Early Treatment of Depression and Outcome

In a group of patients with first-episode depression, the duration of untreated symptoms was inversely associated with response and remission.

Methods: Study subjects were 133 adults (mean age, 41 years) who presented to a university hospital psychiatry department with first-episode unipolar major depression. Patients were stratified by self reported duration of untreated symptoms. All received treatment with fluvoxamine (Luvox) monotherapy, flexibly dosed between 25 and 150 mg/day for 8 weeks. Psychosocial treatments and most concomitant medications were prohibited. Treatment response and remission were defined as a $\geq 50%$ decrease in Hamilton Rating Scale for Depression (HAM-D) score and a final score of $\leq 7$, respectively.

Results: The mean baseline HAM-D score was 21, indicating moderate depression in the sample as a whole. Mean scores at 8 weeks ranged from 6 to 14 and varied in a linear fashion by duration of untreated illness. Overall, the odds of both response and remission significantly decreased ($p \leq 0.04$) as duration of untreated illness increased. (See table.) Response and remission rates were substantially lower in patients who experienced symptoms for $\geq 12$ weeks before receiving medication.

Discussion: These results suggest that early treatment of first-episode depression may substantially improve patients’ odds of achieving response and remission with fluvoxamine.

Okuda A, Suzuki T, Kishi T, Yamanouchi Y, et al: Duration of untreated illness and antidepressant fluvoxamine response in major depressive disorder. Psychiatry and Clinical Neurosciences 2010;64 (June):268–273. From Okehadama Hospital Fujita Mental Care Center; and other institutions, Japan. Funded by the Japanese Ministry of Education, Culture, Sports, Science and Technology; and other not for profit sources. The authors did not include a statement disclosing potential conflicts of interest.

<table>
<thead>
<tr>
<th>Block</th>
<th># of Patients</th>
<th>Duration of Untreated Symptoms</th>
<th>Response Rate</th>
<th>Remission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>24</td>
<td>2–3 weeks</td>
<td>75%</td>
<td>71%</td>
</tr>
<tr>
<td>B</td>
<td>23</td>
<td>4–7 weeks</td>
<td>78%</td>
<td>65%</td>
</tr>
<tr>
<td>C</td>
<td>28</td>
<td>8–11 weeks</td>
<td>71%</td>
<td>57%</td>
</tr>
<tr>
<td>D</td>
<td>29</td>
<td>12–24 weeks</td>
<td>41%</td>
<td>24%</td>
</tr>
<tr>
<td>E</td>
<td>29</td>
<td>$\geq 25$ weeks</td>
<td>24%</td>
<td>10%</td>
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</tbody>
</table>
Antidepressants and Triptans

In 2006 the FDA issued a preliminary warning about increased risk of serotonin syndrome with concomitant use of an SSRI or SNRI with a 5-hydroxytryptamine receptor agonist (triptan) for migraine. The warning was based on 29 reported cases, and since its release many patients have been counseled to discontinue at least one of the medications. A group of migraine experts from the American Headache Society reviewed these individual cases and determined the evidence is insufficient to warrant that recommendation.

Serotonin syndrome is an adverse drug reaction characterized by a triad of mental status changes, dysautonomia, and neuromuscular dysfunction. Symptoms can include anxiety; agitation; confusion; hyperthermia; diaphoresis; akathisia; muscle rigidity; myoclonus; and tremor. These can range from mild to life-threatening. If serotonin syndrome develops, the suspected agents are stopped and treatment is generally symptom driven and supportive. Symptoms resolve within 24 hours for most patients. Diagnosis is dependent on medication use and exclusion of other disorders. Several sets of diagnostic criteria for serotonin syndrome have been published and at least 1 (the Sternbach Criteria, see box) has been validated.

When the representatives from the American Headache Society applied these criteria to each of the 29 reported cases, about one-third (10 of 29) met criteria for the syndrome. Based on a previous study examining triptan prescriptions in a national pharmacy database, the authors estimated that nearly 1 million patient-months of exposure to combined treatment occurred in the U.S. during the time the 29 cases were reported. Based on the relative infrequency of reported cases and the low quality level of the evidence, the authors suggest concurrent use of SSRIs and SNRIs with triptans should not be limited because of concerns about serotonin syndrome. They do however warn that because serotonin syndrome can be potentially serious and/or life-threatening, caution is warranted.

Topiramate and Burning Mouth Syndrome

Burning mouth syndrome (BMS) is a chronic condition characterized by oral pain and burning with no visible cause. It has been linked to several antidepressants and anxiolytics. Topiramate has been used successfully to treat burning mouth syndrome. This appears to be the first report of the agent causing the syndrome.

A 54-year-old female continued to experience migraine and tension-type headaches despite prophylactic treatment with propranolol and symptomatic treatment with sumatriptan. Topiramate was added to her regimen and titrated to 125 mg/day. Other recent additions

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2Evans R, Tepper S, Shapiro R, Sun-Edelstein C, et al: The FDA alert on serotonin syndrome with use of triptans combined with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors: American Headache Society position paper. Headache 2010; 50 (June):1089–1099. From Baylor College of Medicine, Houston, Tex.; and other institutions. The study was conducted without external funding. Several study authors disclosed commercial relationships with pharmaceutical-industry sources, but the America Headache Society limits the participation of authors with substantial conflicts of interest.
included lisinopril and gabapentin. The headaches improved but progressively worsening oral dryness and burning pain developed. Gabapentin discontinuation did not improve the burning mouth symptoms, and topiramate and lisinopril were also stopped. Symptoms resolved gradually over 3 weeks but recurred with topiramate rechallenge. According to the Naranjo probability scale,* the association with topiramate is “probable” but can not be considered definite.

Zinc deficiency has been suggested as a possible factor in the pathogenesis of BMS in some patients. Another recent study found that zinc replacement therapy reduced self-reported pain by 50% in patients with a zinc deficiency.2

1 Friedman D: Topiramate-induced burning mouth syndrome. Headache 2010; doi 10.1111/j.1526-4610.2010.01720.x. From the University of Rochester, N.Y. The author did not include a statement disclosing potential conflicts of interest.


Drug Trade Names: gabapentin—Neurontin; lisinopril—Prinivil, Zestril; propranolol—Inderal; sumatriptan—Imitrex; topiramate—Topamax

*DSee Reference Guide.

Duloxetine for Social Anxiety Disorder

A preliminary manufacturer-sponsored study supports duloxetine as effective treatment for generalized social anxiety disorder.

Background: Paroxetine, sertraline, and extended-release venlafaxine are the only FDA approved options for treating social anxiety disorder. About one-third to one-half of patients do not respond to these treatments, and other options are needed. Duloxetine is effective in generalized anxiety disorder, and 2 case reports suggest it may be useful in social anxiety as well.

Methods: Study subjects (mean age, 36 years; 36% female) underwent a structured clinical interview to confirm a DSM-IV diagnosis of generalized social anxiety disorder. Those with a history of schizophrenia, other psychosis, bipolar disorder, or substance abuse and those receiving psychotherapy for social anxiety disorder were excluded. Patients with depression, panic disorder, PTSD, and other anxiety disorders were not excluded provided social anxiety was the predominant disorder. Symptoms were generally severe and chronic (mean duration of illness, 25 years), and nearly half of the patients had undergone a previous medication trial.

All patients (n=39) received 6 weeks of open-label treatment with 60 mg/day duloxetine. Patients who did not achieve a Liebowitz Social Anxiety Scale (LSAS) score of <30 were then randomized to either an additional 18 weeks of double-blind treatment with duloxetine at 120 mg/day or continued at 60 mg/day with an added placebo. The primary outcome measures were the LSAS and the Clinical Global Impression Improvement (CGI-I) scale. Responders were patients who achieved a CGI-I rating of "much" or "very much improved", and remission was defined as an LSAS score of ≤30.

Results: During open-label treatment, the mean LSAS score decreased significantly from 91 to 70 (p<0.0001), and the CGI-I score also improved significantly (p<0.0001). A total of 10 patients (26%) achieved response; 28 patients went on to randomized treatment. At the 24-week endpoint, the mean LSAS score was further decreased to 60 (p<0.003, compared with week 6). The 120-mg/day dose was associated with a numerically larger decrease in LSAS score (21 vs 7 points). The between-group difference did not reach statistical significance, but the effect size* of 0.57 was moderate. CGI-I results followed a similar pattern. Of the 15 patients randomized to 120 mg/day duloxetine, 9 (60%) responded and 5 (33%) achieved remission. Of the 13 patients who continued duloxetine at 60 mg/day, 4 (31%) responded and 1 (8%) achieved remission. Quality of life was also improved. Duloxetine did not have a significant effect on comorbid depressive symptoms, but symptom scores were low at baseline.
Adverse effects were those generally associated with duloxetine including nausea (n=15); sedation (n=13); dry mouth (n=10); sexual dysfunction (n=9); and others. During randomized treatment 2 patients in the 60-mg group discontinued treatment: 1 because of an elevation in liver enzymes that was unrelated to study treatment and the other after a study medication overdose. There were no serious adverse events in the 120-mg group.

**Discussion:** The overall response and remission rates in the full intent-to-treat sample (44% and 23%, respectively) suggest duloxetine efficacy is similar to approved treatments for social anxiety disorder.

**Study Rating**—17 (100): Although the trial began with open-label treatment, the randomized portion of the study met all criteria for a randomized controlled trial.

Simon N, Worthington J, Moshier S, Marks E, et al: Duloxetine for the treatment of generalized social anxiety disorder: a preliminary randomized trial of increased dose to optimize response. CNS Spectrums 2010;15 (7):436–443. From Massachusetts General Hospital, Boston. **Funded by Eli Lilly. The authors disclosed commercial relationships with multiple pharmaceutical-industry sources including Eli Lilly, manufacturer of Cymbalta.**

**Drug Trade Names:** duloxetine—Cymbalta; paroxetine—Paxil; sertraline—Zoloft; venlafaxine—Effexor

*See Reference Guide.

### Generic Extended Release Effexor Approved

The FDA has approved the first generic formulation of *Effexor XR* (venlafaxine). It will be available in 37.5-, 75-, and 150-mg strengths. Generic venlafaxine will carry the same warnings as *Effexor*, including the boxed warning about suicidal thoughts and actions in children, adolescents, and young adults.

FDA approves first generic Effexor extended release capsules to treat major depressive disorder. FDA News Release; available at www.fda.gov.

### Intramuscular Paliperidone

Medication adherence in the management of schizophrenia can be addressed in some cases by using depot medications. The newly approved intramuscular formulation of paliperidone is a monthly option. A manufacturer-sponsored phase-3 trial studied its efficacy and safety.1

**Methods:** A multinational controlled trial of adults (mean age, 41 years) with a ≥1 year history of schizophrenia and a Positive and Negative Syndrome Scale (PANSS) score of 70–120 was conducted. The 514 patients were hospitalized for 8 days and started on randomly assigned placebo or IM paliperidone at 25, 50, or 100 mg for 13 weeks. Medications were administered in the gluteal muscle on days 1 and 8 and then every 4 weeks. Patients who had never been exposed to risperidone or paliperidone underwent an oral tolerability challenge before randomization. Response was defined as a ≥30% decrease in the PANSS score.

**Results:** Improvements in PANSS scores were significantly greater with all paliperidone doses than with placebo (p<0.02 for all comparisons), and response rates ranged from 38% to 52% with active treatment. Extrapyramidal symptoms were similar with active and placebo treatment. Parkinsonism, the most frequently reported, affected 5% of the placebo group and 6% of the paliperidone group. Mean body weight, body mass index (BMI), and prolactin levels increased in a dose-dependent manner with paliperidone (range of increase, 4–44 ng/mL); ≤2% of patients in each paliperidone group experienced a prolactin-related adverse event. There were no clinically important changes in lipid or glucose levels. Significant QTc prolongation did not occur. Injection site reactions were infrequent, and those that occurred were generally mild and self-limiting.

**Discussion:** Of note, U.S. study sites contributed about 55% of the patient population. Other sites were in Bulgaria, Romania, Russia, and South Africa. The primary outcome analysis found
patients enrolled outside of the U.S. showed greater PANSS score improvements. The authors suggest the disparity may be related to greater mean BMI in U.S. populations. Also noteworthy, attrition was high; about 50% of randomized patients completed the 13 weeks of treatment.

An extension of another double-blind IM paliperidone study found schizophrenia symptoms and social performance improved over 1 year of open-label treatment. About three-fourths of patients completed the 12-month study, and the most common adverse effects were insomnia, worsening schizophrenia, nasopharyngitis, headache, and weight gain. Prolactin-related events occurred in 3% of patients (mainly women), and extrapyramidal symptoms affected 6%.

**Study Rating**—16 (94%): This study met most criteria for a randomized controlled trial, but the authors did not discuss any potential limitations or bias that may have affected the results.

1 Nasrallah H, Gopal S, Gassmann-Mayer C, Quiroz J, et al: A controlled, evidence-based trial of paliperidone palmitate, a long-acting injectable antipsychotic, in schizophrenia. *Neuropsychopharmacology* 2010; doi:10.1038/npp.2010.79. From the University of Cincinnati College of Medicine, Ohio; and other institutions. Funded by Johnson & Johnson Pharmaceutical Research and Development, LLC. The primary study author disclosed a commercial relationship with Johnson & Johnson, and all other authors are employees of the company.


**Drug Trade Names**
- paliperidone, intramuscular—Invega Sustenna
- risperidone—Risperdal

**Pre-Pregnancy Medication Changes in Bipolar Disorder**

Women with bipolar disorder who are planning pregnancy have limited medication choices because many of the commonly used drugs (e.g., valproate, carbamazepine, lithium) can be teratogenic. A retrospective review examined the maternal outcomes after preconception medication changes in 32 women (mean age, 34 years) with bipolar disorder or a single hypomanic/mixed episode who presented to a perinatal psychiatry clinic for preconception advice.

**Methods:** Thirty-two women with DSM-IV bipolar I disorder (n=24), bipolar II (n=6), or a single previous manic episode (n=2) were studied. Nearly all women (30 of 32) had a previous hospitalization for bipolar disorder (mean, 2; range 0–10). The course of bipolar illness in the 12 months following the consultation was extracted from each patient’s medical records.

**Results:** After considering illness severity, teratogenic effects, and patient preference, physicians made treatment recommendations. No medication change was advised for 9 women (28%), 4 (13%) were advised to discontinue medication, and 19 women (59%) were switched to an alternate medication. The most common switching strategy was to replace an antiepileptic with an atypical antipsychotic (57%).

During follow-up, 15 women achieved pregnancy. Complete data was available for 26 women, of whom 5 (19%) experienced a bipolar relapse: depression in 2, hypomania in 1, and a mixed episode in 2. Four of the 5 recurrences occurred in the first 6 months, and all were managed on an outpatient basis. One of these women had discontinued pharmacotherapy as a result of the preconception consultation.

**Discussion:** This appears to be the first report of maternal outcomes after preconception counseling. Although the sample is small, the results suggest treatment adjustments in women planning pregnancy do not result in destabilization for most patients.

Wieck A, Kopparthi S, Sundaresh S, Wittkowski A: One-year outcome after preconception consultation in women with bipolar disorder [letter]. *Journal of Clinical Psychiatry* 2010: 71 (June):806. From Manchester Mental Health and Social Care Trust, U.K.; and other institutions. **The study was conducted with no external funding, and the authors report no conflicts of interest.**

**Drug Trade Names**
- carbamazepine—Epitol, Tegretol
- valproate—Depakene, Depakote
Depression and GERD

A nested case-control study using a large U.K. primary care database found depression independently associated with gastroesophageal reflux disease. Tricyclic antidepressant use increased the risk.

Methods: Data for >40,000 patients, aged 10–79 years, with a first clinical diagnosis of depression and >44,000 age- and gender-matched patients without depression were evaluated. No patient had previous heartburn or GERD complaints. Patients were followed for 5 years or until onset of GERD (mean follow-up, 3.3 years).

Results: GERD developed in 1854 of the patients with depression and in 1210 of those without depression. The incidence for 1000 person-years was 14.2 and 8.3 in the groups, respectively. After adjustment for age and gender, the hazard ratio* for GERD in patients with depression was 1.72. After further adjustments, the ratio of 1.31 remained significant. Depression severity did not affect risk, and the association between depression and GERD persisted after controlling for antidepressant use. Other mental illnesses, including anxiety and stress disorders, also increased the odds for development of GERD.

Treatment with a TCA was associated with an increased risk beyond that associated with untreated depression (odds ratio* [OR], 1.7), but SSRI use was not. Few patients received high-dose TCA therapy, and a dose relationship could not be examined. However, duration of TCA use did amplify risk: the OR for GERD in patients treated for ≤3 months was 1.48, compared with 2.06 in those treated for >3 months.

Discussion: This appears to be the first study to find a significant increase in GERD risk among patients with depression. Further study should address the pathophysiology of the association.

Martin-Merino E, Ruigomez A, Rodriguez L, Wallander M-A, et al: Depression and treatment with antidepressants are associated with the development of gastro-oesophageal reflux disease. Alimentary Pharmacology and Therapeutics 2010;31 (10):1132–1140. From the Spanish Centre for Pharmacoepidemiologic Research, Madrid, Spain; and other institutions. Source of funding not stated. Several authors disclosed commercial relationships with pharmaceutical-industry sources.

*See Reference Guide.

Topiramate Did Not Improve Resistant Schizophrenia

Adjuvative topiramate did not improve schizophrenia symptoms in patients with an incomplete clinical response to clozapine.

Background: Topiramate is active in several neurotransmitter systems involved in schizophrenia. It has had promising effects in an animal model of psychosis and mixed effects in uncontrolled clinical studies and several small controlled trials.

Methods: Study subjects were 60 outpatients (mean age, 32 years) with schizophrenia and partial or no response to clozapine. Mean duration of illness was about 5.5 years, and all patients had been receiving clozapine monotherapy at the highest tolerable dose for at least 1 year. They received 24 weeks of randomized double-blind adjuvant topiramate or placebo. Topiramate was started at 25 mg/day and increased in 25-mg increments weekly until 100 mg/day was reached. This dosage was continued for 8 weeks and then increased again using the same schedule to 200 mg/day. Clinical and neurocognitive function were assessed at baseline and at weeks 12 and 24.

Results: Eleven patients withdrew from topiramate treatment and 6 from the placebo, most because of noncompliance with the study visit schedule. In the 43 patients who completed the study, topiramate augmentation had no significant effect on positive or negative symptoms,
affective symptoms, or overall symptoms. Topiramate also had no effect on neurocognitive function. The "bizarre behavior" score of the Scale for the Assessment of Positive Symptoms (SAPS), which evaluates social and sexual behaviors, aggression, and stereotypies, was reduced significantly with topiramate (p<0.002). Adverse effects were generally mild to moderate and included asthenia, sedation, and paresthesia.

**Discussion:** Topiramate does not appear to be an effective adjunct to clozapine in patients who continue to have residual symptoms. The authors caution that the topiramate dose, chosen to minimize the risk of cognitive impairment, may have been too low to be effective.

**Study Rating**—15 (88%): This study met most criteria for a randomized controlled trial, but the funding source was not disclosed.


Drug Trade Names: clozapine—*Clozaril*; topiramate—*Topamax*

*See Reference Guide.

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**Omega-3 Supplements for Major Depression**

In a large placebo-controlled trial, omega-3 fatty acid supplementation produced statistically significant though modest effects in patients with depression and no comorbid anxiety disorders. Supplementation was not effective in patients with comorbid anxiety.

**Background:** Meta-analyses of previous studies suggest that omega-3 fatty acids have promising antidepressant effects, but these analyses were based on studies with small sample sizes and mixed designs with a variety of supplement formulas.

**Methods:** The present study enrolled 432 patients who met criteria for unipolar major depression lasting 4 weeks or more. To maximize the representativeness of the study population, patients with comorbid anxiety disorders or chronic or treatment-resistant depression were included; substance abuse and bipolar disorder were exclusion criteria. About 40% of participants were receiving antidepressant medication at baseline. Those not taking an antidepressant either were intolerant of at least 2 prior drugs or refused medically recommended treatment. Approximately one-fourth were taking other psychotropic medications, and about 15% were receiving psychotherapy.

During the 8-week study, patients received 3 capsules daily of randomized, double-blind omega-3 fish oil (1,050 mg/day EPA and 150 mg/day DHA) or a sunflower oil placebo containing enough fish oil to give it a fishy taste. The primary outcome measure was the 30-item self-report Inventory of Depressive Symptomatology (IDS-SR30).*

**Results:** Depression symptoms improved in both treatment groups. The decrease in IDS-SR30 scores did not differ substantially between the 2 treatments (25% vs 29%; p=0.08). Effect sizes* were small: 0.11 for the IDS-SR30 and 0.10 for the Montgomery-Asberg Depression Rating Scale (MADRS), the secondary study outcome. However, patients without comorbid anxiety disorder improved significantly with omega-3 supplementation (p=0.007; effect size, 0.27 for the IDS-SR30). Efficacy did not differ according to gender, baseline use of antidepressants, or the usual amount of fish in the diet.

**Discussion:** The authors judged the overall benefits of fish oil "trivial", but suggest that they may deserve further investigation in patients without comorbid anxiety disorder and in those unwilling to take antidepressant medications. The inclusiveness and heterogeneity of the study
sample may have reduced the ability to detect an antidepressant effect. The effect size is not impressive, but neither is that of conventional antidepressants: only 0.31 according to a recent meta-analysis that included unpublished data. Given the safety and tolerability of the supplements, patients and clinicians may want to consider them even with a lower efficacy level than antidepressant drugs.

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

Lesperance F, Frasure-Smith N, St-Andre E, Turecki G, et al: The efficacy of omega-3 supplementation for major depression: a randomized controlled trial. *Journal of Clinical Psychiatry* 2010; doi: 10.4088/JCP.10m05966blu. From the University of Montreal, Quebec, Canada; and other institutions. Funded by Isodis Natura, a distributor of polyunsaturated fatty acids and other dietary supplements; and the University of Montreal Hospital Center. Several study authors disclosed commercial relationships with pharmaceutical-industry sources.

*See Reference Guide.

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**Reference Guide**

**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.

**Inventory of Depressive Symptomatology (IDS):** A 30-item measure designed to assess clinician- and/or self-rated severity of depressive symptoms. The IDS assesses all the symptom domains designated necessary to diagnose a major depressive episode in the DSM-IV. The IDS can be used to screen for depression, but it is most often used as a measure of symptom severity.

**Naranjo Probability Scale:** A 10-point scale used to determine the likelihood that an adverse reaction is caused by an implicated medication. Based on scores, associations are considered doubtful, possible, probable, or highly probable.

**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.

**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.

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