Quetiapine Augmentation in the Elderly

Adding quetiapine (Seroquel) to an antidepressant appears to be effective and well tolerated in elderly patients with resistant depression.

A retrospective chart review was conducted of 20 elderly inpatients with depression treated at a single center between 2006 and 2008. All patients were aged ≥60 years and had been unsuccessfully treated with at least 1 adequate antidepressant trial in the current depressive episode. Patients previously exposed to quetiapine were excluded.

Thirteen patients were female, and the mean age of the group was 74 years. The mean duration of the current episode was 4 months. Before receiving quetiapine augmentation, patients had not experienced clinically meaningful improvement while receiving an SSRI (n=9), a heterocyclic (n=7); an SNRI (n=3), or bupropion (n=1). Quetiapine was added to antidepressant therapy and titrated to a mean of 70 mg/day (range, 12.5–200 mg/day). Mean Clinical Global Impression (CGI) Severity* scores decreased from 6.4 to 3.25 (p<0.03) after an average of 4 weeks. The average CGI Improvement rating was "much improved."

Five patients complained of somnolence but chose to continue quetiapine. One patient discontinued therapy because pre-existing suicidal tendencies worsened. Quetiapine is not FDA approved to treat depression, and prospective studies are needed to establish its efficacy and safety.

Tadger S, Paleacu D, Barak Y: Quetiapine augmentation of antidepressant treatment in elderly patients suffering from depressive symptoms: a retrospective chart review. Archives of Gerontology and Geriatrics 2010; doi 10.1016/j.archger.2010.06.012. From the Abarbanel Mental Health Center of Tel-Aviv University, Israel. The authors disclosed no potential conflicts of interest.

*See Reference Guide.

Quetiapine for Hyperhidrosis in Social Anxiety Disorder

Axillary hyperhidrosis, or excessive sweating, is relatively common in social anxiety disorder and affects about 30% of patients. Treatment usually consists of topical agents, surgery (e.g., liposuction), or temporary gland denervation with botulinum toxin. In controlled trials,
paroxetine and fluoxetine have been shown to have small positive effects. There are now 3 cases of hyperhidrosis improvement with low-dose quetiapine.

The first patient, a 53-year-old man, had moderate social phobia and associated hyperhidrosis that had not responded to topical treatment, anticholinergic medication, or botulinum toxin injections. After taking 25 mg quetiapine off-label as a sedative, the patient noted an absence of excessive sweating for about 6 hours. He requested continued quetiapine, which he used at 12.5 to 50 mg as needed for 12 months. He reported excellent control of hyperhidrosis for 6–12 hours after each dose. Mild sedation and dry eyes and mouth were the only noted adverse effects of quetiapine treatment.

The other patients were 19-year-old female twins. Both had social phobia and axillary hyperhidrosis. They experienced marginal improvement with topical agents but were unwilling to undergo surgery or botulinum toxin injections. They were treated with 12.75–25 mg quetiapine as needed 1–2 hours before an anxiety-provoking situation and reported a near complete absence of sweating. Both experienced mild dose-dependent dry mouth and sedation.

Quetiapine is approved for treatment of depression, bipolar disorder, and schizophrenia in the range of 400–800 mg/day. The authors suggest that low-dose treatment may block alpha-adrenergic receptors thus causing a decrease in sympathetic neuron overarousal that leads to reduced sweating. Although these cases provide only preliminary evidence supporting quetiapine in hyperhidrosis, based on the robust effects, controlled trials appear to be warranted.


Drug Trade Names: fluoxetine—Prozac; paroxetine—Paxil; quetiapine—Seroquel

### Lamotrigine-Associated Aseptic Meningitis

Aseptic meningitis is a rare but serious adverse effect that can occur with lamotrigine (Lamictal). An FDA review of adverse event reports identified 40 cases of lamotrigine-associated aseptic meningitis. These were characterized by headache; fever; nausea; vomiting; stiff neck; rash; photophobia; and myalgia. Symptoms developed an average of 16 days after starting treatment (range, 1–42 days), and 35 patients were hospitalized. In most cases, symptoms resolved with lamotrigine discontinuation. In 15 patients rechallenged with lamotrigine, symptoms recurred within 24 hours. Some of the affected patients had underlying autoimmune disease and some cases appeared to be a hypersensitivity or generalized drug reaction.

Lamotrigine is commonly used to treat seizures in patients as young as 2 years and adult bipolar disorder. The label will be updated to reflect the risk of meningitis and a medication guide will now be required with each filled prescription.


### More on Antiepileptics and Suicide

An FDA meta-analysis found risk for suicidality was increased 2-fold in patients receiving an antiepileptic; relative risk was greater among patients treated for epilepsy than for psychiatric conditions. A new study of antiepileptic-associated suicidal acts suggests the underlying condition being treated contributes more to suicidality than the use of antiepileptic drugs.

Methods: Data were collected for more than 5 million patients from a primary care database in the U.K. Patients were representative of the general population, and those with a personal or family history of suicidality were excluded. They were followed for a mean of 6 years. The incidence of
suicide-related acts (i.e., suicide attempts, completed suicides) was calculated in separate cohorts of patients with epilepsy, depression, bipolar disorder, and none of these disorders.

**Results:** A total of 8212 patients attempted suicide, including 464 whose attempts were successful. Crude incidence of suicidal acts was highest among patients with bipolar disorder, followed by depression (see table), regardless of antiepileptic use. In a case-control analysis adjusted for potential confounders (e.g., age, duration of illness, alcohol abuse), epilepsy and depression were associated with a 50% increase in risk for suicide-related acts and the increase associated with bipolar disorder was 2-fold. Adjusted odds ratios* (OR) by treatment indication for treated vs untreated patients are also presented in the table; only the association in patients with depression was statistically significant.

<table>
<thead>
<tr>
<th>Incidence of Suicidal Acts per 100,000 Patient-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiepileptic Users</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Bipolar Disorder Only</td>
</tr>
<tr>
<td>Unipolar Depression Only</td>
</tr>
<tr>
<td>Epilepsy Only</td>
</tr>
<tr>
<td>No Epilepsy, Depression, or Bipolar Disorder</td>
</tr>
</tbody>
</table>

**Discussion:** Generally, the present results do not support the FDA conclusion that suicide risk is increased in patients with epilepsy treated with an antiepileptic. However, an association was found among patients with depression. Consistent with results of a previous pharmacoepidemiologic study, no evidence was found that antiepileptic use in bipolar disorder increases risk beyond that of the disorder itself.


*See Reference Guide.

**Ketamine for Bipolar Depression**

A single infusion of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine had rapid antidepressant effects in patients with bipolar depression.

**Background:** Glutamatergic dysfunction, particularly in the NMDA receptor complex, is involved in the pathophysiology of bipolar disorder. In addition, the glutamatergic modulator riluzole has been shown to have antidepressant effects in patients with bipolar disorder. The present study was undertaken to evaluate the antidepressant effects of directly targeting the NMDA receptor with ketamine.

**Methods:** Study participants were 18 inpatients with bipolar I or II depression without psychotic features. Patients were required to have a current major depressive episode of at least 4 weeks in duration and to have failed at least 1 adequate antidepressant trial as well as a trial of a mood stabilizer. Study treatment was carried out at the NIMH. All patients remained on stable doses...
of lithium or valproic acid throughout the study. No other medication was permitted for the 2 weeks preceding each study treatment. In a randomized, crossover fashion, patients were administered IV ketamine 0.5 mg/kg or a saline placebo. Depression was evaluated using several standardized measures 60 minutes before infusion and then at 40, 80, 110, and 230 minutes postinfusion. Measures were repeated on 6 occasions during the 2 weeks after infusion.

Results: Changes in Montgomery-Asberg Depression Rating Scale (MADRS) scores, the primary outcome measure, reflected a large and rapid response to ketamine. Patients had significantly fewer depressive symptoms beginning at 40 minutes (effect size,* 0.5), and the improvement remained statistically significant, compared with placebo, 3 days after ketamine infusion. The largest effect was seen at 2 days post-infusion (effect size, 0.8).

Response rates (≥50% decrease in MADRS score) were 71% with ketamine and 6% with placebo. Of the patients who responded to ketamine, 9 (56%) did so within 40 minutes of the infusion. The antidepressant effects of ketamine were supported by secondary outcome measures, the Hamilton Rating Scale for Depression, Beck Depression Inventory, and visual-analog scale for depression. Anxiety symptoms also decreased significantly after ketamine administration. Young Mania Rating Scale scores were lower following ketamine infusion, from 80 minutes through day 2 post-infusion.

Transient dissociative and perceptual disturbances were the primary adverse effects of ketamine and these could potentially have compromised the study blind. Two patients had increased blood pressure and tachycardia during the ketamine administration. These effects resolved within minutes of completing the infusion.

Discussion: Ketamine infusion has previously shown similar rapid antidepressant effects in unipolar major depressive disorder. The present findings are particularly striking because complex polypharmacy characterized the patients’ histories: the mean number of failed antidepressant trials was 7, and 55% of the patients failed to respond to ECT. This proof-of-concept study identifies the NMDA receptor as a potential target for antidepressant drug development in bipolar disorder. Ketamine is approved only for anesthesia and procedural sedation, and a longer-acting agent would be useful.

DiazGranados N, Ibrahim L, Brutsche N, Newberg A, et al: A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Archives of General Psychiatry 2010;67 (August):793–802. From the NIMH; and other institutions. Funded by the NIMH; and the National Association for Research on Schizophrenia and Depression (NARSAD). The authors did not disclose commercial relationships that pose potential conflicts of interest.

Drug Trade Names: ketamine—Ketalar, and others; riluzole—Rilutek; valproic acid—Depakene, Depakote

Ketamine Infusion Reversed Suicidal Ideation

Suicidal ideation was rapidly diminished by infusion of ketamine in patients with severe, treatment-resistant depression.

Methods: The 33 study inpatients had a mean illness duration of 26 years; 61% had a history of suicidal ideation and 30% had previously attempted suicide. All had been unmedicated for at least 2 weeks before ketamine infusion. At initial evaluation, 10 patients had elevated scores (4 or higher) on the Scale for Suicide Ideation (SSI). During pre-infusion observation (mean, 8 days), the initial level of suicidal ideation was sustained in these patients. All patients underwent an open-label infusion of 0.5 mg/kg ketamine hydrochloride, over 40 minutes, followed by 230 minutes of observation.

Results: After infusion, study participants had significant improvement in mean SSI scores, as well as scores on the suicide items of the Hamilton Rating Scale for Depression (HAM-D) and
the Montgomery-Asberg Depression Rating Scale. The effect size* on the SSI measure for the full sample was very large (1.05) at 40 minutes and moderate (0.45) at 230 minutes. In the 10 patients with clinically significant suicidal ideation, the effect size was 2.36 at 40 minutes and 1.27 at 230 minutes. These patients also had significant improvement in HAM-D total scores (p<0.001). Nine of the 10 patients had an SSI score of <4 within 40 minutes and the additional patient within 80 minutes. Five of these patients reached an SSI score of 0 within 40 minutes and another within 80 minutes. Of the patients with lower initial SSI scores, one had an 1-point increase in SSI score (from a baseline of 3 to 4) within 80 minutes. Other adverse effects were transient perceptual disturbances in the first hour after infusion.

Discussion: These results should be viewed as preliminary. It is not known whether ketamine reduces suicidal ideation in patients without major depressive disorder, nor is the duration of improvement known. Results of this study suggest that directly manipulating the glutamatergic system is a promising avenue for treating suicidal ideation. At present, emergency tranquilization with benzodiazepines or antipsychotic drugs is recommended in patients at acute risk of suicide. The high rate of suicides during emergency treatment or inpatient hospitalization and after starting an antidepressant suggests that a rapidly-acting treatment may prevent suicides during these brief periods of high risk.

DiazGranados N, Ibrahim A, Brutsche N, Ameli R, et al: Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *Journal of Clinical Psychiatry* 2010; doi: 10.4088/JCP.09m05327blu. From the NIMH; and the Department of Health and Human Services, Bethesda, Md. Funded by the NIMH; and the National Alliance for Research on Schizophrenia and Depression. The authors disclosed no commercial relationships that pose potential conflicts of interest.

Antidepressant Step Therapy Increased Costs

Step therapy plans are increasingly being implemented by insurance plans. With this system, insurance plan members are required to try a prespecified first-line medication (usually a generic agent) before receiving coverage for a second-line agent. Research has shown this reduces pharmacy spending, but the effects on other medical spending and service utilization have not been previously studied.

Methods: Study data were compiled from the Thomson Reuters MarketScan Research Database of employer-sponsored insurance plans. Claims made by employees of 2 firms that had recently implemented a step therapy protocol and 2 that did not have such a program were considered. The total sample comprised nearly 270,000 patients, including 60,796 who received antidepressant therapy (15,552 in step therapy programs and 45,244 in comparison plans). Service utilization and costs were extracted from the database and compared between the groups.

Results: Implementing the step therapy plan created a shift toward generic medication use and also fewer days of antidepressant use, thus reducing pharmacy costs. This reduction was offset by a 5% increase in overall outpatient office visits during the first quarter of program participation. Inpatient admissions increased by 17% and emergency department visits increased by 37% during the same period. Specifically, mental health service utilization of all 3 types increased with step program participation: mental health outpatient visits by 19% (p<0.001), mental health admissions by 21% (p<0.001), and emergency department visits by 18% (p=ns). Consequently, service utilization costs were 8–28% higher in the step program group and the effects increased over the first year after implementation.

Discussion: Although pharmacy costs were reduced, other spending increased, negating the cost savings of the program. The reduction in the number of days of antidepressant use with the step program is concerning as it might result from patients not filling prescriptions due to
coverage limitations and the associated administrative difficulties in obtaining approved medications. Psychiatric symptoms, adverse effects, and patient functioning could not be evaluated using the current claims data source, but the authors suggest the increase in mental health specific costs could stem from lesser effectiveness or poorer tolerability of the step 1 medications. In addition, they suggest that when allowed a range of options, physicians can take patient-specific characteristics into account and prescribe more individualized medication, which in turn will likely increase adherence and efficacy.

Mark T, Gibson T, McGuigan K, Chu B: The effects of antidepressant step therapy protocols on pharmaceutical and medical utilization and expenditures. *American Journal of Psychiatry* 2010; doi 10.1176/appi.ajp.2010.09060877. From Thomson Reuters; and Pfizer. *Funded by Pfizer*. Three of the study authors are employed by Thomson Reuters (contracted by Pfizer) and the other by Pfizer.

### Pharmacotherapy for Social Anxiety Disorder

A group of physicians with clinical expertise in treating social anxiety disorder collaborated on an 8-step treatment algorithm based on a mailed questionnaire regarding optimal first choice medication and other treatment issues.¹

**Diagnosis.** An accurate diagnosis may be challenging in social anxiety disorder because it can be misconstrued as “normal” shyness. After establishing the diagnosis, which requires marked and persistent fear or anxiety that interferes with functioning,² specific target symptoms should be identified. These may include social fear, avoidance, and somatic symptoms. Comorbidity must also be identified.

**Complications.** Comorbid conditions such as substance abuse may require that pharmacotherapy for social anxiety be delayed. In addition, concurrent medications for comorbid psychiatric or medical conditions may influence initial medication choice. Before beginning drug therapy for social anxiety, these potential complications must be addressed.

**Pharmacotherapy.** SSRIs are currently the first-line treatment for social anxiety disorder and there is substantial evidence for their efficacy and safety. Evidence also supports their usefulness in many of the common comorbidities. Venlafaxine is also approved for social anxiety disorder treatment. Choice among these agents should be based on patient and/or family history of response when possible. MAOIs are supported but dietary and other restrictions limit their use, and benzodiazepines are useful but withdrawal symptoms can be problematic. Limited evidence supports the anticonvulsants gabapentin, pregabalin, and possibly levetiracetam, and the atypical antipsychotics olanzapine and quetiapine. Patients with situation-specific social anxiety (e.g., fear of public speaking) may be medicated on an as-needed basis, typically with a beta-blocker or benzodiazepine.

Target symptom improvement and adverse effects must be monitored. When a patient cannot tolerate the initial SSRI, it should be replaced with an alternate SSRI or an agent from a different class. The dose-response curve of SSRIs is relatively flat in social anxiety disorder. See table for optimal SSRI dosage ranges. Some evidence suggests better response at higher dosages. A trial of at least 12 weeks should be completed before determining a medication is ineffective. Augmentation for partial response is a common strategy in psychiatry, but little evidence supports it in social anxiety disorder.

Patients who respond to optimized therapy should continue treatment without change for at least 1 year. Gradual taper should precede medication discontinuation and the addition of

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>20–60 mg/day</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10–20 mg/day</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20–60 mg/day</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>50–300 mg/day</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20–60 mg/day</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50–200 mg/day</td>
</tr>
</tbody>
</table>

¹ Mark T, Gibson T, McGuigan K, Chu B: The effects of antidepressant step therapy protocols on pharmaceutical and medical utilization and expenditures. *American Journal of Psychiatry* 2010; doi 10.1176/appi.ajp.2010.09060877. From Thomson Reuters; and Pfizer. *Funded by Pfizer*. Three of the study authors are employed by Thomson Reuters (contracted by Pfizer) and the other by Pfizer.

² Mark T, Gibson T, McGuigan K, Chu B: The effects of antidepressant step therapy protocols on pharmaceutical and medical utilization and expenditures. *American Journal of Psychiatry* 2010; doi 10.1176/appi.ajp.2010.09060877. From Thomson Reuters; and Pfizer. *Funded by Pfizer*. Three of the study authors are employed by Thomson Reuters (contracted by Pfizer) and the other by Pfizer.
cognitive behavioral therapy (CBT) may be useful during this phase. Patients whose symptoms do not respond to adequate first-line therapy should undergo a comprehensive re-evaluation to confirm the social anxiety diagnosis and to reconsider comorbidity. Psychosocial factors that may be complicating the course and medication nonadherence should be evaluated as reasons for nonresponse.

A substantial number of patients with social anxiety disorder do not respond to first-line treatment, and switching to another SSRI or venlafaxine may be useful after an initial failed trial. For treatment-resistant disease, MAOIs are recommended.

In addition to the pharmacotherapy addressed in the algorithm, psychoeducation is vital to the success of social anxiety disorder treatment. CBT may be a useful alternative or adjunct but there is little evidence on the optimal sequence of the treatments.

A substantial number of patients with social anxiety disorder do not respond to first-line treatment, and switching to another SSRI or venlafaxine may be useful after an initial failed trial. For treatment-resistant disease, MAOIs are recommended.

In addition to the pharmacotherapy addressed in the algorithm, psychoeducation is vital to the success of social anxiety disorder treatment. CBT may be a useful alternative or adjunct but there is little evidence on the optimal sequence of the treatments.

Rationale for Oxytocin in PTSD

Oxytocin is believed to be involved in stress regulation and social withdrawal and may dampen stress hyper-reactivity in patients with PTSD as well as increase the activity of social reward circuits. Although not directly studied, it may be a theoretically promising approach for augmentation of interventions such as CBT.

Exposure-based treatments of PTSD, such as CBT, restore extinction learning, allowing the patient to relearn appropriate responses to the fear stimulus. Higher levels of oxytocin have been associated with more effective fear extinction. Studies have also shown basal plasma oxytocin levels to be inversely associated with norepinephrine, blood pressure, and heart rate and positively associated with faster recovery of the HPA axis from an acute stress challenge. PTSD has features such as numbing and inability to benefit from offered social support that suggest an impaired reward system. By increasing social reward signals, administration of oxytocin could increase trust and enhance the therapeutic alliance by increasing the patient's sense of safety.

MDMA (pharmacologic "ecstasy"), now in clinical trials for PTSD, is associated with increased release of oxytocin, which may underlie its prosocial effects. The authors suggest administration of oxytocin itself might have more direct and powerful results. While chronic administration is unlikely to have an effect, it may be useful to administer oxytocin in short bursts during planned emotional learning experiences. To prevent PTSD, it may be administered once, in combination with psychological first aid, after acute traumatization.

Venlafaxine/Bupropion Interaction

Combination treatments play an important role in resistant depression, and large-scale studies such as the STAR*D support the combination of venlafaxine and bupropion. Venlafaxine is a cytochrome (CYP) 450 2D6 substrate, but its active metabolite desvenlafaxine is not. Concurrent
use of a CYP450 2D6 inhibitor, such as bupropion, can increase plasma venlafaxine levels and decrease desvenlafaxine levels.

Three female patients, ages 38, 47, and 55, years, with major depressive disorder were receiving medication regimens that included venlafaxine but continued to experience symptoms. Drug monitoring showed 1 patient to be a poor metabolizer, 1 was characterized as normal, and the third as an extensive metabolizer. Bupropion was added to each woman’s regimen to control residual symptoms. In the woman considered a normal metabolizer, the addition of bupropion dramatically increased levels of venlafaxine and its active metabolite. The patient experienced severe serotonergic adverse effects (e.g., agitation, headache, insomnia); bupropion was stopped and venlafaxine reduced. Adverse effects resolved and serum levels normalized. Venlafaxine levels increased with the addition of bupropion in the other 2 patients as well. However, a reduction in venlafaxine dosage normalized the levels and both women had positive outcomes with combined treatment.

As the interaction was manageable and the outcome positive in 2 of these 3 patients, the authors do not suggest the coadministration be avoided. Rather, they recommend that “the pharmacokinetic interaction of venlafaxine and bupropion should be taken into account, and the combination of the 2 drugs should be accompanied by therapeutic drug monitoring,” particularly in poor metabolizers.

Paslakis G, Gilles M, Deuschle M: Clinically relevant pharmacokinetic interaction between venlafaxine and bupropion: a case series [letter]. *Journal of Clinical Psychopharmacology* 2010;30 (August): 473–474. From the Central Institute of Mental Health, Mannheim, Germany. The authors have no conflicts of interest to disclose.

Drug Trade Names: bupropion—Wellbutrin; venlafaxine—Effexor

---

**Reference Guide**

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

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

**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.