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Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Antipsychotic Update

Learning objectives for this issue: **1.** Describe the evaluation, treatment, and history of patients at risk for psychosis. **2.** Assess some of the scientific and historical background of atypical antipsychotics. **3.** Compare and contrast first-generation and second-generation (atypical) antipsychotics. **4.** Understand some of the current findings in the literature regarding psychiatric treatment.

The Psychosis Prodrome

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Dr. Loewy and Dr. Rose have disclosed that they have no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

Nearly all psychiatrists have met with an adolescent or young adult patient who was depressed and anxious, with some odd ideas or experiences—no florid psychosis, but perhaps with a family history of psychosis—and wondered, "Is this patient headed for schizophrenia?" Similarly, most clinicians have seen patients with schizophrenia who went without treatment for the first few years of their disorder and wondered, "Might this person be less impaired if he or she had received treatment earlier?"

At the crossroads of these experiences lies the concept of the psychosis prodrome and early intervention/prevention efforts. But without evidence of a florid psychotic episode, when should one intervene? With whom? How? These questions are still under active research across the globe and were recently debated hotly during the development of the DSM-5. In this article, we hope to walk you through some of the most recent evidence in treating prodromal psychosis, or the "clinical high risk"

Continued on page 2

Atypical Antipsychotics: Where is the Science, Where is the Evidence?

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Dr. Gillman has disclosed that he has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

Any psychiatrist who has practiced during the last decade has probably written more than a few prescriptions for an atypical antipsychotic. But do these drugs provide any clear advantages over their predecessors? This is a question that is best answered by science, not by anecdote or by popular impression. Unfortunately, good science on this topic is hard to find. Pharmaceutical companies have exerted a tremendous influence not only over academic departments and the scientific literature, but also practitioners' expectations. In this article we will concentrate on science, bypassing the well-publicized issues regarding infamous key opinion leaders (KOLs) and the numerous well-documented examples of fraud and deceit in the literature (which make it especially difficult to dissect out where the good science actually is).

To put it bluntly, the evidence—or rather the lack of evidence—suggests that the notion of "atypicality" has been more of a marketing concept than a pharmacological reality. The idea of atypicality arose quite early. In fact, it arose even before people realized (in the late 1980s) that clozapine (Clozaril), which had been around for more than 15 years, may have been more effective than other drugs available from the early 1970s on. The definition of "atypical" was linked initially with differences in the way these drugs affected how rats climbed up poles (eg, Costall B et al, *Br J Pharmacol* 1978;63(2):381P–382P). That

Continued on page 3

The Psychosis Prodrome
Continued from page 1

(CHR) syndrome.

The Definition of Clinical High Risk

In 1996, Drs. Patrick McGorry and Alison Yung published a definition of the psychosis prodrome based on the first symptoms described in retrospective interviews with schizophrenia patients and family members (Yung AR and McGorry PD, *Schizophr Bull* 1996;22(2):353–370). Sixteen years later, this definition has been used in hundreds of studies to identify and follow CHR patients over time. The two largest studies to date found a similar rate of transition to full psychosis—35% over 2.5 years—with diminishing transition rates over time, but some occurring as far as 10 years later (Fusar-Poli P et al, *Arch Gen Psychiatry* 2012;69(3):220–229). In this literature, "full psychosis" is defined as complete loss of insight and full conviction in hallucinations and delusions, occurring in both primary psychotic disorders such as schizophrenia and also primary mood disorders such as major depressive or bipolar disorders with psychotic features.

The CHR "attenuated psychosis syndrome" requires repeated subthreshold hallucinations or delusions with no full conviction that experiences are real, occurring at least weekly, with recent onset or worsening, and causing distress or impairment. This syndrome was the prototype for the now-rejected DSM-5 diagnosis.

These distinctions between full and attenuated psychosis are somewhat arbitrary, of course, and may differ from the way these terms are used in typical clinical practice, where patients present with symptoms existing on a continuum from mild to extremely severe. For our purposes, however, this distinction is an important one with significant implications for treatment. A clear result of research in schizophrenia suggests that reducing the "duration of untreated psychosis" (DUP) has beneficial effects for patients' symptoms, psychosocial functioning, and quality of life. These benefits can last for decades, above and beyond future treatment success and other factors that influence prognosis. This imperative to treat full psychosis as quickly as possible raises the question of what to do in the more murky area of attenuated psychosis.

Treatment Data in the CHR Population

Only six randomized controlled trials have been conducted with the CHR population (Marshall M and Rathbone J 2011, *Cochrane Database Syst Rev,* (6):CD004718), most using antipsychotic medications such as risperidone (Risperdal) or olanzapine (Zyprexa) alone, or in combination with psychosocial treatments such as family interventions and cognitive behavioral therapy (CBT). Three studies showed a statistically significant difference in the rate of psychotic transition between active treatment and control groups at the end of treatment (six to 12 months), but only one continued to show a significant difference in rates of psychosis six months after treatment ended, suggesting that if there is an effect of "preventing" psychosis onset, the benefit is lost once active treatment is discontinued.

The strongest effects were actually found for CBT, omega-3 fatty acids, and combined psychosocial treatment (CBT, family treatment, skills groups, computerized cognitive training), rather than antipsychotics. And in one of the largest studies, cognitive therapy and risperidone, either alone or in combination, had no benefit for preventing psychosis onset compared to placebo. Together, these studies suggest that antipsychotic treatment may not have a significant preventative or neuroprotective effect in attenuated psychosis, though it does tend to reduce the intensity and frequency of psychotic symptoms, whether attenuated, mild, or severe. Given the especially high metabolic risks for these drugs in adolescents (Sickich L et al, *Am J Psychiatry* 2008;165(11):1420–1423), we would advise against their regular use in the CHR population, except in the very rare cases where the distress and/or impairment caused by a given attenuated psychotic symptom is deemed to be severe or rapidly worsening over time.

Clinical Pearls in the CHR Population

Having worked with the CHR population clinically, and having struggled to integrate the current literature with our own experience, we have identified some helpful guiding principles that we feel apply to adolescents and young adults with attenuated psychosis who have come to clinical attention:

1. **The CHR syndrome is common, so don't be surprised by it and don't overreact to it.** Though psychosis can, of course, become chronic and impairing, the understanding that attenuated psychotic symptoms are actually quite common and don't always become severe can help reduce the urge to overtreat young people with medications that can cause long-term side effects.
2. **Psychosis is on a continuum, just like everything else.** Along with the goal of avoiding over treatment, we must recognize that psychotic symptoms exist on a normal continuum of

Continued on page 3

The Psychosis Prodrome

Continued from page 2

human experience, and interventions should be tailored to the particularities of the symptom clusters themselves. We recommend the staging model described by McGorry and colleagues as a guide (McGorry PD et al, *Austral New Zealand J Psychiatry* 2006;40(8):616–622).

3. **Depression and anxiety are expected.** While our diagnostic nomenclature assumes that primary mood disorders are discrete from primary psychotic disorders, in our experience, the population at risk for the development of psychosis is one that is also likely to exhibit depression and anxiety. Don't let the thought that this "might not be a 'real' mood disorder" stop you from treating what's there using standard depression and anxiety treatments.
4. **Marijuana is a causal risk factor for the development of full psychosis.** Be aware that marijuana not only worsens the course of psychosis, but for those who are at high risk, it can sometimes trigger or accelerate the course of psychosis to the point of being a causal risk factor in and of itself (Large M et al, *Arch Gen Psychiatry* 2011;68(6):555–561). Aggressively assess and treat marijuana use in young adults who are already exhibiting signs of attenuated psychosis.
5. **Childhood trauma impacts course.** Like marijuana, childhood trauma is probably a causal risk factor for the eventual development of psychosis, is common in CHR patients, and may predict transition to full psychosis (Vares F et al, *Psychol Med* 2012;42(5):1025–1036). While patients are often assessed long after the actual traumas have occurred, it is important to screen for, validate, and treat the effects of childhood trauma in the high-risk population. Alternatively, don't dismiss attenuated psychosis in the context of trauma as "just" trauma-related, as these patients are actually at very high risk for developing schizophrenia.
6. **Be on the lookout for cognitive decline.** The data suggest that, by the time people with concerning symptoms come to clinical attention, many have already suffered a decline in their motivation, attention, processing speed, and verbal memory. Consider cognitive decline to be one of the most important prognostic factors in the high risk population. It is especially helpful to educate families about negative and cognitive symptoms, which are not willful behaviors.

Prevention and Recovery: The Primary Goals of CHR Intervention

Recent research suggests that psychotic transition may not be as important an outcome as functional status, which is often poor and remains quite poor for some patients with impairing negative and cognitive symptoms, despite never formally crossing the "full psychosis" threshold (Yung AR et al, *Schizophr Res* 2010;120(1–3):1–6). Therefore, it is often most helpful to work closely with families to provide psychoeducation and support, even with young adults, and use cognitive behavioral therapies or vocational/educational supports to improve functioning. Recent studies have shown some promise that computerized cognitive training software may improve the neurocognitive deficits that are untouched, or sometimes worsened, by antipsychotic medications (Barlati S et al, *Curr Pharm Des* 2012;18(4):534–541).

TCPR'S VERDICT: One of the most important aspects of treating this population is providing safety, support, and hope. Many of us unintentionally communicate our fear of providing a schizophrenia diagnosis to a young person, based on experiences with the devastating outcomes for the worst cases. However, there is now evidence to suggest that recovery is possible with early and rigorous intervention to return a young person back to functioning after the onset of psychosis.

For those practicing near a CHR research center, we highly recommend taking advantage of their diagnostic and treatment services for your patients, or simply for consultation (www.schizophrenia.com/earlypsychosis.htm#clinics). For those in the San Francisco Bay Area, you can reach us at 415-476-7278.

Atypical Antipsychotics: Where is the Science, Where is the Evidence?

Continued from page 1

is not a facetious remark: such simplistic behavioral tests were the common assays of the day. But they are decidedly not a reliable way of assessing drug effects—never mind that they are also far distant from what we want the drugs to do in humans suffering from psychosis.

On such grounds, drugs such as chlorprothixine (Cloxan) and thioridazine (Mellaril) were regarded as atypical at that time, but not now. Obviously, those seeking to develop new drugs more similar to clozapine hypothesized about what pharmacological properties would differentiate them from older drugs, differences that might therefore provide a lucrative advantage.

Before considering such differences, however, it is important to note that the evidence for the superiority of clozapine and other atypicals is actually quite weak: the reliability of symptom and side effect assessments is poor, and the degree of superiority is certainly small, less than a half-point on the seven-point Clinical Global Impression (CGI) scale (Lepping P et al, *Br J Psychiatry* 2011;198(5):341–345). Doctors may find this rather surprising, but then again, they have been inculcated with dubious and biased evidence. All of this suggests that we are dealing with a (rather expensive) castle built on sand; indeed, the general finding in medical research is that effects of small degree are of dubious significance, and frequently false (Siontis KC et al, *Int J Epidemiol* 2011;40(5):1280–1291).

What Does "Atypical" Mean?

Atypical antipsychotics (also called

Continued on page 5

Q&A With the Expert

This Month's Expert

Old Versus New Antipsychotics

Robert Rosenheck, MD

Professor of Psychiatry, Epidemiology and Public Health, and the Child Study Center
Yale Medical School

Dr Rosenheck has disclosed he received research support from Pfizer Pharmaceuticals to analyze CATIE data and has served as a consultant to Otsuka Pharmaceuticals on a long acting injectable antipsychotic. Dr. Balt has reviewed this article and found no evidence of bias in this educational activity.

TCPR: You were an investigator on the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) trial, an effectiveness study comparing four atypical antipsychotics (olanzapine [Zyprexa], quetiapine [Seroquel], risperidone [Risperdal], and ziprasidone [Geodon]) and one first generation antipsychotic (perphenazine [Trilafon]). Briefly, what did this trial reveal?

Dr. Rosenheck: Basically, the CATIE trial showed that the new drugs have no advantage over the old drug used (perphenazine) except that olanzapine and quetiapine make you gain weight. Unfortunately, it hasn't really changed the way psychiatrists use antipsychotics today.

TCPR: How is it possible that the NIMH spent $50 million on this study and yet its results have no impact on practice?

Dr. Rosenheck: One reason is that drug companies did a good deal to minimize the impact of CATIE. They had meetings in which they essentially diverted attention from CATIE. They sponsored editions of commercial journals in which articles criticized CATIE. We published a study in *JAMA* that showed that olanzapine showed no advantages over haloperidol (Haldol) (Rosenheck R et al, *JAMA* 2003;290(20):2693–2702), but it, too, was ignored. Drug company influence essentially nullified the informational value of CATIE. Psychiatrists seem to be more influenced by what key opinion leaders tell them than what the science tells them. Also, it has been hard for science to affect practice because people developed practice habits and beliefs before these studies were completed that are hard to change.

TCPR: Did this happen with other trials, too?

Dr. Rosenheck: Yes. For example, the authors of EUFEST (European First Episode Schizophrenia Trial) initially hypothesized that in first-episode schizophrenia, atypical antipsychotics would be superior to haloperidol, but the objective measures showed that wasn't true (Kahn RS et al, *Lancet* 2008;371:1085–1097). And the subjective measures were highly biased; the study was done in the early 2000s at the height of the enthusiasm for atypicals. The TEOSS (Treatment of Early Onset Schizophrenia Spectrum Disorders) study was another study of first-episode schizophrenia in which molindone (Moban) did just as well as risperidone and olanzapine (Sikich L et al, *Am J Psychiatry* 2008;165(11):1420–1431). Interestingly, the olanzapine arm of the study had to be stopped prematurely by the data-safety monitoring board for the trial because it caused such adverse metabolic consequences. But this has had no impact on policy or practice. The CUtLASS (Cost Utility of the Latest Antipsychotic Drugs) trial also found that the new drugs are not superior to the older drugs (Jones PB et al, *Arch Gen Psychiatry* 2006;63:1079–1087).

TCPR: So why are these drugs so widely used?

Dr. Rosenheck: It's interesting to see the process our profession went through. We have sometimes been fraudulently led to believe things about these medications that aren't true. Eli Lilly paid a $1.4 billion judgment for marketing olanzapine for off-label uses—at the time, the largest criminal penalty ever paid by a US company. The Justice Department summary said that they had trained their sales staff to break the law. As discussed in an exposé in *The New York Times,* the key reason for this was to get the drug to the primary care market, and to use this antipsychotic for people who had anxiety and other disorders. [Eds note: you can read about Lilly's campaign to market olanzapine to primary care at Spielmans GI, *Soc Sci Med* 2009;69(1):14–20.] Not surprisingly, there has been widespread use of olanzapine for anxiety (Comer JS et al, *Am J Psychiatry* 2011;168(10):1057–1065).

TCPR: What does this mean for how we should use these medications?

Dr. Rosenheck: The drugs are largely off-patent. So from the cost perspective it doesn't matter anymore. But when the drugs were first marketed they clearly were not cost effective. I prefer to use the economic term "dominant choice." A dominant choice is a drug that works better and costs less. Perphenazine was a drug that worked just as well as all the atypicals and cost significantly less. This was the "dominant choice."

TCPR: So what questions then should we be asking and what should we be looking for in the science when new drugs come out and are promoted to us?

Dr. Rosenheck: First of all, more research must be done on these drugs. The problem is that independent research is often done many years after drug companies have had a chance to shape opinions. But if the science contradicts what everybody already believes, there will be reluctance to believe in the science. After all, who would want to believe that the great step forward was an illusion?

> **The problem is that independent research is often done many years after drug companies have had a chance to shape opinions.**
>
> Robert Rosenheck, MD

TCPR: Can you describe any advantages of the atypical antipsychotics?

Dr. Rosenheck: One of the frequent statements is that we need lots of different antipsychotics because if a patient doesn't respond to one, they may respond to another. I only know of two actual studies of that possibility, both of which failed to support it (Essock SM et al, *Am J Psychiatry* 2006;163(12):2090–2095; Rosenheck et al, *Schizophr Res* 2009;107:22–29). So if your patient isn't doing well and you switch them, they may do better, but that doesn't show that the second medication was more effective than the first.

You would have to do some kind of randomized trial where you would leave some patients on the first drug and then randomize other patients to be switched. Nobody has an incentive to do those trials.

TCPR: Can we use the unique receptor-binding profiles of atypical antipsychotics to predict efficacy?

Dr. Rosenheck: I don't think there is any evidence to support that as a basis for clinical decision making. In the end it depends on how you think medicine should be practiced: do we make decisions about patients on the basis of things that *could be* or do we make decisions on the basis of *data that we have?* And when things *could be,* do we falsely conclude that they are, or can we somehow test these hypotheses? The thing that sadly seems to happen in our field is that we substitute speculation for truth because there is much we don't know.

TCPR: What are your thoughts about the uses of atypical antipsychotics in non-psychotic illnesses such as anxiety and mood disorders?

Dr. Rosenheck: The problem is that the data on depression and the long-term treatment of mania and bipolar disorder are based on six- or eight-week trials. We don't know the trade-off between benefits and risks over the longer term, and these tend to be longer term illnesses. Most studies that are done these days are by drug companies that need two, usually short-term, trials to get FDA approval for their drug to go on the market, and that is what drives the clinical science of psychiatry.

TCPR: What could be an alternative to these short-term trials?

Dr. Rosenheck: In the past, the NIMH was responsible for testing the effectiveness of medicines. But today they say they are about the business of understanding the basic science of mental illness. This shift occurred in 1990, when employees of a drug company first appeared as authors in a major medical journal in an article about Prozac. This is commonplace today. If you were working for a company, would you see it as in your career interest to publish a paper that said that the company's drug was less than wonderful? This is how our field operates.

TCPR: How might independent evaluation of therapeutics work?

Dr. Rosenheck: I've put forth the idea that once a drug sells more than $1 billion of product, the company should be required to pay a very small tax (1% or 2%) that would fund an independent comparative effectiveness trial of the value of that drug as compared to other available drugs. There is little incentive for anyone to fund those studies, but these are precisely the studies that practitioners need. Psychiatrists know that they should give antipsychotic drugs for schizophrenia; the question is, is any drug better than any other drug, and what are the differences in long-term side effect profiles? Few studies examine these questions over longer periods of time, which is what we need to guide practice. The companies have little incentive for doing studies of this type because they obviously want to show that their drug is superior as quickly as possible. Some have proposed that the federal government should fund agencies to do comparative effectiveness research. The federally funded Patient Centered Outcomes Research Institute (PCORI) has been funded to do this kind of work, which has been an important step forward.

TCPR: Is there anything unique to psychiatry that might make us more susceptible to using medications without sufficient evidence?

Dr. Rosenheck: Yes. We don't have a single disease with a known etiology. We don't have a single biomarker of any mental illness. At the current stage, we don't have evidence that our diagnoses are clinically meaningful because drug companies have shown that some drugs are good for many distinct mental illnesses. The original dream of *DSM-III* was that you would be able to find the right drug for the right illness at the right time. But the drug companies have led us to believe, whether true or not, that their drugs are good for many, many mental illnesses.This is because we don't have a reliable definition for any mental illness and no mental illness has any known etiology, except perhaps for post-traumatic stress disorder.

TCPR: Hopefully your comments will make us wiser consumers of information.

Dr. Rosenheck: I think the deeper issue is that psychiatrists need to be aware recent legal actions suggest that fraudulent information has been provided to the public for the purpose of misleading them. Do psychiatrists want to know this? Do they want patients to know it?

TCPR: But shouldn't we know it?

Dr. Rosenheck: Actually, I find that audiences are very interested in these findings, but find them disconcerting. Our patients are in extraordinary pain, and it is not just that they are in pain, but that their lives are severely impacted at a very young age. Their ability to function is markedly impaired in many cases. These are horrible diseases, but we don't know what causes them, and we have treatments that seem to be effective—but we don't know how, and our sources of information are imperfect in some cases. I think that the main thing that psychiatry has to offer is that people who are in the field have extensive experience being with people who have mental illnesses, and the best of them are adept at actually listening to them, which is a good thing.

TCPR: Thank you, Dr. Rosenheck.

Atypical Antipsychotics: Where is the Science, Where is the Evidence?

Continued from page 3

second-generation antipsychotics or SGAs) are not a class in any meaningful pharmacological sense, but the idea sure is an advertising executive's dream come true. Various different drugs claim various different sorts of atypical features, which inevitably reminds one of *Through the Looking Glass* when Humpty Dumpty said, "A word means what I want it to mean, nothing more, nothing less." Atypicality seems to have moved through several phases of pseudo-explanation—first, meso-limbic selectivity, then 5-HT2A mechanisms; now dopamine dysregulation has been run up the flagpole, but it is hard to know who is saluting it.

It gets worse. Not only are we dealing with a heterogeneous group of drugs, we are also dealing with a

Continued on page 6

Research Updates IN PSYCHIATRY

Section Editor, Glen Spielmans, PhD

Glen Spielmans, PhD, has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

ANTIPSYCHOTICS

Some Popular Antipsychotics May Not be Effective in Patients over 40

Atypical antipsychotics are widely prescribed for a number of psychiatric diagnoses, but their real-world effectiveness has rarely been evaluated in anything other than short-term trials. A recently published study finds that four commonly used antipsychotics (aripiprazole [Abilify], olanzapine [Zyprexa], quetiapine [Seroquel], and risperidone [Risperdal]), when used in patients over age 40 with schizophrenia or psychosis associated with other conditions, may not be effective—and cause frequent side effects.

Investigators studied 332 psychiatric outpatients, mean age 66.6 years, for up to two years. Most (61%) did not have a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder. In fact, depression, PTSD, and dementia were highly represented. All were considered candidates for atypical antipsychotics by their psychiatrists. Each patient was given the opportunity to identify one or two (or none) of the drugs as "unacceptable"; patients were randomized to one of the two, three, or four remaining drugs on their list, at doses determined by their prescribers.

Surprisingly, none of the four drugs provided any symptomatic improvement as observed on the total Brief Psychiatric Rating Scale (BPRS) or BPRS psychosis subscale, and no drug emerged as more effective than any other. (There was no placebo control for ethical reasons.) The one-year incidence of metabolic syndrome was 36.5%, likewise with no significant difference among the medications. Serious adverse events were observed in 23.7% of the patients and nonserious events in 50.8% across the two-year study period. Serious events included deaths, hospitalizations, and emergency room visits.

The median length to discontinuation of medication was short, only 26 weeks. The proportion of patients who stayed on their drug of choice for the entire two years ranged from only 18.5% (aripiprazole) to 21.4% (quetiapine). Reasons for discontinuation included side effects (51.6%), lack of effectiveness (26.9%) or other reasons. No individual diagnosis had a better outcome, and certain perceived "advantages" of individual drugs were not borne out (for example, metabolic syndrome was not less common with aripiprazole). The quetiapine arm was discontinued by the study's safety monitoring board because of the significantly higher incidence (38.5% vs 19.0% for all other drugs) of serious adverse effects with this drug (Jin H et al, *J Clin Psychiatry* 2012; epub online ahead of print).

TCPR's Take: This study should not be dismissed as yet another appeal to use caution when prescribing antipsychotics in older patients. It actually sends an even more powerful message: these four atypical antipsychotics had no significant effect on psychopathology as measured by total BPRS score or the BPRS psychosis subscale. The most prominent "positive" finding, in fact, was the appearance of side effects in more than half the patients. Moreover, the study population was adults over 40 (not exactly the "elderly"). The authors conclude that the results are "worrisome" and "sobering" and we concur. If atypicals are to be used at all in this population, they're probably best used in the short-term only, and discontinued if adverse effects arise.

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Atypical Antipsychotics: Where is the Science, Where is the Evidence?

Continued from page 5

heterogeneous illness: not schizophrenia, but the schizophrenias. (And then there are the uses of these drugs for non-psychotic conditions like depression and anxiety, which are beyond the scope of this article.) The very real and meaningful difficulty of accommodating clinical trials to this heterogeneity has been swept regularly under the carpet, both for schizophrenia and for the non-psychotic conditions for which these drugs are used. That may be permissible—or even required—to get drugs to market, but it is disastrous for clinical science.

There are two key questions that really must be answered. The first concerns whether the evidence for the proposed theoretical basis—meso-limbic selectivity, the 5-HT2A/D2 ratio, or anything else—has been supported by time and independent replication. The second is whether drugs that exhibit those properties have been reliably and reproducibly shown to be significantly different in the ways predicted. More than two decades into this story neither of these requirements has yet been met.

Regarding notions of "atypicality," meso-limbic selectivity has been claimed for some drugs, but PET studies in humans have failed to replicate such claims, so it is not currently possible to show whether possession of such properties (if they even exist) results in noticeable clinical differences (Kegeles LS et al, *Arch Gen Psychiatry* 2010;67(3):231–239). The development of selective 5-HT2A antagonists has fizzled out (Ebdrup BH et al, *Expert Opinion Investig Drugs* 2011;20(9):1211–1223) because of failed clinical trials, although some still support this idea. To the extent that 5-HT2A/2C/1A, or any other receptor acting as feedback modulation may influence the activity of dopamine pathways, the magnitude of change induced is likely to be small (ie, within the normal physiological range) and temporary.

Practice: Clinical Assessment

The current climate promotes and funds research geared to licensing

Continued on page 7

CME Post-Test

To earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post-test. You must answer at least four questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by January 31, 2014. As a subscriber to *TCPR,* you already have a username and password to log on www.TheCarlatReport.com. To obtain your username and password or if you cannot take the test online, please email info@thecarlatreport.com or call 978-499-0583.

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Below are the questions for this month's CME post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning objectives are listed on page 1.

1. The two largest studies of prodromal psychosis (so-called clinical high risk, or CHR) found what rate of transition to full psychosis over 2.5 years (Learning Objective #1)?
   [ ] a) 10% [ ] b) 20% [ ] c) 35% [ ] d) 75%

2. Among the various studies of treatment of patients at clinical high risk for psychosis, which of the following showed the strongest effects for preventing psychosis (LO #1)?
   [ ] a) CBT, omega-3 fatty acids, and combined psychosocial treatment
   [ ] b) Cognitive therapy and risperidone, either alone or in combination
   [ ] c) Risperidone (Risperdal)alone
   [ ] d) Olanzapine (Zyprexa) alone

3. According to Dr. Ken Gillman, the meso-limbic selectivity of atypical antipsychotics causes differences in clinical outcome that are supported by the literature (LO #2).
   [ ] a) True [ ] b) False

4. Which of the following studies demonstrated that atypical antipsychotics are more effective than first-generation antipsychotics, according to Dr. Robert Rosenheck (LO #3)?
   [ ] a) CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness); but not TEOSS (Treatment of Early Onset Schizophrenia Spectrum Disorders) or CUtLASS (Cost Utility of the Latest Antipsychotic Drugs)
   [ ] b) TEOSS, but not CATIE or CUtLASS
   [ ] c) CUtLASS, but not CATIE or TEOSS
   [ ] d) None of these studies showed that atypicals are more effective than typicals

5. In the 2012 Jin et al study of atypical antipsychotics, which of the four drugs studied provided symptomatic improvement as observed on the total Brief Psychiatric Rating Scale (BPRS) in the study group (LO #4)?
   [ ] a) Aripiprazole (Abilify), and olanzapine (Zyprexa)
   [ ] b) Quetiapine (Seroquel)
   [ ] c) Risperidone (Risperdal)
   [ ] d) None of the four drugs provided symptomatic improvement as observed on the total BPRS

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Atypical Antipsychotics: Where is the Science, Where is the Evidence?

Continued from page 6

drugs for marketing, while little funding goes towards long-term research in outcomes or head-to-head trials. As such, answers to whether SGAs provide any clear advantage over FGAs are unlikely to emerge in the near future. It is clear a huge increase in independently and publicly funded long-term research is vital.

We should also remember that the (usually short-term) assessment of drugs used for chronic disorders may not translate into meaningful long-term disease outcomes. If we are to rely on short-term drug trials, then the interim surrogate outcome measures (like subjective rating scales) must be reliably demonstrated to be related to long-term outcomes, not just symptoms over a four to six week trial. But this is simply not the case in most psychiatric research, so we must remain extremely skeptical about any presumptions concerning longer term beneficial effects or lesser side effects of these drugs. The recent reality-check concerning the minimal benefits of beta-blockers in vascular disorders is an excellent case in point, these being another group of drugs that have been in use for a number of decades (Bangalore S et al, *JAMA* 2012;308(13):1340–1349).

The existing evidence to support the claims for superiority of SGAs is marginal at best and dishonest at worst. Many trials remain unpublished, and effect sizes in unpublished trials are far lower than those reported in published trials (Turner EH, *PLoS Med* 2012;9(3):e1001189). Some observers claim there are "no important differences between any of the antipsychotics" (Kendall T, *Br J Psychiatry* 2011;199:266–268) and even the purported advantage of SGAs in terms of extrapyramidal side effects—including tardive dyskinesia—has been called into question (Peluso MJ et al, *Br J Psychiatry* 2012;200:387–392). In brief, there is no single advantage of SGAs that has been independently replicated. In fact, many recent reviews are beset with caveats about uncertainty and significance, and all of the differences are small, on the order of magnitude generated by

Continued on page 8

Atypical Antipsychotics: Where is the Science, Where is the Evidence?

Continued from page 7

observer errors, bias, and the sponsorship effect.

This non-superiority of the SGAs has led the British Association for Psychopharmacology (BAP) to conclude: "No double-blind trial comparing an SGA with an FGA in the acute treatment of first-episode schizophrenia has shown an efficacy advantage for the SGA, with the single exception of a head-to-head, first-line treatment trial of clozapine versus chlorpromazine conducted in China.... These results challenge the almost exclusive use of SGAs for the treatment of first-onset schizophrenia and schizoaffective disorder" (Barnes TR, *J Psychopharmacol* 2011;25(5):567–620). The Cochrane reviews also sing from the same sheet of music.

TCPR'S VERDICT: The proposed notion of atypicality has never had sufficient evidence to support, never mind prove, any of the claims made. In fact, any existing evidence has only become weaker, not stronger, with time. After three decades, the clinical evidence of material advantages remains sparse and characterized by bias and fraud. Long-term studies are needed, but are less likely to be achieved by the research funding arrangements in place in most Western countries.

For an extended version of this article with an expanded reference list, please visit Dr Gillman's website at www.psychotropical.com.