Long-term intermittent treatment with *Ginkgo biloba* did not prevent cognitive decline in a randomized controlled trial of older adults.

**Background:** *Ginkgo biloba* has long been touted by many as an herb that can decrease or delay cognitive decline in older adults. However, the Ginkgo Evaluation of Memory (GEM) study demonstrated no difference from placebo in the rates of dementia with long-term *G. biloba* treatment. The authors were curious about the potential effects of *G. biloba* on more subtle cognitive decline. They wondered if it might decrease memory decline associated with mild cognitive impairment (MCI) and with natural aging.

**Objective:** To determine whether *G. biloba* (240 mg/day) changes the rate of decline in cognitive function in older adults, and to identify modifiers of this effect, including age, race, gender, education, and *APO*E4 allele status.

**Participants/Methods:** 3072 adults aged 72 to 96 years (mean, 79.1 years) were randomized to receive either placebo or 120 mg *G. biloba* twice a day for several years’ duration. Most participants demonstrated normal cognitive function at study entry. Individuals with MCI were included, but those with dementia were not. Cognitive function was assessed with an annual comprehensive neuropsychological test battery designed to assess multiple domains of cognition, including verbal learning, recall, visuospatial ability, attention, psychomotor speed, and executive functioning. Adherence to treatment was only 60%, assessed by patient and proxy interviews.

**Results:** At baseline, those assigned to the placebo group outperformed those assigned to the *G. biloba* group by 3 out of 10 cognitive measures, although this difference was not likely to be clinically significant. The authors measured the rate of change of cognitive performance to prevent skewing of the results. There were no group differences in the rate of change in performance on any of the cognitive domains.

**Conclusions:** Based on these and previous results from the GEM study, *G. biloba* does not appear to have any effect on memory decline in older adults.

**Reviewer’s Comments:** Given the large number of adults taking *G. biloba*, one wonders about its placebo effect and how robust it might be for cognitive performance. It would have been nice if the authors had included a no-treatment group to investigate the placebo effect in this context. *G. biloba* joins many other agents initially touted as "cognitive enhancers" now proven ineffective in slowing memory decline, including vitamin E and estrogen replacement therapy. (Reviewer-Charlotte O. Ladd, MD, PhD).

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Keywords: Cognitive Function, *Ginkgo biloba*

Print Tag: Refer to original journal article
The idea of a medical food containing nutrients that will facilitate the formation of dendritic spines and synapses in Alzheimer’s disease is appealing, but it is still unclear if this intervention will demonstrate sufficient efficacy.

**Background:** The cognitive disturbances of Alzheimer’s disease (AD) best correlate with loss of hippocampal and cortical synapses. Therefore, a possible therapeutic strategy might involve steps to restore such synapses. Preclinical studies indicate that such an effect can be induced by the co-administration of rate-limiting precursors for membrane phosphatide synthesis, such as the nucleotide uridine, omega-3 polyunsaturated fatty acids, and choline. Making these nutrients more available may also increase synapse formation by increasing dendritic spines in the hippocampus. Facilitating these processes should enhance cognitive function. Souvenaid is a multi-nutrient drink designed to improve synapse formation, and is manufactured by the sponsors of this study, the Danone research center.

**Design/Objective:** The primary goal of this double-blind, randomized, controlled, multi-center trial was to determine the effect of a medical food, such as Souvenaid, on cognitive function compared with a control product in patients with mild AD after a 12-week supplementation.

**Methods:** The trial consisted of a 12-week core study followed by a 12-week similarly designed exploratory and optional extension study. The control multi-nutrient drink did not contain the active ingredients. Co-primary outcome measures were week-12 change from baseline on the delayed verbal recall test of the Wechsler Memory Scale–revised (WMS-r) and the 13-item Modified Alzheimer’s Disease Assessment Scale–cognitive subscale (ADAS-cog).

**Results:** 212 subjects were randomized to either a control or the active product. At 12 weeks, 40% of patients in the active group showed an improvement in WMS-r delayed recall, with 24% in the control group. However, the mean change in the WMS-r was comparable between the active and control groups. The modified ADAS-cog, however, did not change in either group. No significant differences in either of the primary measures were observed at the end of the optional 24-week extension period.

**Conclusions:** There is no clear benefit for this medical food intervention at this time in the treatment of mild AD.

**Reviewer’s Comments:** This study presents a significant potential bias due to its funding source, a large food manufacturer in France. The investigators honestly stated the various post-hoc analyses were conducted in an attempt to demonstrate efficacy. However, they came up with response rates of only 18.2% in the active group versus 7.2% in controls—a barely significant differential response with no clear clinical meaning. Anyone who has witnessed an individual with AD desperately hopes that this line of research will show clear promise in the future. (Reviewer-John G. Koutras, MD).

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Keywords: Nutritional Supplement, Alzheimer's Disease, Synapse Formation

Print Tag: Refer to original journal article
Administering the Mini-Mental State Examination, the clock-drawing test, and the cube-copying task with simple cut-offs helps differentiate dementia with Lewy bodies from Alzheimer’s dementia.

**Background:** Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia, accounting for 10% to 20% of all cases. However, it is frequently mistaken for Alzheimer’s disease (AD) due to their similar clinical features. Identification of DLB is of great importance. Up to 50% of patients have sensitivity to both first- and second-generation antipsychotics, resulting in severe extrapyramidal side effects. These patients also have higher rates of neuroleptic malignant syndrome. DLB seems to exhibit greater attention and visual-perception impairment and less pronounced memory deterioration than AD.

**Objective:** To find easy and practical ways to interpret 3 practical tests in order to identify DLB and differentiate it from AD. The 3 tests used were the Mini-Mental State Examination (MMSE), the clock-drawing test (CDT), and the cube-copying task.

**Participants/Methods:** 33 patients with dementia with Lewy bodies were selected and then matched with mildly or moderately severely impaired patients with Alzheimer’s disease in a 2:1 ratio. Therefore, there were 66 patients with AD. The DLB patients received extensive cranial imaging (including functional imaging) to help rule out other potential causes of dementia. The 1-year rule between the onset of dementia and parkinsonism was applied to differentiate DLB from Parkinson’s disease with dementia. The MMSE was administered and scored for each patient. The CDT was scored according to Shulman’s 5-point scale, in which a score of 5 is given for a perfect clock. The cube-copying task was scored on the basis of whether the drawings demonstrated any 3-dimensionality (3-D).

**Results:** On the MMSE, orientation scores were higher compared to individual total scores, for patients with DB. Otherwise, the only other significant difference on the MMSE was slightly lower attention scores for the DLB group. On the 3-D cube-copying test, only 1 of 60 AD patients failed to produce a 3-D copy, whereas approximately 30% of the DLB group failed. The DLB patients also produced lower scores on the CDT.

**Conclusions:** In at least 2 of 3 identified cut-offs (CDT <5, non-3D cube copying, and orientation/total MMSE score ≥1/3), the sensitivity of identifying DLB patients was 85% and the specificity was 75%.

**Reviewer’s Comments:** This article provides extremely useful clinical information for psychiatrists who treat geriatric patients. These simple-to-administer, familiar, bedside-administered tests can help identify a group of patients with dementia who may respond tragically differently to commonly used medications such as antipsychotics. (Reviewer-John G. Koutras, MD).

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Keywords: Alzheimer’s Disease, Dementia, Lewy Bodies, MMSE

Print Tag: Refer to original journal article
**Does Personality Change Go With Improved Mood on SSRIs?**

*Personality Change During Depression Treatment: A Placebo-Controlled Trial.*

Tang TZ, DeRubeis RJ, et al:

Arch Gen Psychiatry 2009; 66 (December): 1322-1330

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SSRIs appear to change personality measures that have been associated with depression, possibly treating depression by altering personality.

**Background:** Extraversion involves social extraversion, dominance, and a tendency to experience positive emotions. Neuroticism encompasses a tendency to experience negative emotions and emotional instability. Neuroticism appears to predict both the onset and chronicity of major depressive disorder (MDD). Patients have reported that selective serotonin reuptake inhibitors (SSRIs) make them less sensitive to rejection and more outgoing. These changes are consistent with increases in extraversion and decreases in neuroticism. The "state effect hypothesis" debate has been whether these changes in personality measures are due to an improvement in depression (ie, depression causes a state effect that is reversed by SSRIs). However, what if personality dimensions are also modulated by serotonin mechanisms? Molecular, genetic, and PET studies have, in fact, associated neuroticism with serotonin receptor polymorphisms and binding.

**Objective/Design:** To examine self-reported personality changes in a randomized, placebo-controlled, clinical trial of MDD treated with paroxetine.

**Methods:** 240 patients with major depression were included as subjects. All patients met criteria and scored ≥20 on the Hamilton Depression Rating Scale for Depression (HAM-D). The subjects were randomized such that 60 patients received placebo for 8 weeks, 120 patients received paroxetine for 16 weeks, and 60 patients received cognitive therapy for 16 weeks. Depression was measured by the 17-item version of the HAM-D. Personality variables were assessed with the NEO Five-Factor Inventory. After 8 weeks, those in the placebo group were assessed and were offered the opportunity to be switched to paroxetine.

**Results:** Paroxetine and cognitive therapy each outperformed placebo in changing depression, neuroticism, and extraversion. Contrary to the state effect hypothesis (ie, depression changes personality measures), placebo patients reported little changes in neuroticism or extraversion despite considerable depression improvement. Paroxetine patient-reported changes in neuroticism and extraversion were 4 to 8 times as large as the changes reported by placebo patients. In the placebo group that opted to switch to paroxetine, neuroticism and extraversion changed less during the placebo phase than during the subsequent SSRI phase.

**Conclusions:** Paroxetine appears to have a specific, true drug effect on neuroticism and extraversion scores, in addition to antidepressant efficacy in patients with major depressive disorder.

**Reviewer's Comments:** Surprisingly, this study found that personality change can explain the advantage of paroxetine over placebo in antidepressant efficacy, rather than vice versa. This article truly represents a paradigm shift in the way clinicians understand the efficacy of SSRIs for depression—that SSRIs independently change aspects of personality that contribute to their antidepressant efficacy. (Reviewer John G. Koutras, MD).

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Keywords: SSRIs, Introversion/Neuroticism

Print Tag: Refer to original journal article
Training primary care physicians to do a CBT-based intervention as a strategy for addressing possible psychologically driven unexplained medical symptoms is not effective compared to care as usual.

**Background:** Family practitioners commonly see presentations with somatic complaints that are not medically explained. One estimate found that 1 in 6 primary care visits involved medically unexplained symptoms that carried with them significant limitations in daily living. At the same time, some trials have shown that a cognitive-behavioral therapy (CBT)-based intervention can be successful in these cases.

**Objective:** To examine the impact of a family practitioner-delivered CBT intervention.

**Methods:** Participants were recruited from 16 family physician practices. All subjects had unexplained medical symptoms and fulfilled criteria for a DSM-IV Somatoform Disorder. Potentially eligible patients were screened over the phone and needed to score ≥5 on the Physical Symptom Checklist (PSC) or a total score of ≥15 on the Hospital Anxiety and Depression Scale (HADS); patients also and had DSM-IV confirmed somatoform disorder. Study subjects were followed up both by physicians who participated in training to provide the intervention and those who did not. Control subject received "care as usual" from their family physician. The intervention consisted of 5 CBT sessions provided by the family physician, including scheduling activities, relaxation therapy, and challenging of dysfunctional cognitions. Physicians also underwent three 2-hour sessions of supervision by experienced CBT therapists. At baseline and at 6 and 12 months of follow-up, patients were assessed on the PSC and HADS, as well as for impairment on the Medical Outcomes Study Short Form-36; for health anxiety on the Illness Attitude Scale; and a self-rating of symptom severity on a visual analog scale (VAS). Comparable health care utilization was also measured through records of office visits and psychotropic medication use.

**Results:** 31 subjects were in the intervention group, and 34 were in the control group. Both groups showed similar 6- and 12-month improvements on the VAS. Differences in other measures or in care utilization were also not significantly different. The only significant difference of interest was that, across groups, VAS improvement was associated with psychotropic medication use. Intervention effectiveness was limited by the fact that 55% of that group did not complete the 5 sessions.

**Conclusions:** A CBT intervention delivered by family physicians was not more successful than treatment as usual in reducing the presence, severity, or impact of unexplained medical symptoms among patients with a diagnosed somatoform disorder.

**Reviewer's Comments:** As models to deliver care for depression and other disorders in primary care settings get increasing attention, what does the failure of this effort indicate? Several issues could be a factor: the severity or nature of these conditions; the intensity or the consistency with which these methods are applied by primary care physicians; and the small number of interventions performed per physician. Of interest, the use of psychotropic medications did have an impact, all things being equal. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: CBT, Primary Care, Unexplained Medical Symptoms, Somatoform Disorders

Print Tag: Refer to original journal article
Antidepressant and antipsychotic polypharmacy increased from 1996 to 2006, but the use of sedative hypnotics and mood stabilizers did not.

**Background:** There has been growing concern about increasing rates of polypharmacy, or the use of ≥2 psychotropic medications, in psychiatric patients.

**Objective:** To evaluate the percentage and types of polypharmacy in office-based outpatient practices in the United States between 1996 and 2006 using data from the National Ambulatory Medical Care Survey (NAMCS).

**Methods:** The NAMCS is a multistage probability survey of physician-reported information on outpatient care, including prescribed medications, diagnoses, source of payment, and sociodemographic information. Randomly selected psychiatrists provided information on a sample of patients in a 1-week period between 1996 and 2006. Only adult visits were included, yielding 13,079 outpatient visits. Data were analyzed using bivariate and multivariate logistic models to examine time trends in the number of psychotropic medications prescribed over the study period.

**Results:** Between 1996 and 2006, the median number of psychotropic medications prescribed by psychiatrists increased from 1 to 2; the mean number increased from 1.42 to 1.99. The percentage of patients receiving ≥3 psychotropics increased from 16.9% to 33.2% during this same period. Patients most likely to receive ≥2 psychotropics were middle aged; were diagnosed with major depression, bipolar disorder, or schizophrenia; had comorbid diagnoses; and carried public insurance. Men, self-paying patients, and new patients were less likely to receive ≥2 medications. Combinations of antidepressants with other classes were relatively common: 23.1% with sedative hypnotics, 12.9% with antipsychotics, and 12.6% with other antidepressants. Over time, antidepressants were prescribed more often with an antipsychotic or another antidepressant but not with a sedative hypnotic. The percentage of mood stabilizer use did not change over the study period. Polypharmacy type was predicted by diagnosis, risk, and morbidity. The use of ≥2 antipsychotics decreased in depressed patients over time, as did the use of ≥2 sedative hypnotics in the elderly and in patients with schizophrenia. Predictors of antidepressant and antipsychotic polypharmacy were: female gender; a diagnosis of depression, bipolar disorder, or schizophrenia; psychiatric comorbidity; and public insurance.

**Conclusions:** The increased use of antidepressants, antipsychotics, and the combination thereof accounted for much of the increase in polypharmacy over the 10-year period.

**Reviewer's Comments:** The authors express concern over increased polypharmacy, citing drug-drug interactions, increased side effects, and lack of evidence supporting this practice. In fact, some polypharmacy is supported by evidence, especially for the treatment of major depression. There is little evidence in this study to suggest that psychiatrists are prescribing unreasonably; taking an alarmist view from these results is, therefore, not justified. Rather, it should give us pause to re-examine our prescribing practices and encourage further outcome studies. (Reviewer-Charlotte O. Ladd, MD, PhD).

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Keywords: Mood Stabilizers, Antipsychotics

Print Tag: Refer to original journal article
Treatment Gaps for Depression

Depression Care in the United States: Too Little for Too Few.
González HM, Vega WA, et al:
Arch Gen Psychiatry 2010; 67 (January): 37-46

Treatment gaps for depression remain substantial nationwide but are particularly acute for Mexican and African Americans.

Background: It is estimated that most Americans who have major depression are either untreated or undertreated. However, estimates of a treatment gap for this disorder need to be further refined and understood.

Objective: To examine the use of care comparing ethnic subgroups, taking into account characteristics known to be associated with access to health care, the adequacy of care received, and the severity of illness.

Methods: Trained interviewers used the structured, validated, Composite International Diagnostic Interview format to identify individuals with major depression in the past year. Severity of illness was identified by use of the Quick Inventory of Depressive Symptomatology Self-Report. Information about actual care received was gathered in the interviews. The care received was matched against minimum care expected based on the American Psychiatric Association’s Practice Guideline for the Treatment of Patients with Major Depressive Disorder. Variables known to be related to access to care (eg, income, education, and/or health insurance status) were also evaluated.

Results: The total sample was 15,762 subjects. Severity of major depression did not significantly vary by ethnic group. Overall, about 1 in 3 individuals who scored as having had an episode of major depression in the previous year reported antidepressant use. Puerto-Rican and non-Latino whites were more likely; Mexican Americans, Caribbean blacks, and African Americans were least likely. Among those who received pharmacotherapy, only one-third had adequate treatment. Concordant use with guidelines was highest among Puerto-Rican and non-Latino whites; it was lowest among Mexican Americans, Caribbean blacks, and African Americans. The likelihood of psychotherapy use mirrored that by the ethnic differences of likelihood of medication use. However, proportions of guideline-concordant psychotherapy use were higher across groups compared with psychopharmacology. Overall, 1 in 5 individuals with major depression in the past year received guideline-concordant therapy of some type, with greater likelihood among Puerto Rican and non-Latino whites. Having health insurance was associated with an increased likelihood across groups of receiving depression care, but not of receiving guideline-concordant care. However, for Caribbean black and African Americans, neither health insurance nor any other enabling factor explained their lower pharmacotherapy use.

Conclusions: Americans do not tend to get treatment, and are even less likely to get guideline-concordant treatment, for major depression. The differences are most pronounced among Mexican Americans and African Americans, despite similarity in illness severity.

Reviewer’s Comments: These subgroup differences, especially among Caribbean blacks and African Americans, underscore the mix of important structural and cultural preferential factors that affect whether people get care. This is true even when controlling for health insurance and other access variables. However, one is struck by the overall disconnect between recommended care and received care. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Depression, Treatment Gap, Ethnicity

Print Tag: Refer to original journal article
The effectiveness of antidepressants relative to placebo appears to increase with severity at baseline, showing substantial benefit for those with severe depression, and perhaps no marginal benefit versus placebo for those with mild to moderate illness.

**Background:** Antidepressants have apparently been subject to thousands of controlled clinical trials over half a century of clinical research. However, the data supporting antidepressant advantage compared to placebo is based on a higher severity of illness, which some studies suggest is not always typical of actual medication use. For example, one study found that 71% of patients in an outpatient practice scored <22 on the Hamilton Depression Rating Scale (HDRS), a common cut-off score in antidepressant trials.

**Objective:** “To estimate the relative benefit of medication versus placebo across a wide range of initial symptom severity in patients diagnosed with depression.”

**Methods:** The authors surveyed randomized, placebo-controlled antidepressant trials from 1980 through March 2009. Studies had to include HDRS scores and patients across a full spectrum of major or minor depression disorder. In addition, patient-level data had to be available from the authors. The authors of this study then constructed a larger cohort that included information on relative treatment response comparing medication and placebo across a broader range of severity of HDRS scores than is commonly reported. Six studies met these criteria.

**Results:** When comparing treatment and placebo, the magnitude of differences in change in HDRS scores was related to a function of the HDRS baseline score. For patients with a score of <23, the differences between medication and placebo were statistically small. The statistical magnitude of superiority of antidepressant over placebo achieved an accepted threshold of significant effect at an HDRS score of 25.

**Conclusions:** Antidepressant benefit, compared to placebo, appears to be minimal for patients with score-defined mild or moderate symptoms, but the benefit is substantial for those with severe depression.

**Reviewer’s Comments:** While this study received substantial press coverage, its message probably should not surprise most psychiatrists—antidepressants are effective for more severe illness. However, the ability in actual practice to reliably identify where that severe and less severe line is, and thus to better target the benefit of these agents, does not seem to be resolved by this new attention. The power of placebo indicates the value of contact, outreach, and support to those with less severe spectrum of illness as part of a stepped spectrum of potential treatments. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Antidepressant Effectiveness, Depression Severity

Print Tag: Refer to original journal article
Do Psychiatrists Do What They Are Told?

Metabolic Testing Rates in 3 State Medicaid Programs After FDA Warnings and ADA/APA Recommendations for Second-Generation Antipsychotic Drugs.

Morrato EH, Druss B, et al:

Arch Gen Psychiatry 2010; 67 (January): 17-24

Using Medicaid data, physicians apparently do not respond with changed practices in response to published recommendations for metabolic screening for individuals starting SGAs.

Background/Objective: In the face of Food and Drug Administration warning labels about the metabolic risks of second-generation antipsychotics (SGAs), and consensus recommendations as to best practice for managing and screening for them, have clinicians changed their practice? Actual screening practices by clinicians in the face of these now long-standing recommendations and increased patient risks are not well known. The study here asks this question of the care of patients who rely on Medicaid for their care, and among whom antipsychotic use is more common, using California, Missouri, and Oregon state Medicaid databases.

Methods: A study cohort was retrospectively created using claims data between January 1, 2002, and December 31, 2005, before and after public recommendations. A total of 109,451 enrollees with a new SGA prescription were identified, and Current Procedural Terminology (CPT) codes over time for glucose and lipid testing were followed. Prior mental illness diagnoses were recorded for patients as was pre-existing diabetes, hyperglycemia, dyslipidemia, heart disease, and hypertension using accepted data screening methods such as scanning for ICD diagnoses and prescription patterns. A control group of patients initiating albuterol were also tracked in the same way.

Results: Glucose and lipid testing rates did not increase (0.9% change) when comparing the pre- and post-warning periods. While interestingly only 31% of patients continued to use SGAs at 6 months after their prescription started, even those who were persistent users did not have clinically higher rates of testing at baseline, and rates of change in trend use of lipid and glucose testing were statistically similar to the albuterol group. While testing was substantially higher among SGA patients with a history of pre-existing diabetes, these differences were statistically similar to, and in most cases outperformed by, testing rates in individuals with pre-existing disease in the albuterol cohort.

Conclusions: Actual rates of glucose and lipid screening among Medicaid recipients started on SGAs before and after national consensus recommendations for such screening showed no significant change when comparing rates before and after warnings.

Reviewer’s Comments: While these data reflect the picture as of 2005, and habits may have changed given only increased concern and attention to these issues since then, it does reinforce the often very slow response to adoption of new, even if expert consensus, practices. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: SGAs, Guidelines, Adherence

Print Tag: Refer to original journal article
Antipsychotic prescriptions doubled in this toddler population, with relatively few of these children having even received a mental health evaluation.

Background: Within one large, privately insured population under managed care, the percentage of children aged 2 to 4 years treated with antipsychotic medications increased from 0.04% in 1996 to 0.09% in 2001. Adverse effects may be especially pronounced in these young children. A different 6-month study of children aged 2.5 to 6 years found that there was a 15.4% increase in mean weight from baseline to end point among risperidone-treated children. An analysis of 2001 Tennessee Medicaid claims data reported that most new use of antipsychotic medications by children aged 2 to 5 years is for ADHD and disruptive behavior disorders.

Objective: To examine trends in antipsychotic drug treatment within a large population of privately insured children aged 2 through 5 years between 2000 and 2007.

Methods: Service and pharmacy claims are examined from the MarketScan Research Databases, which include information from privately insured individuals and their family members from >150 employers in the United States. Patient cohorts were limited to children aged 2 through 5 years. First- and second-generation antipsychotics were included.

Results: Although the overall percentage of very young children who received any psychotropic medication changed little between 2000 and 2007, there was a marked increase in the percentage that filled prescriptions for antipsychotic medications and smaller increases in the percentage that filled prescriptions for alpha2-agonists and stimulants. However, there were significant decreases in the percentages that filled prescriptions for antidepressants, mood stabilizers, and anxiolytics. During this time period, stimulants were the most commonly prescribed class of psychotropic medications. The rates of antipsychotic treatment were substantially higher for boys than girls and for children aged 4 or 5 years versus those aged 2 or 3 years. Children diagnosed with bipolar disorder had the highest rate of antipsychotic treatment. Risperidone accounted for roughly three-quarters of the total antipsychotic prescriptions, with aripiprazole a distant second at 14%.

Conclusions: The annual rate of antipsychotic medication use in very young children approximately doubled between 2000 and 2007.

Reviewer's Comments: Unfortunately, most of the children treated with antipsychotics in this study did not receive a mental health assessment, a psychotherapy visit, or treatment from a psychiatrist during the year of antipsychotic use. This study probably just identifies the tip of the iceberg as it does not examine records of patients who are publicly insured and have been found to have comparatively higher rates of antipsychotic treatment. (Reviewer-John G. Koutras, MD).

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Keywords: Antipsychotics, Toddlers, Preschool Bipolar Disorder

Print Tag: Refer to original journal article
Panic-Disordered Patients Over Generalize Conditioned Fear

Overgeneralization of Conditioned Fear as a Pathogenic Marker of Panic Disorder.

Lissek S, Rabin S, et al:


Panic-disordered patients exhibit exaggerated fear responses to stimuli several orders of approximation apart from a conditioned stimulus, indicating overgeneralization and a lower threshold of threat reactivity.

Background: Classical conditioning is thought to play a central role in the development and perpetuation of panic disorder. Neutral cues in the environment can become conditioned to trigger panic if paired with a panic attack. Perpetuation of panic disorder is thought to occur in part due to overgeneralization of these conditioned stimuli. This hypothesis has not been systematically tested in a laboratory setting.

Objective: The authors hypothesized that, compared to control subjects, patients with panic disorder exhibit overgeneralization to stimuli related to a conditioned stimulus. They tested this hypothesis by measuring the generalization gradient, or slope, of fear response to stimuli that were progressively distinct from a conditioned stimulus.

Participants/Methods: The authors recruited 19 patients with panic disorder and 19 healthy control subjects. Acquisition of conditioned fear involved pairing a mild electrical shock (unconditioned stimulus) to a circle with a specific diameter (conditioned stimulus = CS+). Generalization was assessed by presentation of varying sized circles, grouped into 4 classes of differentiation from the CS+ (class 4 = closest approximation; class 1 = farthest approximation); the circle farthest in diameter from the CS+ was considered the safety cue. Fear-potentiated startle was measured with an electromyogram (EMG) of the blink reflex associated with a loud burst of white noise (102 dBA) presented after half of the trials in each phase (pre-acquisition, acquisition, and generalization) and during inter-trial intervals. Subjects were asked to rate their level of risk (Likert scale of 3) and anxiety (Likert scale of 10) associated with the stimulus.

Results: Participants acquired conditioned fear-potentiated startle to the CS+. The strength of potentiation did not differ between groups. Compared to control subjects, panic-disordered patients rated their risk of shock and associated anxiety higher for the safety cue and smaller for the danger cue. Control subjects demonstrated a quadratic decline in conditioned fear as the stimulus differentiated from the conditioned cue. Potentiation in control subjects generalized only to class 4 stimuli, not to class 1, 2, and 3 stimuli, responses, which did not differ from the safety cue. Panic disordered patients exhibited potentiated responses to classes 4, 3, and 2 stimuli compared to the safety cue, with a linear slope decline.

Conclusions: These data support the hypothesis that patients with panic disorder exhibit stronger fear generalization, indicative of lower thresholds of threat reactivity following conditioning.

Reviewer’s Comments: Because this study was not prospective, we do not know whether the tendency to over generalize predates or follows the onset of panic disorder. Regardless, it is likely to perpetuate and exacerbate the disorder, often leading to agoraphobia. The authors propose several treatment approaches for further research, including the use of D-cycloserine to improve discrimination by increasing the accuracy of learning. (Reviewer-Charlotte O. Ladd, MD, PhD).
A New Way to Extinguish Conditioned Fear

Preventing the Return of Fear in Humans Using the Reconsolidation Update Mechanisms.

Schiller D, Monfils M-H, et al:

Nature 2010; 463 (January 7): 49-53

A reminder of the conditioned stimulus just before the extinction process prevents spontaneous recovery of fear later on.

**Background:** Fear responses in mammals can be manipulated using Pavlovian principles of conditioned fear and extinction. This is the basis of exposure therapy for the treatment of anxiety disorders. One limitation of this type of therapy is that the results may be short lived; that is, fear may return under stress. The authors sought to enhance fear extinction by taking advantage of reconsolidation, conceptualized as a window of time during which "new information is incorporated into old memories," potentially offering an opportunity to "re-write" old memories. This hypothesis relies on the premise that memories are reconsolidated each time they are retrieved.

**Objective:** The authors hypothesized that by introducing new memories within the reconsolidation window they might permanently eliminate conditioned fear.

**Participants/Methods:** To test this theory, 65 subjects were recruited and divided into 3 groups. All were exposed to fear conditioning with partial reinforcement. On day 1, subjects were presented with 2 colored squares. One square was paired with a mild electrical shock 38% of the time (conditioned stimulus = CS+); the other square was never paired with a shock (CS-). Twenty-four hours later, all subjects completed an extinction process in which they were exposed to both colored squares and no shock. Two of the 3 groups were reminded of the CS+ before the extinction process, one group 10 minutes beforehand and the other 6 hours beforehand. Subjects returned on day 3 and were again exposed to both colored squares without shock pairing. The differential fear response was measured by the skin conductance response (SCR) to the CS+ minus the CS-. A smaller group of subjects (n=19) was retested a year later with CS+ following 4 unpaired shocks after a period of re-extinction. Results were analyzed using a 2-way analysis of variance, with group and time as main effects.

**Results:** Subjects developed fear acquisition to the CS+ and subsequently extinguished this fear. However, the conditioned fear returned spontaneously both 24 hours later and 1 year later EXCEPT in those subjects who received a cue of the CS+ 10 minutes before the extinction process began.

**Conclusions:** The authors hypothesize that this reminder cue initiated a "reconsolidation window" during which time extinction re-wrote the memory, thereby permanently erasing fear of the conditioned stimulus.

**Reviewer's Comments:** This experiment earned its way into the journal *Nature* by virtue of its elegant design, clean results, and potential for improving the way we approach treatment of anxiety disorders. The next step is to study whether or not this observation translates into more effective clinical extinction of fear. Consideration should be given to combining the use of D-cycloserine with extinction in the reconsolidation period to further enhance this effect in both the laboratory and clinical settings. (Reviewer-Charlotte O. Ladd, MD, PhD).

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Keywords: Conditioned Fear, Anxiety

Print Tag: Refer to original journal article
After controlling for actually having a mental disorder, returning military identify other prominent factors (ie, activity restriction and suicidal ideation) that determine whether they would in fact seek mental health care.

**Objectives:** People do not always perceive their need for mental health care based on clinically defined need. Increasing research seeks to understand help-seeking behavior for mental health services. There does not appear to be a close relationship between having a DSM diagnosis, believing one needs mental health services, and actually receiving mental health services. A range of sociodemographic, clinical, and development-historical features appear to mediate the relationships between these only tenuously related steps. The author's here are particularly concerned about how these factors play out in terms of returning military personnel, who have high burdens of illness and traumatic exposure, but also resistances to seeking help.

**Methods:** The authors look at deployed, active-military Canadian soldiers. This is because soldiers have been surveyed on several related measures of interest here including the use of a well-validated measure of perceived need, the Perceived Need for Care Questionnaire (PNCQ). Also gathered were a range of sociodemographic variables, information as to deployment (minimum of 3 months) such as number, frequency, and combat exposure, and the use of the World Health Organization Composite Diagnostic Interview (CIDI), which can identify ICD-10 and DSM-IV defined diagnoses. Soldiers were also asked questions as to functional impairment and activity restrictions, as well as suicidal ideation in the prior 12 months.

**Results:** Data on 8,441 active military were obtained. An endorsement of perceived need for care differed by diagnosis, with panic disorder showing the strongest association. Higher income soldiers were also more likely to perceive a need for care as were women, those aged 35 to 44 years, regular service membership, and junior rank. Deployment with combat exposure and witnessing atrocities was related to perceived need for a range of care; not having exposure was associated only with a perceived need for information. When controlling for having a mental disorder, statistically significant predictors of perceived need were long-term restriction on activities and suicidal ideation.

**Conclusions:** Many factors, including having an illness, modify the degree that deployed soldiers perceive a need for mental health care, especially suicidal ideation and activity limitations after controlling for having a mental disorder.

**Reviewer’s Comments:** This study underscores, especially in high-risk populations, the need to not only screen populations for disorder, as the U.S. military is now doing, and to also identify and establish efforts to engage and address barriers to perceived need for care. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Soldiers, Perceived Need for Care

Print Tag: Refer to original journal article
Depression onset is influenced heavily by proximal risk factors that perpetuate the illness long after they are removed.

**Background:** Depression is both highly prevalent and highly treatable. The prevalence of depression is determined by the rate of disease onset (incidence) and its duration. Cross-sectional research has provided information on risk factors for depression onset and recovery. This is the first study to simultaneously examine risk factors for depression onset and recovery in a general practice cohort.

**Objective:** To compare the relative rank and weight of 39 risk factors in the onset of, and recovery from, depression.

**Methods/Participants:** 10,045 patients were recruited from general practice settings in 7 countries and interviewed at baseline, 6 months, and 12 months. Data were collected on 39 proposed risk factors, including sociodemographics, personal and family psychiatric history, relationship satisfaction, substance use, job satisfaction, major life events, childhood trauma, social support, and living environment. Continuous variables were converted to binary status, categorized as either above or below the mean. The authors used a model for interval censored data fitted for each of the 39 variables.

**Results:** The rate of onset of depression in the study was 4.87% in the first 6 months and 3.43% in the second 6 months. The rate of recovery was 67.45% after the first 6 months and an additional 48.82% after the second 6 months. Hazard ratios for individual risk factors were greater for onset than recovery and were negatively associated with one another, except for gender and alcohol use. The incidence density fraction, an estimate of the percentage of cases directly related to a given risk factor, was >50% for 22 of the 39 risk factors for depression onset, but only 3 risk factors for depression recovery. Nine of the top 10 risk factors for onset and recovery were time-dependent.

**Reviewer’s Comments:** The data presented here support the illness model of depression and encourage movement toward preventive psychiatry to reduce the prevalence of depression. The study was not conducted in the U.S. and was limited to individuals who sought general medical care; thus, the generalizability of these findings remains uncertain. (Reviewer-Charlotte O. Ladd, MD, PhD).

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Keywords: Risk Factors, Depression

Print Tag: Refer to original journal article
Cognitive Therapy for Depression Shows Promise in Preventing Recurrence

Long-Term Effects of Preventive Cognitive Therapy in Recurrent Depression: A 5.5-Year Follow-Up Study.

Bockting CLH, Spinhoven P, et al:

J Clin Psychiatry 2009; 70 (December): 1621-1628

High-risk groups continue to have recurrent depressive episodes, but there is some benefit to group cognitive therapy for relapse prevention.

**Background/Objective:** Recurrent major depression is projected to rank second on a list of 15 major diseases in terms of burden in 2030. A crucial part of the treatment and management of depression is the prevention of recurrences in high-risk groups, primarily those with a history of recurrent depressive episodes. There is accumulating evidence that cognitive therapy (CT) applied during the acute depressed phase has enduring preventive effects on relapse and recurrence. The preliminary finding at the 2-year mark for this study cohort demonstrated that augmenting treatment as usual (TAU) with CT resulted in a significant protective effect that intensified with an increasing number of previous depressive episodes reported. For patients with ≥5 previous episodes (41% of the sample), CT reduced the rate of relapse from 72% to 46%. This report is on the 5.5-year follow-up of this cohort.

**Participants/Methods:** 172 patients with a history of at least 2 depressive episodes in the previous 5 years were treated for the acute depressive episode (with medication and/or psychotherapy). After remission, the patients were randomly assigned to TAU, community care, or CT (TAU + CT). CT consisted of 8 weekly 2-hour group sessions that focused on enhancing positive experiences and identifying and changing dysfunctional attitudes as well as formulating specific relapse prevention strategies. Relapse/recurrence of depression was assessed using the Structured Clinical Interview for DSM-IV; the assessors were blinded to the treatment condition.

**Results:** Overall, 79% of patients had experienced relapse at least once during the 5.5-year follow-up period. The beneficial effect of CT became statistically significant in patients who had a history of ≥4 previous episodes. Over the total study period of 66 months, the cumulative rate for relapse/recurrence for the 90 patients with ≥4 previous episodes was 95% for TAU patients and 75% for TAU + CT, a 20% difference in favor of the CT group.

**Conclusions:** The addition of a CT group intervention to the management of major depressive disorder was associated with a substantial and enduring effect on relapse/recurrence over a 5.5-year follow-up period.

**Reviewer’s Comments:** CT intervention appears to be more effective at increasing the time to first relapse for most of the patients and significantly decreasing the number of relapses only in those who had ≥4 prior episodes. The actual relapse rates in recurrent depression are still dramatically high, even in those with the CT intervention. (Reviewer-John G. Koutras, MD).

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Keywords: Cognitive Therapy, Recurrent Major Depressive Disorder

Print Tag: Refer to original journal article
In rural south India, psychosocial stresses and conditions, rather than psychiatric morbidity per se, are risk factors for suicide.

**Background:** India has experienced high rates of suicide, especially in rural areas. The reasons for this and ways to address it have been an area of active concern and investigation. However, exploring this particular question invites larger ones. In particular is the question of the relative contribution of psychosocial stress and psychiatric morbidity that is one’s social context versus one’s psychiatric condition. Much of the psychiatric literature has highlighted the importance of suicide occurring in the context of psychiatric disorder, in particular major depression, with the emphasis, therefore, on getting people into treatment. But that literature largely comes from Western contexts. Work in low- and middle-income countries point to social, economic, and cultural factors as primarily impacting suicide risk. Overall, research comparing these categories of risk is limited.

**Objective/ Design:** This study was a retrospective psychological autopsy series of 100 cases of consecutive suicides in a south India region along with similar psychological profiles of 100 matched living controls.

**Methods:** All deaths in a health catchment area, or "block" in the Indian state of Tamil Nadu have been reviewed by verbal autopsy since 1985 along rigorous methods that engage the deceased family, neighbors, local healers, etc. The psychological autopsy interview is a commonly used semi-structured interview design that assists the construction of a likely DSM-IV diagnosis as well as gathers context information. Interviews were also performed on 100 controls pair-matched by age, gender, and location.

**Results:** 37% of the suicide group and 16% of the control group had at least one Axis I disorder. For the suicide group, these included alcohol dependence (16%) and adjustment disorders (15%). Major depression, dysthymia, and schizophrenia accounted for only 2% each. Psychosocial factors showed pronounced differences between the 2 groups. Living alone and a break in a significant relationship in the past year were significantly more common in the suicide group, which was also twice as likely to have identified stress and lack of confidants. Indeed, on multivariate analysis, the only factors that remained significantly predictive of suicide were ongoing stress and chronic pain, and not psychiatric morbidity.

**Conclusions:** Psychosocial stress and isolation, and not psychiatric morbidity per se, appear as risk factors for suicide in this population.

**Reviewer's Comments:** This study reminds us (and the authors also point this out) that this work furthers the view that depression itself has shown too often capture some heterogeneous kinds of features that perhaps undermine its status as a clear condition, such as patients that seem to have prognoses or patterns tied varyingly to context and social conditions, underlying coping and developmental features, and autonomous mood patterns. Literally broadening the contexts and settings in which these issues are studied can lend insightful perspective on the nature of psychiatric illness and risks. (Reviewer-Gary S. Belkin, MD, PhD, MPH).
A concise ultra-brief screening instrument derived from a separate anxiety and depression screen appears to be an effective screen for both anxiety and depressive disorders.

**Background/Objectives:** Anxiety and depression-spectrum disorders collectively represent the most common ambulatory mental health conditions that are treated and also capture a substantial burden of disability in the population. There are several available, reliable, validated screens that can initially identify individuals who likely fall into each of these groups of disorders. The Patient Health Questionnaire (PHQ)–2, a simple 2-question subset of the PHQ–9 depression screen and tracking scale, has an 83% sensitivity and 90% specificity for major depression. A similarly easy and brief 2-question Generalized Anxiety Disorder-2 (GAD-2) has varying, but generally good specificity as well, for several key anxiety disorders (GAD, panic, social anxiety, and post-traumatic stress disorder). The authors here did the math and decided to combine these 4 screening questions into what they call the PHQ–4 and to see the degree that doing so retained the value of the sum of these parts in terms of providing a single very brief instrument that could quickly identify people at likely risk of having 1 of these priority conditions.

**Participants/Methods:** 2149 subjects were recruited from 15 primary care clinics. In these clinics, patients were asked to complete a questionnaire that included the full 7-question GAD Scale, and the PHQ–8 (the well-known PHQ–9 without the question about suicide, but which has shown to have high correlation with each other). They also provided sociodemographic information and the Medical Outcomes Study Short Form that measures functional status. A structured DSM-IV diagnostic interview was also conducted. Responses to the first 2 questions of the GAD-7 and PHQ-8 were compared to the overall scores and interview-based diagnosis.

**Results:** Factor analysis of the variation in scores found that the discrete anxiety and depression factors explained 84% of the variance in scores. The magnitude of the PHQ–4 score was significantly related to escalating functional impairment and days reported of disability.

**Conclusions:** A combined brief screen appears to effectively identify individuals at high risk of having an anxiety and/or depressive disorder.

**Reviewer’s Comments:** Such a combined screen might be attractive for primary care settings in identifying initial patients at risk. It is also consistent with work in other parts of the world to consider the idea of common mental disorder, which considers overall distress and impairment along mood and anxiety symptoms, as a valuable construct as these conditions often overlap. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: PHQ–4, Screening Instruments, Anxiety, Depression

Print Tag: Refer to original journal article
Even Very Low Lead Levels Associated with ADHD

Confirmation and Extension of Association of Blood Lead With Attention-Deficit/Hyperactivity Disorder (ADHD) and ADHD Symptom Domains at Population-Typical Exposure Levels.

Nigg JT, Nikolas M, et al:

J Child Psychol Psychiatry 2010; 51 (January): 58-65

Lead levels that are lower than averages in the U.S. are still associated with ADHD symptoms and reversible by stimulant medications, which may be masking the problem.

**Background/Objective:** Blood lead levels ≥10 µg/dL has been associated reliably with attention-deficit/hyperactivity disorder (ADHD) and related behaviors, with the only dispute being the magnitude of the effect. Even at lower blood levels, lead has been linked to reduced intellectual functioning. Recent findings point to an association with ADHD even very low exposures, such as <5 µg/dL. This study is the first to use a new spectroscopy technology (inductively coupled plasma mass spectrometry [ICPMS]), which has detection limits for lead that are 3- to 8-fold lower than other methods typically used clinically or in ADHD research.

**Methods:** 236 children aged 6 to 17 years completed the study. To confirm ADHD and comorbid diagnoses, the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-E) was completed. To estimate full-scale IQ, children completed a 3-subtest short form of the Wechsler Intelligence Scale for Children (WISC-4th Ed.) For teachers, ADHD symptoms were assessed on the ADHD Rating Scale. The Conners served as a normed, dimensional measure. Blood samples were obtained and lead levels assayed using ICPMS.

**Results:** Child blood levels ranged from <0.3 (undetectable; n=3) to 2.20, with a mean of 0.73. These levels are equal to or lower than recent averages in Western Europe and the United States. The blood levels in this study were the lowest ever evaluated in relation to ADHD to date. Blood lead level was reliably associated with hyperactivity and impulsivity. On the Conners, both cognitive and hyperactivity/impulsivity were reliably related to blood lead levels. For children who had never been treated with stimulant medication, there was a reliable relation of blood lead to hyperactivity. For the children who had been treated, the relation disappeared. These results suggested that medication treatment masked the relation of lead to hyperactivity. The association of blood lead with inattention (or cognitive problems) was observed in parent and teacher Conners ratings and in teacher, but not parent, DSM-IV ratings.

**Conclusions:** Even very low levels of lead are associated with ADHD symptoms, particularly hyperactive symptoms, but also inattention or cognitive problems, supporting the view that a cut-off of 10 µg/dL for lead screening captures those at risk for developing ADHD symptoms via lead exposure.

**Reviewer’s Comments:** The results of this study may have even further implications beyond lead. As the authors noted, lead can serve as a model insult affecting frontal-striatal circuitry in ways that are relatively well understood, guiding investigations into other potential environmental toxins. (Reviewer-John G. Koutras, MD).

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Keywords: ADHD, Blood Lead Levels, Stimulants

Print Tag: Refer to original journal article
Parents with mental illness are more likely to smoke and to have low socioeconomic standing, both of which increase the risk of SIDS.

**Background:** Sudden infant death syndrome (SIDS) is defined as any unexplained death of an infant in the first year of life. Parental smoking and prone sleeping are risk factors for SIDS. The incidence of SIDS declined dramatically in many countries after risk reduction campaigns educated new parents about these risk factors. However, SIDS remains prevalent among disadvantaged families, with 75% of SIDS cases in the U.K. occurring among the 15% to 20% of the poorest families.

**Objective:** To compare the relative risk of SIDS in Swedish infants of parents with and without mental illness before and after the 1992 risk reduction campaign.

**Participants/Methods:** A Swedish birth cohort included 2,480,320 children born between 1978 and 2004. The authors used several national databases and registries to obtain information on birth, death, parental psychiatric hospitalizations, antenatal tobacco use, and sociodemographics. Parents were assigned to low socioeconomic status if they either received welfare or failed to complete upper secondary schooling. The authors fitted an unconditional logistic regression model, and data were presented as odds ratios (OR) or relative risk (RR) estimates.

**Results:** The rate of SIDS during the 27-year period was 6 per 1000 births. Among the SIDS victims, 11.2% had at least 1 parent who had been hospitalized psychiatrically in the 5 years before birth. The OR for SIDS was 3.1 for maternal general psychiatric admission and 6.5 for maternal inpatient substance abuse treatment. The OR was 3.5 for paternal psychiatric admission and 2.8 for inpatient substance abuse treatment. If both parents were hospitalized, the OR was 6.8 for general psychiatric admissions and 9.5 for admissions related to substance abuse. Time since admission decreased the potency of the effect of substance abuse treatment, but not general psychiatric hospitalization. Parents with a history of any psychiatric hospitalization were more likely to have obstetrical complications, adverse social circumstances, and to smoke. Obstetrical factors had little confounding effect on SIDS risk. Both maternal smoking and social adversity were confounding factors for parental psychiatric admission. The RR associated with parental psychiatric admission increased after the risk reduction campaign.

**Conclusions:** Much of the relative increased risk of SIDS associated with parental mental illness appears to be associated with social adversity. This group was more likely to receive welfare, have low educational attainment, be single parents, and smoke prenatally. The authors postulate that mothers in this group may have difficulty receiving or acting on risk reduction information.

**Reviewer’s Comments:** This article highlights the necessity to identify expecting mothers with a psychiatric history and educate them individually about the risk of SIDS with maternal smoking and infant sleeping position. Because prepartum smoking influences risk more than postpartum smoking, efforts to decrease smoking in pregnancy should be increased. (Reviewer-Charlotte O. Ladd, MD, PhD).

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**Keywords:** SIDS, Parental Mental Illness

**Print Tag:** Refer to original journal article
Simulated Voices -- Hear Them to Believe Them

Cultivating Empathy for the Mentally Ill Using Simulated Auditory Hallucinations.

Bunn W, Terpstra J:


Measured empathy in medical students for the mentally ill can increase with a simulated hallucinations exercise.

**Background/Objectives:** Empathy for patients has been known to play a role in how doctors react to patients and to the quality of that relationship, clinical outcomes, and patient follow-through with treatment. Indeed, the Association of American Medical College has established the promotion of empathy as a proposed learning objective, and the literature contains many studies looking at the effectiveness of a range of interventions aimed to do that, including role performance, reflective writing or literature courses, communication skill trainings, and hospital experience scenarios. The authors point out that there is more limited attention to such strategies, specifically for enhancing empathy for the mentally ill. This study looks at an experiential intervention, the experience of auditory hallucination.

**Methods:** The study included 150 medical students who participated in a 6-week psychiatry rotation during the 2005 to 2007 academic years at the University of Utah. One hundred students completed the Jefferson Scale of Physician Empathy-Student Version (JSPE-S). This validated instrument queries rated responses from strongly disagree to strongly agree across a range of attitudinal statements. Students completed some simple neurocognitive tests and then listened to a 40-minute simulated auditory hallucination presentation on earphones. Another sample of 50 students were randomly selected to complete the testing, but were not exposed to the simulated hallucinations. All students then completed a follow-up JSPE-S.

**Results:** After participating in the exercise when it included listening to the audio recording, student empathy scores showed a statistically significant average increase of 2.65 points. The comparison students showed no interim difference (increase of 0.1).

**Conclusions:** Empathy scores substantially increased for medical students who were exposed to a simulated auditory hallucination exercise compared to those who were not.

**Reviewer’s Comments:** While the authors identify that one problem with this sort of research is that it looks at short-term rather than sustained empathy attitudes, their study does not seem to explore whether this specific brief exercise has enduring effects on attitudes, especially in light of research showing that empathy decreases through medical school. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Empathy, Simulated Hallucinations

Print Tag: Refer to original journal article
When assessing for suicide risk, always obtain a history for substance abuse and prior psychiatric hospitalizations, as well as prior suicide attempts.

**Background/Objective:** In the U.S., >30,000 people die from suicide every year, and suicide accounts for 4% of all deaths among adults 18 to 65 years of age. Two comprehensive meta-analyses estimated that 2% to 6% of individuals with affective disorders will die by suicide. Suicide is a rare event, and risk assessment requires the use of very large samples, so there are very few studies that have examined the relationships between >2 risk factors. This exploratory analysis was designed to derive an empirically based set of interactions related to rates of suicide in the Veterans Affairs (VA's) National Registry for Depression (NARDEP).

**Methods:** The NARDEP includes data for demographic factors, diagnostic characteristics, pharmacy data, and service utilization for VA patients with depression. This study uses data from 1999 to 2004. Participants were included if they (1) had been diagnosed with a depressive disorder and had been prescribed an antidepressant or (2) were diagnosed with depression during 2 separate medical visits in the study period. Patients were excluded if they had bipolar disorder, schizophrenia, or schizoaffective diagnoses. The sample was divided into primary and replication samples: 589,825 (66.4% of the original sample) in the primary sample; 298,034 (33.6%) in the replication sample. A total of 1,892 patients were identified in the total sample as having died of suicide for this study cohort.

**Results:** The data mining analysis split the sample into those with or without a substance use disorder and identified the most important risk factors in these 2 separate groups. In those with a substance use disorder, African Americans were significantly less likely to commit suicide than any other race/ethnicity group, and there were no other distinguishing variables; in non-African Americans (mostly Caucasians), having been admitted to inpatient treatment at least once in the prior 12 months conferred an additional suicide risk. In those without a substance use disorder, gender is the strongest predictor, with men having a suicide rate 2 to 3 times higher than women. The analysis of the replication sample confirmed the initial findings.

**Conclusions:** Substance use disorder was the strongest indicator of suicide risk in depressed Veterans, followed by non-African race and those with an inpatient stay in the past 12 months.

**Reviewer’s Comments:** Interestingly, among depressed VA patients who do not have substance abuse, gender is not among the top 3 risk factors. Unfortunately, in this sample, no reliable data were available on prior suicide attempts, which have typically conferred the highest risk for completed suicide. (Reviewer-John G. Koutras, MD).

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Keywords: Suicide, Substance Abuse, Veterans

Print Tag: Refer to original journal article
**SSRIs Without Clear Evidence of Benefit for Borderline Personality Disorder**

*Pharmacotherapy for Borderline Personality Disorder: Cochrane Systematic Review of Randomised Trials.*

Lieb K, Völmi B, et al:

Br J Psychiatry 2010; 196 (January): 4-12

Few studies qualified for this review, and those that did demonstrated no supporting evidence for SSRIs in borderline personality disorder, but did demonstrate some evidence for aripiprazole, valproate, and topiramate.

**Background/Objective:** In a recent U.S. study, the lifetime prevalence of borderline personality disorder has been estimated at approximately 5.9%. Suicidal behavior reportedly occurs in 84% of patients with borderline personality disorder. Comorbid mood disorders or substance use disorder are considered the most relevant risk factors for suicide completion. This Cochrane review evaluates the available high-quality evidence for pharmacotherapy of the core symptoms of borderline personality disorder.

**Methods:** Studies were identified from searches of multiple available databases. Cross-references from relevant literature were also traced, and researchers in the field were contacted by e-mail and asked for unpublished data. Studies were included if they were double-blind in design. The distinct borderline personality disorder criteria were assessed separately, but were also subsumed into 4 clusters: affective dysregulation (affective instability, emptiness, anger); cognitive-perceptual symptoms (stress-related paranoia/dissociation); impulsive-behavioral dyscontrol (self-mutilating, impulsivity); and interpersonal problems (abandonment fears, unstable relationships). Secondary outcomes included depression and anxiety.

**Results:** In total, data for 1,714 participants were included, with study samples varying in size between 16 and 314 participants. Patients with current suicidal ideation were not eligible for nearly half of the included trials. The study pool consisted of 16 different drug studies. The comparison of first-generation antipsychotics with placebo yielded significant effects for haloperidol in the reduction of anger. Among second-generation antipsychotics, aripiprazole had significant effects in the reduction of the core pathological symptoms of borderline personality disorder. Three olanzapine studies were pooled (with a total of 631 participants), and efficacy was demonstrated for most of the core symptoms as well. Beneficial effects were found for mood stabilizers valproate, lamotrigine and topiramate, but not for carbamazepine. Topiramate improved interpersonal problems, impulsivity, and associated anxiety. There was no clear evidence for the effectiveness of selective serotonin reuptake inhibitors (fluoxetine and fluvoxamine).

**Conclusions:** Symptoms related to interpersonal pathology patterns were significantly affected by the second-generation antipsychotic aripiprazole and the mood stabilizers valproate and topiramate.

**Reviewer's Comments:** To say that the amount of double-blinded studies that met criteria to be included in this review is disappointing would be making a great understatement, especially considering the prevalence of this condition in more intensive treatment settings. For example, quetiapine appears to be fairly widely used for borderline personality disorder, yet there was not 1 study of quetiapine that made it into the review, or, for that matter, risperidone. Topiramate, however, has some encouraging evidence. (Reviewer-John G. Koutras, MD).

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Keywords: Borderline Personality Disorder, Mood Stabilizers, Antipsychotics

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