Memantine plus clozapine may be an effective pharmacologic strategy in the treatment of refractory schizophrenia.

**Background:** Glutamate deregulation may be involved in the neuropathology of schizophrenia, mainly through N-methyl-D-aspartate receptor (NMDAR) dysfunction. Memantine, which is approved for Alzheimer's disease, acts as a nonselective NMDAR antagonist. There have been some mixed results in some preliminary studies about adding memantine to antipsychotics in patients with schizophrenia in terms of improvement in symptoms.

**Objective:** To add memantine to clozapine to investigate whether it would be effective, primarily for the negative symptoms of schizophrenia.

**Design:** Double-blind, placebo-controlled, randomized trial.

**Participants/Methods:** The sample consisted of 21 adult outpatients in Brazil with a history of treatment-refractory schizophrenia being treated with clozapine for the past 10 years, with partial remission of negative symptoms. The subjects were randomized to a 12-week trial of memantine or placebo in addition to clozapine treatment as usual. Memantine was dosed twice daily with the following titration schedule: week 1, 5 mg/d; week 2, 10 mg/d; week 3, 15 mg/d; and weeks 4 to 12, 20 mg/d. Primary outcome measures were the positive and negative symptoms of schizophrenia as measured by the 18-item version of the Brief Psychiatric Rating Scale (BPRS). Secondary outcomes included the Clinical Global Impressions (CGI) scale, and the Mini-Mental State Examination (MMSE). The assessments were conducted at baseline and at weeks 4, 8 and 12.

**Results:** The memantine-treated group reported significant decreases in BPRS total scores, the positive symptoms subscale score, and the negative symptom subscale score compared to the placebo group. The memantine group also reported significantly greater improvement in overall functioning on the CGI. At week 12, patients who received memantine (compared with those who received placebo) showed a significantly greater improvement in their cognitive symptoms scored by the MMSE.

**Conclusions:** Memantine appears to improve positive and negative symptoms, overall level of functioning, and possibly even cognition in clozapine-treated patients with schizophrenia.

**Reviewer's Comments:** Memantine is a fast off-rate (low affinity) type of uncompetitive NMDAR antagonist that blocks only pathological receptor activity and could, theoretically, restore abnormal neurons to a homeostatic state. Clozapine, remarkably, increases the expression of NMDARs. Clozapine also appears to stabilize dopaminergic neurons, dampening both hyperactivity and hypoactivity via an agonist and antagonistic action, respectively, at the NMDA/glycine site. Therefore, it may be that clozapine and memantine, through their NMDA and dopamine modulating properties, may be a match made in psychopharmacological heaven for optimal treatment of refractory schizophrenia. (Reviewer—John G. Koutras, MD).

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Keywords: Clozapine Augmentation, N-Methyl-D-Aspartate Receptor

Print Tag: Refer to original journal article
Children and adolescents who are experiencing their first use of second-generation agents incur significant weight gain as well as metabolic changes, but that seem to vary widely by medication.

**Objectives:** The research reported here was designed to prospectively follow children who had minimal prior exposure, but were just started on olanzapine, quetiapine, risperidone, and aripiprazole in order to assess these drugs’ impact on weight gain and metabolic parameters. Prior studies have been limited by including patients who may have had extensive prior histories of antipsychotic exposure.

**Participants/Methods:** The data here were part of the work of a study with far too long of a name (the Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth [SATIETY] study). Eligible subjects were aged 4 to 19 years, with a ≤1 week history of antipsychotic use, who were started on 1 of the 4 followed medications by their treating clinician. All participants had initial study physical and laboratory parameters obtained within 7 days of onset of use. Initial, tracked, and outcome indicators included waist circumference, weight, body mass index (BMI), fasting LDL, HDL, glucose, and insulin measures. These were assessed at baseline and at weeks 4, 8, and 12.

**Results:** 338 subjects enrolled; 47 received aripiprazole, 52 olanzapine, 45 quetiapine, 165 risperidone. Twenty patients dropped antipsychotic use, but were followed as a comparison group. After an average of 10.8 weeks of treatment, weight increased by 8.5 kg with olanzapine, by 6.1 kg with quetiapine, by 5.3 kg with risperidone, by 4.4 kg with aripiprazole, and by 0.2 kg in the comparison group. There were statistically significant increases for olanzapine and quetiapine for total cholesterol, triglycerides, non-HDL cholesterol, and triglyceride-to-HDL ratios. For risperidone, only triglyceride levels increased. No metabolic end point changes were significant for aripiprazole. Patients on olanzapine had the highest incidence of metabolic syndrome. For all agents except risperidone, body measure parameters were not related to dose, whereas for risperidone, doses >1.5 mg/day were associated with raised weight, BMI, and waist circumference. Metabolic effects related to each agent were related to dose for olanzapine (≥10 mg) and risperidone (≥1.5 mg/d), but not for the other 2 drugs.

**Conclusions:** First-use of second-generation agents in children and adolescents is associated with substantial weight gain and metabolic change, although these effects vary substantially by medication, with the greatest weight and metabolic impact associated with olanzapine and the least impact with aripiprazole.

**Reviewer’s Comments:** This study not only reinforces extending concerns about the effects of second-generation agents found in adults to children, but also reinforces particularly acute concerns with olanzapine. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Second Generation Antipsychotics, Adolescents

Print Tag: Refer to original journal article
Combining the nicotine patch with as needed nicotine lozenges, or possibly nicotine gum, appears to be the most efficacious in preventing smoking relapse, and, fortunately, this combination is available without prescription.

**Background:** The 2008 Update to the Public Health Service (PHS) Treating Tobacco Use and Dependence Clinical Practice Guidelines reported that 5 nicotine replacement therapies (NRTs) and 2 non-nicotine replacement first-line pharmacotherapies (sustained release bupropion [buproprion SR] and varenicline) reliably increase abstinence rates when compared to a placebo control. Research has also supported the efficacy of NRT combinations.

**Objective:** To compare the relative efficacies of the following 5 pharmacotherapies (buproprion SR, nicotine lozenge, nicotine patch, combined nicotine patch and lozenge, and combined buproprion and nicotine lozenge) for nicotine dependence.

**Methods:** Participants were 1504 smokers who agreed to participate in a 3-year smoking cessation (year 1) and health outcomes (years 2 and 3) study conducted in Wisconsin. Inclusion criteria included smoking >9 cigarettes per day on average for at least the past 6 months. Exclusionary criteria were a history of bipolar or psychotic disorders. Patients were randomized to 1 of the following 6 possible treatment conditions: buproprion SR 150 mg twice daily started at 1 week prequit and continued for 8 weeks postquit; nicotine lozenge 2 to 4 mg for 12 weeks postquit; nicotine patch, titrating down for 12 weeks postquit; combination therapy of nicotine patch and lozenge; or combination therapy of buproprion SR and nicotine lozenge. Each treatment arm was matched with placebo tablets, patches, and lozenges. In addition to pharmacotherapy, all subjects received individual 10- to 20-minute counseling sessions on smoking cessation strategies.

**Results:** All active treatments produced higher rates of initial cessation and higher point-prevalence abstinence rates at week 1, end of treatment, and 6 months postquit. Only the 2 combination treatments significantly increased the number of days to lapse (meaning a single episode of smoking) relative to placebo. However, after 6 months postquit, only the patch plus lozenge combination remained efficacious in preventing relapse.

**Conclusions:** Combination therapy, involving either buproprion SR plus lozenge or nicotine patch plus lozenge, increases days to lapse, with the possible long-term advantage of decreasing risk of relapse going to the nicotine replacement combination.

**Reviewer’s Comments:** The only smoking cessation pharmacotherapy that is not included in this study is varenicline as it was not FDA approved at the time of the study initiation. However, a review of the literature produces some evidence, although not controlled study data, for the safety of combining NRT and varenicline. (Reviewer-John G. Koutras, MD).
Primary outcomes may be changed in published trials in order to fit the data, without notification to the reader.

**Background:** Clinical studies often measure treatment effectiveness by a range of outcomes. Areas of expected or presumably more clinically relevant impact are often designated as primary outcomes and, even if other, secondary outcomes, may show significant change, the impact on the designated primary outcome shapes conclusions. Changing the outcomes of interest might be legitimate, but not simply to fit data. The possibility of doing so has been a concern in some research that might do so to retrospectively pick more favorable outcomes.

**Objective:** Keeping all of this in mind, the authors examined clinical trials of gabapentin for off-label use for migraine prophylaxis, bipolar disorders, neuropathic pain, or nociceptive pain to see if results there were "massaged" through changing or selectively reporting outcomes in this way.

**Methods:** The authors did an exhaustive review of published studies on gabapentin for off-label indications, as well as finding internal company research reports. They then looked for changes in primary and secondary outcomes from protocol to published report. They then examined the statistical significance of the initially selected primary outcome measure against the revised primary outcome and then matched this against publication status.

**Results:** A total of 21 trials of gabapentin were identified, 3 of which were for bipolar disorder. Twelve of the trials were published, and within the 12 studies, there were 21 primary outcomes identified. Of those 21 primary outcomes, only 11 were reported without change. Six were not included in the published report, and 4 were reported as secondary outcomes. A total of 12 primary outcomes were actually newly introduced, and 5 outcomes that were initially designated as secondary outcomes were not distinguished from primary outcomes in the published report. There were 180 secondary outcomes in the protocols of the 12 published trials, and 122 of these outcomes were never reported in the papers. The statistical analysis revealed that only 1 of 9 trials published in full had the initial primary outcome, the outcomes identified only in the company internal reports, reach statistical significance.

**Conclusions:** Pharmaceutical industry sponsored studies of gabapentin often had the primary outcome changed, seemingly in order to achieve statistical significance, or were not published in full.

**Reviewer’s Comments:** It appears that once the data are known, the addition or subtraction of primary outcomes can lead to the presentation of chance findings as evidence of a drug’s effectiveness. This strategy is not confined to pharmaceutical industry sponsored trials, but has also been observed with more publicly funded trials. A Canadian study found that 40% of primary outcomes differed from the protocol and published report in the government sponsored trials. (Reviewer-John G. Koutras, MD).
Another Treatment Option for Patients With Borderline Personality Disorder

A Randomized Trial of Dialectical Behavior Therapy Versus General Psychiatric Management for Borderline Personality Disorder.

McMain SF, Links PS, et al:

Am J Psychiatry 2009; 166 (December): 1365-1374

Weekly psychodynamic psychotherapy plus medication management is just as beneficial as dialectical behavior therapy for the treatment of borderline personality disorder.

**Background:** Borderline personality disorder (BPD) affects 1% to 2% of the population, with high morbidity and mortality leading to enormous health care utilization and eventual suicide in 10% of patients. Four out of 5 randomized controlled trials have found Dialectical Behavior Therapy (DBT) more effective than other forms of treatment in reducing suicidal behavior associated with BPD.

**Objective:** To examine how DBT would compare with psychiatric management outlined in the APA Practice Guideline (2001) for BPD. The authors hypothesized that DBT would lead to greater reduction in self-harm behavior in patients with BPD than would general psychiatric management.

**Participants/Methods:** 180 patients with BPD and recent self-harm behavior were randomized to either DBT or general psychiatric management for 1 year. Patients with bipolar disorder, psychosis, or mental retardation were excluded. Participants in both groups received 1 hour of individual therapy per week. Those in the DBT group also received 2 hours of group therapy and up to 2 hours of phone coaching per week. The primary outcomes were severity and frequency of self-harm behavior. Secondary measures included ratings of depression and BPD symptoms, interpersonal functioning, health care utilization, and quality of life.

**Results:** Participants in both groups improved significantly in both primary and secondary outcome measures, but there were no group differences in any measure of treatment response. The only significant group difference was that participants in the general psychiatric management group utilized non-study treatments more than those in the DBT group. Self-reported depression decreased modestly in both groups by approximately 33%.

**Conclusions:** Although the authors were surprised by the study results, it is reassuring that guidelines issued by the American Psychiatric Association in 2001 are as effective as DBT at reducing suicidal behavior, self-rated depression, and interpersonal functioning in patients with BPD.

**Reviewer's Comments:** This study was not controlled, and, therefore, it is not known how much patients would have improved over time with usual care. Another question not addressed is the relative cost between the 2 treatments. There were many more provider hours involved in DBT, but this was heavily weighted toward master's level therapists and psychologists, whereas psychiatrists provided the majority of care in the general psychiatric management group. It will be important in the future to replicate this study with a control group and cost analysis. (Reviewer-Charlotte O. Ladd, MD).

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Keywords: Borderline Personality Disorder, Dialectical Behavior Therapy, Guidelines

Print Tag: Refer to original journal article
CBT for Late-Life Depression--Good, But Not Sufficient

Clinical Effectiveness of Individual Cognitive Behavioral Therapy for Depressed Older People in Primary Care: A Randomized Controlled Trial.

Serfaty MA, Haworth D, et al:

Arch Gen Psychiatry 2009; 66 (December): 1332-1340

Cognitive behavior therapy is more than just a relational opportunity for depressed elderly, but it does not lead to remission in 4 months' time.

Background: Late-life depression is common and often associated with bereavement, social isolation, and medical illness. Although psychotherapy is well suited to address these issues, only 5% of depressed elderly receive such treatment. Meta-analyses support the use of cognitive behavioral therapy (CBT) as a treatment for late-life depression. However, no studies have controlled for the simple relational element of treatment, which may be especially relevant in this population.

Objective: To determine if CBT is superior to treatment as usual (TAU) and to a "talking-support" control in the treatment of late-life depression in a primary care setting.

Participants/Methods: 204 subjects (80% women) ≥65 years of age (mean, 74 years) were randomized to TAU alone, TAU with up to 12 50-minute talking control (TC) sessions, or TAU with up to 12 50-minute CBT sessions. The primary outcome measure was the change in the Beck Depression Inventory (BDI)-II scores from baseline to the end of treatment (4 months), as well as 6 months after treatment. The change in BDI-II scores was adjusted for baseline BDI-II scores and time. Therapists in the TC group showed interest and warmth, but did not offer advice or challenge cognitive distortions.

Results: 80% of participants completed the study, attending an average of 7 therapy sessions in the CBT and TC arms. Adjusted BDI-II scores dropped by 3.07 points in the CBT versus TAU group and 3.65 in the CBT versus TC group. However, only one-third of the participants improved by ≥50% after 4 months of CBT. CBT did not change patients' level of anxiety, as measured by the Beck Anxiety Inventory (BAI).

Conclusions: In this English community population, 4 months of CBT was more effective than either TC sessions or TAU in reducing self-rated depression scores in the elderly. Therefore, CBT is not likely to benefit depressed elders simply by increasing their human contact. However, we do not yet know how best to deliver CBT in this age group. Most participants only attended 7 out of 12 possible sessions, and they certainly did not get "well" with treatment.

Reviewer's Comments: It is unfortunate that no observer rating scales were used to evaluate depression severity, as patients often over- or under-report their own improvement. Furthermore, patients may have been biased by which treatment they received versus the treatment they wanted. Since the majority of participants remained clinically depressed at treatment's end, future studies need to examine longer courses of CBT using both patient and observer rating scales. Given participants' reluctance to fully comply with treatment, however, therapeutic sessions may need to be further modified to accommodate for this population. As the number of elderly adults rises rapidly, it behooves us to identify treatments for late-life depression that are clinically effective and accessible. (Reviewer-Charlotte O. Ladd, MD).

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Keywords: Cognitive Behavioral Therapy, Late-Life Depression

Print Tag: Refer to original journal article
Self-help book guide use to treat social anxiety appears to have sustained improvement effects comparable to a similar method, but boosted with therapist support.

**Background/Objective:** The authors of this study separately completed work that showed the efficacy of an internet-based cognitive-behavioral therapy (CBT) intervention for social anxiety disorder with therapist feedback when compared to traditionally delivered CBT. They decided to explore whether a book form of this intervention (bibliotherapy) was just as effective, and that the degree to which, perhaps, that the therapists’ availability element, however at a distance, was important.

**Methods:** Subjects were recruited through different media announcements and links with anxiety disorder related advocacy or provider groups. Potential subjects completed a standardized anxiety screen online, the Social Phobia Scale (SPS) and the self-rated Montgomery Asberg Depression Rating Scale (MADRS). Subjects needed to meet the criteria for social anxiety disorder, have a score <31 on the MADRS, and not be in other psychological therapy. Also, any psychopharmacology had to be at a stable dose for the prior 3 months. Subjects were randomized to 2 trials, one which involved further randomization to internet-based CBT (ICBT), bibliotherapy, or a waiting list control condition, while the other involved ICBT, bibliotherapy alone, bibliotherapy with internet-based discussion group or with internet-delivered applied relaxation therapy (IAR). These together generated 5 treatment arms. The manual (bibliotherapy) was organized around modules that explained the cognitive model for social anxiety and introduced cognitive restructuring, guided exposure exercises and attention training, as well as social skills and relapse strategies. The discussion group was part of ICBT and the bibliotherapy (“plus”) group and involved an online forum with other subjects. Internet "therapy" involved email-based support from therapists to review use of, questions about, and feedback for, homework assessment and CBT program steps. This therapy support was available to those in the IAR and ICBT arms. Outcomes assessments were administered over the internet at baseline, immediately upon completion of treatment, and 1 year later.

**Results:** ICBT and bibliotherapy only groups showed significant, and comparable, improvement on all social anxiety and mood measures compared to controls after treatment. ICBT had the greatest effect sizes, but comparable effects were found by those with bibliotherapy users augmented by group discussion. One year later, bibliotherapy users maintained their gains, while ICBT users showed evidence of further improvement with a significant difference in its favor on some scores, such as the Social Phobia Scale.

**Conclusions:** Manual-driven self care alone appears effective for social anxiety, although longer-term improvement may be seen from such methods augmented by limited, structured feedback from a therapist.

**Reviewer’s Comments:** This study furthers the idea of primarily self-driven treatment, and while it seems to still support the value of an expert clinician in the loop, it supports the practice of using even more accessible modes of help, perhaps as a first line of treatment. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Internet CBT, Manual CBT, Bibliotherapy, Social Anxiety

Print Tag: Refer to original journal article
Reduced life stressors may accelerate memory decline in older patients with mild cognitive impairment, but not in control subjects without baseline memory problems.

**Background:** There is increasing evidence that in young adults, chronic stress leads to an allostatic burden of cortisol, which is thought to adversely affect memory via glucocorticoid receptors in the hippocampus and other limbic areas by initiating a cascade of neurotoxic events.

**Objective:** To examine whether chronic stress accelerates cognitive decline in older adults with and without mild cognitive impairment (MCI) and to correlate this finding with baseline diurnal cortisol concentrations.

**Participants/Methods:** Participants were 65 to 97 years old (mean age, 78 years) and lived independently. A total of 102 participants were enrolled in the study (61 cognitively normal patients and 41 patients with MCI), but only 52 patients (25 in the control group and 27 in the MCI group) were followed longitudinally for 1 to 3 years. Stress levels were assessed by the Life Events and Difficulties Schedule administered at baseline and every 6 months. Five salivary cortisol samples were obtained every 6 months between awakening and bedtime. The Mattis Dementia Rating Scale and several memory tests evaluating recall, verbal learning, and logical memory were administered every 6 months for up to 3 years.

**Results:** Cognitively normal patients did not show appreciable changes in dementia rating scores or cognitive function over the 1- to 3-year period regardless of life stress or cortisol concentrations. Patients with MCI demonstrated a significant decline in dementia rating scores and memory assessments, which were exacerbated by chronic stress and somewhat ameliorated by higher cortisol levels. Male gender was often associated with a slower rate of cognitive decline.

**Conclusions:** Chronic stress only accelerated cognitive decline in patients with a baseline diagnosis of MCI. High cortisol was protective in this group, had no effect in the control group, and was not statistically correlated with life stress.

**Reviewer's Comments:** In this study, chronic stress accelerated memory decline in the context of MCI. There are several unknown variables in this study, including the lack of information regarding antidepressant treatment, psychotherapy, and depression scores, all of which can confound both memory function and diurnal cortisol. Although patients were excluded if they met criteria for moderate or severe major depression at baseline, we are not given information regarding psychiatric condition afterward. Furthermore, the authors had no data on whether the participants were exposed to early life trauma, another confounder of adult stress reactivity. (Reviewer-Charlotte O. Ladd, MD).

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Keywords: Mild Cognitive Impairment, Chronic Stress, Cortisol

Print Tag: Refer to original journal article
Young adults diagnosed with MDD commonly exhibit subthreshold bipolar symptoms that are associated with alcohol use disorders, a family history of bipolarity, and increased risk of conversion to bipolar disorder I or II over time.

**Background:** The National Comorbidity Survey Replication found that when bipolar disorder (BPD) criteria were relaxed to include subthreshold manic symptoms, the prevalence of a bipolar spectrum illness doubled from 2.1% to 4.4%.

**Objective:** To determine if major depressive disorder (MDD) might be over diagnosed at the expense of bipolar spectrum illness due to rigidity in the current DSM-IV BPD criteria. The authors investigated how many individuals diagnosed with MDD would be reclassified as having a subthreshold BPD with relaxed criteria for hypomania.

**Participants/Methods:** Data were collected through the prospective, longitudinal Early Developmental Stages of Psychopathology (EDSP) study. Subjects, 14 to 24 years of age, were followed longitudinally for 8 to 9 years with at least 3 diagnostic interviews. Subthreshold BPD was defined as 1 of the following: (1) elevated mood for ≥4 days noticeable by others, but without a sufficient number of accompanying symptoms or (2) irritable mood expressed as increased arguments with verbal or physical aggression and 3 accompanying symptoms of hypomania, but NOT noticeable by others.

**Results:** 2210 subjects completed the final assessment; 488 (23.2%) were diagnosed with MDD via DSM-IV criteria. After using the study's mood disorder spectrum criteria, 286 (58.6%) of these were classified as "pure" MDD, and 202 (41.4%) were classified as having subthreshold BPD. Three percent met criteria for BPAD I and 1.4% for BPAD II. Participants with subthreshold BPD were more likely than those with pure MDD to have comorbid panic disorder, alcohol use disorder, and a family history of bipolarity. Subjects with subthreshold BPD converted to BPD I or II more often than those with MDD over time; predictors of conversion included early onset of depression, symptoms observable by others, and mood lability.

**Conclusions:** Early onset of observed depression, alcohol misuse, panic disorder, and a family history of manic/hypomanic symptoms might be red flags for the presence of subthreshold bipolarity in patients currently diagnosed with MDD according to DSM-IV.

**Reviewer's Comments:** The prevalence of MDD was high in this study and associated with low socioeconomic status, limiting generalizability of the results. Advantages of this study include its longitudinal format over a critical window of vulnerability for mood disorders. It will be important to follow these subjects into middle age, monitoring severity of mood symptoms, substance use, suicidality, and personality disorder diagnoses. (Reviewer-Charlotte O. Ladd, MD).

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Keywords: Depression, Bipolar Disorder

Print Tag: Refer to original journal article
Older paternal age appears to be associated with offspring who are more assertive/willful, impulsive and hostile, whereas advanced maternal age may decrease the risk for these behaviors.

**Background:** There is mounting evidence that advanced paternal age (APA) has been linked to schizophrenia, to autism spectrum disorders, and even bipolar disorder. There are many more germline cell divisions during the development of a sperm compared to an oocyte. Each time the cell divides, the replication of the genome introduces the possibility of copy error mutations. There is a somewhat larger body of evidence that has mostly reported an association between advanced maternal age (AMA) and superior behavioral/cognitive measures in children.

**Objective:** To explore the association between paternal and maternal ages and behavioral measures in children using a large prospective birth cohort.

**Participants/Methods:** The Collaborative Perinatal Project (CPP) recruited pregnant women from 12 university-affiliated hospital clinics in the U.S. from 1959 to 1965. The final sample size for this study was 21,753 offspring from this project. The mean maternal age was 24.8 years, and the paternal mean age was 28.4 years. The offspring of the women were followed up at regular intervals until the children reached age 7 years. At age 7 years, psychologists administered a battery of cognitive and motor tests to the children. Based upon this interaction and a period of free play, psychologists provided structured ratings of the child's behavior. The study design then separated the ratings into 2 factors: "internalizing behavior," which includes shy/withdrawn behaviors and "externalizing behavior," which includes assertive/willful and/or hostile behaviors. Then, there were 2 models created for the statistical analyses. The first model took into account the other parent's age. The second model adjusted for race, socioeconomic status, and parental mental health.

**Results:** For every 5-year increase in paternal age, there was an increased odd of externalizing behavior by 12% in offspring. Internalizing behaviors did not show any statistically significant associations with APA. In contrast, for every 5 years of increase in maternal age, their offspring were at a 12% decreased risk of higher scores on the "externalizing" measure and a 6% increased risk of higher scores on the "internalizing" scores.

**Conclusions:** The offspring of older fathers show adverse behavioral outcomes during early childhood, whereas those of older mothers have more mixed outcomes.

**Reviewer's Comments:** This most surprising thing of all is that these findings occur from a sample where the mean age of parenthood may have been "older" for the early 1960s, the period of time for this dataset, but would not be considered particularly older parentage today. It would be very interesting to look at offspring of parents who are around 40 years old. (Reviewer-John G. Koutras, MD).

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Keywords: Externalizing Behaviors, Internalizing Behaviors, Advanced Parental Age

Print Tag: Refer to original journal article
Parent Training and Risperidone Work Better Together for Autism

Medication and Parent Training in Children With Pervasive Developmental Disorders and Serious Behavioral Problems: Results From a Randomized Clinical Trial.

Aman MG, McDougal CJ, et al:


Combined treatment of risperidone and parent training is superior to risperidone alone in the treatment of severe behavioral disturbances in children with PDDs.

Background: Pharmacotherapy is common among individuals with pervasive developmental disorders (PDDs), with community-based surveys suggesting a prevalence rate of approximately 45% and up to 83% for the past year. Risperidone was approved in 2006 by the Food and Drug Administration for children with autism accompanied with irritability. The authors of this study developed a parent training (PT) curriculum that teaches behavioral principles and management techniques to parents of children with PDD.

Objective: To test whether risperidone plus PT would be superior to risperidone alone in children with PDD and serious behavior problems.

Participants/Methods: Subjects were aged 4 to 13 years and had a diagnosis of either PDD not otherwise specified (PDD NOS), Asperger's disorder, or autism as confirmed by the Autism Diagnostic Interview-Revised (ADI-R). Exclusionary criteria included patients with a diagnosis of bipolar disorder. A total of 124 participants were randomized into this 24-week, multisite, parallel-group trial. The trial used blinded evaluation with a planned 2:1 randomization to combined risperidone and parent training (COMB) and risperidone only (MED), respectively. During the first 8 weeks, the risperidone could be titrated upwards weekly. The risperidone dosing range was up to 1.75 mg for children weighing up to 20 kg and up to 3.5 mg/day for children weighing over 35 kg. The majority of weekly PT sessions concluded at 16 weeks. The primary outcome measure was the Home Situations Questionnaire (HSQ), and the secondary outcome measures included the Aberrant Behavior Checklist (ABC).

Results: The HSQ score decreased 71% for COMB compared with 60% for MED, with an effect size in the small range of 0.34. The ABC Irritability, Stereotypic Behavior and Hyperactivity Noncompliance subscales showed significantly greater improvement over time in the COMB group, with an effect size in the medium range of 0.48. By week 24, the mean dosage of risperidone was higher in the MED group than in the COMB group.

Conclusions: Combined treatment composed of parent training and risperidone or aripiprazole showed added benefit in reducing serious behavioral problems in children with PDD, utilizing lower doses of medication than when medication was used alone.

Reviewer's Comments: The behavioral intervention takes longer to have more significant additive effects to medication, which is a finding that appears to be almost universal in studies with similar designs for psychiatric disorders. Also, patient/family satisfaction is usually higher in the combined group. (Reviewer-John G. Koutras, MD).

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Keywords: Risperidone, Behavioral Management, Autism Spectrum Disorders

Print Tag: Refer to original journal article
Further follow-up of outcomes from Mexico’s highly visible cash transfer program, Oportunidades, indicates extended benefits to children over time, as well as the value of longer enrollment in the program.

**Background/Objective:** Poverty is a consistent risk factor for poor developmental and health outcomes in children the world over. Conditional cash transfer (CCT) programs have been developed in several countries under the assumption that a certain threshold of additional income support will substantially incentivize participation in specified health, health education, and preventive services that are a condition for receipt of the money. One of the first countries to develop a CCT program was Mexico. Only the evaluation of Mexico's program, Oportunidades, has included measures of behavior.

**Methods:** Oportunidades targeted poor, rural families in randomly chosen communities. Cash transfers of 20% to 30% of household income were provided on condition of child attendance at school and child and family member attendance at specified preventive medical care and health education visits. The forms of the CCTs were as food stipends and education scholarships. Assessment and follow-up measures included: height, weight, Wechsler abbreviated intelligence scale, and an adapted parental interview-based assessment of behavior through a rated strengths and difficulties questionnaire. These outcomes were compared with similarly matched nonparticipating control families over a 10-year period and measured against participation itself (case vs control), amount of payment, characteristics of families participating, and length of enrollment.

**Results:** 1064 children in the "early" group and 687 in the "late" group (enrolled 18 months later) were followed. Program participants continued to outperform nonparticipants. Within the program, an additional 18 months enrollment had no effect relative to later enrollment 10 years after the program started, overall, in terms of body mass index, height, or cognitive or language assessment scores. However, reported behavioral problems were significantly less in the earlier group with longer program exposure, and height for age was significantly better for those as well in the early group when comparing children of mothers with no formal education. Also, the amount of cash provided was itself significantly related to higher verbal and cognitive scores and fewer behavioral problems.

**Conclusions:** An extended observation of a widely followed CCT program supplementing income in exchange for health care and education participation among high-risk families and their children showed persistence of outcomes over a decade. It also showed the value of an additional period (18 months) of enrollment, and additional specific benefits on behavior and growth outcomes for children of poorly educated mothers, and on cognition and behavior outcomes with larger absolute cash transfers.

**Reviewer’s Comments:** Studies like this would also be helpful to include other quantitative or more qualitative data as to the impact on family and child attitudes towards self-care and self-improvement to identify the ways such an approach does, or does not, foster ongoing practices that will sustain these gains. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Conditional Cash Transfer, Child Development

Print Tag: Refer to original journal article
Converting From Autism to PDD-NOS

Inter-Rater Reliability and Stability of Diagnoses of Autism Spectrum Disorder in Children Identified Through Screening at a Very Young Age.
van Daalen E, Kemner C, et al:
Eur Child Adolesc Psychiatry 2009; 18 (November): 663-674

Early intervention can help some children "convert" from autism to PDD-NOS.

**Background:** It appears from the current evidence that the diagnosis of autistic disorder made at 2 years is stable in clinically referred samples measured ≥3 years later. Diagnostic stability, however, is less strong for pervasive developmental disorder, not otherwise specified (PDD-NOS). Although differences between children with an early diagnosis of autism spectrum disorders (ASD) who retain the diagnosis and those who lose the diagnosis do exist, the 2 groups are very difficult to differentiate at the time of the initial diagnosis.

**Objective:** To evaluate the inter-rater reliability and stability of ASD diagnoses in children identified through a screening procedure applied at 14 months of age.

**Participants/Methods:** 31,724 Dutch children were screened by physicians using the 4-item early screening of autistic traits (ESAT) scale at their routine 14-month well-child visit. Children who screened positive were referred for a psychiatric evaluation, which consisted of the following measures: the Autism Diagnostic Observation Schedule-Generic (ADOS-G), the Wing autistic disorder interview checklist, the Vineland social emotional childhood scales, and cognitive testing utilizing the Mullen scales of early learning (MSEL). Eighty children were diagnosed with an ASD, and 53 participated in the study. All ASD children were referred to a facility for toddlers with special needs for day care 4 days a week and also received speech and language therapy. The subjects were then re-tested with the above measures at time 2, which was, on average, at 43 months old.

**Results:** 46 children diagnosed with an ASD at time 1 had a stable diagnosis at time 2. The remaining children, those with an "unstable" ASD, showed a significantly higher cognitive score and higher scores on the expressive language subscales than those with a stable ASD diagnosis. The gender of the children in the stable and unstable group was compared, and there was no significant difference.

**Conclusions:** Approximately one-third of children initially diagnosed as having autism at approximately 24 months of age "converted" to a diagnosis of PDD-NOS at approximately 43 months of age.

**Reviewer's Comments:** This article reinforces what has become increasingly observed clinically: interventions are more likely to decrease the intensity of PDD symptoms, so that some children are less clinically autistic at later ages. Not surprisingly, the children with normal cognitive scores and better expressive language abilities at younger ages are more likely to "convert" from autism to PDD-NOS. (Reviewer-John G. Koutras, MD).

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Keywords: Autism Diagnostic Stability, Early Intervention

Print Tag: Refer to original journal article
Genes and Postpartum Mood Disorder--Is There a Connection?

*Genome-Wide Linkage and Follow-Up Association Study of Postpartum Mood Symptoms.*

Mahon PB, Payne JL, et al:

Am J Psychiatry 2009; 166 (November): 1229-1237

The first study to examine the genetic etiology of postpartum mood symptoms identified potential associations between symptom onset and variation in chromosomes 1q21.3-q32.1, and 9p24.3-p22.3.

**Background:** Postpartum mood symptoms are common and debilitating. The gene search has been on for some time with respect to mood disorders in general, but might there be a specific genetic vulnerability to postpartum mood symptoms and disorder? Especially as rates of postpartum mood episodes are heightened among women with pre-existing depression or bipolar illness, is the enhanced susceptibility to mood change postpartum (a postpartum trigger) mediated by identifiable genes and gene products?

**Objective:** This study is described by the authors as the first genome-wide linkage study of mood symptoms postpartum.

**Methods:** Data were collected from participants in 2 studies, the National Institute of Mental Health (NIMH) Genetics Initiative Bipolar Disorder project and the Genetic of Recurrent Early-Onset Major Depression study. Both studies allowed identification of female subjects with a history of pregnancy, of any mood disorder, and with information from the parent study as to the course of those conditions as well as the postpartum period. Blood samples obtained from subjects allowed for comparative genetic analysis and gene frequencies.

**Results:** 23% of the women had postpartum mood symptoms (manic or depressive). The maximum linkage association for postpartum symptoms was found on chromosome 1q21.3-q32.1. A linkage association was also suggestive for 9p24.3-p22.3.

**Conclusions:** Two potential chromosome regions appear related to susceptibility for onset of mood symptoms postpartum among women with a history of any mood disorder.

**Reviewer’s Comments:** This is a very early step in identifying any unique genetics to explain the vulnerability women have to postpartum mood conditions. The authors also point out that the strongest implicated specific gene in these regions includes those for estrogen binding sites, which plausibly relates these findings to the outcomes of interest, and to potential understanding of ways to predict or prevent these conditions, though likely not anytime soon. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Genome-Wide Linkage, Postpartum Mood Disorder

Print Tag: Refer to original journal article
Primary outcomes may be changed in published trials in order to fit the data, without notification to the reader.

**Background:** Clinical studies often measure treatment effectiveness by a range of outcomes. Areas of expected or presumably more clinically relevant impact are often designated as primary outcomes and, even if other, secondary outcomes, may show significant change, the impact on the designated primary outcome shapes conclusions. Changing the outcomes of interest might be legitimate, but not simply to fit data. The possibility of doing so has been a concern in some research that might do so to retrospectively pick more favorable outcomes.

**Objective:** Keeping all of this in mind, the authors examined clinical trials of gabapentin for off-label use for migraine prophylaxis, bipolar disorders, neuropathic pain, or nociceptive pain to see if results there were "massaged" through changing or selectively reporting outcomes in this way.

**Methods:** The authors did an exhaustive review of published studies on gabapentin for off-label indications, as well as finding internal company research reports. They then looked for changes in primary and secondary outcomes from protocol to published report. They then examined the statistical significance of the initially selected primary outcome measure against the revised primary outcome and then matched this against publication status.

**Results:** A total of 21 trials of gabapentin were identified, 3 of which were for bipolar disorder. Twelve of the trials were published, and within the 12 studies, there were 21 primary outcomes identified. Of those 21 primary outcomes, only 11 were reported without change. Six were not included in the published report, and 4 were reported as secondary outcomes. A total of 12 primary outcomes were actually newly introduced, and 5 outcomes that were initially designated as secondary outcomes were not distinguished from primary outcomes in the published report. There were 180 secondary outcomes in the protocols of the 12 published trials, and 122 of these outcomes were never reported in the papers. The statistical analysis revealed that only 1 of 9 trials published in full had the initial primary outcome, the outcomes identified only in the company internal reports, reach statistical significance.

**Conclusions:** Pharmaceutical industry sponsored studies of gabapentin often had the primary outcome changed, seemingly in order to achieve statistical significance, or were not published in full.

**Reviewer's Comments:** It appears that once the data are known, the addition or subtraction of primary outcomes can lead to the presentation of chance findings as evidence of a drug's effectiveness. This strategy is not confined to pharmaceutical industry sponsored trials, but has also been observed with more publicly funded trials. A Canadian study found that 40% of primary outcomes differed from the protocol and published report in the government sponsored trials. (Reviewer-John G. Koutras, MD).

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Keywords: Research Practices, Off-Label Indications, Publication Bias

Print Tag: Refer to original journal article
Background: Alcohol use disorders present some of the greatest public health burdens. These disorders fuel health conditions and contribute to violence and accidental deaths. Drinkers who misuse alcohol are a highly resistant group to accept and participate in treatment. As is the case with experimentation in more accessible manual or web-based treatment methods for other common disorders (such as depression), there has been increasing work in the past decade. To date, this work has focused primarily on college students on the development of brief, easily accessible ways to help problem drinkers who are unwilling or unable to seek traditional treatment services.

Design: This was a randomized, controlled evaluation of the Internet-based Check Your Drinking (CYD) screener. The CYD screener is a self-administered intervention that profiles a respondent’s drinking and compares it graphically to that of the general population as a way to make problem drinkers aware of the severity and distinctiveness of their use.

Participants: 185 subjects were recruited through a general telephone population sociological survey that included drinking patterns.

Methods: At-risk individuals were followed-up for interest in participating in a study using Internet-based modalities. Eligible subjects needed to meet an AUDIT-C screen severity cutoff and were assigned randomly to receive access to the CYD or to a no-intervention control group with follow-up at 3 and 6 months. Problem drinkers who were provided access to the CYD displayed a 6- to 7-drink reduction in their weekly alcohol consumption (30% reduction in typical weekly drinking) at both the 3- and 6-month follow-up compared to a 1 drink per week reduction among control group respondents. Approximately one-third of invited subjects did not access the program. Drinking for lower-risk drinkers was not affected.

Conclusions: The CYD screener appears to provide a potentially sustainable effect on drinking patterns of those with problem drinking. However, the dynamics of long-term compliance, effect, and self-selection use with respect to targeting beneficiaries remains unclear.

Reviewer’s Comments: The Internet could increase the range of help-seeking options available for drinkers. As reflected in entries just this past year in Practical Reviews, the study and the range of manual and Internet-based self-guided interventions are rapidly expanding but with an unclear impact on integrated treatment with clinical practice. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Alcohol, Internet Treatment

Print Tag: Refer to original journal article
Aripiprazole Decreases Severe Irritability in Autistic Patients

Aripiprazole in the Treatment of Irritability in Children and Adolescents With Autistic Disorder.

Owen R, Sikich L, et al:

Pediatrics 2009; 124 (December): 533-1540

Aripiprazole is a safe, rapidly acting, alternative to risperidone in treating severe irritability in patients with autism.

Background: Approximately 20% of individuals with pervasive developmental disorder experience moderate to severe irritability. Only risperidone has been approved by the Food and Drug Administration (FDA) for the symptomatic treatment of irritability in children and adolescents with autistic disorder.

Objective: To examine the safety and efficacy of flexibly dosed aripiprazole in reducing symptoms of irritability in children and adolescents with autistic disorder.

Design: An 8-week, double-blind, randomized, placebo-controlled study conducted at 20 centers in the United States.

Participants/Methods: 98 subjects who met DSM-IV criteria for autism were randomly assigned (1:1) to either aripiprazole or placebo. Aripiprazole was initiated at 2 mg/day, with a target dosage of 5, 10, or 15 mg/day based on tolerability and perceived treatment response. The primary outcome measure was the Aberrant Behavior Checklist (ABC) irritability subscale score. The main secondary outcome measure was the Clinical Global Impression-Improvement (CGI-I) score. Subjects were also monitored for extra-pyramidal effects using standardized measures.

Results: The mean decrease from baseline in the caregiver-rated ABC irritability subscale score was significantly greater for patients who received aripiprazole than placebo, with an effect size of -0.87. On the CGI-I, 67% were rated very much improved on aripiprazole versus 16% in placebo at week 8. Differences became apparent by week 2, as defined by a ≥25% reduction in the ABC irritability subscale score. No significant differences were found between placebo and aripiprazole on extrapyramidal symptom measures. Aripiprazole was associated with a significant decrease in serum prolactin levels compared with placebo at the end point. Aripiprazole was also associated with a greater incidence of weight gain, 2 kg versus 0.8 kg on placebo.

Conclusions: Aripiprazole appears to be rapidly effective at decreasing severe irritability in patients with autism, at least for the 8-week duration of this study. However, it also appears to be associated with more rapid weight gain than placebo.

Reviewer's Comments: Aripiprazole recently received FDA approval based on this trial and a companion study that appeared in the November issue of the Journal of the American Academy of Child and Adolescent Psychiatry (JAACAP). Both studies were sponsored by the manufacturer and used similar designs, except that the one by Marcus and colleagues appearing in the JAACAP used randomization to 5, 10, and 15 mg fixed dosages and found no clear added benefit to doses >5 mg. A useful follow-up study would involve comparison of longer-term efficacy with an active comparator arm of risperidone, as well as relative propensity for weight gain. (Reviewer- John G. Koutras, MD).

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Keywords: Autism, Irritability, Second-Generation Antipsychotics

Print Tag: Refer to original journal article
Most antiepileptic drugs are associated with a decrease in suicide attempts in patients with bipolar disorder.

Background: In 2008, the Food and Drug Administration (FDA) issued a warning to health care providers. The warning said that antiepileptic drugs (AEDs) were significantly associated with suicidality based on a meta-analysis of 199 placebo-controlled trials demonstrating twice the risk of suicidal ideation and behavior in patients treated with 1 of 11 AEDs versus placebo. These studies involved the use of AEDs for any condition, including epilepsy, bipolar disorder, migraine prevention, and pain syndromes. Bipolar disorder is associated with a high rate of suicide. It is important to understand the relative risk of suicidality with and without mood stabilizer treatment in this population.

Objective: To determine if AEDs pose a risk of increased suicidal behavior in patients with bipolar disorder.

Participants/Methods: Medical claims data were collected from the PharMetrics Patient Centric Database from 2000 to 2006. A total of 47,918 patients with a diagnosis of bipolar disorder I, II, or not otherwise specified were included. ICD-9 codes of self-harming behavior were used to identify individuals with suicidality. Patients were divided into 1 of 3 groups based on prescribed mood stabilizer: AED without lithium, lithium monotherapy, or neither AED nor lithium.

Results: Group analysis revealed no increase in suicidal behavior in bipolar patients taking AEDs compared to patients taking neither AEDs nor lithium. AEDs were not associated with a mean increase in suicide attempts, but patients treated with topiramate or carbamazepine had a higher suicide attempt rate than did untreated patients. Of note, patients prescribed mood stabilizers appeared to be more ill at baseline. Patients who received AEDs or lithium had much higher pre-treatment rates of attempted suicide (72 per 1000 and 99 per 1000, respectively) than did patients who were never prescribed mood stabilizers (15 per 1000).

Conclusions: Lithium and most AEDs given to patients with bipolar disorder decreased suicidal behavior, with the exception of topiramate and carbamazepine. Topiramate should be avoided in patients with bipolar disorder, with evidence of increased suicidality from both this study and the FDA meta-analysis. Future studies on carbamazepine are needed.

Reviewer’s Comments: This study differs from the FDA meta-analysis in that it assessed only suicidal behavior, not suicidal ideation or completed suicide. Limitations of the study include its retrospective design with no information on illness severity, treatment adherence, or comorbid disorders such as epilepsy or pain for which the AED may have been prescribed. (Reviewer-Charlotte O. Ladd, MD).

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Keywords: Antiepileptic Drugs, Bipolar Disorder, Suicide Attempts

Print Tag: Refer to original journal article
Measures of stress sensitivity predict later depression. The connection is moderated both by genetic liability and environmental conditions.

**Background/Objective:** One model for understanding how genetic vulnerability to depression might work is through the phenomenon of stress sensitivity. This testable and measurable response to minor stresses can be assessed as a predictor of later depression. Interestingly, not only do we question how predictive such a phenomenon is, but we would also like to know what moderates that risk. These questions were put to a test using a twin cohort involved in a longitudinal set of studies in Belgium.

**Methods:** 218 twin pairs comprised the East Flanders Prospective Twin Survey, which has recorded multiple births since 1964. Over the years, baseline and follow-up assessments have included the following: the Structured Clinical Interview for DSM-IV Axis I disorders to determine current and lifetime diagnoses; a scaled and standardized interview of stressful life events, the Childhood Trauma Questionnaire; and a method for identifying stress sensitivity that uses self-rating of time-dependent responses to an unpredictable audio stimulus emitted from a wristband device at varying time intervals during a 5-day period. Genotyping was also completed for the genes encoding the serotonin transporter (5-HTTLPR) and brain-derived neurotrophic factor (BDNF), both of which are implicated in depression risk.

**Results:** Data were obtained on 502 twins. Stress sensitivity at baseline was, as expected, significantly associated with increased depressive symptoms at follow-up and the risk of a diagnosis of major depressive disorder. This was true for those with and without a history of depression at baseline, although a positive history strengthened the association. Sixteen percent of those with high, 10% of those with moderate, and only 6% of those with low stress sensitivity developed depression. The interaction was significantly greater between co-twin depression and stress sensitivity among monozygotic twins, sharing 100% genome, than with dizygotic pairs, sharing 50%; this indicates genetic modulation of this effect and the so-called Met allele of the tested BDNF polymorphism. Variation in the 5-HTTLPR gene was associated with increased stress sensitivity-depression symptom risk. Negative life events were negatively related to the sensitivity-depression relationship; that is, the higher the levels of stress sensitivity, the lower the effect of life events were as a predictive factor on later depression.

**Conclusions:** Stress sensitivity appears to be a pre-onset attribute of depression, especially when genetic liability is high as reflected in certain genotypes, and when sensitivity is at such a level that competing potentially moderating environmental influences are, therefore, low.

**Reviewer’s Comments:** The study suffers from its retrospective design and key variables (especially life events), upon which much of the analysis and ideas about the threshold that gene-driven stress dynamics might overwhelm any contribution of environmental effects. This "horse-out-of-the-barn" idea with respect to the balance of genetic-stress response and environmental factors, however, may be biased by life event recall. Therefore, this study was limited in how well it could explore the genesis of this dynamic (ie, the role of negative events early on in the evolving stress-sensitivity-genetic relationship). (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Stress Sensitivity, Depression, Twin Study

Print Tag: Refer to original journal article
Novel Pharmacologic Approaches to Refractory OCD


Koran LM, Aboujaoude E, Gamel NN:

J Clin Psychiatry 2009; 70 (November): 1530-1535

D-amphetamine may be an effective SSRI/SNRI augmenting agent for OCD, although this trial is inconclusive.

Background: 2 small, double-blind, placebo-controlled studies found that a single dose of dextroamphetamine (d-amphetamine) 30 mg was clearly superior to placebo in immediately relieving symptoms of obsessive-compulsive disorder (OCD). There have also been 4 case reports of Adderall augmentation of selective serotonin reuptake inhibitors (SSRIs).

Design/Objective: This 5-week, double-blind, caffeine-controlled study tests the hypothesis that d-amphetamine, added after an adequate selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) trial, is more effective than caffeine in reducing OCD symptoms in patients whose symptoms have been refractory.

Participants/Methods: 24 subjects were included. The 11 women and 13 men all met DSM-IV criteria for OCD and had a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of ≥20 after 12 weeks of treatment with an established effective dose of an SSRI (citalopram, escitalopram, or fluoxetine, ≥20 mg/day; paroxetine ≥40 mg/day; or sertraline ≥50 mg/day) or with a clinically reasonable dose of an SNRI (venlafaxine 225 to 300 mg/day or duloxetine 60 to 120 mg/day). None of the subjects had a diagnosis or a clinical picture of attention deficit-hyperactivity disorder. Subjects were randomly assigned to receive either d-amphetamine 30 mg or caffeine 300 mg. Caffeine was chosen as a "placebo" since it can also induce elevated moods and energy levels, as well as side effects such as nervousness and jitteriness. In the first week using the study medication, subjects were evaluated and had to experience a mean Y-BOCS score decrease of ≥20% to be continued into the study's 4-week double-blind extension phase. Six of 12 subjects in the d-amphetamine group and 7 of 12 subjects in the caffeine group were continued in the trial. At the week 5 rating, the mean Y-BOCS score decreases were 48% for the d-amphetamine group and 55% for the caffeine group. Four subjects (33%) in the d-amphetamine group and 6 subjects (50%) in the caffeine group met the criterion for a full response.

Conclusions: Augmentation of SSRI/SNRI with d-amphetamine was not more effective than caffeine augmentation in reducing subjects' OCD symptoms. However, both compounds act through dopamine mechanisms, and both resulted in significant improvement in OCD symptoms in a treatment-refractory population.

Reviewer's Comments: The authors were extremely careful in trying to eliminate factors that would lead to a type 1 error: using caffeine as a placebo (to minimize the risk of the subjects' realizing they were not on d-amphetamine), and utilizing the Montgomery-Asberg Depression Rating Scale to be sure that underlying depression improvement did not match improvement for OCD symptoms. However, the choice of caffeine, the small sample size, and other methodological issues led to an inconclusive trial. The possibility of d-amphetamine, or Adderall, as an augmentation agent remains intriguing. (Reviewer-John G. Koutras, MD).

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Keywords: Dextroamphetamine, SSRI/SNRI, OCD

Print Tag: Refer to original journal article
AAS dependence is an emerging problem and poses some unique challenges conceptually, with no clear direction for more targeted treatment.

**Background:** Anabolic-androgenic steroids (AAS) are a family of hormones that include testosterone and numerous synthetic testosterone derivatives. AAS users can greatly increase their muscle mass, often well beyond the limits attained by natural means. In Western societies, including the United States, the lifetime prevalence has been estimated at 3%. AAS users generally self-administer their drugs for blocks of time, which are known as "cycles." Cycles typically last 8 to 16 weeks, separated by drug-free intervals lasting months or years. Many individuals use only a few cycles of AAS, with a cumulative lifetime exposure of <12 months. If a man uses AAS in cycles, rather than continuously, the hypothalamic-pituitary axis can rebound during the drug-free intervals, restoring normal endogenous testosterone production. However, some individuals progress to nearly unbroken AAS use, which may progress to adverse medical, psychological, and social effects.

**Objective:** To explore this syndrome of AAS dependence.

**Methods:** A thorough review of the available literature was performed, in part utilizing the PubMed database.

**Results:** Approximately 30% of illicit AAS users develop dependence. Despite AAS use often beginning in the high school years, AAS dependence appears to occur primarily in the late-20s age period. Furthermore, adverse psychiatric and medical effects would probably not surface until the 30s. Since AAS use began increasing in popularity in the 1980s, and it is estimated that >1 million American boys initiated AAS use as teenagers in the last 20 years, the full impact of AAS dependence may just be emerging. Dependent AAS users have a much higher lifetime prevalence of non-alcohol substance dependence than non-dependent AAS users, with most of the differences accounted for by opioid abuse and dependence. It appears that opioid use in dependent AAS users begins both before and after the onset of AAS use. In animal studies, hamsters will self-administer testosterone sometimes to the point of death. Animal studies also suggest that AAS can modify opioid systems.

**Conclusions:** Like nicotine, AAS use does not cause an acutely intoxicating effect and causes minimal performance impairment. However, AAS use clearly can result in dependence, which may be related to the risk of opioid abuse.

**Reviewer's Comments:** Although there are minimal effects on performance (cognitive, etc.), the irritability, aggression, and mood swings associated with AAS use may impair social relationships. Among AAS users, those who progressed to AAS dependence did not show a greater level of body image disturbance. One possible hypothesis as to why some individuals progress to AAS dependence is that these subjects are more biologically vulnerable to the dysphoric effects of AAS withdrawal. (Reviewer-John G. Koutras, MD).

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Keywords: Anabolic Steroids, Animal Models, Dependence

Print Tag: Refer to original journal article
Primary care providers might identify depression more through symptoms than through diagnostic criteria or categories with unclear implications for real-world treatment choices.

**Background/Objective:** Depression is common, costly, and apparently increasing. Much of this illness and the treatment for it originate from primary care settings. This study is part of a line of work examining how primary care physicians recognize and define depression. One comparison of primary care diagnoses of depression with standard diagnostic instruments showed low sensitivity (36.4%) but higher specificity (83.7%). Perhaps those physicians do not identify patients as having depression if they have milder symptoms. Better understanding of how practitioners define and sort patients into illness categories is important to understand in order to design better strategies to treat patients in these settings.

**Methods:** The authors took advantage of the British National Health Service (NHS) database, in which general practitioners enter standardized information on the content and findings of office visits, including coded lists of diagnoses and symptoms. Sociodemographic information was also captured. The authors scanned patterns of diagnostic codes for depression and depressed mood symptoms from 1996 to 2006 in 298 U.K. general practices.

**Results:** Data were obtained on 2,982,024 patients aged ≥16 years. There were 255,667 incident cases of depression diagnoses, and 156,907 incident cases of identified depression symptoms. The incidence of diagnoses decreased from 22.5 per 1000 person-years at risk (PYAR) to 14.0 per 1000 PYAR. Symptom incidence tripled over the same period, from 5.11 to 15.5 per 1000 PYAR. The combined incidence of identified diagnoses and problem symptoms, however, remained relatively stable over the 10-year period. Diagnoses and symptoms were identified twice as often in women than in men, and twice as often among those in the most economically deprived category than in those in the least deprived category.

**Conclusions:** British general practitioners appear to have been identifying depression as a problem with overall consistency, but with a marked shift in the designation of the problem as one of a disorder as opposed to specific symptoms.

**Reviewer's Comments:** The authors offer various interpretations for this inversion of how to label the problem of depression. These range from the possibility of a move to describe more mild illness as no illness at all, to a change in the sensitivity of reporting a mental illness in a national database. Whatever the reason, the phenomenon points to the complexity of how primary physicians approach this disorder in order to enhance the likelihood of diagnosis and treatment. I was surprised these authors did not include information that was also in the NHS database on whether prescribing or treatment practices changed and differed by describing the conditions as symptoms versus disease. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Depression Primary Care, Diagnosis, Symptoms

Print Tag: Refer to original journal article