Valbenazine for Tardive Dyskinesia

The newly approved vesicular monoamine transporter 2 (VMAT2) inhibitor valbenazine (Ingrezza) improved tardive dyskinesia (TD) and was well tolerated in a phase III trial.

Background: Valbenazine is the first FDA-approved drug to treat antipsychotic-induced TD, which affects as many as 20–30% of patients with chronic antipsychotic exposure. Previously, treatment options included stopping the antipsychotic, reducing the dosage, or using off-label medications. VMAT2 inhibitors modulate release of dopamine into the synapse and may offset the movement-related adverse effects of antipsychotics.

Methods: Study subjects, aged 18–85 years, had a diagnosis of schizophrenia, schizoaffective disorder, or mood disorder and had been experiencing moderate-or-severe dopamine receptor blocker-induced TD for ≥3 months. Patients taking strong CYP3A4 inducers, dopamine agonists and precursors, MAOIs, stimulants, or other VMAT2 inhibitors were required to undergo a 30-day washout prior to study screening. Participants received 6 weeks of randomized, double-blind treatment with 40 or 80 mg/day valbenazine or placebo, and TD symptoms were assessed every other week. The study’s primary efficacy endpoint was change from baseline to week 6 in the 7-item Abnormal Involuntary Movement Scale (AIMS) dyskinesia score in patients taking the 80-mg dose, compared with placebo. AIMS examinations were video recorded and scored by a pair of expert clinicians. The key secondary endpoint was the Clinical Global Impression of Change–Tardive Dyskinesia (CGI-TD).

Results: A total of 234 patients were randomly assigned to treatment, and 205 (88%) completed the study. Two-thirds had a diagnosis of schizophrenia, schizoaffective disorder, or mood disorder and had been experiencing moderate-or-severe dopamine receptor blocker-induced TD for ≥3 months. Patients taking strong CYP3A4 inducers, dopamine agonists and precursors, MAOIs, stimulants, or other VMAT2 inhibitors were required to undergo a 30-day washout prior to study screening. Participants received 6 weeks of randomized, double-blind treatment with 40 or 80 mg/day valbenazine or placebo, and TD symptoms were assessed every other week. The study’s primary efficacy endpoint was change from baseline to week 6 in the 7-item Abnormal Involuntary Movement Scale (AIMS) dyskinesia score in patients taking the 80-mg dose, compared with placebo. AIMS examinations were video recorded and scored by a pair of expert clinicians. The key secondary endpoint was the Clinical Global Impression of Change–Tardive Dyskinesia (CGI-TD).

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(≥50% reduction in AIMS dyskinesia score) was 40% in the 80-mg/day valbenazine group (p<0.001 vs placebo), 24% in the 40-mg/day group (p=0.02 vs placebo), and 9% in the placebo group. The number needed to treat* with 80 mg/day valbenazine for 1 response was 4. The 2 treatment groups did not differ from placebo in the CGI-TD score. However, an analysis limited to 179 patients with a recorded AIMS score and a detectable plasma level of valbenazine at week 6 (if assigned to valbenazine) and no important efficacy-related protocol deviations showed about a half-point improvement relative to placebo (p=0.011).

The most frequently reported adverse effects of valbenazine were somnolence, akathisia, and dry mouth, each affecting about 1–5% of patients. No deteriorations in psychiatric stability or drug-related changes in laboratory results, physical examinations, vital signs, or electrocardiograms were observed.

**Discussion:** The present study results provide initial support for a favorable risk–benefit profile for both valbenazine doses. Patients who completed the current trial have gone on to a 42-week extension period of valbenazine treatment, results of which will be reported separately.

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


*See Reference Guide.

### Antidepressants and Smoking

Smoking tobacco reduces serum levels of several antidepressants, according to a systematic review. While very limited, published data suggest smoking is associated with lower levels of fluvoxamine, duloxetine, venlafaxine, trazodone, and mirtazapine.

**Background:** There is a lack of consensus on whether clinical outcome is correlated with plasma levels of SSRIs and other newer antidepressants. Nevertheless, it appears that subtherapeutic levels could jeopardize clinical response. Furthermore, most antidepressant adverse effects are dose dependent. Elimination of antidepressants is almost completely dependent on hepatic cytochrome P450 (CYP) enzymes, many of which are induced by compounds in cigarette smoke.

**Methods:** A comprehensive literature search identified 21 studies comparing steady-state metabolism of newer antidepressants in smokers and nonsmokers. The review included 7 studies of fluvoxamine; 2 each of fluoxetine, sertraline, venlafaxine, duloxetine, and mirtazapine; and 1 each of escitalopram, citalopram, trazodone, and bupropion. The studies comprised a total of 2375 patients, 733 of whom were smokers. No studies of paroxetine, milnacipran, or agomelatine were identified. All of the antidepressants evaluated are metabolized by CYP isoenzymes.

**Results:** Fluvoxamine levels were consistently decreased in smokers. However, most of the fluvoxamine studies were conducted in Japan in a population that differs from others in CYP enzyme activity. Studies of sertraline, escitalopram, and citalopram have shown no effect of smoking on serum levels, but many of these studies were based on a particularly young study population and did not exclude the possibility of interactions with other drugs. In 1 study, levels of norfluoxetine, the active metabolite of fluoxetine, were significantly higher in smokers than nonsmokers, which could suggest the possibility of accumulation and increased risk of serotonin syndrome.

Study results have been more consistent for SNRIs and other non-SSRI antidepressants. In 2 studies, average venlafaxine levels were significantly lower in smokers than in nonsmokers.
Strong evidence, from 2 large randomized clinical trials, suggests serum levels of duloxetine are significantly lower in smokers than nonsmokers. Smoking was also associated with significantly reduced levels of trazodone and mirtazapine. In a single study that included only 17 smokers, smoking did not influence bupropion levels.

**Discussion:** Although it is difficult to draw implications from many of the studies because of small sample sizes, failure to account for exposure to other drugs, and limitation to a single ethnic group or age group, these findings may help direct the choice of antidepressant treatments and dosages and highlight the possibility of adverse effects in patients who quit smoking.


**Common Drug Trade Names:** agomelatine (not available in U.S.)—Valdoxan; bupropion—Wellbutrin; citalopram—Celexa; duloxetine—Cymbalta; escitalopram—Lexapro; fluoxetine—Prozac; fluvoxamine—Luvox; milnacipran—Savella; mirtazapine—Remeron; paroxetine—Paxil; sertraline—Zoloft; trazodone—Desyrel; venlafaxine—Effexor

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**Quetiapine vs Lithium Maintenance**

Following a first episode of mania successfully treated with lithium plus quetiapine (Seroquel), lithium monotherapy was superior to quetiapine monotherapy as maintenance treatment. This finding, unexpected in the context of other research, suggests that lithium may have greater efficacy in the early stages of bipolar disorder or in more severely affected patients.

**Methods:** The study recruited patients, aged 15–25 years, who were experiencing a first episode of mania (the majority with psychotic features). Nearly half of the patients had comorbid cannabis use disorder, and nearly one-third had comorbid alcohol use disorder. All patients (n=40; mean age, 21 years; 78% men) received treatment with lithium plus quetiapine as part of a routine care protocol. Quetiapine dosage was determined by the treating clinician, and lithium dosages were based on serum level targets of 0.8–1.0 mEq/L. Following clinical stabilization, 1 of the 2 drugs was gradually withdrawn, by random assignment. Patients and their psychiatrists knew which drug was being continued, but evaluators and others connected with the study did not. Patients were assessed for mania, depression, clinical status, functioning, and other outcomes at regular intervals, ending at 12 months.

**Results:** After 12 months, patients who received lithium fared significantly better than those who received quetiapine in terms of depression, psychotic symptoms, overall psychopathology, and functional outcomes. However, differences in Young Mania Rating Scale (YMRS) scores did not differ between the 2 treatments, and the Clinical Global Impression for Bipolar Disorder (CGI-BP) mania scale was higher in the quetiapine group only at 9 months. According to post-hoc analyses, although most patients were euthymic at study entry, the quetiapine group showed a significant worsening of depression, measured with the Montgomery Asberg Depression Rating Scale (MADRS) during treatment, while the lithium group did not.

The groups differed significantly at 12 months on the Brief Psychiatric Rating Scale (BPRS) psychosis subscales (p=0.047), and the quetiapine group showed a greater deterioration from baseline than the lithium group (p=0.004), as well as greater severity of positive symptoms (p=0.005). In terms of overall psychopathology, the quetiapine group had a statistically significant worsening in BPRS total score from baseline to 12 months (p=0.008), while the lithium group continued to improve (p=0.023). The lithium group showed improvement in CGI-BP severity scores and measures of function (Global Assessment of Functioning [GAF], Social and Occupational Functioning Assessment Scale [SOFAS]), with only modest differences in Quality of Life Scale scores. (See table, next page.)
Discussion: These results were surprising given the failure of other maintenance studies to find differences in efficacy between typical antipsychotics and mood stabilizers. Patient selection may explain much of the difference. Lithium may be more effective in first-episode patients and in those with an index episode polarity of mania.

Berk M, Daglas R, Dandash O, Yucel M, et al: Quetiapine v. lithium in the maintenance phase following a first episode of mania: randomised controlled trial. *British Journal of Psychiatry* 2017; 10.1192/bjp.bp.116.186833. From Deakin University, Melbourne, Australia; and other institutions. *Funded by AstraZeneca. Six study authors disclosed financial relationships with commercial sources, including AstraZeneca; the remaining 11 authors declared no competing interests.*

Topiramate for Skin-Picking Disorder

In a pilot study, topiramate (*Topamax*) reduced skin-picking behavior to a clinically significant extent. Other pharmacologic and psychological treatments for this disorder have had limited success.

Methods: Study subjects (n=10; 8 women; mean age, 24 years) were adults who engaged in recurrent skin picking resulting in lesions, with clinically significant distress or impairment and repeated prior attempts to stop. Skin picking was not attributable to the physiological effects of substance use or a medical condition, or to another psychiatric disorder, although comorbid conditions (e.g., social anxiety disorder, major depression, drug/alcohol dependence) were common. After a washout of previous medications, study patients were started on 25 mg/day topiramate, followed by very gradual increases until clinical response, up to a maximum of 100 mg b.i.d. Participants were followed for 12 weeks, and the primary outcome measure was the mean amount of time spent picking per day, as reported in a diary. Other outcome measures were the Skin Picking Impact Scale, a modification of the Yale-Brown Obsessive Compulsive Scale (SPS-Y-BOCS), Beck Anxiety and Depression Inventories, and Clinical Global Impression (CGI) Severity (S) and Improvement (I) scales.

Results: Study patients had skin-picking onset at an average age of about 16 years (range, 12–34 years) and had gone a mean of nearly 5 years before seeking any treatment. All had multiple prior treatments, including antidepressants, antipsychotics, mood stabilizers, habit-reversal therapy, and cognitive behavioral therapy. Patients reported interference with social and work activities, inability to control the behavior, and anxiety, interpersonal rejection, and depression.

By the end of follow-up, the amount of time spent skin picking was reduced from a baseline mean of 85 minutes per day to 30 minutes per day. Seven patients reported no skin picking at follow-up. Clinician-rated measures indicated that 3 patients were much improved and 4 were very much improved on the CGI-I, and the mean CGI-S rating improved from markedly to mildly ill. The patients most likely to improve were those with relatively mild skin picking of short duration, those with good family support systems, and those who were married and more educated. All secondary outcome measures showed improvement, including the SPS-Y-BOCS and measures of anxiety and depression. A single patient dropped out of the study.
because of intolerable dizziness and sedation. Three others had milder adverse effects—nausea, drowsiness, headache, confusion—but these were limited to the first week of treatment.

**Discussion:** These results suggest that topiramate warrants further study for skin-picking disorder, especially in view of the limited success of psychological therapies, SSRIs/SNRIs, opioid antagonists, atypical antipsychotics, and glutamatergic agents. Skin-picking disorder may share a common pathway with other obsessive-compulsive syndromes such as body dysmorphic disorder, Tourette’s disorder, and trichotillomania, which suggests a glutamatergic dysfunction and possible efficacy of glutamatergic drugs. Topiramate modulates GABA-ergic neurotransmission and may also help reverse dopamine reward dysfunction.

Jafferany M, Osuagwu F: Use of topiramate for skin-picking disorder: a pilot study. The Primary Care Companion for CNS Disorders 2017; doi 10.4088/PCC.16m01961. From Central Michigan University College of Medicine, Saginaw. This study was conducted without funding. The authors declared no competing interests.

### 5-α Reductase Inhibitors and Depression, Suicide

Despite concerns based on pharmacovigilance sources, use of 5-α-reductase inhibitors (5-ARIs) was not associated with an increased rate of suicide in a large cohort of older men with benign prostatic hyperplasia (BPH). The drugs were, however, associated with a temporary increase in depression and self-harm.

**Background:** The potential adverse neurologic effects of 5-ARIs are a growing concern. There have been postmarketing reports of self-harm, suicidal ideation, and suicide in men taking these drugs, and depression is now included as an adverse event in the product monographs. There are also multiple lines of evidence supporting plausible biological mechanisms, including the role of 5-α reductase in production of neuroactive steroids and the involvement of testosterone in depression via the neuroendocrine stress response.

**Methods:** A cohort of men, aged ≥66 years, who received treatment with dutasteride or finasteride for BPH between 2003 and 2013, was identified from Canadian healthcare databases. Each patient was matched with a control, who was selected from the general population based on index date, history of depression or self-harm, and a 44-item propensity score.* The index date for cases was the date of prescription filling and for controls, a date was randomly selected. Risk was assessed for the period of continuous drug usage from the index date until 12 months after discontinuing the medication. The primary study outcome was suicide. Secondary outcomes were self-harm requiring emergency treatment or psychiatric hospitalization and new onset of depression.

**Results:** The study population consisted of >93,000 pairs of exposed and unexposed men with a mean age of 75 years. About half of patients took dutasteride and half finasteride. Baseline rates of psychotropic use, which ranged from <1% for mood stabilizers to about 15% for antidepressants, did not differ between exposed and unexposed men.

The absolute risk of suicide was low—0.04% in both patients and controls. Use of a 5-ARI was not associated with suicide risk (hazard ratio,* 0.88). Absolute rates of self-harm and depression were 0.18% and 1.95%, respectively in the treated group, compared with 0.14% and 1.37% in controls. Compared with unexposed men, risk of self-harm was increased during the first 18 months of 5-ARI use (hazard ratio, 1.88; p<0.01), but not afterward. Risk of depression was increased throughout the period of 5-ARI use, up to >3 years, although the highest risk was in the first 18 months (hazard ratio, 1.94, dropping to 1.22 afterward; p<0.01 at all time points).

**Discussion:** These results suggest that neither finasteride nor dutasteride is associated with increased suicide risk in older men with BPH and that the potential benefits of treatment likely outweigh the small increase in risk of self-harm and depression. However, discontinuation of...
these drugs may be appropriate if self-harm or depression occurs shortly after they are started, and the associations should be evaluated in younger men receiving treatment for alopecia.

Welk B, McArthur E, Ordon M, Anderson K, et al: Association of suicidality and depression with 5α-reductase inhibitors. JAMA Internal Medicine 2017; doi 10.1001/jamainternmed.2017.0089. From Western University, Canada; and other institutions. One study author disclosed a financial relationship with a commercial source; the remaining 5 authors declared no competing interests.

Common Drug Trade Names: dutasteride—Avodart; finasteride—Propecia, Proscar

*See Reference Guide.

Activating and Sedating Effects of Atypicals

Second-generation antipsychotics differ considerably in their propensity to cause activating and sedating side effects, according to an analysis of clinical trial data from multiple sources. Individual patient preferences can vary with regard to which type of adverse effect is least tolerable. Assuming equivalent efficacy, these differences can have important implications for treatment selection.

Methods: The investigators reviewed pivotal clinical trial data from the product labeling as well as the "gray" literature—i.e., unpublished sources available on the Web. For each of the first-line, oral second-generation antipsychotics indicated for treating schizophrenia, the researchers identified frequencies of activating and sedating side effects and calculated the absolute risks and numbers needed to harm (NNH).*

Results: Based on the statistical calculations, the authors separated the atypicals into 4 distinct categories: predominantly activating, predominantly sedating, similarly activating and sedating, and neither activating nor sedating. (See table.)

Among activating effects, akathisia occurred at highly varied rates among the atypicals. Rates were higher with lurasidone, cariprazine, risperidone, olanzapine, asenapine, and aripiprazole than with placebo, with NNH values ranging from 11 to 31. Rates did not differ from placebo for paliperidone, ziprasidone, quetiapine extended release, brexpiprazole, or iloperidone.

Few statistically significant associations were observed for individual agents and other activating effects: iloperidone with agitation and with insomnia (lower risk than placebo) and extended-release quetiapine with insomnia (lower risk than placebo).

Somnolence and sedation are often combined in clinical trial reports and were combined in the present analysis. Risk of sedating adverse effects were higher than placebo for olanzapine, risperidone, quetiapine (extended and immediate release), ziprasidone, lurasidone, asenapine, and iloperidone, with NNH estimates ranging from 10 to 33. Aripiprazole, paliperidone, and brexpiprazole were similar to placebo, and there was no information on cariprazine or risperidone.


Common Drug Trade Names: aripiprazole—Abilify; asenapine—Saphris; brexpiprazole—Rekulti; cariprazine—Vraylar; iloperidone—Fanapt; lurasidone—Latuda; olanzapine—Zyprexa; paliperidone—invega; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon

*See Reference Guide.
Acute Kidney Injury Risk with Antipsychotics

Risk of hospitalization for acute kidney injury (AKI) was elevated in patients taking certain atypical antipsychotics, relative to haloperidol, according to a retrospective cohort study. However, the absolute excess risk of these events was small.

Background: A recent large database analysis found associations of some earlier second-generation antipsychotics with AKI and related events in patients aged >65 years. The present study adds information about agents that have become more widely used in recent years and in a broader patient population.

Methods: Claims data were analyzed from a managed care prescription database covering >14-million patients in 2007–2013. Patients were included in the analysis if they had a diagnosis of schizophrenia or bipolar disorder and had ≥1 claim for haloperidol, aripiprazole, fluphenazine, olanzapine, quetiapine, risperidone, or ziprasidone. Because AKI hospitalizations are rare, only antipsychotics that had a sufficient number of prescriptions to make reliable incidence estimates were included. The primary outcome was hospitalization for AKI during active treatment with any of the study drugs or within 30 days of discontinuation. Secondary outcomes included any of the known causes of AKI: hypotension, acute urinary retention, neuroleptic malignant syndrome (NMS) and rhabdomyolysis, and pneumonia. Patients receiving haloperidol were the reference group for incidence comparisons. Because events that occurred during overlap of 2 study medications could be attributable to 1 of the drugs or to both drugs, a separate sensitivity analysis using episodes without overlap was conducted to provide a clean comparison.

Results: The final sample consisted of >172,000 patients. The overall incidence of AKI in patients exposed to a study medication was 25 per 1000 exposures, ranging from a minimum of 12.9 per 1000 exposures to fluphenazine, to 29 per 1000 to quetiapine. After adjustment for multiple factors, the incidence was significantly elevated, relative to haloperidol, for olanzapine, quetiapine, and ziprasidone. (See table.) Risks of the 4 predisposing events did not follow a consistent pattern, but risk elevations were statistically significant for: quetiapine and hypotension; quetiapine and NMS or rhabdomyolysis; and olanzapine and pneumonia (p<0.05 for all). As a class, second-generation antipsychotics had a significantly higher risk of AKI than first-generation agents (hazard ratio,* 1.3). Results were similar in the sensitivity analysis excluding episodes of medication overlap.

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Incidence per 1000 Person-Years</th>
<th>Adjusted Hazard Ratio</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>20.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>27.5</td>
<td>1.34</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>29</td>
<td>1.35</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>23.2</td>
<td>1.34</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

**Risk with aripiprazole, fluphenazine, and risperidone did not differ significantly from haloperidol.

Discussion: These newer data suggest AKI risk is not a class effect of second-generation agents, and that AKI risk should not be a major concern in prescribing antipsychotics. However,
caution may be warranted when prescribing olanzapine, quetiapine, or ziprasidone for elderly patients and those at risk for kidney disease. In addition, high-risk antipsychotics should be considered as a potential cause when AKI occurs.

1Jiang Y, McCombs J, Park S: A retrospective cohort study of acute kidney injury risk associated with antipsychotics. CNS Drugs 2017; doi 10.1007/s40263-017-0421-4. From the University of Southern California, Los Angeles; and the University of California, Los Angeles. This study was conducted without funding. The authors declared no competing interests.


Common Drug Trade Names: aripiprazole—Abilify; fluphenazine—Prolixin; haloperidol—Haldol; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon

*See Reference Guide.

Reference Guide

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 1 group has half the risk of the other group.

Number Needed to Harm: A measure of how many patients need to be exposed to a risk-factor to cause harm in 1 patient that would not otherwise have been harmed. Lower NNH, indicates more attributable risk.

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

Propensity Score 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.

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 are posted at www.alertpubs.com.

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