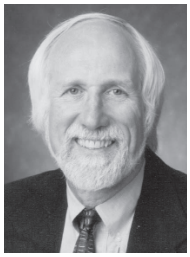
Q&A With the Expert

This Month's Expert:

William Carpenter, M.D.

Choosing the Right Antipsychotic



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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.

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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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