Cariprazine vs Risperidone for Negative Symptoms

In a manufacturer-sponsored study, cariprazine monotherapy was superior to risperidone monotherapy at reducing predominant negative symptoms of schizophrenia.1

Background: Cariprazine has a unique activity profile, with especially potent affinity for the dopamine D$_3$ receptor. The importance of this receptor in modulating mood and cognition suggests possible efficacy of cariprazine in treating negative symptoms.

Methods: Study subjects had a diagnosis of schizophrenia (DSM-IV-TR) with a duration of ≥2 years and had been clinically stable for ≥6 months but continued to have a Positive and Negative Syndrome Scale (PANSS) negative symptom score of ≥24 plus a score of ≥4 on at least 2 of the 4 core negative PANSS symptoms: blunted affect, passive social withdrawal, lack of spontaneity, and flow of conversation. Those with a history of nonresponse to risperidone or who had received the drug within the prior 6 weeks were excluded. Participants were randomly assigned to double-blind treatment with either cariprazine or risperidone. During the first 2 post-randomization weeks, study medications were cross-titrated with patients’ previous antipsychotics. Following the taper, patients received monotherapy for 26 weeks at target dosages of 4.5 mg/day cariprazine or 4 mg/day risperidone. Patients could receive lorazepam or a similar agent for agitation, sedatives for sleep, or a limited number of agents for extrapyramidal symptoms, but no other psychotropics were permitted. The primary efficacy outcome was change from randomization to treatment week 26 in the PANSS factor score for negative symptoms.

Results: A total of 460 patients (mean age, 40 years; 58% men) received study medication. Of these, 456 completed ≥1 assessment and were included in the intent-to-treat analysis. The mean baseline PANSS negative symptom score was 28 in each treatment group. Patients who received cariprazine had a significantly larger reduction in the negative symptom score than those receiving risperidone (8.6 vs 7.2 points; p=0.0022; effect size*, 0.31). Rates of response, defined as a ≥20% reduction from baseline in PANSS negative symptoms, were 69% with...
cariprazine and 58% with risperidone (odds ratio,* 2.08; p=0.0022). These rates translate to a number needed to treat* of 9 to achieve 1 additional response with cariprazine, relative to risperidone.

Several secondary efficacy measures also favored cariprazine. Statistically significant differences were observed in change from baseline on the Clinical Global Impression–Severity (CGI-S) scale (p=0.0052) and the CGI–Improvement scale (p<0.0001), although the absolute mean differences versus risperidone were small. Scores on the Personal and Social Performance Scale indicated greater cariprazine-related improvement in self-care, personal and social relationships, and socially useful activities, but not in disturbing and aggressive behaviors. Further analysis indicated that improvement in negative symptoms was not related to improvement in positive symptoms, depression, or extrapyramidal symptoms.

Editorial.* Although some second-generation antipsychotics may be more effective than conventional agents at reducing negative symptoms, previous research suggests they lack a direct effect on primary negative symptoms and improvement is secondary to reductions in positive symptoms. Although the absolute differences in improvement between the groups in this study were small and effect sizes were not robust, the number needed to treat for cariprazine is below the cutoff of 10 that is generally accepted to indicate clinical significance.

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

Common Drug Trade Names: cariprazine—Vraylar; risperidone—Risperdal

*See Reference Guide.

Adjunctive Citicoline in Depression

In a randomized trial, adding the dietary supplement citicoline to citalopram (Celexa) was superior to citalopram monotherapy at reducing symptoms of depression.

Background: Animal models have shown that citicoline increases the amount of acetylcholine, noradrenaline, dopamine, and serotonin in different parts of the brain. It has shown promise in treating cognitive deficits in patients with brain injury, craving and depression in patients with substance use disorders, and mood in patients with bipolar disorder.

Methods: Study participants (n=54; mean age, 36 years; 15 men) had a diagnosis of major depressive disorder of at least moderate severity. All patients received treatment with citalopram, increasing from 20 mg/day in the first week to 40 mg/day in weeks 2–6. In addition, patients received randomly assigned, double-blind citicoline (100 mg every 12 hours) or placebo. The primary study outcome was change from baseline in Hamilton Rating Scale for Depression (HAM-D) score.

Results: The treatment groups did not differ in depression severity at baseline, with mean HAM-D scores of 25 and 24 in the citicoline and placebo groups, respectively. After 6 weeks of treatment, combined therapy resulted in a larger decrease in HAM-D scores than citalopram monotherapy (mean scores, 6.5 and 10, respectively; p=0.021). The between-group difference was statistically significant as early as treatment week 2. Remission (i.e., HAM-D score of ≤7) occurred by week 6 in 72% of patients receiving combination therapy and 44% of those receiving monotherapy (odds ratio,* 3.27; p=0.04). Rates of response and early improvement
were also higher with combination therapy, although not significantly. Citicoline and placebo were associated with comparable adverse effects, with no serious events or death in either group. Only 4 of the 54 patients (2 from each group) did not complete treatment.

**Study Rating**—15 (88%): This study met most criteria for a randomized trial; however, the source of funding was not stated.

Roohi-Azizi M, Arabzadeh S, Amidfar M, Salimi S, et al: Citicoline combination therapy for major depressive disorder: a randomized, double-blind, placebo-controlled trial. *Clinical Neuropharmacology* 2017;40 (January–February):1–5. From Tehran University of Medical Sciences; and Mashad University of Medical Sciences, Iran. **Source of funding not stated.** The authors declared no competing interests.

**Monthly Aripiprazole Maintenance**

Once-monthly injectable aripiprazole delayed the time to mood episode recurrence in a 52-week placebo-controlled withdrawal trial within a 4-phase manufacturer-sponsored study of patients with bipolar I disorder.¹

**Methods:** This multicenter study enrolled patients who met DSM-IV-TR criteria for bipolar I disorder and who were currently experiencing a manic episode (excluding those with rapid cycling). In phases 1 and 2, patients not already taking the drug were converted to oral aripiprazole monotherapy over 4–6 weeks and then assessed for clinical stability over the next 2–8 weeks. During phase 3 (this study), all patients received open-label aripiprazole injections every 4 weeks for up to 28 weeks. Finally, those who met the study’s stability criteria for ≥8 consecutive weeks were randomly assigned to 52 weeks of double-blind treatment with long-acting injectable aripiprazole or placebo. The primary efficacy endpoint was time from randomization to recurrence of any mood episode, including hospitalization for a mood episode; exceeding thresholds on the Young Mania Rating Scale, the Montgomery-Asberg Depression Rating Scale, or the Clinical Global Impression for Bipolar Disorder-Severity Scale; need for another medication; a serious adverse event; or active suicidality.

**Results:** A total of 466 patients began treatment with oral aripiprazole, 425 entered the open-label stabilization phase, and 266 (mean age, 41 years; 58% women) began the placebo-controlled phase. The overall recurrence rate in the active treatment group was about half that in the placebo group. (See table.) Recurrence risk with once-monthly aripiprazole was significantly lower for manic episodes (p<0.0001) and approached significance for mixed episodes (p=0.06). Risk of depressive recurrence was not reduced. However, patients had few depressive symptoms at study entry and the number of depressive recurrences was low. Notably, monthly aripiprazole did not increase the number of depressive recurrences.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aripiprazole</th>
<th>Placebo</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence of any mood episode</td>
<td>27%</td>
<td>51%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Median time to discontinuation for any reason</td>
<td>345 days</td>
<td>170 days</td>
<td>p=0.0026</td>
</tr>
<tr>
<td>Discontinuation for adverse event</td>
<td>17%</td>
<td>26%</td>
<td>p=ns</td>
</tr>
</tbody>
</table>

Adverse events were similar to those reported for oral aripiprazole. There were minimal differences between groups in extrapyramidal symptoms. Aripiprazole was associated with a modestly higher rate of clinically significant weight gain (18% vs 13%), but no clinically significant elevation in prolactin.
Discussion: Currently, injectable risperidone (administered every 2 weeks) is the only long-acting injectable antipsychotic approved for maintenance treatment of bipolar disorder. Results of the present study support the safety and efficacy of once-monthly aripiprazole for these patients and are consistent with a meta-analysis suggesting that the efficacy of long-acting injectable antipsychotics is similar to that of oral agents.²

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


Common Drug Trade Names: aripiprazole, injectable—Abilify Maintena; risperidone, injectable—Risperdal Consta

*See Reference Guide.

Lithium, Sertraline, and Bipolar Switching

In patients with bipolar II depression, lithium monotherapy, SSRI monotherapy, and the combination were all associated with similar rates of switching to hypomania and similar antidepressant efficacy in a randomized trial. Combination therapy was associated with a higher rate of discontinuation.

Methods: Study subjects (n=142; mean age, 39 years; 54% women) had a structured clinical interview-confirmed diagnosis of bipolar II disorder and were currently experiencing a major depressive episode, with no- or minimal symptoms of mania. Patients with rapid cycling (42%) were not excluded, nor were those with a history of substance abuse ≥3 months prior to entry. Participants were randomly assigned to 16 weeks of double-blind treatment with lithium at a minimum dosage of 900 mg/day, sertraline at a minimum of 100 mg/day, or combined treatment with both agents. Lithium dosage was guided by the same serum level range as in bipolar I disorder (0.8–1.2 mEq/L), but because the therapeutic range for bipolar II disorder is not precisely known, lower levels were permitted in patients who could not tolerate levels >0.8 mEq/L. To maintain the blind, serum samples were collected from all participants and a single unblinded, nonrating physician at each study site characterized lithium levels as subtherapeutic, therapeutic, or toxic to guide dosage changes. The primary study outcome was a switch to hypomania or mania, based on scores on the Young Mania Rating Scale or the Clinical Global Impression for Bipolar Disorder (CGI-BP) severity scale. The secondary efficacy outcome was response, defined as a sustained decrease of ≥50% on the Inventory of Depressive Symptomatology—Clinician Rated or a decrease of ≥2 points on the CGI-BP depression severity score, without hypomania or mania.

Results: The treatment groups did not differ in likelihood of incurring a treatment-emergent adverse effect, and rates of study drop-out due to adverse effects (24–29%) did not differ between the groups. However, the overall dropout rate was significantly higher for combined therapy (71%) than for lithium or sertraline monotherapy (55% and 42%, respectively; p=0.03). The response rate was 63% overall and did not differ statistically among treatments. Combined therapy did not accelerate the antidepressant response.

During the study period, hypomania developed in 20 patients (14%) and was severe in 3 (1 in each treatment arm). Rates of switching did not differ across treatment groups; nor were rapid-cycling patients at greater risk of a switch than others. There were 5 switches to hypomania
with combination therapy, 7 with lithium, and 8 with sertraline. No patient switched to mania. The majority of patients who switched (75%) did so within 5 weeks of starting therapy. History of substance abuse, in particular stimulant abuse or dependence, was associated with a significantly higher risk of switching (p<0.001). In addition, within the lithium groups, patients who switched to hypomania had significantly lower serum levels than those who did not experience a switch (p=0.03).

Discussion: There are currently few guidelines for treatment of bipolar II depression; instead, guidelines for bipolar I are often applied. This study adds to the sparse literature on treatment of bipolar II depression and suggests that it may require a different approach than bipolar I depression. Quetiapine is the only FDA-approved drug for treatment of bipolar II depression.

Altshuler L, Sugar C, McElroy S, Calimlim B, et al: Switch rates during acute treatment for bipolar II depression with lithium, sertraline, or the two combined: a randomized double-blind comparison. American Journal of Psychiatry 2017; doi 10.1176/appi.ajp.2016.15040558. From the David Geffen School of Medicine at UCLA, Los Angeles, CA; and other institutions. Funded by the NIMH; and other sources. Four study authors disclosed financial relationships with commercial sources; the remaining 8 authors declared no competing interests.

Common Drug Trade Names: quetiapine—Seroquel; sertraline—Zoloft

Solifenacin and Donepezil Dosing

In a first-in-patients study, co-administration of solifenacin, a peripheral anticholinergic approved for treatment of overactive bladder, allowed patients to tolerate increased doses of donepezil. The increased donepezil doses resulted in better clinical outcomes.

Background: It has been suggested that profound underdosing contributes to the lack of efficacy of donepezil and other cholinesterase inhibitors in Alzheimer’s disease. However, dose-limiting adverse effects are a major factor contributing to underdosing. A 23-mg strength of donepezil was introduced in 2010 but has found limited acceptance due mainly to GI intolerance.

Methods: This single-blind, dose-escalation, crossover study recruited patients, aged 50–89 years, with a diagnosis of probable Alzheimer’s dementia, according to standard criteria, and who had Mini-Mental State Examination (MMSE) scores of 10–20, indicating moderate impairment. All patients received 10 mg/day donepezil for ≥12 weeks before study entry. Those taking memantine at stable doses for ≥8 weeks were allowed to continue.

All patients received 6 tablets of single-blind study medication per day throughout the study. At entry, patients received 10 mg/day donepezil plus placebo for 2 days. On day 3, 10 mg/day solifenacin was introduced and then increased to 15 mg/day after 1 week. Remaining placebo tablets were subsequently replaced with donepezil, increasing in weekly 5-mg increments to 25 mg/day and then at biweekly intervals until the patient’s first intolerable dose or the protocol-specified maximum of 40 mg/day. When titration was completed, patients were received maintenance with 15 mg/day solifenacin and the maximum tolerated dose of donepezil for 12 weeks. The primary study outcome was the maximum tolerated dose of donepezil during coadministration of solifenacin. Cognitive effects were a secondary study outcome.

Results: The 41 study participants had a mean age of 73 years, and 54% were women. The mean baseline MMSE score was 16.5. The average duration of donepezil treatment before study entry was >2 years, and 61% of patients were also taking memantine. Of the 11 patients who did not complete the study, none withdrew because of a drug-related adverse effect. Solifenacin was not associated with observable cognitive decline, neuropsychological dysfunction, or other evidence of centrally mediated adverse effects. Of the 33 patients who completed donepezil dose titration, all reached a maximum tolerated dosage of ≥25 mg/day and all but 4 tolerated 40 mg/day. In all patients who completed the study, the maximum titrated dose was
maintained throughout the final 3 months of the study. GI intolerance was the dose-limiting adverse effect in 3 of the 4 patients whose maximum tolerated dose was 25 mg. No clinically meaningful changes in vital signs, electrocardiogram, or laboratory findings occurred.

Mean scores on the Alzheimer’s Disease Assessment Scale–cognitive subscale (ADAS-cog) improved during the study period, reaching a peak at 18 weeks (after completion of donepezil titration), after which scores declined but remained higher than baseline averages at the 26-week endpoint. Final scores averaged about 2.5 points better than would be expected with 10 mg/day donepezil. A total of 14 patients (61%) were judged to be responders, based on stable or improved ADAS-cog scores. In the 16 patients with evaluable Clinical Global Improvement–Improvement ratings at 26 weeks, both study clinician and caregiver ratings indicated substantial global improvement (p<0.01).

**Discussion:** The present observations support the suggestion that underdosing contributes to the lack of donepezil efficacy and suggests that more aggressive dosing may now be possible. Further study is now needed in a fully powered, randomized, controlled trial.

Chase T, Farlow M, Clarence-Smith K: Donepezil plus solifenacin (CPC-201) treatment for Alzheimer’s disease. *Neurotherapeutics* 2017; doi 10.1007/s13311-016-0511-x. From Chase Pharmaceuticals, Inc., Washington, DC; and Indiana University School of Medicine, Indianapolis. **Funded by Chase Pharmaceuticals Corporation. The authors did not include disclosure of potential conflicts of interest.**

**Common Drug Trade Names:** donepezil—*Aricept*; memantine—*Namenda*; solifenacin—*VESIcare*

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**Dopamine-Serotonin Stabilizer in Schizophrenia**

In a phase II trial, RP5063, an investigational dopamine-serotonin stabilizer, was superior to placebo in acute exacerbation of schizophrenia or schizoaffective disorder. The agent has a complex profile of partial agonist and antagonist activity of different dopamine and serotonin receptor subtypes, which differentiates it from approved atypical antipsychotics that are either D2 antagonists or D2 partial agonists.

**Methods:** The multinational study enrolled patients who had received a diagnosis of schizophrenia or schizoaffective disorder ≥1 year prior to screening, who were experiencing an acute exacerbation of ≤4 weeks, and who had a history of response to antipsychotic medication. Study patients were randomly assigned to double-blind, inpatient treatment with 1 of 3 dosages of RP5063 (15, 30, or 50 mg/day), placebo, or 15 mg/day aripiprazole (*Abilify*; included as an active control for sensitivity analysis only). Additional antipsychotics and other psychotropics were not permitted. The primary efficacy endpoint, assessed after 28 days of treatment, was change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score.

**Results:** A total of 234 subjects (mean age, 36 years; 75% men) were randomized; 80% completed the study. Of the patients who withdrew, 3 (1 in the 50 mg RP5063 group and 2 in the aripiprazole group) did so because of adverse effects. About 95% of patients had schizophrenia, and all were markedly ill at baseline (mean PANSS score, 88.2). The 15- and 50-mg doses of RP5063 were associated with significant improvement in the PANSS total score relative to placebo (see table, next page), with statistical differences apparent as early as day 15. The 30-mg dose was numerically superior to placebo, and the lack of significance was attributed to a high rate of discontinuation for reasons that were not related to the medication. Between 37% and 46% of the RP5063 dosage groups had a ≥2-point improvement in the Clinical Global Impression–Improvement scale score by day 28, compared with 19% of the placebo group. RP5063 was associated with improvements in both PANSS positive and negative subscale symptoms. The differences were statistically significant versus placebo for positive symptoms in the 50-mg RP5063 group and for negative symptoms with 15 and 50 mg. There were no significant differences among the groups in changes from baseline on measures of cognition.
Only 1 patient stopped taking RP5063 because of a drug-related adverse event. Insomnia and agitation were the most frequent adverse events associated with RP5063, and extrapyramidal symptoms and akathisia affected ≤10% of the 3 dosage groups. There were no clinically relevant changes in weight, body mass index, or waist circumference within or between the treatment groups. RP5063 was associated with modest decreases in prolactin and with no changes in laboratory measurements or electrocardiogram.

**Discussion:** Although preliminary, these results suggest that RP5063 may be effective in schizophrenia and schizoaffective disorder and have a favorable adverse-effect profile that could improve treatment compliance.

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


*See Reference Guide.

**Antipsychotic Adverse Effects: Patient Perspectives**

Patient perspectives on the burden of adverse effects associated with atypical antipsychotics differ from those of clinicians, according to a focus group- and interview-based study. Because adverse effects differ substantially among second-generation agents, these observations argue for an adverse event-tailored approach when choosing a treatment.

**Methods:** The study was carried out at 2 qualitative research centers in the U.S. Study participants were community residents who had previously volunteered to participate in research opportunities, had a clinician-administered diagnosis of major depressive disorder (n=25) or schizophrenia (n=17), received an atypical antipsychotic within the past year, and had experienced ≥1 adverse event. The study also included 4 psychiatrists who provided direct care to patients with these disorders and had experience prescribing second-generation antipsychotics. The patients with depression and the psychiatrists participated in separate guided focus groups, and the patients with schizophrenia were interviewed individually. Patients were asked to list all side effects they had experienced, estimate their frequency, and rank them according to how bothersome they were. Clinicians listed all adverse effects known to them and then ranked them by frequency, clinical importance, and level of patient-perceived aggravation.

**Results:** The most commonly prescribed antipsychotics for depression were quetiapine and aripiprazole (each 24%), while patients with schizophrenia most often were given a prescription for olanzapine or risperidone (each 24%). The 4 psychiatrists had treated a total of about 600 patients with major depressive disorder and 300 with schizophrenia within the past year, including 35% and 57%, respectively, for whom an atypical antipsychotic was prescribed.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline Mean</th>
<th>Endpoint Mean</th>
<th>Significance vs Placebo</th>
<th>≥30% PANSS Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg RP5063</td>
<td>87.6</td>
<td>67.4</td>
<td>p=0.02</td>
<td>41%</td>
</tr>
<tr>
<td>30 mg RP5063</td>
<td>88.7</td>
<td>73.3</td>
<td>p=ns</td>
<td>26%</td>
</tr>
<tr>
<td>50 mg RP5063</td>
<td>85.9</td>
<td>66.7</td>
<td>p=0.016</td>
<td>39%</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>91.7</td>
<td>82.4</td>
<td>—</td>
<td>16%</td>
</tr>
<tr>
<td>Placebo</td>
<td>89.8</td>
<td>78.4</td>
<td>—</td>
<td>22%</td>
</tr>
</tbody>
</table>

Change from baseline to study end in PANSS total score
The adverse effects most often reported by all patients were cognitive issues including decreased attention and reduced ability to concentrate, remember, or recall (57%); weight gain and/or increased appetite (55%); low energy (48%); excessive sleepiness (36%); and extrapyramidal symptoms (36%). The most bothersome side effects according to both patient groups were cognitive issues (57%), weight gain and/or increased appetite (55%), extrapyramidal symptoms (36%), and sleepiness (36%). The patterns differed somewhat between patient groups: cognitive issues, weight gain, and excessive sleepiness were the most bothersome in patients with depression, while weight gain, low energy, and anxiety were the most bothersome to patients with schizophrenia. Nearly half of patients in each group reported experiencing reduced sexual desire, but this was not generally rated as among the most bothersome effect.

Adverse effects that were considered the most clinically important by ≥2 of the 4 psychiatrists were metabolic syndrome (all 4 physicians), neutropenia (3), and weight gain, hyperglycemia, and QT prolongation (2 each). Physicians rated weight gain as the most bothersome to patients, followed by reduced sexual desire, extrapyramidal symptoms, akathisia, and hormonal issues.

Discussion: This research is part of an effort to develop a tolerability index that will accommodate patient preference for avoiding specific adverse effects of atypical antipsychotics. Low energy, somnolence or sedation, and cognitive issues were more bothersome to patients than clinicians believed. Many of the effects judged clinically significant by psychiatrists are not amenable to patient self-reporting, and other differences may be attributable to clinical terminology or to patients’ greater tendency to attribute their experience to their illness rather than its treatment. Interestingly, cognitive issues, frequently reported by patients as bothersome, are not mentioned in the prescribing information of any of the atypicals studied.


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

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:** 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.

**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 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 are posted at www.alertpubs.com.