Omega-3 fatty acids appear to have modest efficacy in unipolar and bipolar depressive disorders but not in mania, according to a meta-analysis.¹

**Background:** Epidemiologic studies have linked dietary fatty acid intake and depression, but the results of clinical trials examining supplementation have been inconsistent. The present meta-analysis was undertaken to determine efficacy of supplemental omega-3 fatty acids in depressive and manic mood states.

**Methods:** Randomized clinical trials (n=21) in which patients with an active mood disorder received at least 4 weeks of omega-3 fatty acids were identified. Eight studies were excluded because they did not include a placebo control, they involved pediatric patients, or diagnoses were not confirmed. The remaining 13 studies were reviewed. Patients had either bipolar disorder (n=231) or major depressive disorder (n=365), and symptoms were measured using standardized instruments. All trials used omega-3 fatty acids as adjunctive treatment at a median daily dose of 2 g. Changes in depressive symptoms and mania were the primary outcomes.

**Results:** Effects of omega-3 fatty acids in depressed mood states were modest and varied in statistical significance depending on the method of analysis. The overall pooled standardized mean difference* (SMD) was -0.47. Results of individual studies were highly or moderately inconsistent. Treatment effects were similar in unipolar and bipolar depression and greater at higher doses. Omega-3 fatty acids had no effect on manic mood states (SMD, 0.12).

**Discussion:** In general, the authors judged the quality of included studies to be inadequate, and they caution that the success of the blind was questionable in several studies. However, these results support those of earlier analyses that were based on smaller data sets. The optimal omega-3 dosage and preparation remains to be determined. All studies included in this analysis used fatty acids as an adjunct to antidepressants or mood stabilizers. A recent controlled trial of monotherapy with a combined supplement of eicosapentaenoic acid and docosahexaenoic acid adds further support to the efficacy of fatty acids in major depression.²
Currently, 2 clinical trials of the supplements are being conducted in pediatric bipolar disorder and further research in adults with depression appears to be warranted.

**Study Rating*—18 (100%): This study met all criteria for a meta-analysis.**

1 Kraguljac N, Montori V, Pavuluri M, Chai H, et al: Efficacy of omega-3 fatty acids in mood disorders—a systematic review and metaanalysis. *Psychopharmacology Bulletin* 2009;42 (September 1):39–54. From Mayo Clinic College of Medicine, Rochester, Minn.; and the University of Illinois, Chicago. **Funded by the National Alliance for Research on Schizophrenia and Depression (NARSAD); and other sources. The authors did not include disclosure of potential conflicts of interest.**


*Reference Guide Item.*

**Can N-Acetyl Cysteine Improve Impulse Control?**

Pathological nail biting is part of the compulsive-impulsive spectrum and is similar to other compulsive grooming disorders such as trichotillomania and skin picking. There is little data on treatment of nail biting, but some preliminary research suggested serotonergic drugs may be useful. Case reports have shown N-acetyl cysteine (NAC), a commonly used nutraceutical with a variety of actions, can reduce compulsive pathological grooming behaviors,¹ and a single patient with treatment-resistant OCD improved with add-on NAC.² Pathological gambling was also improved in a small trial.³

In a clinical trial of add-on NAC in bipolar disorder, several patients spontaneously reported they had reduced or stopped compulsively biting their fingernails.⁴ Nail biting was not a target symptom in the trial, and no behavioral suggestions were offered. However, 2 female patients with long-standing compulsive nail biting who received 1000 mg b.i.d. add-on NAC reported that they had stopped nail biting (1 with conscious effort and the other unconsciously). Both women were in their 40s and they noted the behavioral change at 2 and 16 weeks, respectively. Although both had made unsuccessful efforts to stop nail biting in the past, they were able to refrain from the behavior during 6–7 months of follow-up while receiving NAC. A third patient, a 46-year-old male, reported an unconscious reduction in nail biting during the NAC trial.

It is unclear how NAC acts on compulsive-impulsive behaviors, but it may be related to glutamate or glutathione modulation. It is also possible that NAC-associated reductions in stress or anxiety may underlie the improved impulse control. Further study of NAC in impulse control disorders may be warranted.

4 Berk M, Jeavons S, Dean O, Dodd S, et al: Nail-biting stuff? The effect of N-acetyl cysteine on nail-biting. *CNS Spectrums* 2009;14 (July):357–360. From the University of Melbourne, Australia; and other institutions. **The source of funding for the clinical trial was not stated. The authors disclosed commercial relationships that might pose conflicts of interest.**

**Topiramate-Induced Cough**

For patients with migraine, topiramate (*Topamax*) is a first-line treatment, but adverse effects are common and cause 20–25% of patients to discontinue treatment. Paresthesia, dizziness, somnolence, and abnormal thinking are among the common effects, but cough has not previously been reported.

Three patients, aged 35–47 years (2 females), received topiramate for prophylaxis of migraine without aura. None of the patients were taking other medications or had a history of respiratory
disorder. Intractable cough developed in all 3 patients during topiramate titration. Physical exams and laboratory and imaging studies ruled out medical causes for the cough, which persisted in all patients until topiramate was stopped. Within days of stopping the drug, the cough resolved in all 3 patients and has not recurred with alternate prophylactic treatment.

**Discussion:** Although none of topiramate’s actions appear related to development of cough (as is the case with angiotensin converting enzyme inhibitors), secondary causes were ruled out, and the rapid resolution after stopping therapy clearly indicates an association with topiramate treatment.


### Does Valproate Reduce Olanzapine Concentrations?

Valproate and olanzapine are commonly used together in patients with psychotic disorders. Because they are metabolized via common pathways, the potential for a pharmacokinetic interaction exists but has not been formally studied.

**Methods:** Study subjects were 18 outpatients with bipolar or schizoaffective disorder who had been receiving 5–20 mg/day olanzapine for at least 1 month but required the addition of a mood stabilizer. All received 600–2000 mg/day adjunctive valproate for 4 weeks. Concomitant medications were permitted but remained unchanged during the study. Olanzapine compliance was monitored by pill count and serum measures and valproate compliance by serum measurement. Plasma olanzapine concentrations were measured at baseline and after 2 and 4 weeks of add-on treatment.

**Results:** Mean plasma olanzapine levels decreased from 32.9 ng/mL at baseline to 27.4 ng/mL at 2 weeks (p=0.02) and to 26.9 ng/mL at 4 weeks (p=0.001). Olanzapine concentrations were lower in the 8 patients who reported smoking at baseline than in those who did not. Although the changes were statistically significant, they were considered clinically modest. Values fell below the suggested therapeutic range of 20–50 ng/mL in 3 smoking patients. No patient experienced clinical worsening or a relapse of psychotic symptoms.

**Discussion:** There are several possible pharmacokinetic mechanisms that could underlie this interaction, but they were not addressed in the present study. The authors suggest further research to help determine if there are situations in which the interaction would be clinically important.

Spina E, D’Arrigo C, Santoro V, Muscatello M, et al: Effect of valproate on olanzapine plasma concentrations in patients with bipolar or schizoaffective disorder. *Therapeutic Drug Monitoring.* Published online October 27, 2009 at www.journals.lww.com; doi 10.1097/FTD.0b013e3181c590e. From the University of Messina, Italy; and other institutions. **Funded by the University of Messina. The authors did not include disclosure of potential conflicts of interest.**

**Drug Trade Names:** olanzapine—*Zyprexa*; valproate—*Depakene, Depakote*

### Discontinuing Desvenlafaxine

As a follow-up to a suggestion that desvenlafaxine (*Pristiq*) discontinuation symptoms may be clinically important, a pooled analysis of these symptoms in controlled trials was undertaken. Desvenlafaxine did cause some symptoms. A few patients who discontinued without taper experienced a full discontinuation syndrome (≥4 symptoms). Duration of antidepressant use did not appear to affect the incidence or severity of symptoms.

**Background:** Stopping a serotonin reuptake inhibitor can cause a discontinuation syndrome characterized by anxiety; dysphoria; disequilibrium; GI and flu-like symptoms; and sensory and sleep disturbances. Often the symptoms occur within hours of the last medication dose.
Drug half-life, metabolite profile, dosage, and abruptness of discontinuation are believed to affect whether or not symptoms develop. Because desvenlafaxine has a relatively short half-life of about 11 hours (compared with 21 hours for paroxetine and 4–6 days for fluoxetine) and no active metabolites, discontinuation symptoms may be likely.

Methods: Data were pooled from 9 placebo-controlled trials of desvenlafaxine in >3500 adult outpatients with major depressive disorder. Eight trials were short-term (8 weeks) and 1 included 6 months of maintenance treatment. Desvenlafaxine was dosed at 50–400 mg/day. The taper schedule generally comprised halving the dose on a weekly basis until 100 mg/day was reached and then discontinuing without further taper. Patients who received 100 mg/day during active treatment could undergo a similar taper at their physician’s discretion and the 50 mg/day dose was not tapered. The Discontinuation-Emergent Signs and Symptoms (DESS) checklist* was administered to patients at the final evaluation of their therapeutic dose and then on at least 2 occasions 1–4 weeks after the last dose. Spontaneous reports of adverse effects were also considered.

Results: Symptom data were available for 1549 patients. About 40% of those discontinuing short-term desvenlafaxine reported emergent symptoms, most commonly dizziness, nausea, irritability, and diarrhea. Of patients treated for ≥6 months, more than half reported symptoms including nausea, dizziness, and headache.

Mean DESS scores during the taper and poststudy periods ranged from <1 to 6, and they increased significantly from the final study evaluation to the first measure after stopping treatment. On average, patients experienced 1 or 2 specific symptoms and they often resolved within 1 week. Increases were significant only with low doses that were not tapered. Six patients met criteria for a discontinuation syndrome; all stopped 100 mg/day desvenlafaxine without taper. Length of treatment did not affect presence or severity of discontinuation symptoms.

Discussion: Discontinuation symptoms were common after stopping both short- and long-term desvenlafaxine treatment and most resolved rapidly. The symptom profile was similar to that seen with SSRIs.

Montgomery S, Fava M, Padmanabhan S, Guico-Pabia C, et al: Discontinuation symptoms and taper/post-study-emergent adverse events with desvenlafaxine treatment for major depressive disorder. International Clinical Psychopharmacology 2009;24 (November):296–305. From Imperial College School of Medicine, London, U.K.; and other institutions. Funded in part by Wyeth Research; and other sources. The authors did not include a statement disclosing potential conflicts of interest.

*Reference Guide Item.

Using a collaborative care model improved guideline adherence in a group of patients with bipolar disorder.1

Background: Evidence-based treatment guidelines can enhance quality of care, but only if they are implemented in clinical practice. Research has shown that guidelines for bipolar disorder and other serious mental illnesses are not routinely followed. The Texas Medication Algorithm Project found guideline adherence improved in a collaborative care environment.

Methods: The Department of Veterans Affairs conducted a large multicenter trial designed to reduce the gap between efficacy and effectiveness in bipolar disorder. This multicenter study enrolled 306 veterans hospitalized for bipolar disorder who were randomized at discharge to collaborative care or continued usual care for 3 years. Collaborative care combined 3 manual-
ized elements: group psychoeducation to enhance self-management skills; an updated simplified summary of VA practice guidelines for pharmacotherapy of mania with monthly technical support for providers; and access to psychiatrists and nurse care managers in specialty clinics to ensure continuity of care. Usual care providers received the printed guidelines without specific training or ongoing support. The effects of collaborative care on physician adherence to treatment guidelines for mania was investigated by examining patient records at 6-month intervals for 1 or more of the following:

- Lithium with a serum level $\geq 0.5\text{mEq/L}$ confirmed within the previous 6 months
- Valproate with a serum level $\geq 45\text{ mcg/dL}$ confirmed within the previous 6 months
- Carbamazepine with a serum level $\geq 4\text{ mcg/dL}$ confirmed within the previous 6 months
- Second generation antipsychotic dosed to $\geq 2\text{ mg/day risperidone equivalents}$

Results: Guideline adherence was significantly better in the collaborative care arm where treatments were nearly twice as likely (odds ratio,* 1.74; $p=0.04$) to be guideline compliant. Regardless of treatment assignment, guideline adherence was better early in treatment (50–60% of cases). At 1 year, 20–30% of usual care treatments were compliant. The decline was slower in the collaborative care arm where compliance remained at about 40% in the third year. Failure to prescribe antimanic medication was the most common nonadherent practice, as opposed to failing to properly manage prescribed medication. Patient outcomes were not discussed in the present analysis. However, it was previously reported that the collaborative care patients spent fewer weeks experiencing mania and/or any affective episodes and that they had improved social functioning and better quality of life. 

Discussion: It is unclear which elements of the collaborative care program investigated were responsible for the improved guideline compliance, and the results cannot be extrapolated to other guidelines or patient populations.


Drug Trade Names: carbamazepine—Epitol, Tegretol; risperidone—Risperdal; valproate—Depakene, Depakote

*Reference Guide Item.

Response and Remission in First-Episode Schizophrenia

A trial of patients with first-episode schizophrenia spectrum disorders found similar rates of discontinuation among atypical antipsychotics and higher rates with low-dose haloperidol. 

A follow-up analysis has found response and remission rates higher with the atypicals.

Methods: The European First-Episode Schizophrenia Trial enrolled 498 patients aged 18–40 years with first-episode schizophrenia. Participants were randomized to haloperidol (n=103), amisulpride (n=104), olanzapine (n=105), quetiapine (n=104), or ziprasidone (n=82) at 50 centers in Europe and Israel. All medications were flexibly dosed within the following ranges: 1–4 mg/day haloperidol; 200–800 mg/day amisulpride; 5–20 mg/day olanzapine; 200–750 mg/day quetiapine; and 40–160 mg/day ziprasidone. Neither patients nor clinicians were blinded to treatment assignment. Clinical status was assessed using multiple standardized measures and response was defined as at least a 50% decrease in Positive and Negative Syndrome Scale (PANSS) total score within 12 months of starting treatment. Remission was a score of 3 or less on the PANSS items for delusions, conceptual disorganization, hallucinatory behavior, blunted affect, social withdrawal, spontaneity, mannerisms/posturing, and unusual thought content, each maintained for 6 months.
**Results:** In addition to the discontinuation rate differences (72% with haloperidol vs 33–53% with atypicals; see *Psychiatry Drug Alerts* May 2008 issue for complete results), the initial study found the mean PANSS score at 12 months decreased by about 40% in all treatment groups with no significant differences between them. The present analysis found atypicals produced significantly greater response and remission rates than haloperidol. The 37% response rate with haloperidol was significantly lower than with atypicals (p=0.001): 67% with amisulpride, 67% with olanzapine, 56% with ziprasidone, and 46% with quetiapine. Remission rates followed a similar pattern: 17% with haloperidol, 40% with amisulpride, 41% with olanzapine, 28% with ziprasidone, and 24% with quetiapine (p=0.01). There were no significant differences between the atypicals in response or remission rates.

**Discussion:** In the response analysis, missing observations were addressed using the last observation carried forward* method and nonremitters were assumed to be continued nonremitters. These approaches may explain why significant differences were found between the groups in the present analysis but no between-group differences in mean PANSS scores were reported in the initial paper.


**Drug Trade Names:**
- amisulpride (not available in the U.S.)—Deniban, Solian, Sulamid
- haloperidol—Haldol
- olanzapine—Zyprexa
- quetiapine—Seroquel
- ziprasidone—Geodon

*Reference Guide Item.

**Patient Preferences: Buprenorphine/Naloxone**

Buprenorphine is used to treat opioid addiction and concerns exist about patients injecting it. The opioid antagonist naloxone can precipitate withdrawal when injected by individuals using opioid agonists. Thus combining the agents could allow patients to continue taking buprenorphine while reducing opportunities for inappropriate use.

Patients undergoing a switch from buprenorphine to an equivalent dose of buprenorphine/naloxone were surveyed during the first 5 days of the switch about their preference between the agents. The 53 study subjects were long-term (at least 6 months) users of buprenorphine at a stable dose. Many (40%) had a history of buprenorphine misuse. They were questioned within 1 hour of administration of sublingual buprenorphine on days 1 and 2 and combined buprenorphine/naloxone on days 3, 4, and 5.

Global satisfaction with treatment and well-being within the past 24 hours ratings were the same with both agents. Participants preferred the tablet characteristics of the combined buprenorphine/naloxone: smaller tablet size, better taste, and shorter dissolution time. On the fifth day 54% of patients said they preferred the new agent, 31% preferred buprenorphine alone, and 15% had no preference. Seventy-one percent said they wanted to continue with buprenorphine/naloxone, including 16 of 21 who had a history of injecting buprenorphine.


**Drug Trade Names:**
- buprenorphine—Subutex
- buprenorphine/naloxone—Suboxone
- naloxone—Narcan
D-Cycloserine Enhanced CBT

In a small group of patients with panic disorder, adding D-cycloserine (Seromycin) to cognitive behavioral therapy had a large positive effect on outcomes.1

**Background:** Results of research into the combined use of pharmacotherapy and CBT in panic disorder have been disappointing. Although combining antidepressants and CBT has been shown to have advantages over either treatment alone, the added benefit is lost when the medication is stopped. The partial NMDA receptor agonist D-cycloserine has been shown to reduce fear response in patients with phobias, and it was effective as augmentation in OCD2,3 and in a small study of social anxiety disorder.4

**Methods:** Adults aged 18–65 years with at least moderately severe panic disorder with or without agoraphobia participated in a brief 5-session CBT program. The 28 participants were randomized to receive either 50 mg D-cycloserine or placebo 1 hour before sessions 3 through 5. Symptom severity was evaluated using the Panic Disorder Severity Scale (PDSS) 1 week and 1 month after patients completed the CBT program, which comprised increasingly intense interoceptive exposure and cognitive restructuring techniques.

**Results:** All patients completed the treatment protocol, but 1 was lost to follow-up before the 1 month follow-up. The mean baseline PDSS score was 14. Posttreatment scores (at 1 week) were significantly lower in the D-cycloserine group at about 3.5 compared with 7 in the placebo group (p=0.007; effect size,* 1.11), and the improvements were maintained at 1 month. Clinically significant change, indicated by a ≥5 point decrease in PDSS score to a final value of <5, was evident at 1 week in 77% of the D-cycloserine group, compared with 33% of the placebo group. At 1 month, no additional D-cycloserine patients showed clinically significant change, but the rate increased to 53% with placebo. No adverse effects were reported.

**Discussion:** Although the study sample was small and the CBT program was brief, D-cycloserine appeared to have positive additive effects over CBT alone. These effects may have been related to extinction memory consolidation (the process by which recent memories are crystallized into long-term memory). These effects have been verified in both animal and human studies of the agent.

**Study Rating*—15 (88%):** This study met all criteria for a randomized controlled trial except that the source of funding was not stated.

**Editor’s Note:** D-cycloserine is an antibiotic used to treat acute urinary tract infections (when conventional therapy fails) and tuberculosis. Although it was effective in this study and in other anxiety disorders, the contraindications include depression and severe anxiety.5

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5. Facts and Comparisons 4.0 online.

*Reference Guide Item.*
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Discontinuation-Emergent Signs and Symptoms (DESS) Checklist: A quantitative measure of 43 symptoms associated with medication discontinuation. Each item is scored as absent (0) or as new or worsened (1); the maximum total score is 43. Treatment discontinuation syndromes are typically defined as DESS scores of 4 or more.

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 treatment 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 one group has half the risk of the other group.

Last Observation Carried Forward (LOCF): A method of data analysis in which missing data for individual patients is replaced by the last observed value of that variable.

Odds Ratio: A comparison of the probability of an event in two groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Risk Ratio: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (nonexposed) group.

Standardized Mean Difference (SMD): The difference of the means of two treatment arms divided by the pooled standard deviation. In this way, the treatment effect in each study is expressed in standard units (instead of in original units) and the results of all studies can be combined. Although the SMD is not a perfect measure of effect size it provides a method of computing a standard measure of effect across different studies.

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 have been posted at www.alertpubs.com.