Repeated Ketamine for Depression: What We Don’t Know

Preliminary research has demonstrated rapid and robust positive effects of ketamine (Ketalar) infusion on depressive symptoms, but controlled trials are needed to confirm the clinical efficacy as well as to establish optimal dosing. Safety of repeated ketamine infusions, while theoretically plausible, has not been systematically established. In addition, the level of physiological monitoring necessary during infusion (e.g., for blood pressure changes and respiratory depression in the presence of other medications) is unknown, as is the potential for repeated infusions to cause neurotoxicity. Although it has not been reported in the existing research and has not been methodically evaluated, ketamine does have abuse and dependency potential, particularly in patients with current or past drug abuse.

The positive effects reported are encouraging, but it is important to note that improvement is transient, often lasting only a few days. A recent case report described a patient who, in addition to antidepressants and augmentation strategies, received more than 40 ketamine infusions spaced several days apart over about 5 months. Her depression improved, cognitive function did not decline, and no dependency was observed.


Inhaled Loxapine for Psychotic Agitation

An investigational inhaled formulation of loxapine (Adasuve) appears to be an effective non-invasive treatment option for agitation in inpatients with schizophrenia or bipolar disorder. Effects are rapid and comparable to those of intramuscular antipsychotics and benzodiazepines. Concerns remain about the agent’s potential for pulmonary side effects.
Inhaled loxapine was investigated in 2 Phase III clinical trials: 1 in patients with schizophrenia, and 1 in patients with type 1 bipolar disorder. The present review was based on publicly available FDA briefing documents from the manufacturer, the FDA’s own briefing document, and questions prepared by the FDA’s Psychopharmacologic Drug Advisory Committee.

The clinical trials were multicenter, inpatient studies in 344 patients with schizophrenia and 314 with bipolar disorder, manic or mixed episode. Participants were randomized to either 5 or 10 mg inhaled loxapine or placebo. Up to 3 doses of study medication were permitted, with the second dose at least 2 hours after the first and the third dose at least 4 hours after the second. Use of multiple doses was at the investigator’s discretion. Intramuscular lorazepam was used as rescue medication. The primary outcome was decrease from baseline in the Positive and Negative Symptoms of Schizophrenia-Excited Component (PANSS-EC), a 5-item scale consisting of 7 point ratings for tension, excitement, hostility, uncooperativeness, and poor impulse control. Study medication was used in patients with an initial score of ≥14 on the PANSS-EC and a score of ≥4 (moderate) for 1 or more item.

In both studies, onset of anti-agitation effects (i.e., statistical superiority to placebo) was evident at 10 minutes. Effect sizes* were larger for the 10-mg dose, which is expected to be the recommended dose. For this dose, effect sizes at 2 hours were 0.6 in schizophrenia and 0.94 in bipolar disorder. In the comparison of 10 mg loxapine vs placebo, the numbers needed to treat* to achieve the PANSS-EC response was 3.2 in schizophrenia and 2.2 in bipolar disorder.

Early-phase clinical trials have raised concerns about the pulmonary adverse effects of inhaled loxapine. Patients with clinically significant pulmonary disease were excluded from these trials. Rates of pulmonary adverse events were low, despite participants’ high rates of cigarette smoking. In separate Phase I safety trials in patients with asthma or COPD, inhaled loxapine sometimes resulted in bronchospasm consistent with a time-limited irritant effect. This effect was mild or moderate and resolved with bronchodilator therapy. If approved, the drug’s labeling will likely warn against its use in persons with active airway disease.

Availability is expected to be limited to facilities with access to short-acting beta-agonist bronchodilators or possibly even with full respiratory support and staff trained in airway management.


From New York Medical College, Valhalla, N.Y. This analysis was conducted without external funding. The study author disclosed financial relationships with multiple commercial sources, including Alexza, manufacturer of Adasuve.

Drug Trade Names: lorazepam, intramuscular—Ativan; loxapine—Adasuve

*See Reference Guide.

SSRIs and Pancreatitis Risk

A large Swedish population-based study found no support for an association between SSRIs and acute pancreatitis.

Background: Known risk factors, including heavy alcohol consumption and gallstones, are found in a majority of cases of acute pancreatitis, while 25% of cases are idiopathic. Several adverse event reports have attributed acute pancreatitis to SSRIs, and serotonin is known to affect pancreatic function.

Methods: A nationwide population-based cohort study was conducted using administrative databases. The investigators identified all Swedish residents, aged 40–84 years, experiencing
a first episode of acute pancreatitis in 2006–2008. Each case was matched with 10 controls for age, gender, and year. Exposure was defined as the dispensing of an SSRI prescription before the date of hospitalization for acute pancreatitis or, in controls, a randomly selected index date. Current use was defined as exposure within the 114 days before the index date. Past exposure was assessed for up to 3.5 years before the index date.

Results: The study included 6161 case patients with acute pancreatitis and 61,637 controls. Current and past use of an SSRI were overrepresented in cases compared with controls, but so were many other possibly influential factors, including chronic diseases, lifestyle factors, and diseases related to alcohol overconsumption. In an analysis adjusted only for age and gender, current SSRI use was associated with statistically significant increased risk of acute pancreatitis (odds ratio,* 1.5). However, the risk was no longer increased in a statistical model that also included alcohol; chronic obstructive lung disease; ischemic heart disease; obesity; diabetes; opioid use; education level; and marital status (odds ratio, 1.1). For most categories of past use, odds ratios also approached zero after adjustment. Adjusting for the number of distinct medications further reduced the odds ratio to 1.0. Results did not differ in subgroup analyses by gender, age (less than or greater than 65 years), and SSRI dosage.

Discussion: Results of this study were similar to those of population-based studies in the U.K. and Denmark, in which apparent excess risks associated with SSRIs were reduced by adjusting for confounding factors. Relying only on case reports of adverse reactions would probably exaggerate the appearance of elevated risk of acute pancreatitis with SSRIs.


*See Reference Guide.

**NSAID Augmentation in Schizophrenia**

Results of randomized controlled trials show moderate but significant positive effects of NSAID augmentation in patients with schizophrenia.

Background: Evidence is mounting that supports a role for central nervous system inflammation in the pathogenesis of schizophrenia. Augmentation of antipsychotics with anti-inflammatory drugs has been evaluated in several studies, but sample sizes were small. The present meta-analysis was undertaken to increase the power of previous research and to clarify the role of NSAIDs in schizophrenia.

Methods: A literature search identified 5 randomized controlled trials of NSAID augmentation in patients with a schizophrenia spectrum disorder. The primary outcome measure was the Positive and Negative Syndrome Scale (PANSS), and the standardized mean differences between active and placebo augmentation were calculated.

Results: The 5 studies comprised a total of 264 patients who were treated with risperidone, olanzapine, clozapine, or amisulpride. Four of the studies evaluated 400 mg/day adjunctive celecoxib for 5–8 weeks, and the other study evaluated 1000 mg/day aspirin for 3 months. Mean durations of illness ranged from about 1 to ≤10 years.

NSAID augmentation produced a moderate reduction in the severity of schizophrenia symptoms overall (effect size,* 0.43; p=0.02). The effects on positive symptoms were moderate (effect size, 0.34; p=0.02). While the reduction in negative symptoms was smaller (effect size, 0.26), it remained statistically significant (p=0.03). There was no apparent difference in
efficacy between celecoxib and aspirin. Augmentation was well tolerated, and common NSAID adverse effects (e.g., GI upset) did not differ between the active and placebo groups.

**Discussion:** NSAIDs are a broadly acting class of drugs and are considered generally safe and mild. These results should be considered cautiously because the number of studies identified was small and treatment durations were short. However, based on these positive effects, additional research appears to be warranted.

**Study Rating**—16 (89%): This study met most criteria for a systematic review/meta-analysis, but the quality of individual studies was not assessed.

**SSRIs and Driving Safety**

Although some adverse effects of SSRI antidepressants may impair driving performance, evidence from experimental and pharmacoepidemiologic studies is limited and conflicting, according to a review undertaken to summarize the evidence on SSRIs and traffic safety. SSRIs have milder adverse effects than older antidepressants and might be expected to produce less driving impairment. Potentially relevant side effects include anxiety, agitation, sleep disturbances, and headache; suicide and self-harm; and treatment-discontinuation reactions (e.g., dizziness, fatigue, or anxiety).

**Methods:** A literature search identified 15 full-text reports on the relationship between use of any of the 6 SSRIs available in Europe (i.e., citalopram; escitalopram; fluoxetine; fluvoxamine; paroxetine; sertraline) and driving impairment or accident risk. Of these studies, 10 were experimental (including 6 that comprised only healthy subjects) and 5 were pharmacoepidemiologic studies.

**Results:** The experimental studies were conducted using laboratory tests of cognitive and psychomotor function, driving simulators, and on-the-road tests. These studies’ results generally suggest that SSRIs do not constitute a high risk to traffic safety unless used at high doses or in combination with other psychotropic medications or substances. These results should be interpreted cautiously because they may not generalize to clinical populations; sample sizes tended to be too small to show a statistically significant effect; there was limited information on the possible contribution of substance use or comorbidity; and the experimental tests may not reflect the complexity of real driving.

Results of the 5 pharmacoepidemiologic studies of SSRIs and driving were conflicting. A study conducted in the U.K. found no association between SSRI exposure and risk of being in a traffic accident, but studies from Norway and the Netherlands found increased risk with SSRI exposure. A Canadian case-crossover study* found that in patients with dementia, SSRIs and other newer antidepressants were associated with greater accident risk than older antidepressants. In a second Canadian study of antidepressant-treated patients aged ≥65 years, those taking an SSRI were more likely to cause an accident than those treated with a first-generation antidepressant, but only if they were also receiving benzodiazepines or strong anticholinergic drugs.
Based on the available evidence, no clear relationship between SSRI use and traffic safety can be confirmed. However, because some research does suggest the relationship exists, additional experimental and epidemiologic research should be conducted to provide clarification on the relationship.

R avera S, Ramaekers J, de Jong-van den Berg L, de G ier J: Are selective serotonin reuptake inhibitors safe for drivers? What is the evidence? Clinical Therapeutics 2012; published online ahead of print; doi 10.1016/j.clinthera.2012.04.002. From the University of Groningen, the Netherlands; and other institutions. Funded by the European Community. The authors declared no conflicts of interest.

Drug Trade Names: citalopram—Celexa; escitalopram—Lexapro; fluoxetine—Prozac; fluvoxamine—Luvox; paroxetine—Paxil; sertraline—Zoloft

*See Reference Guide.

**Antidepressants in Early Parkinson’s Disease**

A potential disease-modifying effect of antidepressants in Parkinson’s disease has been suggested but not investigated directly. Results of a retrospective cohort study suggest that in patients with Parkinson’s disease, antidepressant drugs, particularly tricyclics, delay the need for dopaminergic therapy.

**Methods:** The effects of antidepressant use on progression of Parkinson’s disease were evaluated in a secondary analysis of 2064 patients with recently diagnosed Parkinson’s disease who had participated in 6 clinical trials of other potential neuroprotective therapies. The studies had enrolled patients regardless of antidepressant therapy (except for the exclusion of MAOIs), who were then followed for 6 months to 2 years. Patients were required to have been on a stable antidepressant regimen for 60 days preceding enrollment. Time to initiation of dopaminergic therapy, a surrogate for disease progression, was the primary endpoint of the present analysis.

**Results:** Of the 2064 patients, 451 were taking an antidepressant during their study participation. Most of the participants taking an antidepressant when they entered a clinical trial had no depression or mild depression. Moderate/severe depression was present in 17% of patients receiving an SSRI, 7% of those receiving a TCA, 3.5% of those receiving an SNRI, and 6% of those receiving an atypical antidepressant (i.e., bupropion, mirtazapine, trazodone).

Overall, antidepressant use was associated with a delay in onset of dopaminergic therapy (449 vs 363 days; p=0.002). After stratification for class of antidepressant, the median time to therapy and the percentage of patients not receiving dopaminergic therapy at 1 year was higher for amitriptyline and for atypical antidepressants than for non-use of antidepressants. After controlling for depression and other potential confounders, patients taking tricyclics (particularly amitriptyline) were less likely to progress to dopaminergic therapy than those not taking an antidepressant (hazard ratio,* 0.3; p=0.004). In this adjusted analysis, SSRIs and SNRIs were not significantly associated with the outcome. Antidepressant use did not affect the rate of change in the Unified Parkinson’s Disease Rating Scale (UPDRS), a measure of disability and impairment.

**Discussion:** Results of preclinical studies suggest SSRIs and amitriptyline have various neuroprotective effects, particularly on dopaminergic neurons, and research has shown that depression in Parkinson’s disease is more likely to respond to TCAs than to SSRIs. As such, it is possible that the positive effects of TCAs in these patients may be the result of improvement of depression, rather than a disease-modifying neuroprotective effect of the drugs. Tremor may also have influenced whether subjects received TCAs, as their anticholinergic properties may attenuate tremor, although any such change in these patients was insufficient to drive differences in UPDRS motor scores.

**Drug Trade Names:**
- Citalopram—Celexa
- Escitalopram—Lexapro
- Fluoxetine—Prozac
- Fluvoxamine—Luvox
- Paroxetine—Paxil
- Sertraline—Zoloft

*See Reference Guide.
In addition to its primary aim, this study highlights the inadequacy of treatment of depression in Parkinson’s disease, a comorbidity that affects 40–50% of patients with the disease. Of the patients experiencing depression at baseline in this study, 248 (71%) were not receiving an antidepressant.

Paumier K, Siderowf A, Auinger P, et al: Tricyclic antidepressants delay the need for dopaminergic therapy in early Parkinson’s disease. Movement Disorders 2012; published online ahead of print; doi 10.1002/mds.24978. From the University of Cincinnati, Ohio; and other institutions. Funded by the Parkinson’s Disease Foundation; and other sources.

Drug Trade Names: amitriptyline—Elavil, Endep, and others; bupropion—Wellbutrin; mirtazapine—Remeron; trazodone—Desyrel, and others

*See Reference Guide.

### Pregabalin/Clozapine Interaction

A 34-year-old male with a 14-year history of paranoid schizophrenia had been receiving 800 mg/day clozapine for 6 months. His only other medication was the antihypertensive metoprolol. He was admitted with a psychotic exacerbation associated with stressful family events, and ≤2 mg/day lorazepam was added as it had improved previous stress-related exacerbations in this patient. Shortly after admission, the patient’s serum clozapine level was 497 ng/mL. Psychotic symptoms resolved within the following week, and the lorazepam was stopped; however, the patient continued to experience nonspecific anxiety. On the basis of reportedly successful augmentation with pregabalin in anxiety with schizophrenia (an off-label use), 150 mg pregabalin b.i.d. was started. Within 1 more week, the anxiety had completely resolved. Serum clozapine measurement prior to discharge found an elevated concentration of 844 ng/mL. Results of other laboratory analyses, including measures of liver enzymes, inflammatory markers, and creatinine, were unremarkable and hepatitis screening was negative. No clinical adverse effects occurred, and pregabalin was continued. Following a subsequent rise in anxiety, pregabalin was increased to 300 mg b.i.d. At this dosage, the patient’s serum clozapine level was 1106 ng/mL. Pregabalin was reduced to 300 mg/day, and the clozapine level fell to 500 ng/mL.

Clozapine is metabolized via cytochrome P450 pathways, while pregabalin has not been considered to be hepatically metabolized. A competitive inhibition of the active renal elimination of clozapine by pregabalin is possible. Although the mechanism is unclear, according to the Naranjo probability scale,* it is "probable" that the serum clozapine elevation in this patient was related to pregabalin administration.

Gahr M, Schmid M, Schonfeldt-Lecuona C: Pregabalin-associated elevation of clozapine serum levels. Pharmacopsychiatry 2012; published online ahead of print; doi 10.1055/s-0032-1311645. From the Ulm University, Germany. The authors declared no conflicts of interest.

Drug Trade Names: clozapine—Clozaril; lorazepam—Ativan; metoprolol—Lopressor, Toprol; pregabalin—Lyrica

*See Reference Guide.

### Vilazodone for Major Depressive Disorder

The recently FDA-approved antidepressant vilazodone has a unique mechanism of action. It blocks serotonin reuptake and is a partial agonist of 5-HT1A receptors. The mechanism is similar to the common strategy of combining an SSRI with the available 5-HT1A receptor partial agonist buspirone. Theoretically and in animal models, these properties of vilazodone might be expected to result in a robust antidepressant effect, more rapid onset of action, and reduced potential for sexual side effects. These preclinical suggestions have yet to be confirmed in clinical trials, and there have been no head-to-head comparisons with other antidepressants.
There are theoretical advantages to beginning treatment with a single drug that combines multiple mechanisms, rather than multiple drugs. However, the GI side effects of vilazodone call for slower titration, with 2 weeks of initial treatment at less than the maintenance dose. This requirement may offset any potential rapid onset of antidepressant effects. Genetic biomarkers can identify patients at increased risk for GI side effects with vilazodone, as well as those at greater likelihood to have remission. Overall, vilazodone is not as complicated as the strategy of antidepressant augmentation with a second-generation antipsychotic because it does not induce metabolic effects or movement disorders.

Vilazodone was approved for marketing in January 2011, based on two 8-week Phase III clinical trials. It had superior antidepressant efficacy to placebo but was associated with diarrhea, nausea, somnolence, and dry mouth. It did not induce abnormal weight gain. Sexual dysfunction occurred in about 1–2% of patients over and above the rate in the placebo groups. Additional Phase II studies showed superiority to placebo for Clinical Global Impressions and Montgomery-Asberg Depression Rating Scale scores, but not the primary Hamilton Rating Scale for Depression measure. In a long-term study, vilazodone was well-tolerated for up to 1 year. It appears to be as effective as the SSRIs.

Although it might be acceptable as a first-line antidepressant, vilazodone will more likely be used after failure or intolerance of an SSRI or SNRI. It may be particularly useful in patients who experience sexual dysfunction, weight gain, or increased blood pressure with other antidepressants.

Singh M, Schwartz T: Clinical utility of vilazodone for the treatment of adults with major depressive disorder and theoretical implications for future clinical use. Neuropsychiatric Disease and Treatment 2012;8:123–130. From SUNY Upstate Medical University, Syracuse, N.Y. This review was conducted without external funding. The authors disclosed no conflicts of interest.

Drug Trade Names: buspirone—Buspar, and others; vilazodone—Viibryd

### Lamotrigine and Aseptic Meningitis

In 2010 the FDA issued a warning about aseptic meningitis with lamotrigine. A detailed analysis of the their Adverse Event Reporting System (AERS) indicates that the event is rare and should be considered only after bacterial causes have been ruled out.

**Methods:** AERS data were analyzed from December 1994 through November 2009 using a data-mining algorithm to identify higher-than-expected reporting of aseptic meningitis related to 9 different antiepileptic drugs.

**Results:** Between 2005 and 2009, the cumulative rate of aseptic meningitis with lamotrigine was 4.7 times higher than expected. Analyses of the other antiepileptics did not show an increase, even though 1 drug, carbamazepine, was previously labeled as associated with increased risk of aseptic meningitis.

A total of 40 reports of lamotrigine-related aseptic meningitis were identified. Affected patients ranged in age from 1.5 to 79 years, and the majority (n=33) were female. Aseptic meningitis occurred in patients taking lamotrigine for seizures or bipolar disorder as well as for the off-label indications of anxiety and depression. Occurrence of aseptic meningitis was not dose-related. Patients had the typical meningitis symptoms: headache; fever; rash; stiff neck; nausea; and vomiting. A total of 27 reports documented the cessation of meningitis symptoms when the drug was stopped, and in 15 cases the symptoms reappeared with rechallenge. One patient died, but aseptic meningitis was not believed to be the cause.

Cerebrospinal fluid (CSF) profiles in these patients showed features of both bacterial and viral meningitis. The CSF was bacteriologically negative but contained large numbers of white blood
cells, which were predominantly polymorphonuclear leukocytes in two-thirds of cases and lymphocytes in one-third.

**Discussion:** Two mechanisms of action have been proposed for lamotrigine-associated aseptic meningitis: a hypersensitivity reaction to the drug and direct meningeal irritation by the drug. Greater severity of symptoms on rechallenge suggests hypersensitivity. The involvement of other organs in some patients suggests systemic hypersensitivity. A higher-than-predicted rate of an adverse event does not prove causality.


**Drug Trade Names:** carbamazepine—Epitol, Tegretol; lamotrigine—Lamictal

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### Reference Guide

**Case-Crossover Study:** A case-control design involving only cases, which may be used to evaluate whether brief exposures cause a transient change in risk of a rare acute-onset disease or event. The design resembles a retrospective nonrandomized crossover study but differs in having only a sample of the base population-time. Self-matching of cases eliminates the threat of control-selection bias and increases efficiency.

**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.

**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.

**Number Needed to Treat (NNT):** 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.

**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.