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Invega: Can You Say "Patent Extender"?

Janssen's marketing team apparently missed the fact that the word in the English language that sounds most like "Invega" is "inveigle," meaning "to entice, lure, or ensnare by flattery or artful talk or inducements" (*www.dictionary.com*). You may have already heard some "artful talk" from your Janssen reps, who are keen to have you convert your patients from Risperdal to Invega. Will you be doing your patients a favor by taking the plunge? Or will you simply be giving them the same wine in a fancier bottle?

Approved by the FDA on December 20, 2006, Invega is an extended-release formulation of paliperidone, which is the major active metabolite of Risperdal. Invega uses the same delayed-release technology as Concerta, namely, the OROS osmotic drug-release technology. The Invega capsule contains three compartments: two layers of paliperidone and one "push" layer with an osmotically active polymer. Surrounding the whole thing is a semi-permeable membrane that allows water to seep in, causing the drug to slowly escape through a precision-drilled orifice at the one end of the tablet. The result? Twenty-four hours of continuously released paliperidone.

The bottle *is* fancier, but will it make any difference to your patients? The best way to answer this question would be to do a double-blind study comparing Risperdal with Invega. Unfortunately,

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Focus of the Month:
Antipsychotic Roundup 2007

Do Second-Generation Antipsychotics Treat Depression? An Update

By Shalom Feinberg M.D.,
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A lot has happened in the four years since *TCPR* first looked at the role of second-generation antipsychotics (SGAs) in the treatment of depression (*TCPR*, Feb. 2003). The literature has mushroomed, and recently the FDA approved Seroquel (quetiapine) for the treatment of bipolar depression. In this article, we'll take a hard look at the most recent data on the effectiveness of SGAs for depression in its various guises, including treatment-resistant depression (TRD) and bipolar depression (BD).

Seroquel for Bipolar Depression: The BOLDER Studies

Seroquel was approved for bipolar depression on the evidence from two eight-week double-blind placebo-controlled studies called BOLDER I and II, which were funded by AstraZeneca. In its zeal to create a memorable acronym, AstraZeneca derived the study name in the following circuitous manner: BipOLar 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 meeting criteria for bipolar I or II disorder and suffering from major depression at the time of enrollment. Patients were randomized to one of three conditions: Seroquel titrated to 300 mg/HS over four days, Seroquel titrated to 600 mg/HS over one week, or placebo. Exclusion criteria included substance abuse, acute suicidality, refractory depression, chronic depression lasting longer than 12 months, or other recently treated Axis I diagnoses. Unfortunately, a sizeable minority of our real-life patents would not meet the inclusion criteria, which limits the generalizability of the results.

At the eight-week endpoint, both studies showed a statistically significant benefit of Seroquel when bipolar I and bipolar II depression were combined: in BOLDER I there was a 58% response rate to Seroquel vs. a 36% response to placebo, while

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Dr. Feinberg has disclosed that he has no significant relationships with or financial interests in any commercial companies pertaining to this educational activity.

Learning objectives for this issue: 1. Contrast the new antipsychotic Invega with Risperdal. 2. Outline the evidence for the antidepressant properties of the second-generation antipsychotics. 3. Describe a rationale for deciding on a specific antipsychotic for a given patient.

This CME activity is intended for psychiatrists, psychiatric nurses, and other health-care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

Invega: Can You Say "Patent Extender"?

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Janssen chose not to conduct such studies, presumably because the company was afraid of what it might find. So we are left with the task of comparing the two drugs based on other research the company has conducted.

Extended-release formulation. The least controversial difference between the two medications is that Invega is released gradually into the bloodstream, reaching a peak at 24 hours, whereas Risperdal reaches its peak in about one hour. The fact is, however, that when your patients take plain old Risperdal, their livers gradually convert it *into* paliperidone, with the peak paliperidone concentration occurring about three hours after patients take the Risperdal. Thus, although Risperdal reaches its peak in one hour, it gradually releases (via its metabolism) paliperidone over a several-hour time span.

Nonetheless, 24 hours of continuous release is genuinely smoother than a few hours of delayed release, and it theoretically would lead to fewer initial side effects in some patients. But the corresponding potential *dis*advantage of Invega is that it may not quell acute agitation and anxiety, whereas Risperdal often does.

Is Invega easier to dose? Invega's package insert suggests starting with 6 mg QD, which it describes as an effective dose in many patients. Risperdal, with its 24-hour half-life, is also often dosed once daily, so there's no convenience advantage for Invega there. We usually have to titrate Risperdal upward to reach the effective dose of 3-4 mg/day. By contrast, Janssen says that we can start and end with 6 mg, no dose adjustments needed. How believable is this claim? Not very.

For example, we know that in two of the pivotal FDA trials, Invega 6 mg was less effective than Zyprexa 10 mg QD, though the studies did not include enough patients to assess *statistical significance* between the two drugs (Kane, et al., *Schizophrenia Research* 2007;90:147-161 and Marder, et al., abstract presented at ACNP meeting 2005). In both of these studies, researchers had to push the dose of Invega up to *12 mg QD* to equal or exceed Zyprexa's efficacy (imagine how poorly Invega would have looked if it had been compared with Zyprexa 15 mg or 20 mg/day, doses more commonly used in schizophrenia). Invega at 12 mg QD is not well tolerated, resulting in a 26% incidence of EPS, as opposed to a 10% incidence on Invega 6 mg QD and 11% on placebo in the Invega studies.

The bottom line on dosing is that many patients will likely end up needing *more* than 6 mg of Invega, and with upward titration comes side effects. Uh oh–I'm having a flashback to Lexapro's launch, when we were told that Lexapro 10 mg QD would have the same efficacy as Celexa 40 mg QD, with fewer side effects. It didn't quite turn out that way!

Article Summary

The Subject: Invega, an extended-release version of the main metabolite of risperidone, was recently approved for the treatment of schizophrenia.

The Background: Risperidone, Janssen's current antipsychotic, will be going off patent in about a year. Invega will have a longer patent life and will allow Janssen to continue to offer a profitable antipsychotic.

The Bottom Line: Other than causing no drug-drug interactions, Invega has no clear advantages over risperidone and appears to have the disadvantage of causing more cardiac side effects.

Fewer drug-drug interactions. Risperdal is metabolized in the liver primarily by 2D6, so its levels can be affected by drugs that affect 2D6. For example, carbamazepine *decreases* Risperdal levels by about 50%, whereas the 2D6-inhibitor Prozac *increases* Risperdal levels 2.5-2.8 fold. Invega, on the other hand, is metabolized primarily by the kidneys, and so is not subject to drug interactions, nor does its dose need adjusting in patients with liver disease. These are both potential advantages of Invega.

Side effects. EPS: Invega and Risperdal are comparable, though at the more robust dose range of 9 mg to 12 mg QD Invega leads to more EPS than is reported for Risperdal at doses of 6 mg to 8 mg QD (see package inserts of both medications for this data). **Cardiac:** Invega caused QT widening of 12 msec more than placebo at the highest dose tested (8 mg of immediate-release paliperidone, which results in maximum blood levels double that of 12 mg of Invega), similar to Geodon's reported 10 msec drug-placebo difference on 160 mg daily. Is this a big deal? After hundreds of thousands of Geodon prescriptions, most prescribers have become comfortable with its cardiac safety, and we expect the same of Invega. Nonetheless, this is one disadvantage not shared by Risperdal. Invega also caused a 12%-14% incidence of **tachycardia**, about double that of placebo. This has *not* been reported as a side effect of Risperdal. **Hyperprolactine-mia:** No differences between Invega and Risperdal were noted. Both drugs frequently cause hyperprolactinemia, although significant clinical consequences, such as lowered libido in men and amenorrhea in women, are uncommon. **Weight gain:** Probably no difference; both drugs can cause moderate weight gain, but not at the level of Zyprexa or Clozaril.

Cost. Risperdal goes off patent in June of 2008, and we will start seeing cheaper generic risperidone soon thereafter. Until then, Janssen will actually price Invega slightly below Risperdal (and will stop providing Risperdal samples) in order to encourage psychiatrists to prescribe Invega. The company's strategy is to have psychiatrists convert as many patients as possible to Invega before cheap risperidone comes on the market.

Bottom line. When all is said and done, Invega looks like Risperdal *without* drug-drug interactions, but with *more* QT interval prolongation, *more* tachycardia, *possibly more* EPS, and the same amount of *hyperprolactinemia*. Not a very pretty picture. Get ready to be Invega'ed–I mean inveigled–by your neighborhood drug rep soon.

TCPR VERDICT: ***Invega: How fancy the bottle!***

Do Second-Generation Antipsychotics Treat Depression? An Update

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BOLDER II posted a 52% response rate to Seroquel vs. a 37% placebo response rate. Both studies found that dosing at 600 mg/day was no more effective than 300 mg/day. Treatment-emergent mania, a concern when prescribing antidepressants to bipolar patients, did not occur more frequently with Seroquel, at least over the short eight-week trial period.

While the Seroquel data appears to be robust, there are a few caveats to keep in mind. First, in breaking out the data it is clear that **only one of the two studies – BOLDER II – found a significant benefit for Seroquel in bipolar II depression; BOLDER I did not.** Second, Seroquel has not been directly compared with other active antidepressant agents or with mood stabilizers such as lamotrigine or lithium. Third (and crucially), there have been no non-industry sponsored replications of these studies. We emphasize this point because AstraZeneca fully planned the design and selected the statistical methodology used in BOLDER. In an apparent attempt to draw comparison to Lilly's Symbyax study (discussed below) AstraZeneca used similar statistical methodology; it opted for the newer MMRM (mixed-effects model repeated measure) method rather than the standard LOCF (last observations carried forward) technique in its statistics. As *TCPR* discussed in a past article on Cymbalta (duloxetine; Jan. 2004), the MMRM approach *may* enhance reported effect sizes, making active treatments look better than they would otherwise appear if using LOCF.

The bottom line on Seroquel is that it may be a good option as monotherapy for bipolar depression, though more clearly for BP I than BP II patients. In otherwise medically healthy patients, we recommend a fairly rapid dosing schedule, increasing by 50 mg increments over four to seven days, up to 300 mg QHS. Warn your patients about initial sedation while reassuring them that most people accommodate to this intense side effect over time.

What Happened to Symbyax?

Of course, Seroquel is not the first SGA found to be effective for depression: in 2003, the FDA approved Symbyax (a combination of Zyprexa and Prozac) for the treatment of bipolar depression. But we've rarely prescribed it, and chances are you haven't prescribed it much either. Why not? First, it offers limited flexibility as a fixed-dose combination; second, Zyprexa is associated with the metabolic syndrome; and finally, there is concern that the Prozac component might precipitate antidepressant-induced mania in bipolar patients.

How does the Seroquel BOLDER data stack up against the Symbyax data? It's pretty similar. The pivotal study reported a 56% response rate on Symbyax vs. a 30% response rate on placebo (Tohen, et al., *Arch Gen Psychiatry* 2003;60:1079-1088). However, the Symbyax study also compared Zyprexa monotherapy (that is, Symbyax minus the Prozac) with placebo, which is a fairer comparison with the Seroquel monotherapy data. Zyprexa alone did not do very well, posting a 39% response rate, only marginally (but statistically) better than placebo. The implication is that Seroquel monotherapy is a more effective antidepressant treatment than Zyprexa monotherapy, but only a head-to-head comparison of the two will tell.

How About Risperdal?

Although Risperdal has been around longer than any other atypical (except for clozapine), there have been very few studies of this agent for bipolar depression. The only controlled study that we could find on this topic (Shelton and Stahl, *J Clin Psychiatry* 2004;65:1715-1719) was a double-blind trial in which patients continued on prior mood stabilizers and were randomized to either Paxil (paroxetine) or Risperdal monotherapy, or a combination of these two drugs. All three treatments were equally but modestly effective. However, the sample size of only 30 patients was meager, and the study lacked a placebo control, so it offers no definitive conclusions. In the recent multi-center NIMH-funded STEP-BD study of bipolar disorder, Risperdal fared rather poorly as add-on (or augmentation) treatment for refractory bipolar depression (i.e., a less than 5% response rate) in an open-label comparison to lamotrigine and inositol (Nierenberg et al, *Am J Psychiatry* 2006; 163:210-216).

Do SGAs work for Treatment-Resistant Depression?

Until last year, the literature on SGAs for TRD primarily consisted of open studies showing a positive therapeutic role for every SGA as an augmentation agent to an antidepressant. There was only one published double-blind study; it endorsed Zyprexa augmentation of fluoxetine over continued monotherapy with either fluoxetine or Zyprexa (Shelton, et al., *Am J Psychiatry* 2001;158:131-134). But now Zyprexa has some competition. Controlled studies have been presented at major meetings describing successful augmentation of antidepressants with Risperdal and Seroquel, along with

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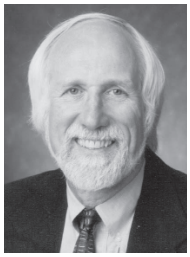
Q&A With the Expert

This Month's Expert:

William Carpenter, M.D.

Choosing the Right Antipsychotic



Editor-in-Chief, Schizophrenia Bulletin*; Professor, Psychiatry and Pharmacology, and Director, Maryland Psychiatric Research Center University of Maryland School of Medicine, Baltimore*

Dr. Carpenter has disclosed that he has served as a consultant to Alza, AstraZeneca, Janssen Pharmaceutica, Merck, Pfizer, and Solvay/Wyeth, and that he has received less than $5,000 for each consultancy. Dr. Carlat has reviewed and edited the content to ensure a balanced and unbiased presentation.

TCPR: Dr. Carpenter, as Editor-in-Chief of *Schizophrenia Bulletin* and a long-time researcher in the field, I'm sure you've seen trends come and go. Lately, we've been hearing a lot about how the older, conventional antipsychotics may be just as good as the newer atypicals. What's your take?

Dr. Carpenter: Interestingly, the CATIE trial was only the latest data set to weigh in on this issue. Even before this, there was the PORT literature review, which was updated in 2002. Neither PORT nor the Cochrane Library Reviews found superiority of atypical antipsychotics over conventionals.

TCPR: And yet, for many years, atypicals have been prescribed much more than the conventionals. What has driven this pattern?

Dr. Carpenter: One of the reasons is that psychiatrists had a lot of negative experience using excessive doses of first-generation drugs and then noticing the immediate adverse effects, such as depression, cognitive impairment, and unpleasant EPS side effects. However, the CATIE trial showed that if you put patients on a moderate dose of medium-potency neuroleptic (about 20 mg QD of Trilafon/perphenazine) they do about as well as patients on the newer atypicals, and with relatively few side effects.

TCPR: The CATIE results also seemed to show that Zyprexa (olanzapine) was more effective than the other atypicals, but there have been some methodological critiques of this finding.

Dr. Carpenter: Right, and one of the issues is that more patients came into the study already taking Zyprexa than any other agent. So some of the greater "effectiveness" of Zyprexa may have been related to the fact that many of the patients who entered the study were already tolerant of that drug, and so they lasted longer before requiring discontinuation. The other issue is that if the CATIE study were done today, it is very unlikely that Zyprexa would win on the "time to discontinuation" measure, because doctors are now more sensitive to metabolic effects and weight gain, and thus are likely to switch from Zyprexa to another agent more quickly.

> **"If the CATIE study were done today, it is very unlikely that Zyprexa would win...because doctors are now more sensitive to metabolic effects and...thus are likely to switch from Zyprexa to another agent more quickly."**
>
> **– William Carpenter, M.D.**

TCPR: But, bottom line, do you feel that Zyprexa is more efficacious in some way than the other atypicals?

Dr. Carpenter: The empirical evidence is mixed. There are a number of circumstances where Zyprexa has not appeared to be superior to comparative drugs, including when the doses of haloperidol were low. And when it appeared to be superior, it has been in large studies where there was only a modest difference, so it is not clear that the difference is clinically significant. So, personally, my own view is that the dopamine antagonists all seem to have very similar efficacy. They do differ in their overall profiles; I think some drugs are more likely to produce cognitive or depressive side effects and Zyprexa may not. But this has to be weighed against its metabolic effects, and it is the metabolic effects that you would predict would take a number of years off people's lives. On the other hand, John Davis did a meta-analysis of a large number of studies on 10 different SGA drugs (this included some not approved for use in the U.S.), and he suggests that four are more effective than the other six, and Zyprexa is one of the better four (David et al, *Arch Gen Psychiatry* 2003;60:553-564). This conclusion is debatable on methodological grounds, but we don't have a definitive answer.

TCPR: My sense is that, despite all this recent evidence about the equivalence of conventionals and atypicals, front-line psychiatrists are still very reluctant to use these older agents. One of the continuing issues is the higher incidence of tardive dyskinesia (TD) with conventionals. Is this a reasonable fear?

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Dr. Carpenter: Yes, TD is being used by some people as kind of a trump card, but I think from a scientific perspective that is absolutely wrong. First of all, we do not actually know the risks for TD of medium-potency, first-generation drugs used at low to moderate doses. We don't know that drugs like Trilafon incur the same high risk of TD as higher-potency agents such as Haldol (haloperidol). Second, if the clinician follows the patient closely and picks up early signs of TD, it is a very reversible condition.

TCPR: So it is not necessarily the neurological catastrophe that many of us assume it is?

Dr. Carpenter: No, it isn't. With close follow-up, it is something we may well be able to manage and prevent. On the other hand, once patients have developed hyperlipidemia, decreased insulin sensitivity, and obesity, it may be very difficult to reverse these conditions. And so the question is, if this were my family member, would I rather potentially take years off his or her life with Zyprexa or clozapine, or expose him or her to the risk of TD?

TCPR: What sort of algorithm would you recommend when deciding on which antipsychotic to use?

Dr. Carpenter: I don't think we have enough good data to lay out a clear algorithm. It's more a matter of clinical reasoning from known adverse effects and playing your best hunch in terms of which might be the most benign for the patient.

TCPR: Can you lead us through this kind of reasoning?

Dr. Carpenter: I would start by asking what the patient's history on the drug is, which compounds he or she has already experienced, and which he or she liked or disliked and why. Knowing a patient tolerated a particular drug and has some confidence in its effect is a good starting point. Then I would try to avoid the adverse effects of greatest concern in the individual patient. You would not select a metabolically dangerous drug for a prediabetic, or a high-prolactin drug for a patient who is very concerned with sexual function. Adherence is always a concern, so I would often consider using long-acting injectables. In our country this has been stigmatized and reserved for our "difficult patients." But some patients prefer injectables; it may be simpler for them. The fact is that many schizophrenic patients have trouble keeping up with the regular dosing and before you know it they end up in an emergency room or in an encounter with the police. Injectables give you longer-lasting protection.

TCPR: What is your strategy with injectables?

Dr. Carpenter: I recommend that clinicians use relatively low doses and that they space out the injections. We did one study with Prolixin Decanoate (fluphenazine) a few years ago where we substituted saline for Prolixin for two out of every three injections in patients who were receiving injections every two weeks over a 54-week period. There were no differences in outcome between the two groups. But we really don't know the optimal dosing routine.

TCPR: What other decision-making guidelines would you recommend?

Dr. Carpenter: I try to match up a person to medications based on side-effect profiles. If I had a patient who is too skinny and doesn't like it, exercises like a fanatic, and has no history of heart disease in the family, I would be more willing to consider clozapine or Zyprexa and monitor him or her closely. If the patient has had any signs of tardive dyskinesia, I would go for one of the second-generation drugs that is more benign for dyskinesia, like Seroquel (quetiapine). If he or she has had a lot of trouble with EPS, then I would pretreat with an anticholinergic and then go for either a low-dose moderate-potency first-generation drug, such as Trilafon, or one of the second-generation drugs with a low EPS profile. If the patient complains about sexual dysfunction, I'd avoid compounds that raise prolactin, such as Risperdal (risperidone) or the newly approved Invega (paliperidone).

TCPR: What are your opinions about Geodon (ziprasidone) and Abilify (aripiprazole)?

Dr. Carpenter: Both Geodon and Abilify probably came on the market at too low a dose and started getting a reputation as not being as effective as the other dugs. They both appear to be substantially more benign in their side-effect profiles, and hopefully we'll learn how to dose them for better effectiveness. The QT interval problem with Geodon doesn't compare as a public health problem with the frequency of observed metabolic effects with Zyprexa and clozapine, and it is also something that one can monitor.

TCPR: Are there any other important issues in antipsychotics that we haven't covered?

Dr. Carpenter: Yes, I think clinicians ought to be highly sensitive to how influenced we all are by the marketing approaches that are taken by the pharmaceutical industry. Drug companies have relied on developing "me-too" drugs that hit the market with substantial marketing, and this is not advancing the long-term outcomes of people with schizophrenia. There is a tremendous shortfall in novel discovery for drugs; for example, we lack treatments that show a clear benefit for the cognitive impairments and negative symptoms that are associated with poor functional outcomes. Clinicians should pay close attention to sources, with effective firewalls to prevent bias. The Cochrane Library Reviews, the PORT recommendations for evidence-based treatment, and the publicly funded studies such as CATIE and CuTLASS are excellent sources.

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Research Updates IN PSYCHIATRY

PSYCHOSTIMULANTS

College students love to abuse Adderall

Adderall has overtaken Ritalin as the most-abused stimulant among college students. In a survey, 4,580 college students were asked about their illicit use of drugs. Of those reporting stimulant abuse within the prior year (269 students), three times as many abused Adderall as Ritalin (Teter, et al., *Pharmacotherapy* 2006;26(10):1501-1510).

TCPR's Take: Shire, manufacturer of Adderall, has saturated journals and consumer magazines with Adderall ads, and the strategy is working only too well. The company is currently circulating a meta-analysis purporting to show that taking stimulants actually *prevents* future drug abuse (Wilens, et al., *Pediatrics* 2003;111(1):179-185). We're skeptical of the findings, since the article reviews only *retrospective* studies comparing outcomes of kids who either were or were not prescribed stimulants. Children not prescribed stimulants had higher rates of later substance abuse. But these at-risk children may have been subject to a number of confounding factors leading to substance abuse – such as family histories of substance abuse, or disengaged parents who did not seek psychiatric care. The data did not control for any of these crucial social factors. The fact is that stimulants are often diverted, and this should lead us all to be more cautious in our prescribing habits.

ANTIDEPRESSANTS

Bad News for Transcranial Magnetic Stimulation

An FDA advisory panel has recommended that TMS not be approved for the treatment of major depression. Neuronetics, the maker of the NeuroStar device (*www.neuronetics.com*), submitted data from three studies, but only one was a placebo-controlled double-blind trial (Study 101). This study just missed showing statistical significance of the main outcome measure (change in MADRS score after six weeks), although it showed a small TMS benefit on most of the 16 secondary measures. For example, the four-week response rate was 18% in the treatment group vs. 11% in the placebo group. Nonetheless, most panel members thought the improvements were too small to be of great clinical benefit.

TCPR's Take: Many psychiatrists are disappointed, even irate, about the panel's finding, but let's face it, 18% vs. 11% is a very slim efficacy difference upon which to launch what would certainly become an intensively marketed and very expensive antidepressant procedure.

MOOD STABILIZERS/ ANTIPSYCHOTICS

Seroquel vs. Depakote for Impulsivity and Aggression in Teens

We often see teenagers with co-occurring bipolar disorder and aggressive/impulsive behaviors. While Depakote is often effective, we also often prescribe atypical antipsychotics. A new post-hoc analysis provides some evidence to bolster that practice. Thirty-three adolescents with co-occurring bipolar and disruptive behavioral disorders were randomized to receive either Seroquel (quetiapine) 400 mg to 600 mg daily or Depakote (divalproex) dosed to a serum level of 80 mcg/ml to 120 mcg/ml for 28 days. Both drugs reduced scores on the PANSS excited component scale by roughly half at week 4. Depakote was slightly more effective than Seroquel for improving impulsivity and reactive aggression, though the difference wasn't statistically significant (Barzman, et al., *J Child Adol Psychopharmacol* 2006;16:665 - 670).

TCPR's Take: It's always nice to find evidence for something we've already been doing. But a placebo-controlled clinical trial would have been more reassuring than this retrospective study funded by AstraZeneca (maker of Seroquel).

NATURAL TREATMENTS

Omega-3 Fatty Acids for Suicidal Behavior

Omega-3 fatty acids have been studied in a number of psychiatric disorders, including autism, bipolar disorder, depression, and schizophrenia. A new study shows a possible benefit for patients with a history of self-harm. Researchers in Ireland looked at 49 patients who required medical treatment in an emergency department following an incident of self-harm. All patients received standard psychiatric care; half were randomly assigned to receive omega-3 supplementation and the other half to placebo. At the end of 12 weeks, patients who had taken omega-3s showed significantly greater improvements in scores for depression, suicidality, and daily stresses than those who took placebo (Hallahan, et al., *Br J Psychiatry* 2007;190:118-122).

TCPR's Take: Sure, it's only one study, and a small one at that, but patients who present after an episode of self-harm are often complex and difficult to treat. Adding omega-3s might help, and couldn't hurt.

ANTIPSYCHOTIC SIDE EFFECTS

Metformin for Antipsychotic-Induced Weight Gain in Adolescents

Atypical antipsychotics can cause significant weight gain in adolescents. In this study, 39 kids between 10 and 18 years of age were randomized to receive either the antidiabetic drug Glucophage (metformin) or a matched placebo; each was added to their primary antipsychotic medication (Risperdal, Seroquel, or Zyprexa) for 16 weeks. All patients and their participating families received the same three sessions of generic dietary counseling. At week 16 those assigned to placebo had gained an average of 8.8 pounds; those who took metformin along with their antipsychotic lost 0.26 pounds. In addition, measures of insulin resistance – a potential precursor to diabetes – increased significantly in those on placebo and remained stable in those taking metformin.

TCPR's Take: We're encouraged that metformin might help adolescents stay on effective antipsychotics. Unfortunately, another recent study showed metformin was ineffective in preventing weight gain in adults on Zyprexa (Baptista et al, *Can J Psychiatry* 2006;51:192-196). Also, metformin is not a benign drug and carries a black box warning of potentially fatal lactic acidosis. So it's still preferable to choose antipsychotics with less weight-gain liability, like Geodon or Abilify.

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CME Post-Test

To earn CME credit, you must read the articles and complete the quiz below, answering at least four of the questions correctly. 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, 2008. Acknowledgment will be sent to you within six to eight weeks of participation.

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Clearview CME Institute designates this educational activity for a maximum of one (1) AMA PRA Category 1 Credit™. Physicians should claim credit only commensurate 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.

1. Invega (paliperidone ER) is
- [ ] a. An extended-release version of risperidone.
- [ ] b. The main active metabolite of risperidone.
- [ ] c. The purified S-enantiomer of risperidone.
- [ ] d. A new atypical similar to clozapine.

2. The BOLDER studies imply that
- [ ] a. Seroquel is effective for unipolar depression.
- [ ] b. Seroquel is equivalent to Zyprexa in efficacy for bipolar depression.
- [ ] c. Seroquel is ineffective for manic episodes.
- [ ] d. Seroquel is effective for bipolar depression, but more so for bipolar I than bipolar II disorder.

3. All second-generation antipsychotics are FDA-approved for bipolar depression.
- [ ] a. True [ ] b. False

4. An FDA panel decided that transcranial magnetic stimulation (TMS) for depression
- [ ] a. Is just as effective as ECT.
- [ ] b. Is not significantly more effective than placebo.
- [ ] c. Is marginally effective but should be approved anyway.
- [ ] d. Is a good augmenter of vagus nerve stimulation.

5. According to Dr. Carpenter, the risk of tardive dyskinesia with conventionals makes atypicals the treatment of choice.
- [ ] a. True [ ] b. False

PLEASE NOTE: WE CAN AWARD CME CREDIT ONLY TO SUBSCRIBERS

First Name	Last Name	Degree (MD, DO, NP, etc.)
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Phone	Fax	E-mail

Your evaluation of this CME 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? [ ] 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 behavior 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 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.

Second-Generation Antipsychotics —— *Continued from Page 3*

larger positive studies of Zyprexa (see review by Papokostas and Zarate, *Primary Psychiatry* 2007;14:59-65).

Do Geodon and Abilify Have Antidepressant Qualities?

Clinicians who have used Abilify (aripiprazole) have noted that it tends to have a stimulating effect in many patients. For some patients, this is problematic, leading to agitation, akathisia, and, occasionally, worsening psychosis. On the positive side, for some patients this stimulation has an antidepressant effect, and some open data on Abilify augmentation has supported this theory. Bristol-Myers Squibb and Otsuka are currently sponsoring three double-blind studies of Abilify augmentation in TRD (*www.clinicaltrials.gov*). Like Abilify, Geodon suffers from Seroquel envy when it comes to data on the treatment of depression, though this hasn't prevented many of us from using it off-label.

What's the Bottom Line?

For bipolar depression, Seroquel currently has the most convincing data among the SGAs and presents only a moderate liability for the metabolic syndrome. However, we suspect that, if put to an adequate test, all the SGAs would have some efficacy for this disorder. Similarly, Zyprexa augmentation for TRD has been the data leader among the SGAs, but others are right behind. Are all the SGAs *equally* effective for these illnesses? We don't know yet, but stay tuned!

TCPR VERDICT: **Second-generation antipsychotics as antidepressants? Probably.**

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This Month's Focus:
Antipsychotic Roundup 2007

Next Month in *The Carlat Psychiatry Report*: Pregnancy and Menopause in Psychiatry, including a practical approach to using psychotropics in pregnancy, updates on drug safety, and an interview with Louann Brizendine, M.D., author of *The Female Brain*.