According to a preliminary report, stellate ganglion block with bupivacaine, a common pain-management procedure often used to treat face and arm pain, may be effective in treatment-resistant post-traumatic stress disorder.

**Background:** Current treatment options for PTSD are limited to SSRIs and psychotherapies (e.g., cognitive and exposure modalities) or a combination of the 2. However, overall success rates are low (<30%) among veterans and active duty military personnel with combat exposure, and response can take up to 6 months. Previous case reports described promising para-anaesthetic effects of stellate ganglion block in 3 patients with PTSD. The present study further investigated the treatment.

**Patients:** Participants were 8 veterans or active-duty military personnel with PTSD, who had been unsuccessfully treated for at least 1 year. All were evaluated with the 17-item PTSD Checklist, Military Version, which captures anxiety symptoms related to re-experiencing, avoidance, and hyperarousal. Study participants ranged in age from 29 to 66 years (mean age, 43 years); 7 of the 8 were male. All had received the diagnosis of PTSD ≥4 years earlier and had not responded to standard therapies. Most were taking ≥3 medications for PTSD, depression, and other related comorbidities.

**Intervention:** Stellate ganglion block can be administered in an outpatient setting over a period of about 10 minutes. Treatment was delivered with or without sedation, according to the patient’s preference. For the nerve block, bupivacaine was injected into the stellate ganglion (at the level of the 6th cervical vertebra) assisted by contrast imaging.

**Results:** After 1 treatment and an average follow-up of 17 days (range, 1–59 days), 6 of the 8 patients had substantial declines in PTSD symptom scores, ranging from 47% to 73%. The other 2 patients had smaller symptom reductions that were not clinically meaningful. Patients who responded had significant decreases in avoidance and hyperarousal, but not re-experiencing. The 2 patients who had multiple treatments experienced symptom reductions of 59% and 73%.
Although complications (such as infection, bleeding, seizures, and spinal cord trauma) may occur with the procedure, there were no adverse effects in the present case series.

**Discussion:** Since the stellate ganglion has connections with the CNS nuclei that modulate PTSD, the block may work by resetting the area of the brain responsible for anxiety to its pretrauma state, in the same way that sympathetic blocks can reset areas involved in intractable neuropathic pain. Stellate ganglion block may have a calming effect that primarily improves avoidance and hyperarousal. The patients in this series usually felt better within several hours of treatment. It is not known how long the improvement lasts or whether the effects of multiple treatments are cumulative. Stellate ganglion block already has FDA approval for pain management, is relatively inexpensive, and could be rapidly introduced for treatment of refractory PTSD if clinical trials prove its effectiveness.


**Antidepressant Augmentation or Switching**

In patients with partial response to a first-line antidepressant, augmentation and switching strategies produced equivalent rates of response and remission, in an analysis of data from the STAR*D trial. However, in patients who are able to tolerate ≥12 weeks of initial treatment and have milder residual depressive symptoms, augmentation may be slightly more effective.

**Methods:** The STAR*D is a large-scale clinical trial of sequential treatments for unipolar major depression. To mimic real-life clinical practice, patients’ preferences for general treatment strategies were taken into account. Of >4000 patients who entered first-line treatment with citalopram, 1439 did not achieve remission and entered the second study phase. The present analysis included 1292 patients who received citalopram augmented with either bupropion or buspirone or were switched to bupropion, sertraline, or venlafaxine. To compensate for imbalances in patient, disease, and treatment characteristics, the groups were propensity score matched,* based on 47 different covariates that reflected their propensity to receive augmentation. The final study group consisted of 269 propensity-matched patients in each of the 2 treatment groups. Remission was defined as a score of □≤ 5 on the 16-item Quick Inventory of Depressive Symptomatology, Self-Rated (QIDS-SR16) and response as a ≥50% reduction in the score.

**Results:** In the larger study sample (not propensity-matched), patients who received augmentation differed from those switched to an alternate medication in several important ways. They received higher doses of citalopram as monotherapy during the first study phase; spent more time on average receiving citalopram monotherapy (12 vs 8 weeks); were less likely to exit the study’s monotherapy phase because of adverse effects (10% vs 63%); and had somewhat lower residual depression severity scores at the end of monotherapy (11% vs 13%).

In the propensity-matched sample, results of switching and augmentation were nearly identical at the end of the second treatment stage, with equal rates of remission and response (about one-fourth each). Treatment effects on quality of life were also similar. However, patients with the highest propensity for augmentation were more likely to remit with augmentation than with switching (risk ratio,* 1.64; confidence interval,* 0.86–3.16). This difference increased as a function of the length of time on citalopram monotherapy and was
especially large in patients who received monotherapy for ≥12 weeks. Relatively low residual severity of depressive symptoms after monotherapy was also predictive of better outcome with augmentation.

**Discussion:** In clinical practice, augmentation is often favored over switching in patients who tolerate an initial medication trial but achieve only partial response. The present observations provide tentative evidence to support that practice, particularly in patients who complete 12 weeks of initial monotherapy and have less severe residual depressive symptoms.

Gaynes B, Dusetzina S, Ellis A, Hansen R, et al: Treating depression after initial treatment failure: directly comparing switch and augmenting strategies in STAR*D. *Journal of Clinical Psychopharmacology* 2012;32 (February):114–119. From the University of North Carolina at Chapel Hill; and other institutions. Funded by the Agency for Healthcare Research and Quality. All of the study authors disclosed financial relationships with commercial sources, but none were directly related to the study content.

**Drug Trade Names:** bupropion—*Wellbutrin*; buspirone—*BuSpar*; citalopram—*Celexa*; sertraline—*Zoloft*; venlafaxine—*Effexor*

*See Reference Guide.

**Pneumonia Risk with Antipsychotics**

Of the second-generation antipsychotics, clozapine is associated with the greatest risk of pneumonia, particularly when prescribed with other drugs, according to a study in a large cohort of patients with schizophrenia. Pneumonia risk is highest at the beginning of treatment with most second-generation drugs.¹

**Background:** Second-generation antipsychotics have been associated with increased mortality in elderly patient populations,² but the risks have not been investigated in well-designed studies of nonelderly persons with schizophrenia. Specific causes of antipsychotic-related mortality are cardiovascular events and infection, primarily pneumonia. Results of previous studies indicate drugs with high affinity for the histaminergic (H-1) receptor or the muscarinic (M-1) receptor may particularly increase risk of pneumonia.

**Methods:** The relationship of second-generation antipsychotics with pneumonia in patients with schizophrenia was investigated using medical claims data from 2000 through 2008 for the entire population of Taiwan. Cases selected for this case-control analysis were patients, aged 18–65 years, who had their first psychiatric admission for schizophrenia during the study period and subsequently required hospitalization for pneumonia. Each case was matched with up to 4 controls with schizophrenia who were not hospitalized for pneumonia. Cases and controls were matched for age, gender, and year of first psychiatric admission. The study population consisted of 1739 cases and 6949 controls. Investigators analyzed risks for all second-generation antipsychotics available in Taiwan and prescribed with sufficient frequency. First-generation drugs were also included in the analysis as a single category.

**Results:** Nearly all cases and controls had received a first-generation drug at some point. Use of these agents was not associated with pneumonia. Current use of any second-generation drug was associated with increased pneumonia risk. Risk was not increased with recent use (discontinued 1–6 months previously) or past use (>6 months previously). Current use of clozapine was associated with the highest risk, with a 3-fold increase compared with patients never exposed to clozapine (adjusted risk ratio,* 3.18). Risk was also elevated, although less so, with olanzapine, quetiapine, zotepine, and risperidone. (See table, next page.) Amisulpride was not associated with pneumonia. In patients receiving clozapine, but not other agents, risk of pneumonia increased as a function of dose and duration of therapy. Nearly all combinations of clozapine with another drug were associated with increased risk compared with monotherapy. Risk of pneumonia decreased to background levels after 30 days of use for all drugs except clozapine.


**Discussion:** The study authors recommend monitoring patients for signs of pneumonia particularly after they start clozapine and if an additional antipsychotic is prescribed. Pneumonia risk with the different atypicals generally parallels their H-1 and M-1 receptor affinities and may reflect mechanisms such as dry mouth and sedation. The lack of association of first-generation drugs with pneumonia may have been due in part to the grouping of this heterogeneous category of agents, some of which are known to increase pneumonia risk.

1. Kuo C-J, Yang S-Y, Liao Y-T, Chen W, et al: Second-generation antipsychotic medications and risk of pneumonia in schizophrenia. *Schizophrenia Bulletin* 2011; doi 10.1093/schbul/sbr202. From Taipei City Hospital, Taiwan; and other institutions. *Funded by the National Science Council of Taiwan and Taipei City Hospital. The authors declared no conflicts of interest.*


**Drug Trade Names:** amisulpride (not available in the U.S.)—Solian; clozapine—Clozaril; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal; zotepine (not available in the U.S.)—Nipolept, and others

*See Reference Guide.*

### Antidepressants in SAD

Little evidence supports the use of second-generation antidepressants in seasonal affective disorder, according to a Cochrane systematic review.

**Background:** Bright-light and dawn-simulation therapy are recommended for treatment of seasonal depression. However, there is interest in pharmacotherapy because light therapy is time-consuming and has a low rate of compliance.

**Methods:** A comprehensive literature search was undertaken to identify studies of second-generation antidepressants (SSRIs, SNRIs, and other newer agents) in adults who met DSM-IV criteria for SAD. Studies that included patients with bipolar disorder were excluded. The efficacy evaluation was based on randomized clinical trials of ≥4 weeks’ duration; observational studies were also included in a safety analysis.

**Results:** The investigators found only 3 randomized trials that met all inclusion criteria, and the antidepressant compared in all 3 was fluoxetine. All 3 trials had low-to-moderate risk of bias.

In a 5-week trial comparing fluoxetine with placebo in 68 patients, response was measured as a ≥50% improvement on the Hamilton Rating Scale for Depression combined with an 8-item scale for SAD. Response rates were higher with fluoxetine than placebo, but the drug was not statistically superior to placebo (odds ratio* for response, 1.62; 95% confidence interval,* 0.92–2.83).

The other 2 trials compared fluoxetine with light therapy in 136 patients assessed after 5 or 8 weeks. The treatments did not differ in efficacy, with about two-thirds of patients responding to each and about half achieving remission.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients (% of Exposed Patients)</th>
<th>Adjusted Risk Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>336 (19%)</td>
<td>3.18</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>199 (11%)</td>
<td>1.83</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>198 (11%)</td>
<td>1.63</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Zotepine</td>
<td>130 (8%)</td>
<td>1.48</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Risperdone</td>
<td>468 (27%)</td>
<td>1.32</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>56 (3%)</td>
<td>1.14</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Any First-Generation Agent</td>
<td>1018 (59%)</td>
<td>1.38</td>
<td>p=ns</td>
</tr>
</tbody>
</table>

Risk of Pneumonia with Current Antipsychotic Use
Adverse event rates were observed in 2 clinical trials and 3 observational studies that included patients treated with fluoxetine or another second-generation antidepressant (i.e., escitalopram, duloxetine, reboxetine). In these studies, 50–100% of patients experienced adverse effects; 6% of patients treated with light therapy and 15–27% who received pharmacotherapy withdrew from treatment as a result. The most common adverse events were nausea, diarrhea, sleep disturbance, and sexual dysfunction. Risk of bias in the observational studies was considered high.

**Discussion:** Based on these results, it is unclear whether fluoxetine has a role in treating SAD. In the clinical trials, fluoxetine was associated with more adverse effects than light therapy, but logistical and financial concerns might preclude light therapy in some patients.

**Study Rating**—18 (100%): This study met all criteria for a systematic review.

**Adjunctive Clomipramine in OCD**

In a group of patients with obsessive-compulsive disorder, adding low-dose clomipramine to fluoxetine was more effective than adding quetiapine.

**Methods:** Study subjects, aged 18–65 years (n=54), had a primary diagnosis of OCD and a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of ≥16. All had experienced a ≤35% improvement despite ≥8 weeks of treatment with the maximum recommended or tolerated dose of fluoxetine. Before randomization, participants’ fluoxetine dosage was reduced to ≤40 mg/day because of the potential for an interaction between clomipramine and fluoxetine. All patients then received 12 weeks of double-blind, randomized adjunctive treatment with ≤200 mg/day quetiapine, ≤75 mg/day clomipramine, or placebo. The primary efficacy measure was the Y-BOCS.

**Results:** Mean baseline Y-BOCS scores ranged from 25 to 28. At 12 weeks, the least improvement was seen in the quetiapine group; Y-BOCS improvements were 10 points with clomipramine, 7 points with placebo, and <1 point with quetiapine (p<0.001 for clomipramine and placebo vs quetiapine). The number needed to treat* with clomipramine vs quetiapine was 2.4. Response, defined as a ≥35% reduction in Y-BOCS score, was achieved by 8 clomipramine-treated patients (44%), 10 placebo-treated patients (56%), and 6 quetiapine-treated patients (33%). No toxicity was evident with the fluoxetine–clomipramine combination.

**Discussion:** The addition of atypical antipsychotics to fluoxetine is an established second-line treatment for OCD. In this trial, adjunctive clomipramine significantly outperformed quetiapine. The authors suggest that for fluoxetine nonresponders, low-dose clomipramine may be a safe and effective augmentation strategy.

**Study Rating**—17 (100%): This study met all criteria for a randomized controlled trial.
Mortality Risk of Antipsychotics in Dementia

In a large national sample of outpatients with dementia, haloperidol was associated with the highest mortality among commonly used antipsychotic agents, and quetiapine with the lowest mortality. Valproic acid, sometimes used as an alternative to treat neuropsychiatric symptoms of dementia, was associated with comparable mortality to the atypical antipsychotics.

Methods: Investigators analyzed 10 years of data from VA registries maintained to monitor the treatment of serious mental illness. The analysis included 33,604 patients, aged ≥65 years, treated as outpatients for ≥6 months. The analysis was limited to the drugs most often used for behavioral disturbances of dementia in the VA population: haloperidol, risperidone, olanzapine, quetiapine, and valproic acid and related drugs. The study was also limited to patients who received monotherapy (87% of the total) and excluded those who had a seizure disorder.

Results: Risperidone and quetiapine were the most commonly used drugs in this population, in more than 13,000, and 10,000 patients, respectively. Patients using haloperidol were older, sicker, and more likely to be African-American than others. Quetiapine users had significantly higher rates of Parkinson’s disease. Those prescribed valproate were younger, less likely to be African American, and more likely to have comorbid bipolar disorder and other psychiatric illness.

Crude mortality rates for the 6 months following the first prescription were 20% for haloperidol; 12.6% for olanzapine; 12.5% for risperidone; 9.8% for valproate; and 8.8% for quetiapine. Results were similar in an intent-to-treat (ITT) analysis* adjusted for patient-related factors and in a propensity-weighted analysis.* (See table.) The imbalance in patients with Parkinson’s disease, who tend to receive lower drug doses, did not account for the relatively low mortality rates with quetiapine.

Discussion: The possible differential risks with individual drugs should be balanced against what is known of their efficacy. Although it appears to be safe, quetiapine has never been shown to be effective in treating aggression, agitation, or psychosis. Risperidone and olanzapine appear to provide the best balance of safety and efficacy.

Editorial: The serious risks of antipsychotic drug use in patients in dementia are well known, and a new evidence-based best practice guide for preventing and managing behavioral and psychological symptoms is available at www.alzheimers.org.uk/bpsdg. The present study provides important data on the relative risks of different agents and contributes to the understanding of the optimal role of antipsychotics as part of an overall approach to treating behavioral and psychological symptoms of dementia. Rather than resisting prescribing antipsychotics in dementia, clinicians should consider judicious short-term use of the drugs, in

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adjusted ITT Analysis</th>
<th>Propensity-Weighted Analysis</th>
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<tbody>
<tr>
<td></td>
<td>Hazard Ratio*</td>
<td>P Value</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1.00</td>
<td>_____</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1.54</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.99</td>
<td>p=ns</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.73</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>0.91</td>
<td>p=ns</td>
</tr>
</tbody>
</table>
concert with nondrug treatments, pain management, and proactive steps to reduce the poten-
tially fatal complications of antipsychotic use, such as sedation, chest infection, and dehydration.

Management Research, Mich.; and other institutions. Funded by the NIMH. One study author reported financial
relationships with commercial sources.

(January):7–9. From the Alzheimer’s Society; and King’s College, London, U.K.

Drug Trade Names: haloperidol—Haldol, and others; olanzapine—Zyprexa; quetiapine—Seroquel;
risperidone—Risperdal; valproate—Depakene, Depakote

*See Reference Guide.

**IV Ketamine for Resistant Depression**

Results of a literature review suggest that intravenous ketamine (Ketalar) shows promise in
patients with treatment-resistant depression, particularly as a bridge therapy as they await the
onset of action of conventional antidepressants. However, the published evidence appears
insufficient to recommend ketamine as a treatment for depression.

Ketamine, FDA approved as an adjunct to general anesthesia and procedural sedation, is an
NMDA-glutamate receptor antagonist with effects on multiple other neurotransmitter systems.
The present review examined the use of ketamine in patients with refractory major depression.
The review identified case reports of 7 patients, 3 open-label trials, and a single randomized
crossover study. All patients met DSM-IV criteria for major depression, had failed to respond to
≥2 adequately-dosed antidepressants, and were antidepressant-free for ≥2 weeks when they
received ketamine.

The case reports showed positive effects of ketamine on mood, appearing 1–2 days post-infusion
and lasting from several days to weeks. In the randomized crossover trial, 18 patients with
moderate-to-severe refractory depression were administered ketamine or placebo 1 week apart.
In the 13 patients who completed the study, mean Hamilton Rating Scale for Depression
(HAM-D) reductions were substantially greater with ketamine than with placebo at day 1 (56%
vs 10%; effect size,* 1.46). With ketamine, 71% of patients achieved response (i.e., >50% reduction
in HAM-D score), 6 maintained their response for more than 17 days, and 5 achieved remission
within 1 day of ketamine administration. Four patients could not be crossed over to placebo
because they continued to meet response criteria 7 days after ketamine infusion.

Ketamine was also evaluated in 3 open-label studies with varying aims and designs, in a
total of 78 patients. Effect sizes ranged from moderate (in 1 group of ECT-resistant patients)
to large or very large. In an open-label study of 10 patients with resistant depression, ketamine
was administered in up to 6 doses over 12 days. Of the 9 patients who responded to the
initial ketamine infusion and received all 6 doses, all met response criteria after the last dose
and 8 met criteria for remission. Mean time to relapse was 19 days after the last ketamine
dose (range, <1 week to >3 months).

Although these results are generally favorable, they are difficult to interpret. The studies used
varying doses (from 0.15 to 0.5 mg/kg), single or multiple doses, and intermittent or continuous
infusions. Treatment schedules and length of follow up also varied. Trials focused mainly on effi-
cacy, with little analysis of safety or of the abuse potential of ketamine, classified as a Schedule-III
nonnarcotic controlled substance. Adverse effects described in these studies were generally mild
and transient and included changes in vital signs, mild dissociation, headaches, and dizziness.

Covvey J, Crawford A, Lowe D: Intravenous ketamine for treatment-resistant major depressive disorder. Annals of
Pharmacotherapy 2012;46 (January):117–123. From Virginia Commonwealth University Health System, Richmond. The
authors disclosed no competing interests.

*See Reference Guide.
**Reference Guide**

**Confidence Interval:** The range in which the value of a variable in question is likely to fall, usually calculated at 95%. Confidence intervals indicate the reliability of an estimate, and a very wide interval may indicate that more data should be collected before making definite conclusions.

**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.

**Intent-to-Treat:** An analysis based on initial treatment intent, not on the treatment actually administered or completed. In an intent-to-treat (ITT) analysis, everyone who begins treatment is included regardless of treatment completion. ITT analyses are done to avoid the effects of crossover, drop-out, and other factors that could alter the results or inflate the magnitude of effects.

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

**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.

**Propensity Matching:** A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

**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 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.

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