Abstracts

Depression and Dysthymia

Given space limitations and varying reprint permission policies, not all of the influential publications the editors considered reprinting in this issue could be included. This section contains abstracts from additional articles the editors deemed well worth reviewing.

Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review

Gartlehner G, Hansen RA, Morgan LC, Thaler K, Lux LJ, Van Noord M, Mager U, Gaynes BN, Thieda P, Strobelberger M, Lloyd S, Reichenpfader U, Lohr KN.

AHRQ Comparative Effectiveness Reviews. 2011 Dec. Report No.: 12-EHC012-EF.

Background: Depressive disorders such as major depressive disorder (MDD), dysthymia, and subsyndromal depression may be serious disabling illnesses. MDD affects more than 16 percent of adults at some point during their lifetimes. Second-generation antidepressants dominate the medical management of depressive disorders. These drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other drugs with related mechanisms of action that selectively target neurotransmitters. **Objectives:** The objective of this report was to compare the benefits and harms of bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine for the treatment of depressive disorders, including variations of effects in patients with accompanying symptoms and patient subgroups. **Data Sources:** We updated a comparative effectiveness review published in 2007 by the Agency for Healthcare Research and Quality searching PubMed, Embase, The Cochrane Library, and International Pharmaceutical Abstracts up to January 2011. **Review Methods:** Two people independently reviewed the literature, abstracted data, and rated the risk of bias. If data were sufficient, we conducted meta-analyses of head-to-head trials of the relative benefit of response to treatment. In addition, we conducted mixed treatment comparisons to derive indirect estimates of the comparative efficacy among all second-generation antidepressants. **Results:** From a total of 3,722 citations, we identified 248 studies of good or fair quality. Overall, no substantial differences in efficacy could be detected among second-generation antidepressants for the treatment of acute-phase MDD. Statistically significant differences in response rates between some drugs are small and likely not clinically relevant. No differences in efficacy were apparent in patients with accompanying symptoms or in subgroups based on age, sex, ethnicity, or comorbidities, although evidence within these subpopulations was limited. Differences exist in the incidence of specific adverse events and the onset of action. Venlafaxine leads to higher rates of nausea and vomiting, sertraline to higher rates of diarrhea, and mirtazapine to higher rates of weight gain than comparator drugs. Bupropion causes lower rates of sexual dysfunction than other antidepressants. The evidence is insufficient to draw conclusions about the comparative efficacy and effectiveness for the treatment of dysthymia and subsyndromal depression. **Conclusions:** Our findings indicate that the existing evidence does not warrant the choice of one second-generation antidepressant over another based on greater efficacy and effectiveness. Differences with respect to onset of action and adverse events may be taken into consideration for the choice of a medication.

Somatic Treatments for Mood Disorders

Rosa MA, Lisanby SH

Neuropsychopharmacology 2012; 37:102–116

Somatic treatments for mood disorders represent a class of interventions available either as a stand-alone option, or in combination with psychopharmacology and/or psychotherapy. Here, we review the currently available techniques, including those already in clinical use and those still under research. Techniques are grouped into the following categories: (1) seizure therapies, including electroconvulsive therapy and magnetic

seizure therapy, (2) noninvasive techniques, including repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and cranial electric stimulation, (3) surgical approaches, including vagus nerve stimulation, epidural electrical stimulation, and deep brain stimulation, and (4) technologies on the horizon. Additionally, we discuss novel approaches to the optimization of each treatment, and new techniques that are under active investigation.

Ketamine for Depression: Where Do We Go From Here?
Aan Het Rot M, Zarate CA Jr, Charney DS, Mathew SJ
Biol Psychiatry 2012; 72:537–547

Since publication of the first randomized controlled trial describing rapid antidepressant effects of ketamine, several reports have confirmed the potential utility of this dissociative anesthetic medication for treatment of major depressive episodes, including those associated with bipolar disorder and resistant to other medications and electroconvulsive therapy. These reports have generated several questions with respect to who might respond to ketamine, how, and for how long. To start answering these questions, we used PubMed.gov and ClinicalTrials.gov to perform a systematic review of all available published data on the antidepressant effects of ketamine and of all recently completed, ongoing, and planned studies. To date, 163 patients, primarily with treatment-resistant depression, have participated in case studies, open-label investigations, or controlled trials. All controlled trials have used a within-subject, crossover design with an inactive placebo as the control. Ketamine administration has usually involved an anaesthesiologist infusing a single, subanesthetic, intravenous dose, and required hospitalization for at least 24 hours postinfusion. Response rates in the open-label investigations and controlled trials have ranged from 25% to 85% at 24 hours postinfusion and from 14% to 70% at 72 hours postinfusion. Although adverse effects have generally been mild, some patients have experienced brief changes in blood pressure, heart rate, or respiratory rate. Risk-benefit analyses support further research of ketamine for individuals with severe mood disorders. However, given the paucity of randomized controlled trials, lack of an active placebo, limited data on long-term outcomes, and potential risks, ketamine administration is not recommended outside of the hospital setting.

Illness Risk Following Rapid Versus Gradual Discontinuation of Antidepressants
Baldessarini RJ, Tondo L, Ghiani C, Lepri B
Am J Psychiatry 2010; 167:934–941

Objective: Rapid discontinuation of some psychotropic medications is followed by discontinuation symptoms as well as an increased risk of early illness recurrence. Recurrence occurs earlier after rapid than after gradual discontinuation with lithium and antipsychotics. The authors compared illness recurrence after rapid versus gradual discontinuation of antidepressants. **Method:** The authors compared 398 patients with a DSM-IV diagnosis of recurrent major depressive disorder (N=224), panic disorder (N=75), bipolar II disorder (N=62), or bipolar I disorder (N=37). Two-thirds were women, the mean age was 42 years, and patients were treated with antidepressants for a mean of 8.5 months. Antidepressants were discontinued clinically, either rapidly (over 1–7 days; N=188) or gradually (over 14 days or more; N=210), with a mean follow-up duration of 2.8 years; patients who were ill at discontinuation were excluded from the analysis. The authors compared latency to first new illness episodes using survival analysis and Cox multivariate modeling. **Results:** The latency to first illness with rapid discontinuation was 0.4 times that with gradual discontinuation, and the latency after rapid discontinuation was one-fourth the estimated average previous interepisode interval in the same patients. The effect was similar across antidepressant classes and across years; the pace of discontinuation had less effect with drugs of prolonged half-life. The effect also varied by diagnosis (bipolar I ≥ panic > bipolar II ≥ major depressive disorder) but not by episodes per year, duration of index illness, use of concomitant treatment, or antidepressant dose or duration. **Conclusions:** The recurrence risk for depression or panic was much shorter after rapid than after gradual discontinuation of antidepressants. These findings have implications for both clinical management and the design and interpretation of clinical trials.

Atypical Antipsychotic Augmentation in Major Depressive Disorder: A Meta-Analysis of Placebo-Controlled Randomized Trials
Nelson JC, Papakostas GI
Am J Psychiatry 2009; 166:980–991

Objective: The authors sought to determine by meta-analysis the efficacy and tolerability of adjunctive atypical antipsychotic agents in major depressive disorder. **Method:** Searches were conducted of MEDLINE/PubMed (1966 to January 2009), the Cochrane database, abstracts of major psychiatric meetings since 2000, and online trial registries. Manufacturers of atypical antipsychotic agents without online registries were contacted. Trials selected were acute-phase, parallel-group, double-blind controlled trials with random assignment to adjunctive atypical antipsychotic or placebo. Patients had nonpsychotic unipolar major depressive disorder that was resistant to prior antidepressant treatment. Response, remission, and discontinuation rates were either reported or obtained. Data were extracted by one author and checked by the second. Data included study design, number of patients, patient characteristics, methods of establishing treatment resistance, drug doses, duration of the adjunctive trial, depression scale used, response and remission rates, and discontinuation rates for any reason or for adverse events. **Results:** Sixteen trials with 3,480 patients were pooled using a fixed-effects meta-analysis. Adjunctive atypical antipsychotics were significantly more effective than placebo (response: odds ratio=1.69, 95% CI=1.46–1.95, z=7.00, N=16, p<0.00001; remission: odds ratio=2.00, 95% CI=1.69–2.37, z=8.03, N=16, p<0.00001). Mean odds ratios did not differ among the atypical agents and were not affected by trial duration or method of establishing treatment resistance. Discontinuation rates for adverse events were higher for atypical agents than for placebo (odds ratio=3.91, 95% CI=2.68–5.72, z=7.05, N=15, p<0.00001). **Conclusions:** Atypical antipsychotics are effective augmentation agents in major depressive disorder but are associated with an increased risk of discontinuation due to adverse events.

Risk of Suicidality in Clinical Trials of Antidepressants in Adults: Analysis of Proprietary Data Submitted to US Food and Drug Administration
Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, Hammad TA, Temple R, Rochester G
BMJ 2009; 339:b2880

Objective: To examine the risk of suicidal behaviour within clinical trials of antidepressants in adults. **Design:** Meta-analysis of 372 double blind randomised placebo controlled trials. **Setting:** Drug development programmes for any indication in adults. **Participants:** 99 231 adults assigned to antidepressants or placebo. Median age was 42 and 63.1% were women. Indications for treatment were major depression (45.6%), other depression (4.6%), other psychiatric disorders (27.6%), and non-psychiatric disorders (22.2%). **Main Outcome Measures:** Suicidal behaviour (completed suicide, attempted suicide, or preparatory acts) and ideation. **Results:** For participants with non-psychiatric indications, suicidal behaviour and ideation were extremely rare. For those with psychiatric indications, risk was associated with age. For suicidal behaviour or ideation and for suicidal behaviour only, the respective odds ratios were 1.62 (95% confidence interval 0.97 to 2.71) and 2.30 (1.04 to 5.09) for participants aged <25, 0.79 (0.64 to 0.98) and 0.87 (0.58 to 1.29) for those aged 25-64, and 0.37 (0.18 to 0.76) and 0.06 (0.01 to 0.58) for those aged >or=65. When age was modelled as a continuous variable, the odds ratio for suicidal behaviour or ideation declined at a rate of 2.6% per year of age (−3.9% to −1.3%, P=0.0001) and the odds ratio for suicidal behaviour declined at a rate of 4.6% per year of age (−7.4% to −1.8%, P=0.001). **Conclusions:** Risk of suicidality associated with use of antidepressants is strongly age dependent. Compared with placebo, the increased risk for suicidality and suicidal behaviour among adults under 25 approaches that seen in children and adolescents. The net effect seems to be neutral on suicidal behaviour but possibly protective for suicidal ideation in adults aged 25-64 and to reduce the risk of both suicidality and suicidal behaviour in those aged >or=65.

Interpersonal Psychotherapy for Depression: A Meta-Analysis
Cuijpers P, Geraedts AS, van Oppen P, Andersson G, Markowitz JC, van Straten A.
Am J Psychiatry 2011; 168:581–592.

Objective: Interpersonal psychotherapy (IPT), a structured and time-limited therapy, has been studied in many controlled trials. Numerous practice guidelines have recommended IPT as a treatment of choice for

unipolar depressive disorders. The authors conducted a meta-analysis to integrate research on the effects of IPT. **Method:** The authors searched bibliographical databases for randomized controlled trials comparing IPT with no treatment, usual care, other psychological treatments, and pharmacotherapy as well as studies comparing combination treatment using pharmacotherapy and IPT. Maintenance studies were also included. **Results:** Thirty-eight studies including 4,356 patients met all inclusion criteria. The overall effect size (Cohen's d) of the 16 studies that compared IPT and a control group was 0.63 (95% confidence interval [CI]=0.36 to 0.90), corresponding to a number needed to treat of 2.91. Ten studies comparing IPT and other psychological treatments showed a nonsignificant differential effect size of 0.04 (95% CI=−0.14 to 0.21; number needed to treat=45.45) favoring IPT. Pharmacotherapy (after removal of one outlier) was more effective than IPT (d=−0.19, 95% CI=−0.38 to −0.01; number needed to treat=9.43), and combination treatment was not more effective than IPT alone, although the paucity of studies precluded drawing definite conclusions. Combination maintenance treatment with pharmacotherapy and IPT was more effective in preventing relapse than pharmacotherapy alone (odds ratio=0.37; 95% CI=0.19 to 0.73; number needed to treat=7.63). **Conclusions:** There is no doubt that IPT efficaciously treats depression, both as an independent treatment and in combination with pharmacotherapy. IPT deserves its place in treatment guidelines as one of the most empirically validated treatments for depression.

Psychotherapy for Chronic Major Depression and Dysthymia: A Meta-Analysis
Cuijpers P, van Straten A, Schuurmans J, van Oppen P, Hollon SD, Andersson G
Clin Psychol Rev 2010; 30:51–62

Although several studies have examined the effects of psychotherapy on chronic depression and dysthymia, no meta-analysis has been conducted to integrate results of these studies. We conducted a meta-analysis of 16 randomized trials examining the effects of psychotherapy on chronic depression and dysthymia. We found that psychotherapy had a small but significant effect (d=0.23) on depression when compared to control groups. Psychotherapy was significantly less effective than pharmacotherapy in direct comparisons (d=−0.31), especially SSRIs, but that this finding was wholly attributable to dysthymic patients (the studies examining dysthymia patients were the same studies that examined SSRIs). Combined treatment was more effective than pharmacotherapy alone (d=0.23) but even more so with respect to psychotherapy alone (d=0.45), although again this difference may have reflected the greater proportion of dysthymic samples in the latter. No significant differences were found in drop-out rates between psychotherapy and the other conditions. We found indications that at least 18 treatment sessions are needed to realize optimal effects of psychotherapy. We conclude that psychotherapy is effective in the treatment of chronic depression and dysthymia but probably not as effective as pharmacotherapy (particularly the SSRIs).

Comparative Effectiveness of Collaborative Chronic Care Models for Mental Health Conditions Across Primary, Specialty, and Behavioral Health Care Settings: Systematic Review and Meta-Analysis
Woltmann E, Grogan-Kaylor A, Perron B, Georges H, Kilbourne AM, Bauer MS
Am J Psychiatry 2012; 169:790–804

Objective: Collaborative chronic care models (CCMs) improve outcome in chronic medical illnesses and depression treated in primary care settings. The effect of such models across other treatment settings and mental health conditions has not been comprehensively assessed. The authors performed a systematic review and meta-analysis to assess the comparative effectiveness of CCMs for mental health conditions across disorders and treatment settings. **Method:** Randomized controlled trials comparing CCMs with other care conditions, published or in press by August 15, 2011, were identified in a literature search and through contact with investigators. CCMs were defined a priori as interventions with at least three of the six components of the Improving Chronic Illness Care initiative (patient self-management support, clinical information systems, delivery system redesign, decision support, organizational support, and community resource linkages). Articles were included if the CCM effect on mental health symptoms or mental quality of life was reported. Data extraction included analyses of these outcomes plus social role function, physical and overall quality of life, and costs. Meta-analyses included comparisons using unadjusted continuous measures.

Results: Seventy-eight articles yielded 161 analyses from 57 trials (depression, N=40; bipolar disorder, N=4; anxiety disorders, N=3; multiple/other disorders, N=10). The meta-analysis indicated significant effects across disorders and care settings for depression as well as for mental and physical quality of life and social role function (Cohen's d values, 0.20-0.33). Total health care costs did not differ between CCMs and comparison models. A systematic review largely confirmed and extended these findings across conditions and outcome domains. **Conclusions:** CCMs can improve mental and physical outcomes for individuals with mental disorders across a wide variety of care settings, and they provide a robust clinical and policy framework for care integration.

Implementation of Collaborative Depression Management at Community-Based Primary Care Clinics: An Evaluation

Bauer AM, Azzone V, Goldman HH, Alexander L, Unützer J, Coleman-Beattie B, Frank RG
Psychiatr Serv 2011; 62:1047–1053

Objective: This study evaluated a large demonstration project of collaborative care of depression at community health centers by examining the role of clinic site on two measures of quality care (early follow-up and appropriate pharmacotherapy) and on improvement of symptoms (score on Patient Health Questionnaire-9 reduced by 50% or ≤5). **Methods:** A quasi-experimental study examined data on the treatment of 2,821 patients aged 18 and older with depression symptoms between 2006 and 2009 at six community health organizations selected in a competitive process to implement a model of collaborative care. The model's key elements were use of a Web-based disease registry to track patients, care management to support primary care providers and offer proactive follow-up of patients, and organized psychiatric consultation. **Results:** Across all sites, a plurality of patients achieved meaningful improvement in depression, and in many sites, improvement occurred rapidly. After adjustment for patient characteristics, multivariate logistic regression models revealed significant differences across clinics in the probability of receiving early follow-up (range .34-.88) or appropriate pharmacotherapy (range .27-.69) and in experiencing improvement (.36 to .84). Similarly, after adjustment for patient characteristics, Cox proportional hazards models revealed that time elapsed between first evaluation and the occurrence of improvement differed significantly across clinics ($p<.001$). **Conclusions:** Despite receiving similar training and resources, organizations exhibited substantial variability in enacting change in clinical care systems, as evidenced by both quality indicators and outcomes. Sites that performed better on quality indicators had better outcomes, and the differences were not attributable to patients' characteristics.

NOTES