

PSYCHIATRY ALERTS NOS

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Concussion and Suicide Risk

In a Canadian population-based study, concussions were associated with a 3-fold increase in the long-term risk of suicide. Risk was further increased in patients whose concussions occurred on a weekend, presumably as a result of recreational rather than occupational injury.

Methods: Claims data were examined for the entire province of Ontario over a 20-year period. The study cohort consisted of adults who had experienced a concussion but were not hospitalized within 2 days of the event (to exclude those with severe traumatic brain injury). Suicides were identified from official death certificates. The data sources also provided information on psychiatric diagnoses, health care utilization, and mechanism of suicide; but much other information was lacking, including social stress, life events, and other suicide risk factors.

Results: More than 235,000 adults experienced a concussion during the 20-year study period. About half of the patients were men, and the mean age was 41 years. A total of 667 suicide deaths occurred over a median follow-up of 9.3 years, equivalent to an annual rate of 31 deaths per 100,000 persons—3 times the population norm. In patients whose injury occurred on a weekend, the suicide rate was 39 per 100,000, about 4 times the population norm. Suicide was associated with additional risk factors: male gender, low socioeconomic status, a prior psychiatric diagnosis, and a prior suicide attempt. Suicide risk was increased as a function of the number of concussions a person experienced.

Discussion: The implications of concussions are often not considered because of the mistaken beliefs that they cannot be identified on medical imaging, do not require follow-up, and that the neurologic symptoms resolve quickly. Information on concussions is not routinely elicited when assessing a patient's history. However, these results suggest that greater attention to long-term care after a concussion could prevent some suicides.

Fralick M, Thiruchelvam D, Tien H, Redelmeier D: Risk of suicide after a concussion. *Canadian Medical Association Journal* 2016; doi 10.1503/cmaj.150790. From the University of Toronto, Canada; and other institutions. **Funded by the Canada Research Chairs program; and other sources. The authors did not include disclosure of potential conflicts of interest.**

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Postpartum Bipolar/Psychotic Relapse

Women with a history of bipolar disorder or a previous episode of postpartum psychosis have a 1 in 3 chance of relapse during the postpartum period, according to results of a meta-analysis.

Methods: A comprehensive literature search identified all English-language studies investigating patients with a diagnosis of bipolar disorder and/or a history of a psychotic or manic episode following childbirth. Included studies (n=37; 5700 deliveries in >4000 women) were longitudinal in design—i.e., cohort studies, randomized controlled trials, or birth register studies. Information about relapse during the year following delivery was obtained. Relapse was defined as emergence of psychosis, mania or hypomania, depression, or a mixed episode; and/or psychiatric hospitalization.

Results: Overall, women with bipolar disorder had a 37% risk of relapse after delivery. Risk did not differ between women with bipolar I and bipolar II disorder. Women with a history of postpartum psychosis had a 31% risk of relapse. Risk was $\geq 50\%$ in women who had a prior history of postpartum bipolar episodes, but the number of women included in these estimates was small. Pharmacotherapy was highly effective at preventing relapse during the postpartum period, both in women with bipolar disorder and in the limited number of women with a history of postpartum psychosis. In both groups, prophylaxis was effective even when it was not started until delivery.

Discussion: Estimates of postpartum relapse risk in the published literature have been highly variable, making it difficult for women with severe mental disorders to plan their pregnancies and relapse-prevention strategies. Accurate estimation of relapse risk is important because overestimation could distress future parents and lead to excessive medication use, reduced rates of breastfeeding, or unnecessarily altered family planning. Underestimation of risk could lead to ineffective relapse-prevention strategies and to delays in referral for specialized perinatal care.

Wesseloo R, Kamperman A, Munk-Olsen T, Pop V, et al: Risk of postpartum relapse in bipolar disorder and postpartum psychosis: a systematic review and meta-analysis. *American Journal of Psychiatry* 2016;173 (February):117–127. From Erasmus Medical Centre, Rotterdam, the Netherlands; and other institutions. **Funded by the NIMH; and other sources. Four study authors declared financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

Supplement for Compulsive Skin-Picking

N-acetylcysteine, a nonprescription amino-acid supplement, significantly reduced symptoms of excoriation (skin-picking) disorder in a placebo-controlled trial.¹

Background: There is no FDA-approved treatment for excoriation disorder, and no psychological treatment has been clearly effective. *N*-acetylcysteine has 2 potential mechanisms of action in this disorder: It is a cysteine prodrug that increases extracellular glutamate, which may block compulsive behaviors; and its antioxidant properties may confer neuroprotection in the brain. It has also been shown to be effective in patients with trichotillomania,² which is closely related to excoriation disorder.

Methods: Study participants were adults with a primary DSM-5 diagnosis of excoriation disorder. Active treatment consisted of *N*-acetylcysteine started at 1200 mg/day, increased to 2400 mg/day by week 3 and again to the target dosage of 3000 mg/day from week 6 to study end at week 12. Skin-picking symptoms were evaluated in the clinic every 3 weeks. The primary outcome measure was change from baseline in the Yale-Brown Obsessive Compulsive Scale modified for Neurotic Excoriation (NE-YBOCS). This instrument is a 10-item scale assessing picking symptoms during the past 7 days, consisting of 5 items measuring urges and thoughts and 5 items measuring behavior. Secondary outcomes included other symptom measures,

disability, and quality of life, as well as motor inhibition and cognitive flexibility (2 cognitive domains thought to be impaired in persons with excoriation disorder).

Results: A total of 66 patients received randomized treatment: 35 with *N*-acetylcysteine and 31 with placebo. Patients had a mean age of 35 years and had symptom onset at about age 12 years. Nearly 90% were women, about one-third were taking psychotropic medication for other indications, and 85% had never sought treatment for skin-picking. A total of 13 patients did not complete the study, all because of scheduling difficulties.

The *N*-acetylcysteine group showed larger decreases in NE-YBOCS scores than the placebo group, a mean difference of nearly 4 points ($p < 0.05$). *N*-acetylcysteine differed statistically from placebo beginning at the 3-week visit. Effects on the urge/thought subscale were greater with *N*-acetylcysteine than with placebo, but effects on skin-picking behavior were more modest. According to Clinical Global Impression–Improvement ratings, among patients who completed the study, 47% of the *N*-acetylcysteine group and 19% of the placebo group were much or very much improved. Secondary outcome measures, including effects on cognitive function, did not differ between active treatment and placebo. Adverse events of *N*-acetylcysteine were infrequent and mild and included nausea ($n=5$), constipation ($n=2$), dry mouth ($n=1$), and dizziness ($n=1$).

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

¹Grant J, Chamberlain S, Redden S, Leppink E, et al: *N*-acetylcysteine in the treatment of excoriation disorder: a randomized clinical trial. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.0060. From the University of Chicago Pritzker School of Medicine, IL; and other institutions. **Funded by Great American Health; and other sources. Three study authors disclosed financial relationships with commercial sources; the remaining 3 authors declared no competing interests.**

²Grant J, et al: *N*-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. *Archives of General Psychiatry* 2009;66:756–763.

*See Reference Guide.

taVNS for Depression

According to results of a pilot study, transcutaneous auricular vagus nerve stimulation may be an effective noninvasive treatment for depression. The treatment, which uses electrodes applied to the ear, was effective in mild depression, which typically responds poorly to medication, as well as in moderate depression.

Background: Vagus nerve stimulation is an FDA-approved treatment that, because of its invasive nature, is reserved for highly refractory depression. Using the only area on the surface of the body that has afferent vagus nerve distribution, taVNS offers a noninvasive method to deliver treatment.

Methods: Study participants were adults, aged 18–70 years, who met ICD-10 criteria for mild or moderate depression (2 or 3 core symptoms, respectively, plus 2 additional symptoms) and had been psychotropic-free for ≥ 2 weeks. Patients were enrolled and received treatment in 2 cohorts, the first receiving taVNS throughout the 12-week study and the second receiving 4 weeks of sham taVNS before switching to active treatment for 8 weeks. Patients were taught to administer taVNS at home for 30 minutes twice a day. Active taVNS was administered via vagus nerve stimulators that delivered active current to the ear concha. Sham treatment was applied to a part of the outer ear that has no vagus nerve distribution. The primary study outcome was change from baseline to week 4 in Hamilton Rating Scale for Depression (HAM-D) score.

Results: Of 160 participants enrolled in the study (91 in the first cohort, 69 in the second cohort), 148 completed 4 weeks of treatment and 138 completed 12 weeks. A total of 15 patients withdrew from sham treatment because of a lack of effect.

Average baseline HAM-D scores were near 25 in both the active and sham taVNS groups. At the 4-week assessment, HAM-D scores were decreased by 9 points with active taVNS, compared with 3.8 points with sham taVNS ($p < 0.0001$; effect size, * 0.57). When patients were divided into severity subgroups based on initial HAM-D score (mild depression, HAM-D score < 20 ; moderate depression, HAM-D score ≥ 20), both groups showed significant improvement with effect sizes of 0.4 and 0.68 in the mild and moderate groups, respectively ($p = 0.04$ for mild depression, and $p < 0.0001$ for moderate depression). At week 4, there were 24 responders (27%) in the taVNS group and none in the sham treatment group. There were also 3 remissions in the active treatment group. After 12 weeks of treatment, 80% of the first cohort had experienced response and 39% remission. Similar results were observed in the sham treatment group after they switched to active treatment. The only adverse effect of taVNS was exacerbation of pre-existing tinnitus in a few patients.

Discussion: Although preliminary, these results suggest that taVNS may emerge as a first-line treatment for mild-to-moderate depression. Additional study with more rigorous design appears to be warranted.

Rong P, Liu J, Wang L, Liu R, et al: Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: a nonrandomized controlled pilot study. *Journal of Affective Disorders* 2016;195 (May):172–179. From the China Academy of Chinese Medical Sciences, Beijing. **Funded by the National Basic Research Program of China; and other sources. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

***T. gondii* Infection and Aggression**

Evidence of latent *Toxoplasma gondii* infection was associated with aggression in individuals with psychiatric illness.¹

Background: *T. gondii*, a parasite, lives within intracellular structures in the brain of infected hosts and has been linked to several psychiatric illnesses, possibly via low-grade chronic immune activation or anatomic alterations. (The latent infections are common and treatable.)

Methods: This analysis was conducted within a larger study of impulsive aggression in a U.S. population. Study participants included 3 groups: 110 with a lifetime diagnosis of intermittent explosive disorder (IED), 138 with a syndromal psychiatric disorder other than IED, and 110 with no psychiatric illness. Aggression was assessed with the Life History of Aggression Questionnaire, which records aggressive behavior, and the Buss-Perry Aggression Questionnaire, which measures aggression as a personality trait. Other standardized instruments measured impulsivity; lifetime suicidal and self-injurious behavior; and state and trait anger, depression, and anxiety. All participants were assessed for *T. gondii* antibodies after ≥ 4 medication-free weeks.

Results: Of the 358 study participants, 16% were seropositive for *T. gondii*, similar to the seropositivity rate of 14% in the U.S. general population. This included 9% of healthy controls, 17% of psychiatric controls, and 22% of individuals with IED. Seropositive status was associated with the presence of IED ($p = 0.03$ vs. healthy controls), but not with the presence of other psychiatric disorders. Seropositivity was associated with higher composite aggression scores both in an unadjusted model ($p = 0.05$) and after adjustment for impulsivity ($p = 0.011$). Composite impulsivity scores were not associated with seropositivity in an analysis adjusted for aggression. Seropositivity rates were higher in association with syndromal depression, anxiety, and borderline or antisocial personality disorder, but not in individuals with a history of suicide attempt, self-injurious behavior, or substance use disorder.

Discussion: These results suggest a relationship between *T. gondii* and impulsive aggression, both as a dimensional outcome and as a categorical diagnosis. This study may not have been

large enough to detect a relationship with suicidal or self-injurious aggression, which was found in previous research.² Several mechanisms may account for the relationship of *T. gondii* to aggression. Infection may lead to a low-grade chronic state of immune activation, possibly with downstream effects on neurotransmitters involved in aggressive behavior. *T. gondii* cysts may form lesions that alter the anatomy and function of corticolimbic circuits. The infection may also increase expression of genes involved in the production of testosterone, which may be associated with aggression.

¹Coccaro E, Lee R, Groer M, Can A, et al: *Toxoplasma gondii* infection: relationship with aggression in psychiatric subjects. *Journal of Clinical Psychiatry* 2016;77 (March):334–341. From the University of Chicago, IL; and other institutions. **Funded by the NIMH; and other sources. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

²Pedersen M, et al: *Toxoplasma gondii* infection and self-directed violence in mothers. *Archives of General Psychiatry* 2012; doi 10.1001/archgenpsychiatry.2012.668. See *Psychiatry Alerts NOS* 2012;4 (July):40.

CBT for Hoarding Disorder

Preliminary studies indicate that cognitive behavioral therapy (CBT) is effective for hoarding disorder whether the treatment is based on OCD or targeted specifically to hoarding. There is not yet sufficient evidence to compare the relative efficacy of either approach, according to a review.

Generally, treatments for clinically significant hoarding symptoms are the same as those used to treat OCD, most often Exposure and Ritual Prevention (EX/RP). Typical EX/RP programs for OCD consist of 15–20 therapy sessions. For hoarders, exposure may consist of visiting or imagining stores, markets, and other venues that trigger the desire to compulsively acquire things. Through cognitive restructuring, patients learn that anxiety will decrease over time without the use of rituals and that the feared consequences of not hoarding will not occur. Hoarding-specific CBT treatments add motivational interviewing to the techniques of exposure and cognitive restructuring. Since hoarders are not intrinsically motivated by distress over their behavior, additional help is needed from the therapist to motivate change. CBT for hoarding also strives to develop skills such as organization, problem solving, and decision making. Cognitive patterns are addressed by exploring beliefs that may promote hoarding.

A systematic review identified 12 published, peer-reviewed clinical trials of CBT in patients with hoarding disorder. Of these, 6 studies examined traditional CBT techniques, including but not limited to EX/RP. Treatment outcomes were assessed with various versions of the Yale-Brown Obsessive Compulsive Scale. The 2 studies with available effect sizes showed medium-to-large effects. The remaining 6 studies used hoarding-specific CBT. Effect sizes were available from all 5 studies, and ranged from medium to large.

All studies found that hoarding symptoms are difficult to treat. Dropout rates were high, and motivation to participate in treatment was low. EX/RP was helpful, but only partially so. For hoarders who experienced response with EX/RP, effect sizes were large. Effect sizes were smaller for hoarding-specific programs, which are typically longer, requiring about 26 sessions. More research is needed to determine whether hoarding-specific treatment is as effective as EX/RP.

Williams M, Viscusi J: Hoarding disorder and a systematic review of treatment with cognitive behavioral therapy. *Cognitive Behaviour Therapy* 2016;45:93–110. From the University of Louisville and Spalding University, KY. **Source of funding not stated. The authors declared no competing interests.**

Memory Impairment and Depression Recurrence

According to results of a prospective study, residual memory impairment may be a predictive factor for recurrence in patients with remitted depression.

Methods: Study subjects (n=109) with DSM-IV-TR major depressive disorder received treatment at a single hospital and were recruited after they achieved remission. All patients received

antidepressant treatment throughout the study. A comparison group consisted of 211 healthy controls, matched for age, gender, and level of education. Memory function was measured using the logical memory delayed recall subtest of the Wechsler Memory Scale-Revised, which tests recall of a short story immediately after it is told and again after 30 minutes. Patients with depression were divided into 2 groups based on the presence or absence of memory impairment defined as a score ≥ 1 standard deviation below the mean of controls. Patients attended follow-up visits in the clinic every few weeks until their depression returned or the study ended. Recurrence, the primary study outcome, was defined as a Clinical Global Impression–Severity score* of ≥ 4 .

Results: Of the patients with depression, 64 had normal memory function and 45 had memory impairment at study baseline (after achieving depression remission). Patients with memory impairment were older on average than those whose memory was not impaired (55 vs. 45 years; $p < 0.01$), had an older age of depression onset (49 vs. 41 years; $p = 0.01$), and had fewer years of education (13 vs. 14 years; $p = 0.04$). The 2 patient groups did not differ according to gender, number of depressive episodes, total duration of episodes, daily antidepressant dose, or several other factors.

During follow-up, recurrence happened significantly more frequently in the group with memory impairment than in those without (56% vs. 33%; $p = 0.03$). In a multivariate statistical model, memory impairment was associated with a greater risk of recurrence (hazard ratio,* 2.55; $p = 0.006$). Age at onset, number of episodes, family history, and duration of current episode were not associated with risk.

Discussion: Previous research has shown that the number of previous depressive episodes is the most important clinical predictor of recurrence. These results suggest that residual memory impairment may also predict recurrence.

Maeshima H, Baba H, Satomura E, Shimano T, et al: Residual memory impairment in remitted depression may be a predictive factor for recurrence. *Journal of Clinical Psychiatry* 2016;77 (February):247–251. From Juntendo Koshigaya Hospital, Saitama, Japan; and other institutions. **This study was conducted without funding. The authors declared no competing interests.**

*See Reference Guide.

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Clinical Global Impression–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure efficacy.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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