treated with fluoxetine concurrently with eszopiclone 3 mg/day or placebo, while the other trial included patients with insomnia and comorbid generalised anxiety disorder treated with escitalopram concurrently with eszopiclone 3 mg/day or placebo. In the combined dataset, 347 of 1,136 patients (30.5%) had insomnia and comorbid anxious depression. Insomnia was improved by a significantly greater amount with eszopiclone cotherapy than with placebo cotherapy (mean change from baseline on the Insomnia Severity Index: -11.0 vs -7.8, respectively; $p < 0.001$). There were greater reductions from baseline in 17-item Hamilton Depression Rating Scale (HDRS-17) scores at week 8 following cotherapy with eszopiclone compared with placebo when the insomnia items were included (mean change: -14.1 vs -11.2, respectively; $p < 0.01$) or excluded (-10.6 vs -8.9; $p < 0.01$), and HDRS-17 response rates were significantly greater for eszopiclone cotherapy than for placebo cotherapy (55.6% vs 42.0%, respectively; $p = 0.01$; 50.0% vs 44.4% when insomnia items were removed). Remission rates were not significantly different (32.6% vs 27.2%, respectively).

Comment: The association between anxiety and depression is common in clinical practice, and such patients often suffer from insomnia. The insomnia can be a major concern for the patient, such that they come to dread bedtime because they simply 'know' they won't sleep, and also makes their other symptoms worse in that they feel exhausted and unable to think as clearly as they would like. This can feed the cycle of depression and anxiety. Unfortunately, many of the antidepressants we often use in such patients (including fluoxetine and escitalopram, the medications in these two trials) make sleep worse, through a combination of agitation, nightmares and nocturnal sweating. This report shows that the addition of the hypnotic eszopiclone in anxious depression was associated with better sleep and also improvements in the Hamilton Depression Rating Scale scores, even if the sleep items in that scale were excluded; however, response and remission rates were not significantly better when the insomnia items were controlled for. The authors suggest further prospective studies to explore the 'modest antidepressant effects' further, but most clinicians will take little persuasion in using hypnotics in the short term, at least in anxious depressed patients with insomnia, as simply breaking the insomnia cycle seems such an obvious therapeutic target.

Reference: *J Clin Psychiatry* 2011;72(4):473-9.
http://article.psychiatrist.com/dao_1-login.asp?ID=10007147&RSID=79698302714252

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The image shows three overlapping journal covers. The top cover is 'Diabetes & Obesity Research Review', Issue 35 - 2011, featuring a person's hands holding a glucose meter. The middle cover is 'ASCO Annual Meeting 2011 Conference Review', featuring a person's face. The bottom cover is 'Parkinson's Disease Research Review', Issue 1 - 2011, featuring a brain scan image.



The effect of exercise in clinically depressed adults: systematic review and meta-analysis of randomized controlled trials

Authors: Krogh J et al

Summary: These researchers systematically reviewed the evidence from published randomised controlled trials that investigated the effects of exercise in adults with clinical depression. Thirteen trials met the inclusion criteria and were included in the analysis. The pooled result for all 13 studies revealed that depression scores were on average 0.4 of a standard deviation lower in clinically depressed patients randomly assigned to an exercise intervention at the end of that intervention compared to those randomly assigned to a none exercise group. Pooled analysis of 5 trials with long-term follow-up (i.e., that examined outcomes beyond the end of the intervention) suggested no long-term benefit (standardised mean difference, -0.01). Only 3 studies were deemed to be of high quality (adequately concealed random allocation, blinded outcome assessment, and intention-to-treat analysis). A pooled analysis of these trials yielded a more modest estimated beneficial effect of exercise (depression scores 0.19 of a standard deviation lower) than the pooled result for all 13 studies, with no strong evidence of benefit.

Comment: Interest in exercise as an antidepressant has become widespread, and many clinicians advocate regular exercise to their patients as part of a package of care. At the very least, it would seem that such a strategy carries very little risk of adverse consequences and certainly exercise can enhance physical health, including weight loss, and help improve sleep and re-establish circadian rhythms. Thus, secondary mood-enhancing effects might be expected. But whether there is a primary antidepressant effect is a rather more contentious matter. This paper underlines how limited the evidence base is in this regard, with only three trials conforming to 'best practice' in having concealed randomisation, blinded assessments of outcomes and intention-to-treat analyses. That these three trials showed generally less powerful effects for the exercise intervention is not unexpected, but should not be seen totally to negate the positive findings from the less methodologically rigorous studies, and the fact is that the overall combined outcomes (albeit in the face of significant between-study heterogeneity) did favour exercise. One of the questions that this raises is what constitutes a proper 'dose' of exercise as the between-study heterogeneity was largely due to differences in the duration of the intervention: future studies need to address this matter carefully and ensure excellent fidelity to the intervention. It will also be important to establish which type of patient is most likely to benefit from this sort of intervention, and at what stage of the illness trajectory. The fact that any antidepressant effect dissipated once the intervention ceased is not surprising: indeed, we know well that antidepressants don't work unless they are actually being taken!

Reference: *J Clin Psychiatry* 2011;72(4):529-38.
http://article.psychiatrist.com/dao_1-login.asp?ID=10007122&RSID=79698302714364

Efficacy of antidepressants for dysthymia: a meta-analysis of placebo-controlled randomized trials

Authors: Levkovitz Y et al

Summary: These Israeli researchers assessed the efficacy of antidepressants in dysthymic disorder and also compared antidepressant and placebo response rates between dysthymic disorder and major depressive disorder (MDD). A total of 194 randomised, double-blind, placebo-controlled trials of antidepressants for either MDD or dysthymic disorder were eligible for inclusion in the analysis, 17 of which focused on the treatment of dysthymic disorder. Antidepressants were significantly more effective than placebo in dysthymic disorder (risk ratio, 1.75; $p < 0.0001$) and placebo response rates in dysthymic disorder trials were significantly lower than they were in MDD trials (29.9% vs 37.9%; $p = 0.042$). In a comparison of dysthymic disorder and MDD studies, a meta-regression analysis suggested a statistically significant difference in the risk ratio of responding to antidepressants versus placebo, indicating a higher margin of efficacy for antidepressants in dysthymia than in MDD (coefficient of -0.113; $p = 0.007$).

Comment: The late Bob Kendell wrote over three decades ago about the classification of the affective disorders being an area of 'contemporary confusion', and little has changed over the ensuing years. The reliance on 'major depressive disorder' as a putative entity that is generally the inclusion criterion for antidepressant trials, whilst adding reliability and allowing cross-study comparisons, has in many ways been a disservice to those patients who have perfectly legitimate depressive symptoms and associated disability but do not quite meet criteria for major depressive disorder. Indeed, in this meta-analysis, only 17 of 194 studies were of patients with dysthymic disorder. This publication is thus welcome as it weighs the evidence regarding the use of antidepressants in people with dysthymic disorder, often considered a 'lesser' mood disorder but one which can be very disabling. Perhaps unsurprisingly, patients with dysthymic disorder did respond to antidepressants: in fact, outcomes were more robust across studies than in the pooled results for major depressive disorder, and placebo response rates were also lower in dysthymic disorder patients. Hopefully this sort of evidence will open up more focused attention on those forms of depression that don't fit neatly into the Diagnostic and Statistical Manual's diagnostic boxes.

Reference: *J Clin Psychiatry* 2011;72(4):509-14.
http://article.psychiatrist.com/dao_1-login.asp?ID=10007376&RSID=79698302714506

Stepped care and cognitive-behavioural therapy for bulimia nervosa: randomised trial

Authors: Mitchell JE et al

Summary: These researchers sought to establish the relative effectiveness of two treatment approaches for bulimia nervosa: cognitive-behavioural therapy (CBT) augmented by fluoxetine if indicated, versus a stepped-care treatment approach. The study enrolled 293 patients with bulimia nervosa. The interventions consisted of manual-based CBT delivered in an individual therapy format involving 20 sessions over 18 weeks, with fluoxetine added to treatment for those who were predicted to be non-responders after 6 sessions of CBT, or a stepped-care approach that began with supervised self-help, with the addition of fluoxetine for participants who were predicted to be non-responders after 6 sessions, followed by CBT for those who failed to achieve abstinence with self-help and medication management. The intent-to-treat and completer samples revealed no differences between the two treatment conditions in inducing recovery (no binge eating or purging behaviours for 28 days) or remission (no longer meeting DSM-IV criteria). However, the stepped-care method was significantly superior to CBT at the end of 1-year follow-up for some measures, e.g., objective binge eating episodes and compensatory behaviours (defined as the total of episodes of vomiting, laxative use, diuretic use, fasting and driven exercise as measured on the Eating Disorder Examination).

Comment: There is little doubt that cognitive-behavioural therapy has an important role in the treatment of bulimia nervosa. What is problematic is the relative paucity of suitably trained therapists, relative to demand. This situation makes it important to establish how best such face-to-face therapeutic expertise can be deployed and how much use can be made of alternative modes of delivery such as supervised self-help. Another issue is when serotonergic antidepressants should be deployed in this clinical context. This study is informative in this regard, as it shows that a step-wise approach, with only those patients who did not benefit adequately from supervised self-help, going on to receive the serotonergic antidepressant fluoxetine, and if required, face-to-face therapy, was as effective as first-line deployment of one-to-one therapy (with addition of fluoxetine if required). Of even more interest was that 12-month outcomes favoured the stepped-care approach. This study, if supported by others, suggests attention being given by service providers to adopting a more sequential and targeted approach to treating people with bulimia nervosa.

Reference: *Br J Psychiatry* 2011;198(5):391-7.
<http://bjp.rcpsych.org/cgi/reprint/198/5/391>

Independent commentary
 by Professor David Castle,
 Chair of Psychiatry at St Vincent's
 Health and The University
 of Melbourne.

Contact Research Review

Email admin@researchreview.com.au

Phone 1300 132 322



Antidepressant effects, of magnetic seizure therapy and electroconvulsive therapy, in treatment-resistant depression

Authors: Kayser S et al

Summary: Twenty patients with treatment-resistant depression were administered magnetic seizure therapy (MST) or electroconvulsive therapy (ECT) as an add-on therapy to a controlled pharmacotherapy. Antidepressant response (improvement from baseline of 50% in Montgomery Åsberg Depression Scale ratings) was statistically significant and of similar size in both treatment groups. No cognitive side effects were observed. Characteristics in MST- and ECT-induced seizures were comparable, especially regarding ictal activity and post-ictal suppression.

Comment: This paper presents outcomes from the use of MST in treatment-resistant depression. MST is a form of convulsive therapy where the ictus is produced in a much more regionally-targeted manner than is possible with ECT, through the use of magnetic fields. The hope is that this technology can produce effective convulsive therapy with a lower burden of cognitive side effects and shorter post-ictal recovery times: this would be extremely useful for patients and also potentially be cost-saving for services. This open trial randomly assigned 20 patients with treatment-resistant depression to either MST or ECT. Response rates, defined as at least a 50% reduction on the Montgomery Åsberg Depression Rating Scale, were similar in each group. This open trial is encouraging but larger, blinded studies with full assessment of cognitive effects of each treatment modality are required to establish the place of MST in our treatment armamentarium.

Reference: J Psychiatr Res 2011;45(5):569-76.
http://www.sciencedirect.com/science/article/pii/S002239561000275X

Obsessive-compulsive spectrum disorders: a comorbidity and family history perspective

Authors: Brakoulias V et al

Summary: This assessment of rates of comorbidity and family history of obsessive-compulsive spectrum disorders (OCSDs) in patients with obsessive-compulsive disorder (OCD) aimed to determine the strength of the evidence in support of the concept of OCSDs as a new diagnostic classificatory system for inclusion in DSM-V. A total of 77 patients with a primary diagnosis of OCD were assessed by structured clinical interviews that explored comorbidity and family history. When rates of OCSDs and other anxiety disorders (OADs), excluding OCD, were compared, the most prevalent comorbid conditions were OADs: generalised anxiety disorder (34.6%), specific phobia (26.9%), social phobia (21.8%) and panic disorder (19.2%). The proposed OCSDs were less frequently comorbid: tic disorder (12.8%), trichotillomania (5.1%), hypochondriasis (3.8%) and body dysmorphic disorder (BDD) (3.8%). Similar trends were observed for a family history of these disorders. None of the patients reported a family history of an OCSD without a family history of an OAD.

Comment: As we move towards the inevitability of DSM-V, various individuals and groups are lobbying hard to have their views reflected in the new nosology. One of the major proposals is the grouping together of a number of disparate disorders that share certain clinical and other features, under a grouping being referred to as the 'obsessive compulsive spectrum' (OCS). This is somewhat anomalous as it isn't really a spectrum at all, but rather a grouping of disorders. Some of the proposed members of this grouping seem to have much more 'claim' to membership than others. Thus far, much of the argument for inclusion of certain disorders has relied on phenomenological and treatment-response parameters being similar to OCD. This useful paper takes this further, by looking at whether there are clues from comorbidity and family history data to support membership of the OCS. As it happened, it was the other anxiety disorders such as generalised anxiety disorder, social anxiety disorder and panic disorder that were far and away the most prevalent comorbid conditions, and these were also the conditions most likely to be manifest in family members. Of course, this in part reflects the fact that these disorders are more common than the putative OCS disorders in the general population, but does serve to some extent to undermine the OCS concept and support the notion of keeping these disorders in the anxiety disorder grouping in DSM-V.

Reference: Australas Psychiatry 2011;19(2):151-5.
http://informahealthcare.com/doi/abs/10.3109/10398562.2010.526718



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