Repetitive transcranial magnetic stimulation appears to be an effective and safe treatment for depression and psychosis. It should be more widely available to patients who do not respond to pharmacotherapy.

**Background:** Repetitive transcranial magnetic stimulation (rTMS) is a stimulation therapy approved by the Food and Drug Administration in 2008 for the treatment of depression. However, its use remains obscure.

**Objective:** To determine whether rTMS should be brought out of obscurity for the treatment of depression, schizophrenia, and obsessive-compulsive disorder (OCD).

**Design:** A meta-analysis of rTMS for the management of mood and anxiety disorders, psychosis, attention-deficit/hyperactivity disorder (ADHD), Tourette syndrome, bulimia nervosa, and addiction.

**Participants/Methods:** A literature search was conducted to identify parallel, double-blind, randomized, controlled studies investigating rTMS published between 1966 and 2008. Only those psychiatric disorders investigated in at least 3 studies were included in the meta-analysis. Effect sizes were calculated for mean differences in pretreatment versus posttreatment rating scales with rTMS compared to sham treatment.

**Results:** The only psychiatric conditions for which rTMS had been studied sufficiently for meta-analysis were depression, psychosis with auditory verbal hallucinations (AVH), psychosis with negative symptoms, and OCD. Studies investigating rTMS for depression had varied methodologies, and they tested rTMS monotherapy, adjunctive therapy with medication, and cotherapy with medication. rTMS was also compared to electroconvulsive treatment (ECT) in 6 studies of major depression. For depression, rTMS monotherapy performed best (effect size, 0.96) followed by adjunctive treatment (effect size, 0.51) and simultaneous cotherapy with an antidepressant (effect size, 0.37). rTMS for depression was applied over the right or left dorsolateral prefrontal cortex (DLPF), although the location of stimulation did not significantly affect performance of rTMS. rTMS was less effective than ECT for severe major depression, with a weighted effect size of -0.47. In 7 randomized controlled trials, rTMS applied to the left temporoparietal cortex was moderately effective for the treatment of AVH (effect size, 0.54). rTMS was also mildly effective for the treatment of negative symptoms of psychosis in 7 studies (effect size, 0.39). Most of these studies applied rTMS over the left DLPF. In contrast, rTMS was not effective for the treatment of OCD in 3 studies (effect size, 0.15; n=38).

**Conclusions:** Based on these meta-analyses, rTMS should be considered standard treatment for major depression and for both positive and negative symptoms of psychosis that are refractory to pharmacotherapy. rTMS appears to be more effective as monotherapy instead of as adjunctive therapy for major depression. The authors do not recommend the use of rTMS for OCD.

**Reviewer's Comments:** Most participants in these studies were resistant to pharmacotherapy, but it was prudent and cost-effective to try antidepressant or antipsychotic therapy before initiating rTMS treatment for depression and psychosis, respectively. Future studies need to determine the longevity of benefit from rTMS.

(Reviewer-Charlotte O. Ladd, MD, PhD)

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Keywords: Repetitive Transcranial Magnetic Stimulation, Depression, Psychosis

Print Tag: Refer to original journal article
IV infusion of ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, rapidly reduces depressive symptoms in bipolar disorder, but the effect is short-lived.

**Background:** Many patients with bipolar disorder (BPD) remain depressed despite aggressive medication trials, and we have yet to identify treatments that directly target the underlying etiology of this condition. One approach that has proven effective in the short-term treatment of unipolar depression is ketamine, an antagonist of the N-methyl-D-aspartate (NMDA) receptor.

**Objective:** To determine whether ketamine is beneficial for the treatment of depression in BPD.

**Participants/Methods:** Because of the risks of ketamine, including dissociation and nightmares, this initial trial was conducted in patients with treatment-resistant bipolar depression. Patients who had failed at least 1 antidepressant trial were recruited by the National Institute of Mental Health and were hospitalized for 1 month for acute treatment with either lithium or valproic acid at therapeutic serum levels. Patients who did not respond to this strategy (Montgomery-Asberg Depression Rating Scale [MADRS] ≥20) were included in the study, which had a crossover design in which each patient received a single injection of 0.5 mg/kg ketamine and normal saline 2 weeks apart in a blinded fashion. Depression symptoms were assessed immediately before injection and at 40, 80, 110, and 230 minutes after infusion using the MADRS, Hamilton Depression Rating Scale (HAM-D), and the Beck Depression Inventory (BDI). Patients were also assessed 1, 2, 3, 7, 10, and 14 days after infusion. Treatment response was defined as ≥50% reduction in MADRS score; remission was defined as MADRS score ≤8. Data were analyzed using linear mixed models with repeated measures for time and treatment.

**Results:** 55 patients were screened for the study, and 18 met inclusion criteria, of which 5 did not complete the entire study due to unstable mood or anxiety. Most dropouts were receiving valproic acid as their mood stabilizer. Mean lithium and valproate levels were in the therapeutic range (0.77 mEq/L and 74.38 µg/mL, respectively). There was a significant time-drug interaction on MADRS scores: ketamine was associated with fewer depressive symptoms within 40 minutes and lasting for the first 3 days after infusion, inclusive. None of the patients responded to treatment after receiving placebo. Responder criteria were met by 56% of patients at 40 minutes after receiving ketamine and by 44% of patients after 1 day. Remission criteria were met by 13% of patients at 40 minutes after ketamine infusion and by 31% after 1 day. Similar effects were seen when HAM-D and BDI scores were analyzed. At least 10% of patients reported depersonalization side effects, nausea, or headache during the infusion, regardless of medication received.

**Conclusions:** This proof-of-concept study demonstrates that a single dose of ketamine quickly and dramatically improves depressive symptoms in bipolar depression for up to 3 days after infusion.

**Reviewer's Comments:** NMDA antagonism may become a novel treatment strategy for the acute treatment of both unipolar and bipolar depression. (Reviewer-Charlotte O. Ladd, MD, PhD).
Depressed adolescent who do not respond to an SSRI by 6 to 8 weeks of treatment should probably be considered for augmentation with cognitive-behavioral therapy or, possibly, a mood stabilizer.

**Background:** The Treatment of Resistant Depression in Adolescents (TORDIA) study was a 6-site study designed to examine second-step interventions in adolescents with depression who had not responded to an initial selective serotonin reuptake inhibitor (SSRI) trial.

**Objective:** To determine if, in adolescents with resistant depression, remission is more likely among those randomized to cognitive-behavioral therapy (CBT) or venlafaxine rather than another SSRI, if remission is more likely in those who responded by 12-weeks, and if both remission and relapse are predicted by levels of depression at baseline and week 12.

**Design:** A follow-up open study to the initial 12-week study.

**Participants:** 334 adolescents participating in the TORDIA study who met criteria for major depressive disorder (MDD) or dysthymia that persisted despite treatment with an SSRI for at least 8 weeks.

**Methods:** After the first 12 weeks of treatment, nonresponders were randomly assigned to 1 of 4 open-label treatments: (1) switch to another SSRI (paroxetine or citalopram); (2) switch to venlafaxine; (3) switch to another SSRI plus CBT; and (4) switch to venlafaxine plus CBT. Standardized instruments included the Beck Depression Inventory (BDI), the Children's Depression Rating Scale, the Clinical Global Impression Severity Scale, and other measures which screened for substance abuse.

**Results:** During the first 12-week acute phase of the study, 48% of participants responded to treatment, with greater response to medication switch plus CBT (55%) than to medication alone (40%). There was no difference in the response rate between venlafaxine and an SSRI. In this follow-up study, nearly 40% of treatment-resistant adolescents achieved remission after 6 months of randomly assigned treatment. Initial treatment assignment did not affect the rates of remission, but greater clinical severity of depression predicted failure to remit. Initial response at 12 weeks predicted a greater than 3-fold increased likelihood for remission. Venlafaxine did not demonstrate superiority to treatment with SSRIs in achieving remission.

**Conclusions:** Response during the first 12 weeks of SSRI treatment for treatment-resistant depression in adolescents is 3 times more likely to result in eventual remission. The initial assignment of CBT with a new SSRI did not result in any appreciable differences in the course of illness.

**Reviewer's Comments:** One encouraging finding is that adding CBT may be helpful and/or adding a mood stabilizer may also offer benefits. Only 10 subjects received a mood stabilizer, whether a second-generation antipsychotic, lithium, divalproex, or topiramate. Obviously, the mood stabilizer finding needs to be followed up with a larger trial. (Reviewer-John G. Koutras, MD).
Good Question -- Are They Depressed or Just Very Sick?

Pessimism, Worthlessness, Anhedonia, and Thoughts of Death Identify DSM-IV Major Depression in Hospitalized, Medically Ill Patients.

McKenzie D, Clarke D, et al:

Psychosomatics 2010; 51 (July-August): 302-311

Pessimism, worthlessness, loss of interest in activities with others, and thoughts of death are strongly associated with major depression in hospitalized medically ill patients.

Background: Diagnosing depression in severely medically ill patients, including those in an inpatient medical setting, can often be challenging. Many of the diagnostic criteria for Major Depressive Disorder (MDD) have significant overlap with symptoms which are present when someone is severely medically ill, such as decreased energy, change in sleep and appetite patterns, and impaired concentration. Better identification of depression is important, because depression is common in hospitalized medically ill patients, with prevalence rates ranging from 20% to 30%. Depression in the medically ill is also associated with increased health care costs, reduced compliance, and increased morbidity and mortality. Unfortunately, depression may be regarded by some clinicians, as well as by patients and relatives, as an expected or “natural” consequence of illness or hospital stay, further delaying or evading treatment. Prior research conducted by the authors of this study has found that the symptoms of demoralization and anhedonia best differentiate dimensions or types of depression in the medically ill.

Objective: To match the symptoms of demoralization to DSM-IV depression constructs.

Methods: Structured interviews were performed on 312 medically hospitalized patients in Australia, utilizing the Monash Instrument for Liaison Psychiatry (MILP). The key symptoms for demoralization were discouragement/despondency, pessimism, hopelessness, feeling unable to cope, helplessness, worthlessness, loss of confidence, and thoughts of death. The key symptoms of anhedonia were loss of interest in activities with others, being unable to enjoy activities with others, loss of interest in solitary activities, and being unable to enjoy solitary activities.

Results: Only the key demoralization symptoms of pessimism, worthlessness, and thoughts of death were significantly associated with DSM-IV major depression. For anhedonia, only showing less interest in activities with others, loss of interest in solitary activities, and being unable to enjoy solitary activities.

Conclusions: Social anhedonia (inability to experience pleasure deriving from social relationships) appears to be the more important feature of the type of depression commonly seen in physically ill patients.

Reviewer’s Comments: I am a little confused as to how the DSM-IV diagnoses were made in order to compare the diagnosis of MDD to the anhedonia and demoralization symptom findings of the instrument used. In short, was a structured clinical interview for DSM-IV administered? Either way, the findings add some evidence to support the symptom areas that clinicians should focus on in this diagnostically challenging population. (Reviewer-John G. Koutras, MD).

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Keywords: Medical Illness, Depression, Anhedonia

Print Tag: Refer to original journal article
A rapid rate of discontinuation of antidepressants across compound groups and diagnoses significantly reduces the time to onset of a subsequent illness episode.

**Background:** Much of the literature on antidepressants focuses on starting them: which to choose, how to sequence their use, dosing, augmentation, etc.

**Objective:** To determine how the rate of discontinuing antidepressants affects relapse risks for depression and other conditions for which antidepressants are used.

**Methods:** Clinical records from the University of Caligari’s (Sardinia, Italy) Lucio Bini Mood Disorders Center were used. Patients were prospectively followed up with retrievable detailed information as to diagnosis through routine use of standardized, semi-structured interviews, repeated tracking of patients using symptom scales, and detailed information as to treatment duration and dosing. Recovery from major depressive disorder, panic disorder, or for depression as part of bipolar I or II disorder was defined by reported clinical euthymia and a score of ≤7 on the Hamilton Depression Rating Scale. Eligible subjects also had their antidepressant electively discontinued after such recovery, remained clinically stable for at least 1 week after discontinuation, and had follow-up data for at least 1 year after that. The rate of antidepressant discontinuation was classified as either rapid (1–7 days) or gradual (≥2 weeks).

**Results:** Of 398 patients used in the analysis, 62% received tricyclic-like compounds, and 37.4% received new-generation medications. Overall, latency to time of relapse with rapid discontinuation was 0.4 times shorter than that of for gradual discontinuation. Gradual discontinuation was only slightly more common than rapid discontinuation (53% vs 47%, respectively). The latency time to a recurrence after rapid discontinuation was one-fourth that of gradual discontinuation and a fifth as long as the prior latency experienced when discontinuation was done gradually. When controlling for confounding covariates of recurrence (clinical course and severity, demographic and psychiatric history features, etc), discontinuation rate remained a significant factor in relapse latency. Only the type of antidepressant (relapse was sooner with new generation agents irrespective of discontinuation rate) and the elimination half-life (shorter half-life agents had greater impact of discontinuation rate) remained significant predictors, in addition to the discontinuation rates themselves. While significant across disorders, the effect of discontinuation pace varied by diagnosis but not by other clinical features (episodes per year, length of index episode).

**Conclusions:** The recurrence risk for depression and panic disorder is significantly heightened by rapid as opposed to gradual discontinuation of an antidepressant.

**Reviewer’s Comments:** The effect of antidepressant discontinuation rates across medication classes, diagnoses, and target symptoms seems to powerfully underscore the value of slower medication discontinuation and the importance of neurophysiologic adaptation to change in recurrence. While this study seems to reinforce what many already assume, the almost even split in the use of rapid versus gradual discontinuation was surprising. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Antidepressant Discontinuation, Time to Recurrence

Print Tag: Refer to original journal article
Alcohol Abuse and Bipolar Disorder Do Not Mix

Increased Risk for Suicidal Behavior in Comorbid Bipolar Disorder and Alcohol Use Disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

Oquendo MA, Currier D, et al:

J Clin Psychiatry 2010; 71 (July): 902-909

Among adults with bipolar disorder, >50% also have a lifetime alcohol use disorder, which increases their suicide attempt rate from 15% to 25%.

Background: Clinical studies have indicated an increased risk of suicide among patients with comorbid bipolar disorder and alcohol use disorders. There have been no epidemiologic studies to examine this risk in nonclinical populations.

Objective: To determine the risk of suicide in the general population in the context of bipolar disorder and substance abuse.

Design: An analysis of data from the National Epidemiologic Survey on Alcohol and Related Conditions.

Participants/Methods: Employees of the US Census Bureau interviewed 42,093 adults in the United States between 2001 and 2002 using a structured diagnostic interview designed for lay persons—the National Institute on Alcohol Abuse and Alcoholism Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version.

Results: 1643 individuals were identified as having bipolar I or II disorder in the survey, and 54% of these individuals also met lifetime criteria for an alcohol use disorder. Factors associated with this comorbidity included male gender, panic disorder, antisocial personality disorder, and earlier onset of hypomania or mania. Among adults with bipolar disorder, the suicide attempt rate was 15% in those without alcohol use disorders and 25% in those with alcohol use disorders, with an adjusted odds ratio (OR) of 2.25. Logistic regression analysis revealed that the increased risk was not due to an increased rate of other substance use in this cohort. Other independent predictors of suicide attempts were panic disorder (OR=2.13) and antisocial personality disorder (OR=1.56). In contrast to the authors’ hypothesis, other substance use disorders did not increase the rate of suicide attempts in adults with bipolar disorder. The rate of mental health care utilization was low among all individuals with bipolar disorder (33%) and did not differ between those with and without alcohol use disorders.

Conclusions: This epidemiologic study confirms the clinical observation that the rate of alcohol use disorders is very high among adults with bipolar disorder, occurring in most members of this population. Co-occurring bipolar disorder and alcohol use disorders lead to a very high suicide attempt rate of 25%, which climbs even higher in those who also have panic disorder or antisocial personality disorder. Unfortunately, only a minority of adults with bipolar disorder have sought treatment, regardless of their alcohol use.

Reviewer's Comments: Efforts should be made to educate the public about the symptoms, morbidity, and mortality of bipolar disorder and to improve access to psychiatric treatment. Individuals treated for alcohol use disorders should be carefully screened for the presence of bipolar disorder plus panic disorder and vice versa. (Reviewer-Charlotte O. Ladd, MD, PhD).

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Keywords: Comorbid Alcohol Use & Bipolar Disorders, Suicide Risk

Print Tag: Refer to original journal article
The role of mental illness history as a risk factor for suicide attempt might operate differently in the Chinese versus Western context.

**Objective:** To determine the relative prevalence of mental disorders compared to other circumstances as a suicide risk factor in rural Chinese individuals (age range, 15-34 years) and to analyze the interactions between mental illness, social support, and life events as they contribute to suicide risk in this population.

**Methods:** The psychological autopsy method can be a highly structured retrospective review process. For this study, 400 suicides by rural Chinese individuals aged 15 to 34 years were identified in the study provinces through centralized cause-of-death registries and the training of local physicians in suicide death reporting. For each suicide, a healthy, similarly aged comparison subject was identified to also complete an autopsy questionnaire and interview process. That process consisted of trained local interviewers talking with key informants of the deceased or control subject using the Structured Clinical Interview for DSM-IV to generate diagnoses and standardized ratings of social supports and significant recent life events. Sociodemographic information about each decedent and control subject was also obtained.

**Results:** 48% of suicide victims and 3.8% of controls met criteria for at least 1 current mental disorder. Among those, 34.9% were mood disorders, 11.2% were psychotic disorders, and 6.4% were substance use disorders. After controlling for sociodemographic features, social support, and stressful life event ratings, suicide victims were 10 times more likely to have any mental illness diagnosis, and male suicide victims were twice as likely to have a current mental illness diagnosis compared to females. Other contextual risk factors for suicide included low education level, not being married, having long- and short-term significant life events, and having a lower level of social support. But when controlling for relative associations, additive interactions were found only between low levels of social support and the presence of current mental illness as a risk factor for suicide.

**Conclusions:** While a concurrent psychiatric diagnosis is a significant risk factor for suicide among young rural Chinese individuals, the prevalence of psychiatric disorders, especially among women, was lower than that seen in younger suicide victims in the West. The impact of having a diagnosis appears to act through an interaction with poor social supports, and it involves mood disorders in only a plurality of cases.

**Reviewer’s Comments:** I found this study interesting in terms of its use of a structured psychological autopsy method and in the apparent cultural difference regarding the contributions of mental illness and social circumstances to suicide. Psychological autopsy techniques might deserve more attention, not just from the research community, but as a way to better structure quality improvement and event review practices. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: China, Suicide Risk, Psychological Autopsy

Print Tag: Refer to original journal article
Time Spent Depressed Strong Risk Factor for Suicide

Incidence and Predictors of Suicide Attempts in DSM–IV Major Depressive Disorder: A Five-Year Prospective Study.

Holma KM, Melartin TK, et al:

Am J Psychiatry 2010; 167 (July): 801-808

Prospectively, among multiple historical and social support risk factors that impact suicide risk for individuals with major depression, perhaps most dominant is simply the time spent depressed.

Background: Prospectively, many historical and social support factors impact suicide risk for individuals with major depressive disorder (MDD). Trying to winnow down a list of clinically meaningful risk factors for suicidal behavior has proven to be a significant challenge. The authors of this study argue that a good understanding of how risk for suicidal behavior "works" means understanding the dynamics between common risk factors and protective factors over time.

Objective: To investigate variations in the incidence of suicide attempts during different levels of depression among patients with unipolar MDD.

Design: Prospective long-term follow-up study of 249 psychiatric patients with MDD in Finland.

Methods: For 5 years, the Vantaa Depression Study followed up patients with an index episode of depression, prospectively tracking a range of social and clinical features as well as suicide attempts. MDD was identified through structured clinical interview. Baseline clinical measures included (1) several symptom rating scales for depressive symptoms and suicidality, (2) several standardized assessments of occupational and social functioning, and (3) a structured interview to identify and recall significant life events and stressors and quality of social relationships. General medical history and basic sociodemographic data were also obtained. Subjects were reassessed at 6 months, 18 months, and 5 years. Occurrence of suicide attempt was known through these evaluations and review of each patient's medical and psychiatric records.

Results: Of 249 subjects, 36 (14.5%) attempted suicide at least once during the 5-year follow-up, for a rate of 104.1 attempts/1000 patient-years. Cluster B personality traits did not confer higher risk. Risk for a suicide attempt was 21 times greater among those still meeting MDD criteria and was 4 times greater among those in partial remission. After removing nonsignificant variables, the time spent in major depressive episodes, time spent in partial remission, previous suicide attempt, age, and lower perceived social support were the primary predictors of suicide attempts. The time spent in depression was the most powerful predictor and was not significantly affected by other variables.

Conclusions: While state of social supports and prior history are important suicide risk factors over time, the time spent in depression appears to be the strongest cumulative predictor of suicide attempt risk in this study.

Reviewer's Comments: The study did not convincingly measure what it set out to measure, which was comparative cumulative impact of a range of risk and protective factors. For one thing, protective factors seemed less represented than were risk factors among what was measured. Also, some factors, like time spent with a diagnosis, were perhaps more effectively captured than others, like time spent being impulsive or hopeless or time affected by a stressor, thus possibly biasing the findings as to the relative importance of these features. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Suicide, Major Depression, Prospective Risk Factors

Print Tag: Refer to original journal article
Childhood Adversities Impact Lifetime Suicide Risk

*Childhood Adversities as Risk Factors for Onset and Persistence of Suicidal Behaviour.*

Bruffaerts R, Demyttenaere K, et al:

*Br J Psychiatry 2010; 197 (July): 20-27*

Lifetime suicide risk is powerfully predicted by childhood adversities before the age of 18 years.

**Background:** Different research approaches are used to help us understand suicide risk. One concern is that the role of social experiences and developmental factors in suicide risk has been underappreciated.

**Objective:** To conduct cross-national analyses of the associations between a range of childhood adversities and subsequent risk of suicidal behavior.

**Methods:** The World Mental Health Survey was conducted in 21 regionally and economically diverse countries. The survey involved face-to-face structured diagnostic interviews performed by locally trained workers. Sociodemographic and historical information were gathered, including information about prior suicidal behaviors. Individuals “ruling in” for a disorder from this interview, and a probability sample of other respondents, received a more detailed follow-up and focused interview that assessed several areas of special interest, including an inventory recall of childhood adversities. Suicidal behavior histories were obtained using the structured Composite International Diagnostic Interview-3.0 suicidality module that distinguished between ideation, attempts, plans, planned attempts, and unplanned attempts. Childhood adversities included physical abuse, sexual abuse, parental death, neglect, divorce, other parental loss, family violence, physical illness, and financial adversity before the age of 18 years.

**Results:** The data were based on responses from 55,299 subjects. Childhood adversities were common, ranging from 2% to 12% of those randomly interviewed in their respective communities. Overall, lifetime suicide attempt was reported in 2.7% of respondents and ideation was reported in 9.4% of respondents. Among ideators, 55.2% of those with a plan made an attempt, whereas only 15.1% of those without a plan did so. Of the 9 childhood adversities assessed, 8 were associated with significantly increased risk of later suicide attempt and ideation: physical and sexual abuse had the highest odds ratios indicating excess risk (OR= 3.7-5.7 and 2.7-3.4, respectively). Overall, adversities were more strongly associated with attempt and ideation than planning. These associations held when controlling for mental illness history, suggesting that mental disorders had a minimal impact on this association between early adversity and later suicidality. The relationship between adversity and attempt was strong in childhood, waned in teenage years, and strengthened again in later adulthood. Sexual and physical abuses were the only adversities significantly associated with persistence of all suicidal behaviors measured.

**Conclusions:** Even when controlling for mental illness and other factors, childhood adversities, especially aggressive ones, yield substantial risk for later suicidality, particularly impacting the enduring effects on suicidal ideation.

**Reviewer's Comments:** While the study widens the range of dimensions (types of adversities, changing effects over time) to consider in weighing the relative impact of childhood adversity on later suicidal behaviors, the study remains a cross-sectional recollection of longitudinal events, underscoring the need for more prospective studies of these complex factors. The results underscore the potential value of careful history taking of childhood events. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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**Keywords:** Suicide, Etiology, Childhood Adversity

**Print Tag:** Refer to original journal article
Whenever clinically feasible, antipsychotic use should be limited in older adult patients to decrease the risk of a cerebrovascular adverse event.

**Background:** On the basis of data that emerged from clinical trials, the U.S. Food and Drug Administration has issued warnings regarding the increased risk of cerebrovascular adverse events due to second-generation antipsychotic drugs, such as risperidone, olanzapine, and aripiprazole, in elderly demented patients.

**Objective:** To compare the effects of second-generation versus first-generation antipsychotic agents on the risk of cerebrovascular adverse events in older adults dwelling in the community.

**Design:** A propensity-matched retrospective cohort study.

**Methods:** Medical claims data were obtained from 94 different managed care organizations encompassing >60 million patients from January 2000 to June 2008. The data are longitudinal, with a mean member enrollment time of 2 years. To examine the risk of cerebrovascular adverse events, a retrospective cohort design was utilized to compare propensity score-matched older adults taking second-generation versus those taking first-generation antipsychotics. The second-generation antipsychotic cohort involved users of clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. The first-generation antipsychotic cohort involved users of every available first-generation antipsychotic, including thioridazine. The primary outcome measure was the occurrence of hospitalization or emergency room visit due to cerebrovascular adverse events within 1 year after the index date.

**Results:** 39,587 older adult patients were included, with 26,991 patients using first-generation antipsychotics and 12,596 using second-generation antipsychotics. The risk of cerebrovascular adverse events was 7.46% for second-generation antipsychotic users and 6.85% for first-generation antipsychotic users (difference not significant). The duration of therapy between 30 and 90 days and >90 days conferred increased risk compared to <30 days. An almost 3-fold increased risk was associated with concomitant anticoagulant use.

**Conclusions:** There is no significant difference in cerebrovascular adverse events between first- and second-generation antipsychotic use in patients aged ≥50 years. Both types of antipsychotic drugs increase the risk of a cerebrovascular event by approximately 7%.

**Reviewer's Comments:** It is unclear if the higher risk for those who are anticoagulated involves the underlying condition requiring anticoagulation, the risk for a cerebral hemorrhage, or a combination of the two. The pathophysiology for the increased risk of cerebrovascular events with antipsychotics is unclear, but both first- and second-generation antipsychotics are known to increase platelet aggregation due to serotonin changes and are associated with ventricular arrhythmia and thromboembolism. (Reviewer-John G. Koutras, MD).

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Keywords: Cerebrovascular Accident in Elderly, Risk

Print Tag: Refer to original journal article
Children of lesbian parents appear to be psychologically well-adjusted, further supporting the premise that the quality of the parenting matters more than the sexuality of the parents.

**Background:** According to U.S. census data, an estimated 270,313 American children were living in households of same-sex couples in 2005, and nearly twice that number had a single gay or lesbian parent. Despite >30 years of cross-sectional research demonstrating that the psychological adjustment of children is unrelated to their parents’ sexual orientation, the legitimacy of lesbian and gay biological, foster, and adoptive parenting is still under scrutiny. Relatively little has been reported about the psychological well-being of adolescents who have been raised in lesbian families since birth. Prior studies have focused on adolescents who were conceived in heterosexual relationships before their mothers divorced and came out as a lesbian. The US National Longitudinal Lesbian Family Study (NLLFS) was initiated in 1986 to provide prospective data on a cohort of American lesbian families from the time the children were conceived through donor insemination (DI) until they reach adulthood.

**Objective:** To determine the psychological adjustment of adolescents conceived via donor insemination by a lesbian mother and who were living in same-sex–parented families.

**Methods:** In this prospective study, 77 families with 78 17-year-old offspring were analyzed for general well-being using the Child Behavioral Checklist (CBCL) scores and (1) sperm donor status (known, as-yet-unknown, or permanently unknown donor), (2) parental relationship continuity (offspring’s mothers are together or separated), and (3) experiences of stigma. The comparison group drawn from the CBCL database consisted of maternal reports on 49 girls and 44 boys, all aged 17 years.

**Results:** Contrast analyses found that the 17-year-old NLLFS girls and boys were significantly higher in social, school/academic, and total competence ratings and were significantly lower in rule-breaking, aggressiveness, and externalizing problem behavior ratings than the comparison group. No CBCL differences were found among the NLLFS sample analyzed for sperm-donor status or for the status of whether the lesbian parents remained partnered. However, when analyzed for experiencing stigmatization, the results were somewhat mixed, with significantly higher internalizing and total problem behavior scores.

**Conclusions:** Adolescents from lesbian families demonstrate higher levels of social, school/academic, and total competence ratings than gender-matched normative samples of American teenagers.

**Reviewer’s Comments:** Instead of including teacher and self reports, this study is based on parental self-report solely, and a lesbian parent report is probably biased in a study designed to analyze the healthfulness of lesbian parenting. Also, the comparative sample should probably not be "off the shelf" from the CBCL database, but should be carefully collected prospectively in the NLLFS. (Reviewer-John G. Koutras, MD).

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**Keywords:** Lesbian Parenting, Adolescent Adjustment, Psychopathology

**Print Tag:** Refer to original journal article
In a population of individuals with childhood-onset obsessive-compulsive disorder, most stayed in treatment and had subclinical or only mild symptoms at follow-up several years later.

**Background:** Obsessive-compulsive disorder (OCD) is an often debilitating anxiety disorder that usually begins in childhood. The prognosis of childhood-onset OCD is not clear.

**Objective:** To determine the chronicity and morbidity of childhood-onset OCD by evaluating former patients of an OCD clinic at Maudsley Hospital in London.

**Participants/Methods:** All patients (age range, 10-18 years) who received a diagnosis of OCD during a 10-year study interval were invited into the study (n=276). Of these, 142 (41%) participated in the study, which used a computerized screening assessment to determine the presence of current OCD or other Axis I disorders. OCD severity was assessed at baseline and during follow-up using the Yale Brown Obsessive Compulsive Scale (YBOCS). Daily functioning in relationships, work, school, and home was assessed using the Work and Social Adjustment Scale (WSAS).

**Results:** The mean age at diagnosis was 13.5 years, the mean duration of OCD was 3.7 years, and the YBOCS severity at baseline was moderate at 21. The average length of follow-up was 5.1 years, with a mean age at follow-up of 18.6 years. At follow-up, 41% of participants met the criteria for OCD, 25.4% had generalized anxiety disorder (GAD), 15.9% had a depressive disorder, and 15.9% had a tic disorder. YBOCS scores were much less at follow-up than at baseline: one-third of participants scored in the subclinical range at follow-up, one-third scored in the mild range, 30% scored in the moderate range, and 2% scored in the severe range. The mean YBOCS score at follow-up was 14. Most participants reported improvement, with only 8% reporting worsening of symptoms. WSAS scores indicated that most participants had only mild to moderate levels of interference in work and social functioning. Two-thirds of participants had continued treatment for OCD after discharge, with most receiving pharmacotherapy and 25% receiving psychotherapy. The presence of tics at baseline predicted recovery from OCD, whereas chronicity of OCD at baseline predicted persistence at follow-up.

**Conclusions:** In the largest long-term follow-up of pediatric OCD to date, 60% of participants at follow-up at an average of 5 years later did not meet criteria for OCD, perhaps in large part due to ongoing treatment for most patients. Almost two-thirds of participants rated themselves as very much improved with respect to OCD, although 25% met criteria for GAD.

**Reviewer’s Comments:** These are reassuring results in many respects and support the ongoing treatment of/support for children with OCD. Since the duration of OCD at baseline predicted persistence of this illness, early diagnosis and intervention is imperative for children with OCD. Given the relapsing/remitting course of OCD over time, it behooves clinicians to provide timely, evidence-based treatment for those who are newly diagnosed and for those who have experienced a resurgence in symptoms. (Reviewer-Charlotte O. Ladd, MD, PhD).

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Keywords: Childhood-Onset OCD, Outcomes

Print Tag: Refer to original journal article
A structured method for matching psychotherapy type with a given patient improves outcomes for psychodynamic therapy but not for cognitive-behavioral therapy.

**Background:** While there is more than enough evidence that a range of psychotherapies can be effective, the methods are less developed for discriminating which approach is best for which condition or patient.

**Objective:** To study the outcomes-related impact of using systematic treatment selection methods to match patients to either psychodynamic therapy (PDT) or cognitive-behavioral therapy (CBT).

**Methods:** In an established German mental health facility, patients receiving psychotherapy were eligible to be randomized to participate either in psychotherapy as per usual process or psychotherapy as assigned using a systematic selection method. The method was iteratively developed by the psychotherapy unit staff to identify a menu of common therapeutic goals that matched against the different approach assumptions. For example, goals of "ability to fully allow the experience of emotions" sorted to PDT, while "modifying or changing specific behaviors" weighted to CBT. Outcomes included patient-rated questionnaires as to satisfaction and value of therapy 6 months after termination, as well as change in scores on several widely used symptom checklist inventories (the Symptom Checklist-90) and measures of overall quality of life (Short Form-8).

**Results:** 291 patients were randomized. Overall, patients improved as well if they received psychotherapy through the structured treatment selection method compared to receiving psychotherapy as determined by usual care referral methods. However, when comparing the value of this selection method by psychotherapy type, there was a better long-term outcome among those patients who received PDT if they were matched to it through the study method as opposed to usual care practices.

**Conclusions:** Patients who get PDT might improve more from it if that choice was made through a structured selection method.

**Reviewer's Comments:** While this study seems to encourage directions for more careful and successful use of psychotherapy, the narrow detail as to exactly how the criteria were developed and applied is a substantial limitation of the paper and its replicability. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Psychotherapy, Systematic Selection, Efficacy

Print Tag: Refer to original journal article
It is probably best to diagnosis delirium using an assessment instrument other than the Mini-Mental State Examination, such as the Memorial Delirium Assessment Scale (MDAS) or the Confusion Assessment Method (CAM).

**Background:** Health care workers fail to recognize delirium in about 50% of cases. Consensus from an expert panel identified several clinical features of delirium: acute onset and fluctuating course, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, increased or decreased psychomotor activity, and sleep-wake cycle disturbance. Delirium typically presents as either hypoactive (lethargy, psychomotor retardation), hyperactive (vigilance and often hallucinations, psychomotor agitation), or a mixed form which has features of both.

**Objective:** To determine the diagnostic accuracy of various bedside delirium instruments.

**Methods:** Searches of MEDLINE® and Embase® were conducted. Some of the main criteria were that the index instrument be feasible in a clinical setting without requiring special equipment, and that the index instrument could be performed by a nonexpert.

**Results:** 25 studies were suitable for data extraction and synthesis. Eleven bedside instruments with data on diagnostic accuracy met the inclusion and exclusion criteria. Application of the referenced test, a DSM-based diagnosis by a specialized physician, was identical in each study. Of the 11 bedside instruments, positive findings on the Global Attentiveness Rating (GAR), Memorial Delirium Assessment Scale (MDAS), Confusion Assessment Method (CAM), and Delirium Observation Screening Scale (DOSS) all had a likelihood ratio (LR) >5 for diagnosing delirium. The ubiquitous Mini-Mental State Examination (MMSE) was the least useful for identifying patients with delirium (LR, 1.6).

**Conclusions:** The CAM has become the most widely used standardized delirium instrument for clinical and research purposes during the last 2 decades, and its use is supported by this quantitative review.

**Reviewer's Comments:** The authors appeared to favor the use of the CAM, and they state that some training is recommended for optimal use: http://hospitalelderlife program.org/pdf/. In reviewing the CAM, I would also recommend the training, as it seems very subjective and simple. However, the Clinical Global Assessment Scales, for example, are also highly subjective, and yet have been shown to be valid. What is perhaps most interesting is that a simple assessment, such as the CAM, soundly outperforms the MMSE in this analysis. The CAM is a more naturalistic assessment, in that it scores a basic interview with the patient, and perhaps the MMSE is too structured for such a global assessment as investigating delirium. In other words, perhaps you “cannot see the forest for the trees” when using the MMSE, thus giving a higher score if the patient is in the waning phase of their delirium when assessed. (Reviewer-John G. Koutras, MD).

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Keywords: Delirium, MMSE CAM

Print Tag: Refer to original journal article
Oxytocin levels are similar in cohabitating mothers and fathers during the early phases of parenthood. Oxytocin is connected with nurturing in new moms and playful interactions in new dads.

**Background:** Oxytocin is known to stimulate pro-social behavior and maternal behavior in mammals. Parental bonding is critical to healthy development in offspring, and preclinical studies show that the quality of bonding is related to levels of oxytocin. There have been no normative studies to examine the oxytocin concentration in new mothers and fathers.

**Objective:** To collect data on oxytocin concentrations in new parents up to 6 months postpartum and to correlate these values with each other and with parental behavior.

**Participants/Methods:** 80 pairs of new mothers and fathers were recruited into the study, which was conducted in Israel among middle-class adults older than age 20 years and with at least a high school education. The investigators made 2 visits to the participants' home: the first within 1 month of parturition and the second at 6 months after birth. Blood samples were drawn at each visit from both parents for analysis of oxytocin levels. Parent-child interaction was videotaped for 10 minutes at the first visit and scored for several factors: parent gaze, parent affect, parent vocalizations, and parent touch. "Affection parenting" behavior was defined as the sum of positive affect, "motherese" vocalization, and affectionate touch. "Stimulatory parenting" behavior was defined as the sum of proprioceptive touch, object presentation, and stimulatory touch.

**Results:** Oxytocin concentrations were similar in new mothers and fathers and both increased over time from 1 to 6 months postpartum. Oxytocin was not related to any demographic variables, use of medication, method of delivery, feeding style, postpartum interval, or time since breastfeeding. Individual oxytocin levels were highly stable and interrelated between spouses. Parental behavior was associated with oxytocin in a manner that differed between fathers and mothers. Maternal oxytocin concentrations were correlated with affectionate behavior toward the neonate ($r=0.33$). In contrast, paternal oxytocin concentrations were proportional to the time spent in stimulatory parenting behavior ($r=0.3$). The converse was not true: maternal oxytocin was not correlated with stimulatory play and paternal oxytocin was not associated with affectionate play.

**Conclusions:** These data suggest that oxytocin concentrations in new parents increase over time, are stable within the individual, and are interdependent within the couple in a manner that is consistent over time. A similar ‘endocrine fit’ has been observed for other neuroendocrine hormones, including cortisol, vasopressin, and prolactin. Moreover, oxytocin was associated with the more stereotypical behavior associated with each parent: nurturing in women and stimulating behavior in men. This may be related to the degree of reward parents get from these different types of interaction.

**Reviewer's Comments:** Now that normative values have been established in a well-educated, middle-class sample of adults older than age 20 years, future studies should compare oxytocin concentrations through the postpartum period in couples at higher risk. (Reviewer-Charlotte O. Ladd, MD, PhD).

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Keywords: Parenting, Oxytocin

Print Tag: Refer to original journal article
Suicide Risk Not Increased by AED Use in Epilepsy

Suicide-Related Events in Patients Treated With Anti-Epileptic Drugs.

Arana A, Wentworth CE, et al:


The FDA issued a warning regarding an apparent increase in suicidality associated with the use of antiepileptic medications. This study suggests that such a risk may exist, but not for patients with epilepsy.

Background: The U.S. Food and Drug Administration released a safety warning in 2008 that summarized an analysis of aggregated results from clinical drug trials of 11 antiepileptic drugs (AEDs) that showed the risk of suicidality (ideation or behavior) to be two time higher with AEDs than that for placebo. The authors criticize the evidence on which that warning was based because it pooled studies with different or limited definitions of suicidality, did not capture the range of clinical practice, and did not adequately compare diagnostic-specific relative risk.

Objective: To determine if AED use is associated with increased suicidality risks among patients with various diagnoses.

Methods: The authors used The Health Improvement Network (THIN), which is a very large database of >6.7 million patients in the United Kingdom. The data in THIN is standardized and entered in general practitioner's offices to capture various features of treatment in primary care. Within THIN, the authors constructed a cohort of individuals without a family or personal prior history of suicide attempt and who were enrolled in practice for at least 6 months between July 1, 1988, and March 31, 2008. In that cohort, the authors looked for the incidence of suicide-related events among patients with epilepsy, depression, and bipolar disorder, whether or not they used AEDs, and then compared the incidence of such events between use and non-use groups.

Results: >5 million patients were retrospectively followed up for a mean of 6.2 years. The relationship between AED use and suicide-related behaviors varied by diagnosis. The use of AEDs was not associated with a significantly elevated occurrence of suicide-related events among those with epilepsy or bipolar disorder. It was raised, however, among those with depression or those with AED use who did not have depression or epilepsy.

Conclusions: A large population analysis found that AED use was associated with suicide-related behaviors among those with depression. However, AED use was not associated with suicide-related behaviors among those with epilepsy or bipolar disorder.

Reviewer's Comments: This seems an important study, but one that leaves key issues unresolved. The findings suggest that the recent concern and caution about the use of AEDs with respect to suicidality may have been far too bluntly applied. Unfortunately, it allows continued uncertainty as to what to make of all of this because it does not move forward with the precision needed to understand where that risk may lie, such as possibly being different among different medications or how/why AEDs may cause this problem only for certain diagnoses. That said, the relationship with depression should alert clinicians to monitor patients in treatment for depression on AEDs. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Suicide, Anti-Epileptic Medications, Risk

Print Tag: Refer to original journal article
This large population genome-wide association study indicates that many genes and a lot more research will be involved before a clear picture emerges of the genetic basis of depression.

**Background:** A long accumulation of twin and family studies have supported the idea that there is a large genetic component to an individual’s risk of major depressive disorder (MDD), with estimates of the genetic contribution to having MDD ranging widely from 17% to 75%. Precision has been more elusive in the search for particular genetic culprits (particular molecular products and events that lead to MDD).

**Objective:** To identify genes highly associated with the onset of MDD by including only cases with reliably assessed recurrent unipolar depression to create a study sample with more consistently defined and more clearly serious conditions.

**Methods:** Patients seen at 3 clinical centers in the United Kingdom were eligible for study entry if they had DSM-IV or ICD-10–defined recurrent major depression of at least moderate severity using structured clinical interviews. Single nucleotide polymorphism (SNPs) distribution was analyzed and compared to results of 2 other cohort genetic association studies, one in Munich and another in Lausanne.

**Results:** SNPs in a genome location known as *BICC1* had statistical evidence suggestive of an association with major depression. However, when comparing findings from the other large Munich and Lausanne studies for comparison, those showed some evidence for association with a different gene location—*NLGN1* on chromosome 3—and not with *BICC1*.

**Conclusions:** A gene association identified in 1 large (presumably more robustly defined) population for depression did not clearly identify associated genes, nor did it find associated genes that were similar to those found in 2 other large genome-wide association studies.

**Reviewer's Comments:** This study underscores the point that specific genes likely only contribute minor effects on the multiple-factor genesis of depression. One wonders what new breakthroughs, in terms of methodology, beyond broad association searches will be needed to move forward our understanding in this area. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Major Recurrent Depression, Genetic Associations

Print Tag: Refer to original journal article
Microdeletions in genes involved in synaptic connections are associated with autism spectrum disorders and dyslexia.

**Background:** Autism spectrum disorders (ASD) cluster in families, and recent genetic studies have suggested that impairments in synaptic connections may be 1 pathway of vulnerability to these disorders. Both the cadherin and neurexin gene families have been implicated in ASD, as have variations in the copy number of some genes. Related to the neurexin genes is the *CNTNAP2* gene, a microdeletion of which has been implicated in many neuropsychiatric conditions such as schizophrenia, epilepsy, autism, and learning disabilities. Microdeletions in another candidate gene, *DOCK4* (dedicator of cytokinesis), have also been documented in siblings with ASD.

**Objective:** The authors investigated whether microdeletions in similar genes, *IMMP2L-DOCK4* and *CNTNAP5*, were present in a Dutch family with clustered ASD.

**Participants/Methods:** The selected family included a proband and his affected brother as well as first-degree relatives and extended family members. All family members provided saliva samples for DNA extraction and completed a social communication ability assessment, the Social Responsiveness Scale (SRS). A novel microdeletion in *CNTNAP5* led to DNA sequencing of an additional 143 ASD families. DNA was analyzed using quantitative PCR.

**Results:** The *IMMP2L-DOCK4* microdeletion was not found associated with ASD in this family. It was present, however, in several family members with a reading disorder. This microdeletion was then screened for in 606 individuals with dyslexia. Another microdeletion in *DOCK4* was found to co-segregate with dyslexia in this population. A microdeletion in *CNTNAP5* was found in both siblings affected with ASD, inherited from their father, who was also reported to have autistic traits. Genomic analysis of other ASD families revealed several other missense changes in this same gene.

**Conclusions:** This study highlights another candidate risk factor for ASD: a microdeletion in *CNTNAP5* that stops transcription. There were no exonic deletions in this gene among control subjects. This protein is a member of the human contactin-associated protein family, which includes transmembrane proteins thought to be involved in cell adhesion and cell recognition. In contrast, *DOCK4* microdeletions co-segregated with dyslexia. *DOCK4* is involved in guanine-dependent dendritic growth in neural cell lines. The authors postulate that microdeletions in both these genes within the family studied may have contributed to a more severe ASD phenotype in affected individuals, creating an additive effect.

**Reviewer’s Comments:** Future studies in the genetic variation of ASD may help explain the varying phenotypes seen in this spectrum of disorders. (Reviewer-Charlotte O. Ladd, MD, PhD).

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Keywords: Autism Spectrum Disorders, Dyslexia, Genotyping

Print Tag: Refer to original journal article
Tai chi appears to be useful as a treatment for fibromyalgia when added on to ongoing medical treatment.

**Background:** Evidence-based guidelines suggest that fibromyalgia is best managed with a multidisciplinary approach, involving medication, cognitive behavioral therapy, education, and exercise. Tai chi is a Chinese practice which combines meditation with slow, gentle, graceful movements, as well as deep breathing and relaxation, to move vital energy (or qi) throughout the body. Tai chi may be particularly well-suited for fibromyalgia due to its mind-body attributes.

**Objective:** To compare the physical and psychological benefits of tai chi with those of a control intervention that consisted of wellness education and stretching.

**Methods:** 66 participants with fibromyalgia were randomly assigned in equal numbers to either the tai chi or control intervention. The tai chi intervention consisted of twice weekly 60-minute sessions taught by the same tai chi master, lasting 12 weeks. After 12 weeks, participants were encouraged to maintain their tai chi practice with an instructional DVD until the follow-up visit at 24 weeks. The control condition consisted of 60-minute sessions which were composed of a 40-minute educational component taught by a variety of health professionals and 20 minutes of stretching, lasting 12 weeks. Participants were allowed to continue in their usual treatment for fibromyalgia, including medications, for the duration of the study. The primary outcome measure was the change in the Fibromyalgia Impact Questionnaire (FIQ) score from baseline to the end of the 12-week intervention.

**Results:** The observed benefits for tai chi in fibromyalgia patients exceeded specific thresholds for clinically significant improvements in the FIQ score and in the measures used to assess pain, sleep quality, depression, and quality of life. These benefits were sustained at 24 months. The mean significant difference between the tai chi group and controls for the total FIQ score was 18.4 points (-26.9 vs -9.8, respectively).

**Conclusions:** Tai chi appears to be a safe and effective treatment for fibromyalgia.

**Reviewer's Comments:** As the authors noted, this trial did not utilize a double-blind study design (no validated sham tai chi model). However, one can probably devise a sham model, which incorporates Eastern reflections and stretching and would not have a true mind-body interfacing component if taught separately. If the subjects were recruited with knowing that they may be assigned to a Chinese martial-arts-type therapy, such as tai chi, and then ended up with didactic sessions and stretching, as in the control arm, it may come as a disappointment, affecting a placebo response. (Reviewer-John G. Koutras, MD).

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Naltrexone Plus Bupropion Combat Obesity

Effect of Naltrexone Plus Bupropion on Weight Loss in Overweight and Obese Adults (COR-I): A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial.

Greenway FL, Fujioka K, et al:

Lancet 2010; 376 (August 21): 595-605

Naltrexone, either 16 or 32 mg, in combination with bupropion 360 mg, appears to be effective in causing weight loss.

Background: Combined treatment with sustained-release naltrexone and bupropion was developed as a possible obesity treatment, given that this combination would presumably stimulate hypothalamic proopiomelanocortin neurons with bupropion while simultaneously blocking proopiomelanocortin autoinhibition with naltrexone. The synergism of these medications in midbrain dopamine areas reduces food intake, suggesting that another potential mechanism of action might be modulation of mesolimbic reward pathways. Initial studies in overweight and obese adults suggest that treatment with the combination of bupropion and naltrexone produces greater weight loss than the sum of the individual monotherapies.

Objective: To report the results of a large study comparing the efficacy of 2 doses of combination therapy with naltrexone plus bupropion for weight loss.

Methods: The Contrave Obesity Research study was a 56-week phase-3 randomized, double-blind, placebo-controlled study. Participant ages ranged from 18 to 65 years. The body mass index (BMI) ranged from 30 to 45 kg/m2 in those with uncomplicated diabetes or from 27 to 45 kg/m2 in those with controlled hypertension, dyslipidemia, or both. Participants were randomly assigned in a 1:1:1 ratio to receive 1 of the following fixed daily dose combinations of sustained-release naltrexone/sustained-release buproprion: 32 mg/360 mg; 16 mg/360 mg; matching placebo. Doses were divided into twice daily dosing. All patients were given diet and physical activity instruction, although compliance was not assessed. The primary outcome was change in body weight.

Results: 1482 women and 260 men participated. Weight loss in participants assigned to naltrexone plus bupropion, either lower- or higher-dose naltrexone, was sustained for the duration of the 56-week trial and was significantly greater than the placebo group (5%-6% body weight decrease vs 1.3 % decrease for placebo). Greater weight loss and a higher proportion of participants achieving weight loss of ≥5% were seen in the naltrexone 32 mg/bupropion group than in the naltrexone 16 mg/bupropion group. Participants assigned to combination treatment showed significant improvements from baseline to 56 weeks in waist circumference, insulin resistance, and concentration of HDL cholesterol, triglycerides, and high-sensitivity C-reactive protein compared with the placebo group. Adverse events were mostly limited to nausea that was mild to moderate in intensity, transient, and did not result in discontinuation.

Conclusions: Naltrexone/bupropion combination treatment appears to be well-tolerated and effective for weight loss.

Reviewer's Comments: Of course, a 56-week study does not demonstrate that weight loss can be sustained, or furthered, on a medication. A 2-year or greater time period would provide a much fuller picture. One interesting trend was that, around 48 weeks, the naltrexone 16-mg group was gaining back weight, whereas the 32-mg group held steady. (Reviewer-John G. Koutras, MD).

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Keywords: Obesity, Weight Loss, Drug Treatment, Naltrexone, Buproprion

Print Tag: Refer to original journal article
A collaborative care model for the treatment of depression using telemedicine proved clinically effective, but costly.

Background: Rural residents are less likely to receive treatment for mental health disorders, to receive lower quality of care, and to get care later in their illness. Limitations on any health care and adequate numbers of physicians and specialists in rural settings underscore the importance of thinking about collaborative care models for getting access to depression care and to perhaps using telemedicine methods to do so.

Objective: To determine the cost-effectiveness of a rural telemedicine-based depression collaborative care intervention.

Methods: The study used Veterans Affairs (VA) community based outpatient clinics, which are satellites of VA medical centers. Patients were identified using routine annual Patient Health Questionnaire (PHQ-9) for depression screening and were randomly assigned to the study intervention or to usual care. A group of such centers adopted a collaborative care model. That model used PHQ-9 screening and tracking of depression as a guide for care managers to triage patients’ needs and to target routinized psychiatric feedback and review in order to coordinate adherence to stepped care protocols for treatment decisions by primary care providers. The tested intervention used off-site psychiatrists, care manager RNs, and pharmacists to coordinate their interactions for guided care to patients via Web-based and telephonically based tracking of patient scores, progress, and treatment recommendations. These forms of communication were also used to regularly maintain contact with patients using standardized review protocols to track different issues (symptoms, side effects, compliance, etc) according to each patient’s level of care. Patients were followed-up using the 6-month and 12-month scores on the 20-item Symptom Checklist as well as validated functional and quality of life scores. This information added to evidence of response to treatment of depression, depression-free days (DFDs), as well as to calculate any Quality Adjusted Life Year (QALY) change. Patient-recorded expenses as well as costs of services used from VA records, along with QALY data, allowed the authors to measure QALY-adjusted cost-effectiveness of the intervention.

Results: 177 patients had the intervention, while 218 received usual care. The intervention group experienced significantly greater improvement in calculated QALY compared to the controls. However, the intervention was very costly: the incremental cost was $85,634/QALY improvement.

Conclusions: A collaborative care intervention for depression using telemedicine to link off-site collaborating providers (care manager, pharmacist, psychiatric component) to rural primary care practices proved effective at improving outcomes, but it also proved expensive.

Reviewer’s Comments: Using a telemedicine-supported collaborative care model as a solution for access to effective care will need to become further cost-efficient. This effort was more expensive for each QALY gained than was collaborative care used in urban settings. Some potential efficiencies suggested could come from rethinking the use of a pharmacist and more streamlining of documentation tasks. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Collaborative Care, Depression, Telepsychiatry

Print Tag: Refer to original journal article
Computer-delivered interventions for alcohol and tobacco use appear to have a small but meaningful impact on reduction of use.

**Background:** Computer-delivered treatments for substance use disorders offer a promising solution to accessibility issues for group or individual therapy programs by decreasing costs and having greater and more confidential access. During the last 2 decades, several computer-based and computer-aided interventions for substance use have been developed and tested empirically. Some interventions have been used as an adjunct to therapist-delivered treatment, while others have essentially been stand-alone interventions. Core components of interventions have included cognitive-behavioral therapy (CBT), chat features, tailored messaging, and normative feedback (comparing one's substance use to a demographically similar comparison group).

**Objective:** To examine the overall effectiveness of computer-delivered interventions for the use of alcohol and tobacco, as well as to examine whether the program’s effectiveness is associated with any treatment characteristics.

**Methods:** A search was conducted using PubMed and PsychINFO®. The meta-analysis included 42 effect sizes obtained from 34 studies, with a total of 10,632 participants. Studies were coded by the following potential characteristics of treatment moderators: normative feedback, chat features, entertainment features (videos, animation, etc), inclusion of a module devoted to relapse prevention, and number of treatment sessions.

**Results:** The average effect size ($d$) of studies in the meta-analysis was $d=0.20$, which is considered a small effect size. Alcohol studies produced significantly higher effect sizes ($d=0.26$) than tobacco studies ($d=0.13$). No significant differences were found as a function of treatment location, provision of normative feedback, chat feature, entertainment features, emphasis on relapse prevention, or number of treatment sessions.

**Conclusions:** Computer-delivered interventions reduce tobacco and alcohol use significantly with a small effect size.

**Reviewer's Comments:** I believe that computerized substance use treatment modalities hold greater promise than the results of this meta-analysis may suggest. I wonder about the sophistication of the programs developed because a finding of this study was that off-line programs produced significantly higher effect sizes than Web-based programs, which seems very counterintuitive. For example, an online program that utilizes a useful chat feature seems as though it would be more effective than just a computer program. One other finding of this study is that the computer-delivered interventions were more effective for reductions in substance abuse as opposed to abstinence, which is no surprise. (Reviewer-John G. Koutras, MD).

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Keywords: Substance Use Disorders, Alcohol, Tobacco, Online/Off-Line Programs

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