

frequently used criterion for severity refers to more blatant psychotic illness. However, some episodes of blatant psychosis clear up quickly and thus these psychotic patients may not be more severely ill in every respect.

Another potential criterion for severity in people with schizophrenia involves those whose disorder is more likely to be sustained over a longer period of time, or who have a poorer long-term prognosis. To control for this possible confounder, we have utilized the prognostic indices outlined by Vaillant, Stephens and Zigler. These were collected in our studies at index hospitalization. Later we compared the long-term outcome of poor-prognosis schizophrenia patients medicated with antipsychotics for 15-20 years to that of poor-prognosis patients not prescribed antipsychotics for 15-20 years. We also compared a good-prognosis sample of patients prescribed antipsychotics for 15-20 years with a good-prognosis sample of patients not prescribed antipsychotics for 15-20 years. In both comparisons, those patients not on antipsychotics for 15-20 years had fewer symptoms and better outcomes after the first 2-3 years³.

An additional limitation of Correll et al's paper is that they do not fully address the evidence on dopamine supersensitivity psychosis from animals and from humans. They limit their discussion to short-term studies of psychotic relapse

and the potential loss of antipsychotic efficacy, while ignoring the serious risk for the syndrome resulting from continuous long-term antipsychotic treatment.

The clinical picture of dopamine supersensitivity psychosis is well defined and occurs with increasing frequency after two to three years of continuous antipsychotic maintenance use. Studies indicate that the syndrome manifests in 70% of patients with treatment resistant schizophrenia¹¹. Other studies show that the switch to aripiprazole, mentioned by the authors, may actually unmask and intensify psychotic symptoms previously suppressed by stronger D2 antagonists¹². While long-term continuous use of antipsychotics may induce the syndrome, these medications also block psychotic symptoms, which therefore remain largely unrecognized until the "breakthrough" of more severe symptoms occurs and leads to treatment resistance.

While several research groups have described dopamine supersensitivity psychosis as a serious risk of long-term continuous use of antipsychotics, there has been a systematic failure to incorporate this finding into the risk-benefit ratio for continuous use of antipsychotics. The same applies to the possible negative impact of long-term antipsychotic treatment on work functioning³: the block of dopamine receptors may indeed reduce drive and motivation.

Unfortunately, views about the long-term efficacy of antipsychotics are often based on the results from short-term (0-2 years) evaluations. As we have highlighted, there are at least eight major studies which fail to find better outcomes for schizophrenia patients treated on a long-term basis with antipsychotics. These negative results from multiple large well-documented long-term studies are a clear warning sign.

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Disease modifying effects of antipsychotic drugs in schizophrenia: a clinical and neurobiological perspective

Only in psychiatry would the benefits of one of the great pharmacological breakthroughs in the history of medicine be questioned over a half century after its introduction to clinical practice. When H. Laborit, a French Naval Surgeon stationed in Tunisia, serendipitously realized that chlorpromazine, a compound synthesized by the chemist P. Charpentier, could be used for the treatment of schizophrenia, and brought it to the attention of J. Delay and P. Deniker, psychiatrists at St. Anne's Hospital, a chain of

events ensued that changed the course of psychiatry and ushered in the age of psychopharmacology¹. The advent of this antipsychotic prototype was of comparable significance to other therapeutic milestones like the discovery of insulin, antibiotics and L-dopa.

In the ensuing years, numerous studies by eminent researchers in many countries documented the therapeutic efficacy of chlorpromazine, and the other antipsychotics that followed, in relieving the acute psychotic symptoms of schizophre-

nia and preventing their recurrence². And while neurological side effects were prevalent, and in many cases problematic, in most instances they could be managed with dose adjustment or adjunctive medications. Second generation ("atypical") medications in turn provided comparable or (in clozapine's case) superior efficacy, and fewer neurological but more metabolic side effects. However, in both cases, the therapeutic benefits of antipsychotics, when used properly, more than offset their side effects³.

In addition to symptom suppression, longer term studies of patients in their first episode or early stages of illness suggested that antipsychotic drugs, by virtue of their ability to limit the duration and number of psychotic episodes, could impact the clinical deterioration which Kraepelin considered the defining feature of what he termed dementia praecox⁴. In other words, antipsychotics might not just be symptom suppressing, but could mitigate the progression of schizophrenia. If confirmed, this would mean that psychiatry had treatments that could modify the course of the illness, something that had not been achieved with other brain diseases, such as Alzheimer's, Parkinson's and Huntington's.

The evidence for this aspirational therapeutic effect is somewhat circumstantial, but nevertheless compelling, and includes the following.

Treatment studies of first episode patients have consistently found associations between the duration of psychosis prior to treatment and outcome⁵. Specifically, these studies have found that longer periods of active psychotic symptoms prior to first treatment were associated with poorer outcome. What is remarkable is that this relationship was present for outcomes measured in multiple ways, including the time to or level of recovery from the first episode, the time to or likelihood of relapsing after recovery from the first episode, and long-term outcomes measured globally for up to five years after entering treatment for a first episode. Moreover, maintenance treatment studies have demonstrated the prophylactic effect of antipsychotic drugs in preventing relapse; treatment, then, may be responsible for mitigating the course of the illness and producing more favorable outcomes.

Furthermore, numerous investigations of brain morphology (post-mortem and neuroimaging) have demonstrated structural abnormalities in various anatomic regions in schizophrenia patients compared to control subjects. These abnormalities primarily involve volume reductions of gray matter in soft tissue structures (e.g., hippocampus, temporal and

frontal cortices, superior temporal gyrus, thalamus) and volume enlargements of fluid containing structures (e.g., ventricular system, subarachnoid space); but they also include shape anomalies and neurodevelopmental anomalies like cavum septum pellucidum, callosal agenesis and gray matter heterotopias. To the extent that some of these pathomorphologic features represent an atrophic process associated with illness progression, they are a target for therapeutic intervention. Various studies have demonstrated gray matter volume changes consistent with progression in specific anatomic regions, and an association between cumulative intake of atypical antipsychotic medication and less pronounced cortical thinning has been reported⁶. While the correlations of treatment and volume change cannot be confirmed as neuroprotective or disease modifying, they are certainly consistent with that interpretation.

Finally, since the introduction of antipsychotic medications into clinical practice, the frequency of the phenomenologic subtypes has changed. Historically, it was postulated that the less severe forms of schizophrenia were characterized by formed delusions, hallucinations and affective symptoms, and paranoid subtype diagnoses, while the more malignant forms exhibited negative, disorganized and motor symptoms and received hebephrenic and catatonic diagnoses. If there is indeed a continuum of severity in illness subtypes, a unidirectional pattern of change in patients' symptoms and diagnoses should reflect progression of the illness. Studies which have found an association between longer periods of untreated psychosis and a greater number of exacerbations and greater likelihood of developing negative, hebephrenic and catatonic symptoms are consistent with this interpretation. However, since antipsychotics came into use, the proportion of patients with predominant negative symptoms and hebephrenic and catatonic symptoms has decreased⁴.

Given the obvious acute and prophylactic benefits of antipsychotics, and the possibility that they may be disease mod-

ifying, it is hard to understand why there would still be questions as to their effectiveness. In fact, I cannot think of another medication class in other disease areas which has faced similar challenges to its effectiveness after longstanding use and voluminous supportive evidence. Classic "debunking" studies like the Cardiac Arrhythmia Suppression Trial (CAST)⁷ and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)⁸ were either rigorous tests of clinical lore or comparative effectiveness studies. Given the number and consistency of studies, and numerous meta-analyses, I wonder why reviews like that of Correll et al⁹ still need to be written for antipsychotics.

It is my contention that the enduring skepticism and distorted views of the clinical effects of antipsychotic drugs are mostly due to the stigma of mental illness and prejudice toward psychiatry, the medical specialty which is focused on their study and care¹⁰. The stigma historically associated with mental illness is currently perpetuated by lay and professional groups, who oppose the use and deny the efficacy of medication on ideological grounds. They are anti-psychiatry or anti-medical in their ideological orientation, and motivated by biased beliefs. Some lay persons challenge the notion of mental illness, the validity underpinning psychiatric nosology and the evidence supporting the therapeutic basis of psychotropic medications. Some professionals are motivated by factional disputes in mental health care between medical and psychosocial approaches. The latter seek to deny or diminish the evidence that mental disorders have biological bases and are effectively treated with somatic (medications, brain stimulation) forms of treatment, in favor of psychological explanations and psychotherapeutic approaches.

It is certainly appropriate, indeed warranted, to require hard evidence for the efficacy and safety of medical treatments as justification for their clinical use, but it is prejudicial and disingenuous to keep moving the threshold of proof higher and higher because of dogmatically held

views. While we seek and hope for future scientific breakthroughs that will yield better drugs and even greater therapeutic advances, we must recognize and be grateful for what we have, and put them to the best use for our patients¹¹.

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“Will I need to take these medications for the rest of my life?”

Correll et al¹ respond to a growing body of literature that calls into question the long-term use of antipsychotic medications in the treatment of schizophrenia. This recent literature has vexed clinicians who very commonly prescribe antipsychotics on a long-term basis, and who may have held a sense of certainty in the necessity of the therapy.

To address this issue, Correll et al characterize the balance between risks and benefits of long-term antipsychotic treatment. They place past evidence of poor outcomes associated with long-term antipsychotic use in the context of many other benefits (such as that on mortality and relapse prevention), and stratify the literature according to possible bias in each research method. Ultimately, they give an analysis of the benefits and risks of long-term antipsychotic treatment that favors treatment.

In this commentary we focus on applying these principles to working with individuals, particularly people who recently developed schizophrenia. We highlight challenges that will be faced by nearly every clinician who manages this disorder.

First, many – perhaps most – recent onset patients will stop their medication at one time or another. First episode studies have reported up to a 37.1% non-adherence rate² and other studies which include longer observation periods report even higher rates. One naturalistic study in Finland reported non-adherence in 58.4% of its sample, which was confirmed by measuring serum concentration³.

Second, the relationship between clini-

cians and patients with schizophrenia is often skewed toward the patient feeling controlled by others, particularly prescribers or family members. For most other illnesses, patients accept treatment because it makes them feel better or because it protects them from something they wish to avoid. This is often not so in schizophrenia. For young patients with the illness, particularly those who enter a stable remission following a psychotic episode, the most impassioned psychoeducational approaches to improving adherence may not instill a belief that they need to continue their medication.

In addition, nearly all patients will ask the question “Will I need to take these medications for the rest of my life?”. There is only one honest answer to this question, which is “Probably, but I can’t be certain”. Many individuals believe that they will be the *exceptional* patient who will do well off medications. Correll et al cite that perhaps 4-30% of patients stabilized after an acute episode may discontinue antipsychotics without risk of relapse. They add that, currently, we do not have a clinically reliable means of predicting which patients will have this maverick response to antipsychotic discontinuation. A challenge then remains: how to help individuals with recent-onset schizophrenia to make decisions according to an optimal balance of clinical benefit and personal autonomy.

We propose that a reasonable goal during these early years is to assist patients in taking some ownership of their illness and its management. In doing so, one might change the clinician-patient rela-

tionship from one in which the patient may feel controlled by the clinician to one in which the two work collaboratively. A poor relationship with a provider, and the experience of coercion, have been shown to be predictors of negative attitudes towards treatment in those receiving antipsychotics⁴. We emphasize the importance of changing this relationship.

For many, a discussion of the benefits and risks described by Correll et al, combined with the memory of a painful psychotic experience, will suffice. Others may still be skeptical of their need for long-term medication. Prescribers should emphasize the importance of remaining on medications for the first one to two years as well as the potential risks of discontinuation, which includes high rates of relapse^{1,5}. However, if the patient is committed to stopping medication, we concur with the recommendation⁵ that a trial of dosage reduction with possible discontinuation may be carried out with medical supervision and concurrent psychosocial interventions, in a select population. Clinicians may choose to perform a longer and gentler dose-reduction schedule if they sense a higher risk of relapse.

Dose reduction can be characterized as a learning opportunity for the benefit of both the patient and the prescriber. It may yield important data on the patient’s ability to tolerate a period of time on a lower dose of antipsychotic medication, or off of it altogether. Although there are clearly risks associated with this approach, earlier studies⁶ found that careful monitoring of patients for prodromal symptoms can