Asenapine for Bipolar Disorder in Older Adults

In a small uncontrolled study, adjunctive asenapine (Saphris) was effective in older adults with type I or II bipolar disorder with suboptimal response to their ongoing treatments. Asenapine is FDA approved as primary or adjunctive treatment for acute mania or mixed episodes. This study adds new information on its use in an older age group that includes patients with current depression.

Methods: Participants, aged ≥60 years, were experiencing suboptimal response—defined as irritability, agitation, and mood lability or diminished ability to take care of basic personal needs as a result of their illness—to their current bipolar disorder medication. All patients had open-label, flexible-dose, sublingual asenapine added to their current medication for 12 weeks. Responses were evaluated with the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression-Bipolar Version (CGI-BP), Young Mania Rating Scale (YMRS), Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Rating Scale for Depression (HAM-D), as well as various tests of functional and general health status, cognitive function, and patient satisfaction.

Results: A total of 15 patients were enrolled and took ≥1 dose of asenapine. The mean patient age was 69 years (range, 60–80 years), and 2 had a diagnosis of bipolar II disorder. Seven patients also met study criteria for at least mild depression, 3 for a mixed episode, and 1 for mania. Background medications included lithium, mood-stabilizing anticonvulsants, and antidepressants. The mean asenapine dosage was 11 mg/day (range, 5–25 mg/day). Four patients discontinued treatment prematurely, including 3 with severe adverse events. Only 1 of these events, emergence of mixed mania, was thought to be possibly related to the study medication.

On average, patients experienced significant improvement in BPRS scores, as well as the CGI overall, mania, and depression subscales. (See table, next page.) Patients with at least mild mania had a significant improvement in YMRS scores (p<0.01), and those with depression had improvement on the MADRS (p=0.06) and the HAM-D (p=0.01).
There was no significant improvement in ratings of mental or physical health, daily function, or cognition. Of the 11 patients who completed the study, 7 felt that they benefitted substantially from asenapine, and 6 said they would like to continue taking it. Opinions of the sublingual formulation were mixed.

**Discussion:** The average asenapine dose in this study was relatively low, and most adverse effects were mild to moderate and transient. The hypothesis that asenapine would improve residual functional impairment was not supported by the study results.

Sajatovic M, Dines P, Fuentes-Casiano E, Athey M, et al: Asenapine in the treatment of older adults with bipolar disorder. *International Journal of Geriatric Psychiatry* 2014; doi 10.1002/gps.4213. From Case Western Reserve University School of Medicine; and University Hospitals Case Medical Center, Cleveland, OH. Funded by NV Organon/Merck. One study author disclosed financial relationships with commercial sources.

### Adjunctive Armodafinil in Bipolar Depression

In a manufacturer-sponsored trial, adjunctive treatment with the wakefulness drug armodafinil was associated with statistically significant but modest improvement in depression in patients with bipolar I disorder.¹

**Methods:** This multinational study enrolled >400 patients with bipolar I disorder who were receiving maintenance treatment with mood-stabilizing or antipsychotic medication that was required to be stable for ≥4 weeks prior to the onset of the depressive episode. Patients with significant mania or anxiety symptoms were excluded. Participants were randomly assigned to receive 8 weeks of either 150 mg/day armodafinil or placebo. The primary measure of efficacy was the 30-item Inventory of Depressive Symptomatology—Clinician Rated (IDS-C₃₀).

**Results:** Patients who received 150 mg/day armodafinil showed a significantly greater improvement in depressive symptoms than the placebo group (p=0.01). However, the effect size of 0.28 was small. The proportion of patients who experienced response at week 8 (IDS-C₃₀ reduction of ≥50%) was 55% for armodafinil and 39% for placebo (p=0.008). The proportion of patients who achieved remission (IDS-C₃₀ ≤11) was 28% and 22%, respectively, a statistically non-significant difference. Secondary outcome measures tended to favor armodafinil, but not all were statistically significant.

Adverse events were consistent with the known profile of armodafinil. A total of 6 patients experienced suicidal ideation or a suicide attempt: 4 with armodafinil and 2 with placebo. Mania or hypomania was reported by 3 patients in each treatment group.

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS</td>
<td>35</td>
<td>29</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>CGI-BP Mania Severity</td>
<td>2.7</td>
<td>1.9</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>CGI-BP Depression Severity</td>
<td>3.6</td>
<td>1.7</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>CGI-BP Overall Severity</td>
<td>4.4</td>
<td>2.2</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>
Discussion: In spite of decades of research, there have been few advances in the treatment of bipolar depression. Currently only quetiapine, lurasidone, and the olanzapine–fluoxetine combination are approved for this indication. Results of previous studies have suggested strong and rapid positive antidepressant effects with modafinil in patients with bipolar depression. As the R-enantiomer of modafinil, there were strong hopes that armodafinil would show similar effects. Unfortunately, while the improvements in the present study were statistically significant, they were at best clinically modest. However, 2 additional phase 3 studies (currently unpublished) completed since and not yet published showed no statistically significant benefit. Although it appears to be a relatively safe and modestly effective option in a therapeutic area that needs additional options, the manufacturer has abandoned the approval process for armodafinil in bipolar depression.

1Calabrese J, Frye M, Yang R, Ketter T, et al: Efficacy and safety of adjunctive armodafinil in adults with major depressive episodes associated with bipolar I disorder: a randomized, double-blind, placebo-controlled, multicenter trial. Journal of Clinical Psychiatry 2014;75 (October):1054–1061. From Case Western Reserve University School of Medicine, Cleveland, OH; and other institutions. Funded by Cephalon, Inc. (now Teva Pharmaceuticals). All study authors disclosed financial relationships with commercial sources.

2Ostacher M: When positive isn’t positive: the hopes and disappointments of clinical trials [commentary]. Journal of Clinical Psychiatry 2014;75 (October):e1186–e1187. From Stanford University School of Medicine, Palo Alto, CA; and other institutions. The author declared no conflicts of interest.

Drug Trade Names: armodafinil—Nuvigil; lurasidone—Latuda; modafinil—Provigil; olanzapine–fluoxetine—Symbyax; quetiapine—Seroquel

*See Reference Guide.

Transdermal Selegiline in Depression

In spite of FDA approval and demonstrated efficacy in major depressive disorder, transdermal selegiline (Em sam) is rarely used in clinical practice. A recent review highlights some of the potential advantages of transdermal delivery of this MAOI and addresses clinical concerns.

At low doses, transdermal selegiline is a selective MAO-B inhibitor. At approved dosages of 6–12 mg/day, it inhibits both MAO-A and MAO-B. However, because of the transdermal delivery, direct gastrointestinal (GI) exposure and first-pass metabolism in the gut are avoided, thus reducing risk of many MAOI-associated adverse effects. In addition, gradual absorption over 24 hours reduces absorption peaks and may improve tolerability. Transdermal delivery could also be particularly useful in patients with trouble swallowing oral medications. Finally, adverse effects are the most common cause of antidepressant noncompliance and discontinuation. Transdermal selegiline has not been associated with the sexual dysfunction or GI effects typically associated with antidepressants. Skin irritations, insomnia, dry mouth, dizziness, nervousness, and abnormal dreams are the most commonly reported adverse effects of transdermal selegiline, and these appear to occur less frequently than with most other antidepressants.

The potential for hypertensive crisis associated with tyramine ingestion is likely a major factor in physicians’ reluctance to prescribe MAOIs. In contrast to oral MAOIs, however, use of transdermal selegiline at low dosages (<9 mg/day) does not require patients to follow a tyramine-free diet. Although the FDA does require this dietary restriction with higher dosages (9–12 mg/day), studies have shown that the risk of tyramine-associated reactions is low with transdermal selegiline. While the tyramine-free diet is thought to be restrictive and hard to follow, recent research has shown that very few foods actually contain dangerously high tyramine levels and require complete abstinence (i.e., aged chicken liver, air-dried sausage, soy sauce, and sauerkraut). Among the aged cheeses that were previously completely eliminated in the tyramine-free diet, most have a low tyramine content (e.g., mozzarella, cottage, cream, and ricotta) and appear to be safe in moderation.
Drug interactions with MAOIs that can lead to serotonin syndrome are another potentially limiting factor for selegiline. However, interactions between transdermal selegiline and serotonin-promoting drugs have rarely been reported. Evaluation of clinical trial data found that of 100 patients who took a prohibited medication (e.g., decongestants, antitussives, various opioids), only 1 validated case of serotonin syndrome occurred. This was in a patient who was taking several prohibited medications concurrently and applying 2 selegiline patches (12 mg each) at the same time. This suggests that for most patients, the interaction may not be clinically problematic; however, patients who require significant amounts of analgesics and/or sympathomimetics, such as those with asthma or ADHD or those prone to using opiates, should not use transdermal selegiline.

Clinical trials of transdermal selegiline failed to evaluate patients with comorbid anxiety and other disorders for which SSRIs are known to be effective. These trials also did not specifically investigate depressive subtypes (e.g., psychotic, resistant, bipolar) or a variety of patient age ranges. In addition, the registration trials did not include active antidepressant comparators. However, post-hoc analyses have shown possible advantages of transdermal selegiline in terms of suicide prevention and manic switching. Meta-analyses have found that both anxious and nonanxious depression, as well as typical and atypical depression, respond equally well to transdermal selegiline.

Although, according to this review, transdermal selegiline appears to be more effective and safer than generally believed, head-to-head comparisons with other antidepressants are needed.

Asnis G, Henderson M: EMSAM (deprenyl patch): how a promising antidepressant was underutilized. Neuropsychiatric Disease and Treatment 2014;10:1911–1923. From Albert Einstein College of Medicine, New York, NY; and Montefiore Medical Center, Bronx, NY. One study author disclosed financial relationships with commercial sources, but none related to Emsam. The remaining author declared no conflicts of interest.

### Generic Concerta: Therapeutic Equivalence

Based on results of an analysis of adverse event reports and laboratory tests, the FDA has expressed concern about the therapeutic equivalence of 2 generic extended-release methylphenidate formulations. In some patients, the generic products manufactured by Mallinckrodt and Kudco may release active drug at a slower rate than brand-name Concerta. This can inhibit the desired therapeutic effects. Although there are no serious safety concerns and the agents remain FDA approved, they are no longer recommended as automatically substitutable for Concerta at the pharmacy level. The FDA has requested the manufacturers confirm the bioequivalence of their products using revised standards within 6 months or withdraw their products from the market.


### Idalopirdine: Adjunctive Treatment for Alzheimer's

The selective 5-HT6 receptor antagonist idalopirdine had promising effects on cognition in a phase 2 clinical trial in patients with moderate Alzheimer’s disease who were on stable treatment with donepezil (Aricept). Positive results of a phase 2 trial in Alzheimer’s disease are notable, but the study raises questions, according to an editorial. The outcome would have been more convincing if there were positive effects on more than 1 of the multiple cognitive endpoints measured.

**Methods:** The study, conducted in 7 countries, enrolled patients age ≥50 years who met standard criteria for probable Alzheimer's disease. Patients were required to have a mini-mental...
state exam (MMSE) score of 12–19 at baseline, indicating moderate disease severity, and to be receiving stable treatment with 10 mg/day donepezil. Patients were randomly assigned to receive 30 mg idalopirdine t.i.d. or placebo. The primary endpoint was change from baseline in the Alzheimer’s Disease Assessment Scale–cognitive subscale (ADAS-cog) at 24 weeks.

**Results:** Of 278 randomized patients, 272 completed ≥1 post-baseline assessment and were included in the efficacy analysis. A significant improvement in the ADAS-cog score was observed for idalopirdine (mean difference of 2.16 points vs. placebo; p=0.004). There were no differences between treatments in any of the prespecified secondary outcome measures of activities of daily living, neuropsychiatric symptoms, caregiver burden, or a neuropsychological test battery. In an unplanned post-hoc analysis, idalopirdine was associated with an average increase in the mean MMSE score of 0.8 point, compared with a decrease of 0.5 in the placebo group.

Hepatic enzyme elevations were the only adverse effect that occurred more often with idalopirdine than placebo. Of 13 patients who had elevations >2 times the upper limits of normal, 11 withdrew from treatment.

**Discussion:** Based on these results, the manufacturer has launched a full-scale phase 3 development program for idalopirdine. Recent Alzheimer’s research has been characterized by many phase 2 trials, but few with positive results and none that have fulfilled their promise in phase 3, the editorial says. Studies of this and another 5-HT6 receptor antagonist suggest these agents are not effective as monotherapy, only as an add-on to donepezil. Because idalopirdine increases the bioavailability of donepezil, the possibility of a positive pharmacokinetic interaction, not specific to the drug’s mechanism of action, cannot be ruled out.


**Benzodiazepines and Alzheimer’s Risk**

According to results of a population-based case-control study, benzodiazepine use is associated with an increase in risk of Alzheimer’s disease, particularly with long-term use.

**Background:** The negative effects of benzodiazepines on memory and cognition are well documented, and previous studies have suggested a link between use and development of Alzheimer’s. However, it has been unclear if the association is causal or related to increased prescribing for common symptoms (e.g., anxiety, depression, insomnia) that increase with age or early/prodromal Alzheimer’s. The present study was designed to attempt to eliminate bias due to prescription of benzodiazepines for these symptoms (i.e., reverse causality bias), which may represent a prodrome to Alzheimer’s.

**Methods:** The study population consisted of all community-dwelling persons, aged >66 years, living in Quebec, who were covered by the provincial drug plan (about 98% of the population) in 2000–2009. Case patients (n=1796) were those who received a diagnosis of Alzheimer’s disease during the study period, who did not have any previous record of dementia or prescription of a medication for dementia, and who had ≥6 years of follow-up before the date of diagnosis (index date). Each case was matched with 4 controls (n=7184) for age, gender, and duration of follow-up. Exposure was defined as any prescription claim for a benzodiazepine between 6 and 10 years before the index date. Treatments initiated in the 5 years before the
index date were not considered in order to control for possible reverse causality. Cumulative dose was defined as exposure for up to 3 months, 3–6 months, and >6 months (long-term use). Benzodiazepines were categorized as short-acting or long-acting according to a cutoff elimination half-life of 20 hours.

**Results:** Over the study period, benzodiazepines were used by 50% of case patients and 40% of controls. Benzodiazepine use was associated with overall increased risk of Alzheimer’s disease (adjusted odds ratio,* 1.5). The proportion of users with <6 months of exposure did not differ between the groups, but long-term use was more common in patients with Alzheimer’s disease (33% vs. 22%; odds ratios, 1.3 for 3–6 months of exposure and 1.8 for >6 months). Both short-acting and long-acting benzodiazepines were associated with a statistically significant risk increase, which was larger for long-acting agents (odds ratio, 1.70). The analysis was not altered by adjustment for anxiety, depression, or insomnia, conditions thought to be potential prodromes for Alzheimer’s disease.

**Discussion:** The mechanism by which benzodiazepines could induce dementia is unknown but could be related to a limiting of cognitive reserve capacity. These negative effects can be minimized by following prescribing guidelines, which recommend limiting use to 3 months.

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**Anxiolytic Withdrawal and Pseudopheochromocytoma**

A 55-year-old woman was admitted to an emergency unit with paroxysmal malignant hypertension, accompanied by headache; vertigo; tachycardia; lacrimation; nausea; and altered mental status. Her medical history included type 2 diabetes, thyroid disease, and multiple other illnesses. The patient had been experiencing episodic hypertensive crises with altered mental status for about a decade. After a previous detailed workup failed to identify any endocrinologic, neurologic, or cardiovascular cause, these were attributed to panic disorder. She received treatment for 10 years with a combination of antidepressant and anxiolytic drugs. During this period, the frequency of paroxysms was noticeably reduced. However, after 9 years, she appeared to be addicted to her anxiolytic therapy, which was then withdrawn with no apparent ill effects 1 year before the current episode.

During the recent episode, the patient experienced very severe attacks of hypertension (BP as high as 230/100 mmHg), with tachycardia and loss of consciousness. During hospitalization, the attacks occurred 2–4 times/day and resolved spontaneously after 3–5 minutes. She was asymptomatic between attacks. Alpha- and beta-adrenergic blocking agents were started and lowered the patient’s blood pressure but did not reduce the number of daily attacks. An adrenal adenoma was detected during a CT scan, but laboratory testing excluded hormonal abnormalities and the adenoma was judged to be unrelated to her attacks. Endocrine disorders including pheochromocytoma were ruled out, and her physicians focused on her psychiatric illness as a potential cause. When alprazolam (Xanax) was restarted at 0.5 mg b.i.d., the patient improved. Alprazolam was reduced to 0.5 mg/day when sleepiness and fatigue occurred, but the paroxysmal blood pressure increases reappeared. The patient was stabilized on 1 mg/day alprazolam and discharged.

**Discussion:** Pseudopheochromocytoma, an uncommon, potentially life-threatening syndrome presenting as a rapid onset of paroxysmal malignant hypertension and a constellation of related symptoms in the absence of any apparent biochemical or anatomic cause, is caused by...
sympathoadrenal overdrive and is not related to emotional stress, although patients may experience distress as a result of their symptoms. The syndrome may in some cases be caused by withdrawal of drugs that inhibit sympathetic activity. The diagnosis of pseudopheochromocytoma can only be made by ruling out all other secondary causes of the attacks, particularly true pheochromocytoma. Pseudopheochromocytoma may respond to alpha- or beta-blocker therapy. When these agents are not effective, attacks may be prevented with antidepressants, anxiolytics, and/or psychotherapy.


### Review of Pharmacotherapy for Bipolar Depression

At present, only 3 FDA approved medications are available for bipolar depression: the olanzapine–fluoxetine combination, quetiapine (immediate or extended release), and lurasidone (either as monotherapy or as an adjunct to lithium or valproate). Research indicates that all 3 have similar efficacy profiles. In placebo-controlled trials, the numbers needed to treat* (NNT) for response in bipolar depression were 4 for olanzapine–fluoxetine, 6 for quetiapine, 5 for lurasidone monotherapy, and 7 for adjunctive lurasidone. However, the agents do appear to differ substantially in tolerability. A number needed to harm* (NNH) of <10 indicates a potential concern for tolerability during routine use. NNH values below this threshold have been found for the olanzapine–fluoxetine combination for weight gain (NNH, 7) and diarrhea (NNH, 9). For quetiapine, the values were below this threshold for somnolence (NNH, 3) and dry mouth (NNH, 4). There were no NNH values <10 for lurasidone either as monotherapy or adjunctive treatment.

Several agents are commonly used off-label in the treatment of acute bipolar depression. These include lamotrigine monotherapy and antidepressants. In spite of weaker efficacy estimates in terms of treatment response—NNT of 12 for lamotrigine and 29 for antidepressants—they may have tolerability advantages over approved treatments for some patients. Of particular concern is the potential for manic switching with antidepressants. Although this appears to occur rarely (the NNH for this reaction has been calculated at 200), a switch to mania can have serious psychosocial consequences. Aripiprazole and ziprasidone have been investigated as treatments for bipolar depression but have not demonstrated adequate efficacy.

Following response in an acute bipolar depressive episode, there are 5 approved maintenance monotherapy options: lithium; lamotrigine; olanzapine; aripiprazole; and risperidone long-acting injection (LAI). In addition, quetiapine, ziprasidone, and risperidone LAI are approved for use in combination with lithium or valproate for longer-term maintenance. The NNT to avoid relapse for all of these options is <10. Some differences exist between the options in the capability to prevent manic versus depressive episodes. Lithium is substantially more effective at preventing depressive versus manic relapse (NNTs 49 vs. 8). Conversely, valproate and lamotrigine are more effective at preventing manic relapse than depressive (NNTs, 11 and 15, respectively vs. 22 and 23, respectively). Quetiapine is the only agent with an NNT of <10 for both manic and depressive relapse prevention.

Citrom e L: Treatment of bipolar depression: making sensible decisions. CNS Spectrums 2014; DOI 10.1017 / S109285291400056X. From New York Medical College, Valhalla. This review was supported by an educational grant from Sunovion Pharmaceuticals Inc. The author disclosed financial relationships with multiple commercial sources.

**Drug Trade Names:**
- aripiprazole—Abilify;
- lamotrigine—Lamictal;
- lurasidone—Latuda;
- olanzapine—Zyprexa;
- olanzapine–fluoxetine—Symbyax;
- quetiapine—Seroquel;
- risperidone, long-acting injection—Risperdal Consta;
- valproate—Depakene, Depakote;
- 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.

Number Needed to Harm (NNH): 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 (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 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio >1 indicates that the event is more likely to occur in that group than in the comparison group.

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