Add-On Topiramate in PTSD

An 8-week open-label pilot study was conducted in 43 male combat veterans with PTSD. Topiramate (Topamax) was added to their background medications, and PTSD severity, alcohol use, and sleep problems were assessed after 8 weeks. A total of 29 patients completed 8 weeks of treatment and were included in the analysis; 19 of these patients were taking an antidepressant and 4 were taking an antipsychotic.

Results: PTSD severity was significantly reduced with treatment. Mean Clinician Administered PTSD Scale scores decreased from 86 at baseline to 67 at 8 weeks (p<0.01), but a secondary severity measure did not show significant improvement. Nightmares were affecting all of the patients before topiramate treatment but only 62% after 8 weeks of treatment (p<0.001). Although scores on a standardized measure of alcohol use were not significantly improved, the percentage of patients reporting high-risk drinking patterns was reduced from 31% to 14%.

Topiramate was well tolerated. Two patients withdrew from the study because of serious adverse events (i.e., major increase in pain, acute confusion). Other adverse effects, each affecting 1 patient, were blurred vision with normal intraocular pressure, mental dulling, sedation, and nausea/anorexia.

Discussion: This study provides preliminary evidence that topiramate might be effective as add-on therapy in combat-related PTSD. However, the small sample, the short treatment duration, and the lack of control for confounding factors limit the conclusions. Further study, including randomized controlled trials, is warranted.


Varenicline Augmentation for Resistant Depression

Adding varenicline (Chantix) to antidepressants or mood stabilizers improved resistant depression in a small group of patients with nicotine dependence.

Methods: Adults who currently smoked and had a DSM-IV mood disorder with primarily depressive symptoms (n=18; 12 females) were enrolled in the study if they had persistent...
symptoms after ≥6 weeks of treatment with an antidepressant or mood stabilizer. In addition to their current regimen all patients received up to 2 mg/day open-label varenicline augmentation for 8 weeks. Depressive symptoms were the outcome of interest, and although smoking cessation was evaluated, no formal cessation counseling was provided. The primary depression measure was the Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR). Response was defined as a ≥50% decrease in score and remission as a final QIDS-SR score of ≤5. Clinicians rated improvement using the Clinical Global Impression (CGI) scales.

Most patients (n=15) had a diagnosis of major depressive disorder or depressive disorder not otherwise specified and were taking an SSRI, SNRI, or other antidepressant; 3 patients had bipolar disorder and were receiving a mood stabilizer. The mean duration of current mood episode treatment was 81 weeks.

**Results:** The mean QIDS-SR score decreased from 13 at baseline to 8 at study end (p<0.001), and significant improvement was evident at week 2. A total of 8 patients (44%) achieved response and 6 (33%) also achieved remission. CGI-Severity scores also improved significantly (p<0.04) with baseline ratings of "mildly ill" improved to "borderline ill." CGI-Improvement ratings showed 10 patients (56%) as "much improved" or "very much improved," 2 patients (11%) had "minimally worse" depressive symptoms. Cigarette consumption also decreased significantly (p<0.001), and 8 patients (44%) reported abstinence. Improvements in depression were correlated with decreases in cigarette consumption.

Common adverse effects were difficulty sleeping, nightmares, vivid dreams, GI complaints, irritability, and increased appetite. Four patients withdrew before 8 weeks because of adverse effects: 3 because of GI issues and 1 because of worsened mood/irritability. Varenicline did not affect blood pressure or increase body mass index. Although varenicline has been linked to suicidality, there were no significant changes in the QIDS-SR suicide item.

**Discussion:** Patients with a history of depression have high rates of depression after smoking cessation, and research has shown that modulating nicotinic systems can affect mood. This study suggests varenicline augmentation may also have antidepressant properties in treatment-resistant patients. However, because only smokers were included, the effects of augmentation in nonsmokers are unknown. Larger controlled studies are needed to assess the potential antidepressant effects of varenicline in these patients.


From Butler Hospital; and the Warren Alpert Medical School at Brown University, Providence, R.I. **Funded by internal, clinically generated funds at Butler Hospital. Several study authors disclosed having received research support and/or other financial incentives from multiple pharmaceutical-industry sources including Pfizer, manufacturer of varenicline. Varenicline is FDA approved only for smoking cessation.**

**Aripiprazole-Associated Tardive Dyskinesia**

A clinical advantage of atypical antipsychotics is their lower propensity to cause tardive dyskinesia (TD) and other extrapyramidal symptoms. A literature search found 13 cases of atypical antipsychotic-induced TD in previously antipsychotic-naïve patients; none of these cases involved aripiprazole (*Abilify*). Because of its unique receptor profile, aripiprazole is considered relatively safe in terms of TD and has even been suggested to have therapeutic effects in the disorder. Two cases of TD associated with aripiprazole in antipsychotic-naïve patients have now been reported.

A 19-year-old woman with fragile X syndrome had been treated with aripiprazole for anxiety and violent outbursts for 3 years before presenting with dystonia. The aripiprazole dosage had been increased from 7.5 mg to 15 mg/day 3 months before presentation. When no other cause
for the dystonia was found, aripiprazole was stopped and the dystonia rapidly improved. The patient had almost complete resolution after 8–10 months. A 62-year-old man also presented with dystonia after receiving 15 mg/day aripiprazole for 18 months. No other cause was identified and aripiprazole was stopped. The dystonia persisted over the subsequent 18 months despite pharmacological treatment. The patient eventually benefited from deep brain stimulation.


When is Escitalopram Response Unlikely?

A pooled analysis of escitalopram (Lexapro) trials in major depressive disorder (MDD), generalized anxiety disorder (GAD), and social anxiety disorder (SAD) showed that patients with minimal or no improvement within 4 weeks are unlikely to respond by week 8 or 12.

Methods: Data was pooled from randomized controlled trials of escitalopram in MDD (n=14), GAD (n=6), and SAD (n=3). A total of 4357 patients received randomized escitalopram and were evaluated with disorder specific measures. A ≥20% decrease in Montgomery-Asberg Depression Rating Scale, Hamilton Rating Scale for Anxiety or Liebowitz Social Anxiety Scale within 2 weeks was considered an early-onset treatment effect. Response (≥50% decrease in disorder-specific rating scale score) was compared at 8 weeks for MDD and GAD and at 12 weeks for SAD between patients with and without early-onset treatment effects.

Results: The probability of achieving response was greater in patients who demonstrated early treatment effects. In MDD, the eventual response rate in patients with measurable treatment effects at week 2 was 79%, compared with 43% for those without improvement at week 2. In GAD, response rates were 74% vs 38% in patients with and without early improvement, and in SAD the rates were 69% vs 30%. The probability of response decreased as the time to evident treatment effects increased, and response rates for patients with no improvement evident before week 4 averaged about 20%.

Discussion: The authors suggest that treatment changes may be warranted when the probability of response drops to 20% or less. The pattern of response in this analysis suggests that time point is 4 weeks for patients treated with escitalopram for MDD, GAD, or SAD.

Baldwin D, Stein D, Dolberg O, Bandelow B: How long should a trial of escitalopram treatment be in patients with major depressive disorder, generalised anxiety disorder or social anxiety disorder? An exploration of the randomised controlled trial database. Human Psychopharmacology: Clinical and Experimental. Published online March 30, 2009 at www.interscience.wiley.com; doi 10.1002/hup.1019. From the University of Southampton, U.K.; and other institutions. The present analysis was conducted with no external funding, but all trials in the database were funded by H. Lundbeck A/S or Forest Laboratories, escitalopram manufacturing partners. Treatment of social anxiety disorder is an off-label use for escitalopram.

Vegetarian Psychotropics

Many factors influence medication adherence in psychiatry, and vegetarian patients may object to inert ingredients commonly found in prescription medications such as gelatin, animal-derived lactose, and calcium or magnesium stearate. In order to find medications that would be acceptable to vegetarians, the authors of this report surveyed U.K. pharmaceutical manufacturers about the use of animal-derived products in the formulation of all antipsychotic, antidepressant, and antimanic drugs listed in the British National Formulary.

In total, the authors inquired about 99 proprietary preparations of 50 drug compounds. They did not receive any information on the U.K. manufactured formulations of 4 antipsychotics (i.e., clozapine, chlorpromazine, fluphenazine, and pericyazine). In addition, they received
information on only the capsule formulation of haloperidol, not the tablets. According to manufacturer data, 73% of psychotropic drugs available in the U.K. are suitable for vegetarian patients. No capsule formulation of any agent was suitable. However, the manufacturer of duloxetine stated that in vitro testing showed the pellets contained in the capsule are stable for up to 2 hours when mixed with applesauce or juice, thus making it possible for vegetarians to get the full dose without ingesting the offending capsule. See box for a list of non-capsule medications found to be unsuitable.

It appears from this survey that psychotropic medications that should be acceptable to vegetarians are plentiful in the U.K. Most of the agents investigated are also available in the U.S. Although the manufacturing process in the U.S. was not evaluated in the study, our editors examined the U.S. prescribing information for each of the drugs listed as unsuitable and found they would not be acceptable to vegetarians. The prescribing information for many antidepressants, antipsychotics, and mood stabilizers commonly used in the U.S. was also examined, and many were found to be unsuitable. See box for non-capsule U.S. medications that may be suitable for vegetarians. Information on ingredients can be obtained from drug manufacturers, and it is sensible to check with them to see if a drug contains any animal-derived ingredients that would be objectionable to a vegetarian patient.

McAllister-Williams H, Ramplin S: Vegetarian psychotropics: a survey of psychotropic medications suitable for vegetarians [letter]. Human Psychopharmacology: Clinical and Experimental 2009;24 (March):248–249. From the University of Newcastle upon Tyne; and St. Nicholas Hospital, U.K. Dr. McAllister-Williams disclosed receiving fees or research support from multiple pharmaceutical-industry sources; Dr. Ramplin reported no potential conflicts of interest.

**Drug Trade Names:** amitriptyline—Perphenazine—Etrafon; bupropion—Wellbutrin; citalopram—Celexa; divalproex—Depakote; doxepin—Sinequan; duloxetine—Cymbalta; dosulepin (not available in the U.S.)—Prothiaden; flupentixol (not available in the U.S.)—Depixol, Fluaxon; fluvoxamine—Luvox; L-tryptophan (available OTC in the U.S.)—Optima; nortriptyline—Pamelor; olanzapine—Zyprexa; oxcarbazepine—Trileptal; paliperidone—Invega; perphenazine—Trilafon; reboxetine (not available in the U.S.)—Edronax, Vestra; risperidone—Risperdal; selegiline, transdermal—Emsam; sertindole (not available in the U.S.)—Serdolect; sulpiride (not available in the U.S.)—Sulpitil; thiothixene—Navane; trifluoperazine—Stelazine, and others; ziprasidone, intramuscular—Geodon; zuclopenthixol decanoate (not available in the U.S.)—Clopizol

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<td>Geodon, Intramuscular (ziprasidone)</td>
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<td>Lithium Citrate Oral Solution</td>
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Dr. McAllister-Williams disclosed receiving fees or research support from multiple pharmaceutical-industry sources; Dr. Ramplin reported no potential conflicts of interest.
Antidepressants and Diabetes

A recent study used records from the U.K. General Practice Research Database to assess the risk of diabetes with antidepressant treatment.

**Methods:** Patients (n=165,958; aged ≥30 years) who had depression and a new antidepressant prescription but no indication of diabetes between 1990 and 2005 were selected. Timing, duration, and dose of antidepressant treatment were compared between case patients in whom diabetes developed (n=2243) and matched controls (n=8963) in whom it did not. Antidepressant exposure in the 6 months before the index date was considered recent, and dosages were classified as low or moderate/high based on median daily dosages.

**Results:** Recent use of an antidepressant at a moderate or high dose for >2 years increased risk for diabetes by 84%. Risk was increased with TCAs (risk ratio,* 1.77) and with SSRIs (risk ratio, 2.06). Analysis of individual antidepressants showed risk ratios were increased with recent long-term use of amitriptyline (2.5), fluvoxamine (9.1), paroxetine (1.8), and venlafaxine (3.0). Risk estimates were also elevated for clomipramine, nortriptyline, and trimipramine, but few patients received these agents and the increases did not reach statistical significance. No patient in the cohort was treated with an MAOI, or with bupropion, maprotiline, or several other less commonly used tricyclic or tetracyclics. Because these agents could not be evaluated, no assumptions can be made about their association with diabetes. Shorter treatment durations, lower doses, and past use (ending 12–24 months before the index date) were not associated with increased risk.

Andersohn F, Schade R, Suissa S, Garbe E: Long-term use of antidepressants for depressive disorders and the risk of diabetes mellitus. *American Journal of Psychiatry.* Published online April 1, 2009 at www.ajp.psychiatryonline.org; doi 10.1176/appi.ajp.2008.08071065. From the Bremen Institute for Prevention Research and Social Medicine, Bremen, Germany; and other institutions. Funded by the Canadian Foundation for Innovation; the Canadian Institutes of Health Research; and Bayer Schering Pharma AG.

*Drug Trade Names:* amitriptyline—Elavil, and others; bupropion—Wellbutrin; clomipramine—Anafranil; fluvoxamine—Luvox; maprotiline—Ludiomil; nortriptyline—Aventyl, Pamelor; paroxetine—Paxil; trimipramine—Surmontil; venlafaxine—Effexor

*Citalopram Augmentation in Schizophrenia*

Depressive symptoms are common in patients with schizophrenia, and APA guidelines recommend antidepressants for major depression in these patients. However, antidepressant augmentation in schizophrenia has received little study, particularly when symptoms are subsyndromal. Augmentation with citalopram (*Celexa*) appeared to improve depressive symptoms.

**Methods:** Patients (n=198) aged ≥40 (range, 41–75 years) with schizophrenia or schizoaffective disorder who had been experiencing 2–4 depressive symptoms for at least 2 weeks (i.e., subsyndromal depression) were enrolled in this multisite randomized controlled trial. Patients received 12 weeks of augmentation with 10–40 mg/day citalopram or placebo. The majority of patients (90%) were receiving a second-generation antipsychotic either alone or combined with a first-generation agent. The Hamilton Rating Scale for Depression (HAM-D) and the Calgary Depression Rating Scale (CDRS) were the primary outcome measures and response was defined as a ≥50% decrease in score.

**Results:** Augmentation with citalopram produced greater improvements than placebo in HAM-D and CDRS scores (p<0.04). Baseline scores were 14 on the HAM-D and 7 on the CDRS, and they were decreased to 8 and 4 with citalopram treatment and to 10 and 6 with placebo. Using HAM-D scores, 41% of citalopram-treated patients responded, compared with 23% of placebo-treated patients. Using CDRS measurements, 50% and 36% of the citalopram and placebo groups responded. The number needed to treat* was <6 using either measure of response. Secondary
outcome measures showed significant differences between citalopram and placebo in negative symptom improvement, general functioning, and quality of life. Positive symptoms and suicidal ideation were not affected.

The majority of patients completed the 12-week trial: 77 of 104 assigned to citalopram and 72 of 94 assigned to placebo. Outcomes were measured using last observations carried forward.* Most patients experienced adverse effects including GI complaints, difficulty sleeping, musculoskeletal pain, and dry mouth. Serious adverse events (e.g., substance abuse, worsening symptoms, suicidal ideation) occurred in 9 citalopram patients and 13 placebo patients. The most common reason for study withdrawal was nonadherence (n=23; 47%).

Discussion: According to the authors, "when confronted with a patient with schizophrenia who has mild to moderate symptoms of depression, even when those symptoms do not add up to a full diagnosis of MDD, clinicians may consider augmenting antipsychotics with antidepressants." The present study suggests citalopram is effective in this context, but further study is needed with other antidepressants.

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

Zisook S, Kasckow J, Golshan S, Fellows I, et al: Citalopram augmentation for subsyndromal symptoms of depression in middle-aged and older outpatients with schizophrenia and schizoaffective disorder: a randomized controlled trial. Journal of Clinical Psychiatry 2009;70 (April):562–571. From the University of California, San Diego; and other institutions. Funded by NIMH; and the Department of Veterans Affairs. The study authors disclosed receiving support from multiple pharmaceutical-industry sources. Citalopram is not approved for augmentation in schizophrenia.

Treating Panic Disorder in Pregnancy/Nursing

Panic disorder occurs about twice as often in women as in men, and the gender difference is particularly striking in younger adults. In light of the rates of panic disorder in young women, treatment decisions for pregnancy and nursing are important issues.

The course of panic disorder in pregnancy and in the postpartum period appears to be highly variable, and the effects of untreated panic on obstetric outcomes are unknown. Because there is conflicting evidence regarding the safety of antidepressants (a mainstay in the treatment of panic disorder) in pregnant women, the new APA practice guideline for panic disorder recommends considering psychosocial interventions for women who are pregnant, nursing, or planning a pregnancy. Pharmacotherapy may also be indicated, but requires a risk/benefit analysis. Decision-making about treatment and breastfeeding should also involve the infant’s pediatrician.


Antiepileptics in Pregnancy

Children born to mothers who took valproate during pregnancy had lowered IQ scores at age 3 years. Carbamazepine, lamotrigine, and phenytoin did not lower scores significantly.¹

Methods: The Neurodevelopmental Effects of Antiepileptic Drugs study was designed to compare neuropsychiatric outcomes in >300 children exposed in utero to carbamazepine, lamotrigine, phenytoin, or valproate. Mothers were enrolled in the study if they received a single drug to treat epilepsy. Children are expected to be followed to the age of 6 years. The current interim analysis examined IQ scores in 258 of the children tested at age 2 or 3 years.

Results: Mean IQ scores in the 3-year-olds were 92 for those exposed to valproate, 98 for those exposed to carbamazepine, 99 for those exposed to phenytoin, and 101 for those exposed to
lamotrigine. After adjustment for maternal IQ and age, drug dosage, gestational age, and preconceptional folate intake, mean IQ scores of the children exposed to valproate were 6–9 points lower than those of children exposed to carbamazepine, lamotrigine, or phenytoin (p≤0.04). Mothers taking valproate were younger (28 years vs 30–31 years), more likely to have idiopathic generalized epilepsy (70% vs 8–39%), and less likely to breastfeed (31% vs 44–47%). However, the association between valproate use and cognitive outcomes in the children persisted after adjustment for many baseline characteristics and a propensity analysis.

**Discussion:** Previous research has shown the risk of physical malformations associated with antiepileptics is highest with valproate. Taken together, the lowered IQ and physical risks for the fetus suggest valproate should not be used as first-line treatment during pregnancy. Since many pregnancies are unplanned, women of childbearing potential who require antiepileptic medication should be informed of the risks and educated about the importance of prepregnancy planning and counseling.


**Drug Trade Names:** carbamazepine—Epitol, Tegretol; lamotrigine—Lamictal; phenytoin—Dilantin; valproate—Depakene

### Quetiapine Maintenance in Bipolar Disorder

Current guidelines for maintenance treatment of bipolar disorder recommend the use of an atypical antipsychotic with a mood stabilizer or antidepressant in some situations, but with the qualification that the combinations have received little study and additional controlled trials are needed. Recently a double-blind placebo-controlled trial investigated maintenance treatment with the combination of quetiapine plus lithium or divalproex for 2 years.1

**Methods:** In the multicenter study, 1953 adults with bipolar disorder received open-label flexible-dose quetiapine in addition to lithium or divalproex for up to 36 weeks. A total of 1325 patients discontinued treatment during this phase, nearly 40% because of lack of response or adverse events. The 628 patients who completed acute treatment and achieved clinical stability (Young Mania Rating Scale and Montgomery Asberg Depression Rating Scale scores of ≤12 for more than 12 weeks) were then randomized to maintenance treatment with continued quetiapine plus their mood stabilizer or placebo plus the mood stabilizer. They were then followed for up to 2 years with visits conducted at increasing intervals to a final schedule of every other month during year 2. Maintenance doses were flexible in the range of 400–800 mg/day quetiapine and to target serum levels of 0.5–1.2 mEq/L lithium and 50–125 mcg/mL divalproex. The primary outcome was recurrence of mania, depression, or a mixed episode.

**Results:** Five patients took no randomized medication, and the intent-to-treat sample for analysis comprised 623 patients: 310 receiving quetiapine plus lithium or divalproex and 313 receiving placebo plus lithium or divalproex. The median quetiapine dose during follow-up was 519 mg/day and the mean duration of exposure was 240 days, compared with 178 days for placebo. A total of 176 of the 623 patients (28%) completed the follow-up period: 36% of the quetiapine group and 21% of the placebo group.

A recurrent mood event occurred in 63 of the 310 patients (20%) who received quetiapine, compared with 163 of the 313 patients (52%) who received placebo. The time to occurrence was significantly longer with quetiapine than placebo (p<0.0001). Quetiapine was associated with significantly more sedation, weight gain (mean, 12 lbs), and hypothyroidism. Extrapyramidal
symptoms (e.g., akathisia, cogwheel rigidity, restlessness, tremor) were reported by 11% of patients who received quetiapine maintenance and by 10% of those who received placebo. Quetiapine also had a larger influence on blood glucose level and produced adverse effects potentially associated with diabetes (e.g., hyperglycemia, ketoacidosis, polydipsia, polyuria) in 5% of patients receiving quetiapine, compared with 2% in the placebo group. The increase in diabetes-related adverse effects should receive further study.

Discussion: These results suggest that patients who benefit from quetiapine plus a mood stabilizer, albeit a small percentage of the total treated population (32%), are more likely to sustain response if they continue quetiapine during maintenance treatment. A parallel study similar in size and design conducted internationally by some of the same investigators had comparable findings. In that study, the proportion of patients who experienced a recurrent mood event was 19% with quetiapine plus lithium or divalproex and 49% with placebo plus lithium or divalproex.


Drug Trade Names: divalproex—Depakote; quetiapine—Seroquel

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**Reference Guide**

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

**Number Needed to Treat:** Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

**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 (non-exposed) 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.