Scopolamine: Potential as Antidepressant

The anticholinergic medication scopolamine (Scopace) may have potential as an antidepressant, according to a review of 7 studies published since 1988. More investigation is needed to broaden the evidence base and to identify alternative methods of administration.

Scopolamine is a fast-acting agent that binds muscarinic cholinergic receptors and has minimal effects on nicotinic receptors. Peak effects are seen within 15–30 minutes of oral, IM, or subcutaneous administration, and the elimination half-life is 8 hours. The hypothesis that depression results from an excess of cholinergic activity over other forms of neurotransmission supports the possibility that a cholinergic antagonist may have antidepressant effects.

A review of the literature identified 7 studies in which mood and depression were evaluated after scopolamine administration. Early studies, from 1988 and 1991, found little or no effect of scopolamine on mood. However, the remaining 5 studies, from a single group at the NIMH, had positive results.

In the first of the NIMH-funded studies, scopolamine was evaluated for its potential effects on cognitive symptoms in 8 patients with depression. Results showed an overall antidepressant effect in the 5 patients with major depressive disorder and in the 3 patients with bipolar disorder. After this result, scopolamine was tested in a cross-over study of an additional 9 patients with unipolar depression and 9 with bipolar disorder. Participants were given 3 scopolamine infusions 3–5 days apart followed by 3 placebo infusions, or vice versa, in random order. Statistically significant improvement in depression (Montgomery-Asberg Depression Rating Scale) and anxiety (Hamilton Anxiety Rating Scale) were observed in both the unipolar and bipolar groups after scopolamine. Clinical responses were seen at the first assessment, which took place within 3–5 days of the first scopolamine dose. Continued improvement was observed during placebo treatment in the patients who received scopolamine first, which suggests a mechanism of action downstream from receptor blockade.
A third NIMH study was executed to replicate these results with an identical design but in a more homogeneous sample: 22 patients with unipolar depression. Results were similar. The effects of scopolamine lasted for 12–16 days after the final dose. Half of the study patients experienced remission. The most recent study from the NIMH group compared the effects of scopolamine by gender. Although effective in men, scopolamine produced more frequent and larger antidepressant responses in women; and anxiolytic effects were only observed in women. A separate, unpublished analysis of the NIMH results in a group of patients with bipolar disorder confirmed that scopolamine was effective and did not induce mania.

In addition to confirming these promising results, more research is needed to identify alternative routes of administration and effective doses. Other areas of needed research include the potential for nicotinic receptor activation via cigarette smoking to interfere with the antidepressant effects of scopolamine (all studies excluded smokers, which is a problem given the high comorbidity of nicotine dependence and depression) and the potential of scopolamine as a bridge to the onset of action of conventional antidepressants.


TNF Inhibitor for Refractory Depression

In a controlled trial, inhibition of tumor necrosis factor (TNF) with infliximab (Remicade) did not show generalized efficacy in treatment-resistant depression but did relieve depressive symptoms in patients with high baseline inflammatory biomarkers.

Background: Several inflammatory biomarkers, including TNF, have been shown to be elevated in patients with depression and to be associated with a decreased likelihood of antidepressant response. The present study was undertaken to determine whether intravenous infusions of a TNF-specific anti-inflammatory would improve treatment-resistant depression.

Methods: Study participants, aged 25–60 years, were patients with at least moderately severe depression and moderate resistance to treatment, confirmed by the Massachusetts General Hospital Staging method for treatment resistance (which considers both the number and intensity of antidepressant trials). Patients with bipolar depression were included, and stable ongoing antidepressant drug therapy was permitted. Treatment consisted of double-blind randomized 5 mg/kg infliximab or placebo, infused over a 2-hour period at baseline, 2 weeks, and 6 weeks. The primary study outcome was change from baseline on the Hamilton Rating Scale for Depression (HAM-D).

Results: The 60 study participants, including 9 with bipolar depression, had an average age of about 43 years, and 67% were female. The mean baseline HAM-D score was 24 despite patients having received on average 3–5 antidepressant drug trials during the current episode. C-reactive protein (CRP) levels were rather high in the group, with a mean >5 mg/L. The American Heart Association and the Centers for Disease Control and Prevention consider a level of ≥3 mg/L to be a "medium" relative risk for inflammation.

HAM-D scores decreased significantly in both groups by week 12, but patients who received infliximab infusion did not experience a greater decrease than the placebo group. However, baseline levels of CRP were predictive of response to infliximab, which was superior to placebo with a 3-point greater decrease in HAM-D score (p=0.01) in patients with baseline levels >5 mg/mL. Secondary outcome measures, including the Clinical Global Impression–Severity scale, also favored infliximab only in patients with high baseline inflammation. Among patients with high baseline inflammation, response occurred in 62% of those who received
infliximab, compared with 33% of the placebo group. This difference was not statistically significant, possibly because of the small sample size. Placebo was superior to infliximab in patients with lower initial levels of CRP. The effect sizes were moderate to large for infliximab and placebo in opposite directions, depending on a baseline CRP cutoff of 5 mg/mL. When individual HAM-D items were assessed, infliximab was found to relieve a wide range of depressive symptoms including depressed mood, psychomotor retardation, psychic anxiety, and suicidal ideation. Infliximab was well tolerated, with headache as the most frequently reported adverse effect.

Discussion: According to the authors, the 3-point difference between infliximab and placebo in the subset of patients with CRP >5 mg/mL is clinically meaningful and comparable to antidepressant drugs in clinical trials. The superiority of placebo in patients with lower CRP suggests that some level of peripheral inflammatory activity may be necessary for an antidepressant response to TNF inhibition. The authors note that caution may be warranted in the use of anti-inflammatory strategies for patients with depression who have no evidence of increased inflammation.

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

Atypicals: Long-Term Outcome in Older Patients

Treatment outcomes were poor in patients aged >40 years who were treated with 1 of the 4 most commonly used atypical antipsychotics. Over 2 years of follow-up, all drugs had a high discontinuation rate, lack of significant improvement in psychopathology, and a high incidence of metabolic syndrome and other adverse effects.

Methods: Study participants (n=332) were patients aged >40 years with schizophrenia, psychosis associated with mood disorders, post-traumatic stress disorder, or dementia, all of whom were either receiving or were candidates for an atypical antipsychotic. To reflect clinical practice, there were few exclusion criteria and patients and their physicians were given some choice of medication. From a list of the 4 agents—aripiprazole, olanzapine, quetiapine, and risperidone—participants were allowed to exclude as many as 2 drugs, and were then randomly assigned to 1 of their remaining choices. Treatment was open-label, and dosage and other treatment decisions were individualized. Efficacy was assessed at 6 and 12 weeks and then at 3-month intervals for up to 2 years by blinded raters using the Brief Psychiatric Rating Scale (BPRS).

Results: Of the 332 patients enrolled, 16% agreed to be randomized to any of the 4 medications; the remaining patients excluded 1–2 of the study drug options. The most common reason for refusal of a specific antipsychotic was possible side effects, which ranged from 43% for aripiprazole to 78% for olanzapine. Prior lack of efficacy was the reason for 8% of patients to decline olanzapine treatment and for 23% to decline quetiapine.

At baseline, patients had a mean age of 67 years; 39% had a diagnosis of schizophrenia, and 61% were to be treated for "other" indications (i.e., off label). Metabolic syndrome was present in 50% of patients at baseline. Clinicians tended to exclude olanzapine and prefer aripiprazole for patients with metabolic risk factors.
The proportion of patients who discontinued their medication during the 2 years was similar for all drugs, ranging from 79% with quetiapine to 82% with aripiprazole. This discontinuation rate did not reflect adherence to recommendations for limited use; a majority were switched by their physician to another atypical. Adverse effects were the reason for 52% of discontinuations, and lack of efficacy for 27%. Quetiapine was associated with serious side effects in 39% of the patients assigned to that group, compared with 19% for the other drugs combined (p<0.002). This led to early discontinuation of the quetiapine treatment study arm.

None of the drugs resulted in significant improvement on the BPRS total score or the psychosis subscale. The drugs did not differ in their effect on metabolic markers or on the incidence of metabolic syndrome at the end of 1 year, which was 37% among the patients not affected at baseline. The only significant difference was in incidence of metabolic syndrome between aripiprazole and olanzapine (86% vs. 55%; p<0.02).

Nearly 24% of the study patients had a serious adverse event, including death, hospitalization, or emergency room visits for life-threatening conditions. The drugs did not differ in rates of this type of adverse event.

Discussion: These results are worrisome because doses were relatively low and patients were allowed to exclude some antipsychotics for efficacy or safety concerns, the authors say. Given the lack of other effective treatments for psychosis in older patients, these results indicate a need for cautious prescribing of atypicals and the use of alternative, psychosocial treatments when possible.

Jin H, Shih P, Golshan S, Mudaliar S, et al: Comparison of longer-term safety and effectiveness of 4 atypical antipsychotics in patients over age 40: a trial using equipoise-stratified randomization. *Journal of Clinical Psychiatry* 2012;74(January):10–18. From the University of California, San Diego; and other institutions. Funded by the NIH; and the VA. One author disclosed relationships with financial sources; the remaining authors declared no conflicts of interest.

Drug Trade Names: aripiprazole—Abilify; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal

### SSRIs and Birth Outcomes

Evidence, although equivocal, has suggested that SSRI antidepressants used during pregnancy may be associated with congenital anomalies, neonatal withdrawal syndrome, and other adverse outcomes. Less is known about their effects on fetal mortality. According to results of a population-based cohort study, SSRI use during pregnancy is not associated with stillbirth or infant mortality.

Methods: The analysis was based on national registries of pregnancies in Denmark, Finland, Iceland, Norway, and Sweden between 1996 and 2007. All singleton deliveries after 154 gestational days were included. Exposure consisted of ≥1 filled prescription for an SSRI from 3 months before conception until delivery. Study outcomes were: stillbirth; neonatal death within the first 27 days; and postneonatal death between 1 and 12 months. Data was evaluated from >1.6 million births, with SSRI exposure in 29,228 (1.8%).

Results: A total of 135 stillbirths, 74 neonatal deaths, and 40 postneonatal deaths occurred in the women exposed to SSRIs during pregnancy. In an unadjusted analysis, SSRI use was associated with excess risk of stillbirth (crude odds ratio [OR],* 1.25; p=0.01). However, women who used SSRIs during pregnancy were older than others, and were more likely to smoke cigarettes and to have diabetes or hypertension. After adjustment for these and other factors, the risk was no longer statistically significant (adjusted OR, 1.17). In the multivariate analysis, SSRI use was not associated with neonatal death (OR, 1.23) or postneonatal mortality (OR, 1.34).

Discussion: Few studies have examined the association between maternal SSRI use and fetal mortality; those that did have been small and/or failed to control for maternal risk characteris-
tics. In the present study, increased rates of stillbirth and postneonatal death in infants with prenatal exposure to SSRIs appear to be explained by maternal risk characteristics such as cigarette smoking and advanced age.


*See Reference Guide.

**Vasopressin Antagonism for Anxiety/Depression**

Results of preclinical studies suggest vasopressin may modulate the response to stress via activation of the V₁b receptors in the pituitary and in other brain structures. An investigational vasopressin V₁b receptor antagonist, SSR149415, was not effective in clinical trials of depression or generalized anxiety disorder (GAD). It is unclear whether these results indicate failure of the entire class of drugs or whether V₁b antagonists may be useful if used differently.

In 3 clinical trials, the V₁b antagonist was compared with placebo and/or an active control (escitalopram or paroxetine) in 643 patients with major depressive disorder, and in 328 patients with generalized anxiety disorder (GAD). All 3 trials involved 8 weeks of double-blind treatment, and efficacy was measured with standardized rating scales. In addition, 73 patients with major depression participated in a 4-week pharmacodynamic trial of 2 doses of SSR149415 and placebo; efficacy was reported as a secondary outcome. SSR149415 did not show statistical superiority over placebo in any of the trials. Efficacy of the active control drug in the trials that employed one indicates that the studies were adequately designed to detect this outcome.

**Discussion:** SSR149415 is 1 of several V₁b antagonists in development. It is unclear whether this agent’s lack of efficacy is specific, generalized to the entire drug class, or attributable to the use of ineffectively low doses. None of the other V₁b antagonists have advanced to clinical trials for psychiatric disorders. Preclinical studies suggest V₁b receptors are particularly activated during acute stress, and blocking their activity may have limited effects in chronic disorders. These drugs may have a role in the early stages of stress-induced disorders such as posttraumatic stress disorder.

Griebel G, Beeske S, Stahl S: The vasopressin V₁b receptor antagonist SSR149415 in the treatment of major depressive and generalized anxiety disorders: results from 4 randomized, double-blind, placebo-controlled studies. *Journal of Clinical Psychiatry* 2012;73 (November):1405–1411. From Sanofi, Chilly-Mazarin, France; and the University of California, San Diego School of Medicine. Funded by Sanofi. All 3 study authors disclosed financial relationships with commercial sources; 2 of the authors are employed by Sanofi.

**Drug Trade Names:** escitalopram—Lexapro; paroxetine—Paxil

**Antidepressants and Compromised Glycemic Control**

In a large, population-based study, antidepressant use was not associated with abnormal glycemic control or undetected diabetes. This result contradicts observations from earlier studies based on clinician diagnosis of diabetes, and suggests that patients given prescriptions for antidepressants may have higher rates of diabetes because they are more likely to be tested for it.

**Methods:** Data from the U.S. National Health and Nutrition Examination Survey (NHANES), obtained between 2005 and 2010, was used to evaluate the association between antidepressant use and glycemic control. Participants completed the NHANES via computerized interviews administered in their homes. The interview included the Patient Healthcare Questionnaire-9 (PHQ-9) evaluation of depression symptoms, as well as questions about antidepressant prescriptions and diabetes. The present sample comprised 13,478 participants who did not have a previous diagnosis of diabetes and who underwent HbA1c testing. A subgroup of randomly selected patients (n=6141) also underwent fasting blood glucose and insulin testing.
Results: A total of 1069 of the 13,478 NHANES participants (8%) met the study threshold for depression of at least moderate severity (PHQ-9 score, ≥10). Nearly 9% of the sample (n=1164) was taking an antidepressant drug, about two-thirds of these for ≥2 years. Within the complete NHANES sample, 441 patients met the HbA1c screening cutoff for diabetes (HbA1c, ≥6.5%). Of the 6141 who underwent fasting blood glucose measurement, 282 met the cutoff for diabetes (blood sugar, ≥126 mg/dL); 386 of the 5564 screened met the oral glucose tolerance test cutoff (2-hour blood sugar level, ≥200 mg/dL).

The proportion of people who screened positive for diabetes did not differ with regard to antidepressant use. The HbA1c cutoff was surpassed by 3% of those taking antidepressants, compared with 2% of those not taking antidepressants (adjusted odds ratio,* 0.97; p=ns). Results of other diabetes screening tests were also not associated with antidepressant use; nor was insulin sensitivity as measured with the Quantitative Insulin Sensitivity Check Index, computed from other measurements. Further analysis found no association of glycemic control with the presence of significant depressive symptoms, duration of antidepressant use, or any specific antidepressant drug class.

Discussion: Many previous studies have found antidepressant use to be associated with higher rates of physician-diagnosed diabetes, leading to concerns about the effects of these drugs on glycemic control. The present study found better glycemic control in patients taking antidepressants, but the author cautions that persons taking antidepressants may have been tested more often for diabetes, diagnosed, and excluded from the study population. The finding may also reflect improved insulin sensitivity as a result of exposure to some antidepressants.


*See Reference Guide.

Agomelatine Augmentation in OCD

Augmentation of escitalopram with agomelatine (not available in U.S.) resulted in remission of severe, treatment-resistant obsessive-compulsive disorder in a 25-year-old woman.

The patient was referred for psychiatric consultation following emergency-room treatment of vulvar itching and dermatitis caused by excessive washing. She had a 5-year history of OCD symptoms characterized by checking compulsions and ritual washing of hands and genitals as a result of contamination obsessions, all of which interfered with daily activities and work. She reported difficulty sleeping because of the need to perform scheduled washings at night. Before her present evaluation, she had received treatment with fluvoxamine, sertraline plus alprazolam, sertraline plus quetiapine, and clomipramine. All regimens were ineffective and resulted in adverse effects such as weight gain and sexual dysfunction. Concurrent cognitive-behavioral therapy was unhelpful.

On presentation, the patient had a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of 33 with insight and mild depressive symptoms due to secondary demoralization. She had been
taking 30 mg/day escitalopram for about 5 months. Agomelatine was added at a dosage of 25 mg/day. She experienced modest improvement in OCD symptoms after 3 weeks (Y-BOCS score of 25) and reported significant improvement in sleep quality. She was offered a dosage increase, but decided to continue at her current dose. OCD symptoms continued to resolve gradually until she experienced remission (Y-BOCS score of 6) after 12 weeks of treatment. Her OCD symptoms continued in remission at the time of reporting, with ongoing treatment consisting of 20 mg/day escitalopram and 25 mg/day agomelatine.

Discussion: Agomelatine is a new antidepressant with selective melatonergic agonism and 5-HT2c receptor antagonism. Effectiveness in OCD has been reported in individual cases. Previous reports suggest that patients who do not respond to antidepressants at therapeutic doses may improve with much higher doses. The present case suggests that augmentation with agomelatine at a relatively low dose may also be effective. It is unlikely that the patient’s response was the result of a pharmacokinetic interaction. Agomelatine may work by increasing dopamine and noradrenaline levels in the frontal cortex, secondary to 5-HT2c inhibition. An additional mechanism of action may be normalization of disturbed circadian rhythm via the drug’s effects on melatonin.


Drug Trade Names: agomelatine (not available in the U.S.)—Valdoxan; alprazolam—Xanax; clomipramine—Anafranil; escitalopram—Lexapro; fluvoxamine—Luvox; quetiapine—Seroquel; sertraline—Zoloft

### Psychopharmacotherapy in Patients with HIV

Despite a high prevalence of depression and psychosis in patients with HIV, little is known about the effects of psychopharmacotherapy in these patients, according to a systematic review. Evidence supports the efficacy of SSRIs antidepressants, but some drugs in this class may interact with antiretrovirals. Controlled data on the use of antipsychotics is extremely limited.

Depression. The prevalence of depression in patients with HIV is estimated to be double the rate in the general population. Depressed mood, suicidality, hopelessness, and poor concentration may result in poor adherence to antiretroviral medication, leading to worse disease outcomes.

The investigators identified randomized, controlled studies of treatment of depression and psychosis in persons with HIV, published through August 1, 2012. A total of 11 studies of depression treatment were identified. Many of the studies were small, and many excluded women and substance abusers.

Fluoxetine has the most evidence for efficacy in treating depression, with response rates of about 50–75%. Fluoxetine had positive effects in a placebo-controlled monotherapy trial and a small study with a TCA comparator. Results of 2 trials of add-on therapy were mixed; 1 showed adding fluoxetine to group therapy had no benefit, while the other showed more fluoxetine-treated patients experienced symptom improvement. Paroxetine showed benefit in a small trial, and both paroxetine and imipramine were superior to placebo in another slightly larger study. In this trial and another, imipramine was associated with response rates of 80% and 74%. Some other SSRIs have shown promise in small open-label trials. No controlled studies of other antidepressants were identified.

Testosterone has been used to treat depressive symptoms in HIV, but significant efficacy is limited to hypogonadal men. DHEA has had inconsistent results in 2 studies. Stimulants were effective in 2 studies in patients with depression or depressive symptoms and debilitating fatigue associated with HIV.
Psychosis. As many as 6% of patients with HIV may experience psychosis, as a result of HIV itself; substance abuse; antiretroviral toxicity; reemergence of a preexisting condition; or opportunistic infection involving the CNS. Only 1 clinical trial of antipsychotic therapy has been published, in which patients with acute delirium received haloperidol, chlorpromazine, or lorazepam. Chlorpromazine was transiently effective, haloperidol less so. The lorazepam study arm was discontinued early due to adverse effects.

Drug Interactions and Risks. SSRIs, TCAs, and other antidepressant classes may interact with antiretroviral therapies. Serotonin syndrome has been reported in patients combining fluoxetine with antiretrovirals. Pharmacokinetic interactions with antiretrovirals have also been reported for paroxetine and sertraline. Citalopram and escitalopram may be safer choices for administration with protease inhibitors. Patients taking antipsychotics may be at risk for extrapyramidal symptoms, and interactions with antiretrovirals in patients with HIV may further increase this risk by increasing antipsychotic blood levels. QT prolongation and overlapping metabolic side effects may also be a concern with concomitant use of antipsychotics and antiretrovirals.

Hill L, Lee K: Pharmacotherapy considerations in patients with HIV and psychiatric disorders: focus on antidepressants and antipsychotics. *Annals of Pharmacotherapy* 2013;47 (January):75–89. From the University of California, San Diego. Source of funding not stated. The authors did not declare potential conflicts of interest.

**Drug Trade Names**: chlorpromazine—Thorazine; citalopram—Celexa; escitalopram—Lexapro; fluoxetine—Prozac; haloperidol—Haldol; imipramine—Janimine, Tofranil; lorazepam—Ativan; paroxetine—Paxil; sertraline—Zoloft

**Reference Guide**

**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.

**Correction**: In the January 2013 Psychiatry Drug Alerts issue, in the story titled "Tolerability of Clonidine in Tourette Syndrome," the second sentence of the second paragraph should read "The median clonidine starting dosage was 25 mcg/day, and the median maintenance dosage was 50 mcg/day" and the last sentence of the fourth paragraph should read "Patients who had adverse effects were more likely to have started with a higher dosage of clonidine (50 vs. 25 mcg/day; p=0.036) and to be taking additional psychotropic drugs (p=0.019)."

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