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Atypicals for Non-psychotic disorders

By Heidi W. Ashih, MD, PhD
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Dr. Ashih reports no financial relationships with any commercial companies related to this article.

You may have noticed a recent torrent of FDA approvals and clinical trials for atypical antipsychotics in every disorder under the sun–except psychosis. Is this simply an effort by the sponsoring companies to get us to prescribe more antipsychotics? Or are these drugs truly effective for non-psychotic disorders? What's the quality of the evidence?

As the table on page 2 shows, all atypicals are approved for schizophrenia and bipolar mania. Seroquel (quetiapine) & Symbyax (olanzapine-fluoxetine) are the only ones approved for bipolar depression, while Abilify (aripiprazole) is the only one approved for adjunctive treatment of major depression. None are approved for monotherapy of major depression. Some small studies have supported off-label uses of these medications such as Abilify for treatment of borderline personality disorder, and risperidone for irritable aggression of PTSD. Let's review the available evidence for some of the most common non-psychotic uses of the atypicals.

Seroquel for bipolar depression

As we reported in 2007, the BOLDER I & II clinical trials evaluated Seroquel for the treatment of bipolar I or II depression (Calabrese et al., *Am J Psychiatry* 2005;162:1351-1360; Thase et al., *J Clin Psychopharm* 2006;26:600-609). Each study consisted of approximately 500 patients who met criteria for bipolar I or II disorder and suffered from a major depressive episode at the time of enrollment. Patients were randomized to one of three groups: Seroquel titrated to 300 mg QHS over 4 days, Seroquel titrated to 600 mg QHS over 7 days, or placebo. Both studies showed a statistically higher response to Seroquel (approximately 55%) as compared to placebo (37%), with no advantage of the 600 mg dose over the 300 mg dose.

However, several caveats must be noted. First, the data was strongest for depression in bipolar I disorder; one of the trials showed no separation from placebo for bipolar II depression. In addition, the BOLDER studies excluded anyone with substance use within 12 months, acute suicidality, current depression lasting longer than 12 months, other recently treated Axis I diagnoses, or current or previous failure of two full trials (six weeks) of antidepressants. The exclusion of any patients who have failed two prior trials of antidepressants seems particularly restrictive, because the diagnosis of bipolar depression is tricky and can be confused for depression with irritability. By the time you have clearly established a diagnosis of bipolar depression, it is likely that in most cases a patient would have already been through at least

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Learning objectives for this issue: 1. Evaluate the evidence supporting the use of atypical antipsychotics for nonpsychotic disorders. **2.** Describe the major health risks of atypical antipsychotics. **3.** Outline current concepts in the neurobiology of schizophrenia. This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

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two trials of antidepressants – but all such patients were excluded from BOLDER.

Thus, the patients with "bipolar depression" in the BOLDER trials are unlikely to be seen in clinical practice, making it hard to conclude that Seroquel will actually be effective for the patients we see. Also, there are no head-to-head trials comparing Seroquel to mood stabilizers commonly used for bipolar depression, such as Lamictal (lamotrigine) or lithium.

Bottom Line: In patients with bipolar I depression, no significant comorbid disorders and a history of only one prior antidepressant trial, Seroquel (at 300 mg QHS) may be useful; the evidence for bipolar II depression less clear. Warn your patients about substantial weight gain and sedation.

Seroquel for anxiety symptoms

Two small randomized studies compared Seroquel vs. placebo augmentation of SSRIs in patients who had residual symptoms despite monotherapy. One study of 58 patients showed a benefit of Seroquel (mean dose, 182 mg/day) over placebo for both anxiety and depressive symptoms (McIntyre, et al., *Depress Anxiety* 2007; 24(7): 487-94). However, another study of 114 patients showed no benefit of Seroquel (25 mg-100 mg) as an adjunct to fluoxetine for either anxiety or depressive symptoms, although Seroquel was more helpful than placebo for insomnia (Garakani, et al., *Int Clin Psychopharmacology* 2008; 23(5):269-75). Thus, the data on Seroquel augmentation are mixed; higher doses may yield more benefit, but are likely to come with more side effects.

FDA Approved Usages of Atypical Antipsychotics

Atypical antipsychotic	FDA approved indications
Abilify (aripiprazole)	schizophrenia, bipolar mania, agitation in schizophrenia or bipolar I, adjunctive use in major depression
Zyprexa (olanzapine)	schizophrenia, bipolar mania, agitation in schizophrenia or bipolar I, bipolar depression (when combined with fluoxetine as Symbyax)
Seroquel (quetiapine)	schizophrenia, bipolar mania, bipolar depression
Risperdal (risperidone)	schizophrenia, bipolar mania, irritability associated with autistic disorder
Geodon (ziprasidone)	schizophrenia, bipolar mania, agitation in schizophrenia or bipolar I

Seroquel for anxiety disorders

Several smaller randomized placebo-controlled studies have shown no evidence for use of Seroquel either alone or with an SSRI/SNRI for full-fledged anxiety disorders. Though these studies include only 15 to 70 subjects, each showed either no effect or a negative effect of Seroquel on social anxiety disorder, OCD, social phobia, or generalized anxiety disorder. Vaishnavi, et al., *Prog Neuropsychopharmacol Biol Psychiatry* 2007; 31(7): 1464-9; Simon, et al., *Psychopharmacology* 2008;197(4):675-81; Donahue, et al., *J Anxiety Disord*. 2008 Dec 24; Carey, et al., *BMC Psychiatry* 2005;5:5.

However, AstraZeneca has applied to the FDA for the Generalized Anxiety Disorder indication for Seroquel XR (an extended release form of Seroquel). According to the company's website (http://www.astrazeneca-us.com/search/?itemId=2782945), their application is based on the results of four placebo controlled trials evaluating three doses of Seroquel XR: 50 mg/day, 150 mg/day, and 300 mg/day. None of the data have been published, though some positive results were presented at the 2008 APA annual meeting. Whether these results will survive the FDA review process remains to be seen. Given Seroquel's substantial metabolic side effects, we are skeptical that the psychiatric community will embrace it as a treatment for a condition for which there are safer alternative treatments.

Seroquel for insomnia

There are no large, well-designed studies of the Seroquel in the treatment of insomnia. Case reports indicate that dosages of 25-50 mg QHS can be helpful for insomnia of various etiologies. A double-blind placebo-controlled randomized cross-over study of 14 healthy men showed improved sleep architecture, overall sleep time, and sleep efficiency on Seroquel 25 mg- 100 mg given one hour prior to bedtime (Cohrs, et al., *Psychopharmacology* 174:421-429). An open pilot study of 18 outpatients with primary insomnia showed similar benefits, and maintained them for the full six weeks studied (Wiegand et al., *Psychopharmacology* 2008;196(2):337-8). Interestingly, sleep latency was not shortened on Seroquel in either study; people slept better and longer, but didn't fall asleep any faster with Seroquel, a finding that seems inconsistent with common clinical experience.

Abilify for depression augmentation

Two large multi-center randomized, double-blind, placebo controlled trials showed Abilify (aripiprazole) to be an effective adjunct in major depression. (Berman RM et al., *J Clin Psychiatry* 2007;68(6):843-53; Marcus RN et al., *J Clin Psychopharm* 2008;28(2):156-165) Both studies began with eight weeks of antidepressant plus placebo; patients

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Prescribing Atypical Antipsychotics: What are the Risks?

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Dr. Posternak reports no financial relationships with any commercial companies related to this article.

Over the past several years, the use of antipsychotics has expanded dramatically. Aside from the traditional indication, schizophrenia, various members of this class have received FDA approval for bipolar mania, bipolar depression, major depression, and autism, and increasingly they are used off-label for anxiety, insomnia, and agitation.

As with any type of medication that becomes popular quickly, unforeseen side effects have emerged, some minor, others serious. In this article we will briefly review some of the more serious potential risks.

Tardive Dyskinesia (TD). Atypical antipsychotic medications burst onto the scene with much fanfare largely due to their purported lower risk of inducing TD. How well has this promise held up one decade later? In a recent review (Coryell CU et al., *Am J Psychiatry* 2004; 161:414-425) of eleven long-term trials (> one year), investigators confirmed significantly lower annual incidence rates of TD with atypical antipsychotics (0.8%) compared to typical antipsychotics (5.4%). But note that in most of these trials, the typical comparator medication was Haldol, and lower potency typicals pose a lower risk of TD than Haldol. For example, the CATIE study (Clinical Antipsychotic Trials of Intervention Effectiveness) found that the mid-potency typical, Trilafon (perphanizine), did not induce higher rates of TD than atypical agents (Lieberman JA, et al., *NEJM* 2005; 353:1209-23.) While this result has been contested on the grounds that subjects with TD at baseline were not randomized to Trilafon, in fact all statistical comparisons that involved Trilafon excluded patients with TD at baseline. Thus, the patients taking Trilafon were compared with similar patients without TD assigned to atypicals. The risk of TD appears to be cumulative, i.e., higher dosages and longer exposure are associated with higher risk. Other risk factors include the presence of any movement disorders at the initiation of treatment (eg, muscle stiffness, akathisia), the use of anti-cholinergic agents, and substance abuse.

Weight gain, metabolic syndrome, diabetes. We've heard much about the risk of the "metabolic syndrome" (MS) associated with atypicals, but what exactly is the syndrome and how great is the risk? The MS consists of weight gain, increase in waist circumference, increased blood pressure, fasting hyperglycemia, as well as increases in cholesterol and triglycerides (Meyer JM et al., *Schizophr Res* 2008; 101:273-286). Each of these factors in turn contributes to an increased risk of developing diabetes and/or cardiovascular disease. Recent data confirm our long-standing impression that differences exist between the various atypicals. A weight gain of about 10 pounds in 10 weeks can be expected with the worst offenders – Zyprexa (olanzapine) and clozapine, and may continue to increase thereafter until plateauing four to five months after initiating treatment (Allison DB et al., *Am J Psychiatry* 1999;156:1686-1696). Several independent studies have confirmed an increase risk of developing diabetes mellitus with the use of some atypicals, primarily Zyprexa and clozapine; fortunately, the increased risk appears to be small, with an estimated attributable risk of only two to three per 1,000 (Lambert BL, *Pharmacoepid Drug Saf* 2005;14: 417-425). Interestingly, older patients do not appear to be at increased risk for diabetes with these agents. The hypothetical explanation for this surprising finding is that atypicals may not actually cause diabetes to develop *de novo*, but only uncover diabetes in those predisposed to develop it. Elderly patients may therefore be past the at risk window for developing diabetes.

If you don't currently monitor for the MS, you're not alone: a recent evaluation of a large managed care database revealed that few clinicians do (Haupt DW, *Am J Psychiatry* Haupt et al., AJP in Advance, Jan 15, 2009). Part of this may be due to a lack of awareness of what we should actually be doing, so below we report recently published consensus guidelines (Meyer JM and Koro CE, *Schizophr Res* 2004;70:1-17).

Whenever an antipsychotic medication is first prescribed, record the patient's baseline measurements of weight, waist circumference, and fasting plasma glucose, lipids, triglycerides.

1. For lower risk agents (ziprasidone, aripiprazole, and possibly risperidone), check weight, waist circumference, glucose, lipids, and triglycerides **annually**.

2. For higher risk agents (Zyprexa, clozapine, Seroquel), check the same profile **quarterly** for the first year, which may then be decreased to **semi-annually** thereafter if dyslipidemia has not occurred.

Cardiac arrhythmia and risk of death. After reviewing 17 short-term atypical antipsychotic trials in the elderly, a Public Health Advisory issued by the FDA in 2005 noted a doubling of the risk of death in geriatric patients with dementia. A "black box" warning was added for each of the atypicals, and this combined with a lack of any efficacy data has begun to curtail their use in this population. A subsequent analysis of the Tennessee Medicaid program revealed both atypical and typical antipsychotic medications increase the risk of sudden death in the elderly (Wang PS et al., *NEJM* 2005; 353:2335-2341). More recently, a large retrospective study (Ray WA et al., *NEJM* 2009; 360:225-235) found that antipsychotic medications (both typical and atypical) increase the risk of sudden cardiac death, *regardless of age*, by about two-fold, with higher doses being associated with a higher risk for each agent studied. An accompanying editorial (Schneeweiss S and Avorn J, *NEJM* 2009; 360:294-296) infers that this risk causes about three deaths per 1,000 patient years of treatment with antipsychotic medications (this means that if you had 333 patients on antipsychotics, you could expect to cause one sudden cardiac death during that year). In comparison, the rate of death from clozapine due to

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Q&A With the Expert

This Month's Expert:

The Neurobiology of Schizophrenia

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Dr. Jarskog has disclosed that he has no relevant relationships or financial interests in any commercial company pertaining to this educational activity. Dr. Jarskog has disclosed that glycine, D-serine, D-cycloserine, and Glu2/3 receptor agonists are not FDA-approved for the treatment of schizophrenia.

TCPR: Dr. Jarskog, for many years the dopamine theory of schizophrenia has been dominant in the field. What is the current status of that theory?

Dr. Jarskog: The dopamine theory was originally based on the purported mechanism of action of antipsychotic drugs, which is dopamine receptor antagonism. Since these drugs improve psychotic symptoms in patients with schizophrenia, it seemed logical to assume that high levels of dopamine in some part of the brain are a cause of the illness. For a long time, this indirect support was the only real evidence of elevated dopamine in schizophrenia. But, with advances in imaging techniques such as SPECT and PET along with development of dopamine 2 receptor radioligands, it became possible to measure actual baseline levels of dopamine *in vivo* in patients, and it was found that dopamine levels in striatum were approximately twice as high in patients with schizophrenia with acute psychotic symptoms (Abi-Dargham et al., *PNAS* 2000; 97:8104-8109). This was found both in patients who had been previously treated as well as in first-episode neuroleptic-naïve patients, as compared to healthy controls. This was really a dramatic and seminal finding.

TCPR: Does this finding change the way we think about the dopamine hypothesis?

Dr. Jarskog: It doesn't necessarily change our thinking, but it validates the fact that the dopamine receptor is an appropriate treatment target in schizophrenia. But another interesting finding from these studies was that acutely psychotic patients with the highest levels of baseline dopamine responded best to treatment. This suggests that there may be different types of schizophrenia. Patients can have more or less excess dopamine in the subcortical region of the brain.

TCPR: So this could be the beginnings of the first example of the Holy Grail of a lab test in psychiatry where one could envision using a PET scan to determine the amount of dopamine in the caudate putamen and help you decide whether or not a particular patient is going to respond to treatment.

Dr. Jarskog: That is right, in theory. It has some promise, but it is certainly not just around the corner.

TCPR: Aside from this finding, hasn't there been research showing that certain regions of the brain have too much dopamine and others too little dopamine in schizophrenia?

Dr. Jarskog: Right. We believe that the subcortical regions have too *much* dopamine, and there is evidence–although less so–that there is too *little* dopamine in the cortex, especially the frontal cortex.

TCPR: So we basically have a picture of too much dopamine subcortically, which I assume might cause positive symptoms; and too little dopamine in the cortex causing cognitive impairment and negative symptoms.

Dr. Jarskog: Right, although negative symptoms are less well understood in terms of a mechanism.

TCPR: What about the movement problems, the EPS side effects; where do these come from?

Dr. Jarskog: That is due to blocking dopamine receptors in the dorsal striatum, the nigro-striatal pathway. There is a significant hub of neurons controlling gross and fine motor activity, coordination and initiation of movement in that region, and so when you block these D2 receptors, it causes Parkinsonian-like side effects. If you block over 80% of the available D2 receptors in the dorsal striatum you are mimicking Parkinson's disease where symptoms such as tremor and muscle rigidity emerge after loss of about 80% of dopamine neurons.

TCPR: Getting back to the basic neurobiology, in one of your papers, you wrote that, "Synaptic dysconnectivity has emerged as a core neuropathological deficit in schizophrenia." Can you explain this?

Dr. Jarskog: This refers to emerging evidence that there is something wrong with the neuronal synapses in schizophrenia. In post-mortem neurophathological studies, the number of dendritic spines is substantially reduced in the prefrontal cortex in schizophrenia (Glantz and Lewis, *Archives of General Psychiatry* 2000; 57:65-73). There is also evidence of a substantial reduction in the number of proteins specific to synaptic structure and function, such as a 30%-40% reduction of the amount of synaptophysin in the frontal cortex.

TCPR: What is "synaptophysin"?

Dr. Jarskog: Synaptophysin is a protein that is present in almost all synapses, so it is a good marker for synaptic content. Its exact function is not understood but it probably contributes in neurotransmitter release, and a reduction of 30%-40% of synaptic content is really a substantial reduction.

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Q & A With the Expert

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TCPR: I have also heard about studies showing a loss of brain volume over time in schizophrenia.

Dr. Jarskog: Yes. The data show that among patients who are prodromal for schizophrenia (who do not yet meet the criteria for the diagnosis), those who went on to develop psychosis had reductions in gray matter in specific areas of the cortex (Pantelis et al., *Lancet* 2003; 361:281-288). Those that did not become psychotic had no significant change in gray matter volume. Other studies have focused on patients who have been studied longitudinally after the onset of psychosis, and many have also shown some degree of gray matter loss (Cahn et al., *Archives of General Psychiatry*, 2002: 59:1002-1010).

TCPR: I assume the patients in these studies were receiving antipsychotics?

Dr. Jarskog: Yes, and it is not clear whether the loss of gray matter is caused only by the underlying disease or also in part by the use of certain antipsychotics. But there is preliminary evidence from studies of childhood onset schizophrenia that some of this gray matter loss may be related to genetic factors specific to the illness.

TCPR: What is the role of glutamate and GABA in the neurobiology of schizophrenia?

Dr. Jarskog: The initial interest in glutamate came from the observation that the drug of abuse PCP (phencyclidine) is a very strong NMDA (N-methyl-D-asparate) glutamatergic receptor antagonist, and it can temporarily cause all the symptoms of schizophrenia in an otherwise healthy individual. So this led to the theory that schizophrenia may be related to a low glutamate state.

TCPR: What does glutamate normally do in the brain?

Dr. Jarskog: Glutamate is the main excitatory neurotransmitter and glutamatergic neurons are found throughout the brain. Normally, glutamate neurons in the cortex send axons down to dopamine neurons in the mesocortical areas, and when these neurons are stimulated, they send inputs back up to the frontal cortex. But in schizophrenia, there seems to be a decrease in both the number and activity of dopamine neurons projecting up into the frontal cortex. So why would there be such a decrease? The theory is that reduced glutamate activity in the cortex indirectly leads to this decreased dopamine activity.

TCPR: And where does GABA fit into this scheme?

Dr. Jarskog: Glutamate neurons in the cortex also normally project onto subcortical GABA (gamma amino butyric acid) neurons. GABA is the main inhibitory neurotransmitter of the brain. Glutamate neurons normally stimulate GABA neurons that in turn *inhibit* dopamine neurons that extend into the striatum (the so-called mesolimbic dopamine neurons). So, if you have reduced glutamate signaling in schizophrenia, you have reduced activation of these GABA neurons, leading to less inhibition of mesolimbic dopamine neurons, allowing for more dopamine to be transmitted into the striatum, which is consistent with the subcortical *hyper*dopaminergic state.

TCPR: That's quite an elaborate mechanism! Can you tell us the significance?

Dr. Jarskog: Sure. The theory is that in schizophrenia too little glutamate in the cortex leads to less stimulation of mesolimbic GABA neurons, thereby allowing too much dopamine to be released in the mesolimbic area, which leads to positive psychotic symptoms like hallucinations and delusions. But in the cortex, the mechanism is somewhat different: too little glutamate, too little excitation of mesocortical dopamine neurons, and therefore too little dopamine released back in the cortex, accounting for cognitive deficits and possibly negative symptoms.

TCPR: While this is all fairly complex, the good news is that the low glutamate hypothesis dovetails with the dopamine hypothesis.

Dr. Jarskog: Correct, and this has been reassuring to people and it has also spawned a great interest in modulating the glutamate system therapeutically to try to achieve symptomatic response using this mechanism. From what I have said already, it is clear that if you modulate glutamate you ultimately end up affecting dopamine as well.

TCPR: Have any glutamate stimulators been tested in schizophrenia?

Dr. Jarskog: There are a number of different compounds such as glycine, D-serine, and D-cycloserine. These are all indirect agonists at the NMDA receptor (the major glutamate receptor). The problem with glutamate receptors is that if you directly activate the NMDA receptor, you can get excitotoxicity because you have released too much glutamate and that causes cell death. You always have to be concerned about the seizure potential of drugs that modulate glutamate. So we use indirect agonists that just kind of nudge the glutamate receptor into action, and we call them "glutamate modulators."

TCPR: Are they effective in schizophrenia?

Dr. Jarskog: One of the larger studies was published last year, in which glycine and D-cycloserine were tested as an augmentation strategy for patients on antipsychotics, and that study was negative (Buchanan et al., *American Journal of Psychiatry*, 2007; 164:1593-1602). There was no significant effect on cognitive or negative symptoms, which were the main outcome variables. That was disappointing, but we are early in trying to target glutamate receptors. There was another study in *Nature Medicine* a little over a year ago that tested a metabotropic Glu2/3 receptor agonist as monotherapy, and it looked almost as good as olanzapine in acutely psychotic patients with schizophrenia (Patel et al., *Nature Medicine*, 2007; 13:1102-1107). So, it is a work in progress. It remains to be seen if someone who doesn't respond to a conventional dopamine-based antipsychotic could respond to a glutamate-based treatment. That is certainly what we hope.

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Research Updates IN PSYCHIATRY

Section editor, Glen Spielmans, PhD

ANTIDEPRESSANTS

Two New Meta-Analyses Compare Antidepressants

Two recent meta-analyses compared second-generation antidepressants (SGADs) to each other regarding efficacy and safety. One study (Cipriani A et al., *Lancet* 2009; online ahead of print), compared 12 SGADs across 117 controlled trials consisting of 25,298 participants. The researchers used data at the end of eight weeks whenever possible and defined treatment response as 50% or greater improvements on the Hamilton Depression Rating Scale (HDRS) and the Montgomery-Asberg Rating Scale (MADRS), or much improved or very much improved on the Clinical Global Impressions Scale (CGI). Two primary statistical methods were used: a) a traditional meta-analysis of studies that directly compared various ADs to each other and b) a set of complex statistical methods that incorporated data from all studies, even those that did not directly compare the medications. For example, to determine the efficacy and safety of Zoloft (sertraline) versus Paxil (paroxetine), they examined a) studies that directly compared the two drugs and b) studies that compared Zoloft or Paxil to other SGADs. Few differences were found in the direct comparisons: most notably, Prozac (fluoxetine) performed worse than Zoloft, Effexor (venlafaxine), and Remeron (mirtazapine). When incorporating data from direct and indirect comparisons of the drugs, the researchers found that Remeron, Lexapro (escitalopram), Effexor, and Zoloft were significantly more efficacious than Cymbalta (duloxetine), Prozac, Luvox (fluvoxamine), and Paxil. Overall, the authors concluded that Zoloft and Lexapro fared best in combined efficacy and tolerability.

The Agency for Healthcare Research and Quality (AHRQ) sponsored a similar comprehensive meta-analysis of SGADs (Garltehner G et al. *Ann Intern Med* 2008:149;734-750). They found that efficacy differences between newer ADs were negligible, although Remeron had a faster onset of action than Celexa (citalopram), Prozac, Paxil, or Zoloft. They also found that Remeron leads to more weight gain than other medications, that Effexor is linked to higher rates of nausea and vomiting, and that Paxil and Effexor may have the highest rates of discontinuation symptoms. Additionally, Paxil was linked to higher rates of sexual dysfunction than Prozac, Fluvox, Serzone (nefazodone), and Zoloft. Unsurprisingly, Wellbutrin (bupropion) was linked to lower rates of sexual dysfunction than other medications. Both meta-analyses found that Lexapro was more efficacious than Celexa, but the Garltehner et al study concluded that the difference between the two drugs was quite small.

TCPR's Take: The *Lancet* study took more of a "stand" than the AHRQ study, concluding that Zoloft and Lexapro, by slim margins, were the winners in terms of combined efficacy and tolerability. The AHRQ study was less inclined to name a winner, but did provide some useful (though unsurprising) details about relative side effects of different agents. One can argue that the AHRQ study is the more accurate of the two, since these researchers analyzed more raw data, including response rates, change scores, and individual side effects. The *Lancet* researchers looked only at response rates and used rates of drop-out from studies as a proxy for adverse events. Neither study appeared to be influenced by conflicts of interest. Contrary to some papers published over the last decade, neither of these comprehensive reviews found Effexor to be more effective than SSRIs. Ultimately, it appears that our antidepressant prescribing decisions must still be based on a mixture of efficacy data, side effects properties, drug-drug interactions, and clinical judgment.

Atypicals for Non-psychotic disorders

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who did not respond to this treatment were then randomized to receive either Abilify or placebo for an additional six weeks. The average doses for the two studies were Abilify 11 mg and 11.8 mg daily. After six weeks of augmentation, the remission rates on Abilify were 25.4% and 26% (from the two studies), while the remission rates on placebo were 15.2% and 15.7%. This 10% difference was statistically significant, and the FDA granted approval for Abilify as an add-on treatment for depressed patients who have not responded to a standard antidepressant. However, the clinical significance of these findings was questioned in letters to the editor, one of which pointed that, in one of the studies, Abilify produced only a tiny 2.8 point improvement in the MADRS depression scale, and that Abilify did not outperform placebo on patient self-report depression measures in either study (Carroll BJ, *J Clin Psychopharm* 2009;29:91). In addition, Abilify caused akathisia in 25% of patients, a worrisome side effect for chronically depressed patients.

TCPR VERDICT: *Seroquel: Probably useful for bipolar I depression and insomnia; anxiety use questionable. Abilify: Data for depression too weak to have deserved its FDA indication.*

CME Post-Test

To earn CME or CE credit, you must read the articles and complete the quiz below, answering at least four of the questions correctly. Visit www.TheCarlatReport.com to take the test online and print your certificate or mail a photocopy or fax the completed page (no cover sheet required) to **Clearview CME Institute, P.O. Box 626, Newburyport, MA 01950**; **fax (978) 499-2278**. For customer service, please call (978) 499-0583. Only the first entry will be considered for credit and must be received by Clearview CME Institute by February 28, 2010. Acknowledgment will be sent to you within six to eight weeks of participation. This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of the Clearview CME Institute. Clearview CME Institute is accredited by the ACCME to provide continuing medical education for physicians. Clearview CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. Clearview CME Institute maintains responsibility for this program and its content. Clearview CME Institute designates this educational activity for a maximum of one (1) AMA PRA Category 1 Credit™ or 1 CE for psychologists. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

Please identify your answer by placing a check mark or an X in the box accompanying the appropriate letter. Note: learning objectives are listed on page 1.

1. Seroquel (quetiapine) is FDA approved for: (Learning Objective #1)

[ ] a. Schizophrenia and bipolar mania.

[ ] b. Schizophrenia, bipolar mania, and bipolar depression.

[ ] c. Schizophrenia, bipolar mania, bipolar depression and generalized anxiety disorder.

[ ] d. Schizophrenia and maintenance treatment in bipolar disorder.

2. In studies of Abilify (aripiprazole) for adjunctive treatment of depression: (L.O. #1)

[ ] a. Abilify was robustly superior to placebo on all outcome measures.

[ ] b. Abilify was not statistically superior to placebo.

[ ] c. Abilify was modestly superior to placebo on clinician ratings, but not patient ratings.

[ ] d. Abilify caused the same rate of akathisia as placebo.

3. According to a recent study, antipsychotics triple the risk of sudden cardiac death. (L.O. #2)

[ ] a. True [ ] b. False

4. The risk of developing tardive dyskinesia from atypical antipsychotics is: (L.O. #3)

[ ] a. Similar to the risk from conventional antipsychotics.

[ ] b. Lower than the risk from perphenazine, but higher than the risk from haloperidol.

[ ] c. Approximately 5% per year.

[ ] d. Approximately 1% per year.

5. According to the glutamate theory of schizophrenia, reduced glutamate activity leads to decreased dopamine activity in the frontal cortex. (L.O. #3)

[ ] a. True [ ] b. False

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Your evaluation of this CME/CE activity (i.e., this issue) will help guide future planning. Please respond to the following questions:

1. Did the content of this activity meet the stated learning objectives? L.O.#1: [ ] Yes [ ] No L.O.#2: [ ] Yes [ ] No L.O.#3: [ ] Yes [ ] No
2. On a scale of 1 to 5, with 5 being the highest, how do you rank the overall quality of this educational activity? [ ] 5 [ ] 4 [ ] 3 [ ] 2 [ ] 1
3. As a result of meeting the learning objectives of this educational activity, will you be changing your practice performance in a manner that improves your patient care? Please explain. [ ] Yes [ ] No

4. Did you perceive any evidence of bias for or against any commercial products? Please explain. [ ] Yes [ ] No

5. How long did it take you to complete this CME/CE activity? ___ hour(s) ___ minutes
6. **Important for our planning:** Please state one or two topics that you would like to see addressed in future issues.

Prescribing Atypical Antipsychotics: — *Continued from Page 3*

agranulocytosis is about 0.2 per 1000 years of treatment – less than one tenth the risk. Because we have instituted a rigorous risk-management program (ie, regular blood draws) on account of this level of risk with clozapine the authors argue that it only makes sense that we monitor EKGs for antipsychotic medications. Specifically, they recommend obtaining baseline EKGs and repeating shortly after starting the medication to rule out QT prolongation. While it is likely some readers will balk at obtaining EKGs for all their patients on antipsychotics, we feel that this may not be too much of a price to pay in terms of inconvenience if it can prevent a rare side effect as dire as sudden death. But it will likely be a judgment call for individual patients – in general, the higher the dose, and the older and more frail the patient, the more crucial it is to check an EKG.

TCPR VERDICT: ***Atypicals: Lower TD risk is counterbalanced by high risk of metabolic syndrome and cardiac arrhythmia.***

CORRECTION

In the February 2009 issue of *TCPR*, one of the authors of the article, "*Breast Feeding and Psychiatric Medications: An Overview*," was mistakenly omitted. The second author of that article is Deborah Kim, MD, Assistant Professor, University of Pennsylvania Department of Psychiatry. Dr. Kim reports no financial relationships with any commercial companies related to the CME article.

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This Month's Focus: **Antipsychotic Roundup 2009**

Next Month in *The Carlat Psychiatry Report*: Health Policy Issues in Psychiatry, including reviews of mental health parity, the FDA, and health insurance policy of relevance to psychiatrists.