Use of Atypical Antipsychotics: Observations From Clinical Practice

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A psychiatrically well-informed internist colleague recently referred a patient with persistent depression for whom he had prescribed, in a stepwise fashion, a sensible combination of venlafaxine, bupropion, and risperidone. The antidepressants were at reasonable but not quite maximal doses. His question concerning this patient with nonmelancholic, nonpsychotic, recurrent unipolar depression: should he increase risperidone further, or push bupropion or venlafaxine? His patient was only mildly anxious, without a distinct anxiety syndrome, and worried, without frank ruminations. His inclination, guided more by clinical experience than anything he had been taught, was to increase risperidone.

Atypical antipsychotics, available for a decade, are demonstrating efficacy in a number of indications beyond schizophrenic and psychotic disorders. Investigation into their use is increasingly defining the psychopharmacologic literature; however, given their relatively low toxicity, their clinical use appears to be vastly outstripping their strictly "evidence-based" use in clinical practice.

This combination of relatively limited evidence-based guidelines on the use of atypicals in nonpsychotic disorders and their relatively low immediate toxicity often leads to treatment of target symptoms rather than diagnostic syndromes, especially by nonpsychiatrists. This phenomenon may suggest that the atypicals are overutilized in clinical practice, or it may indicate only that scientific investigation necessarily moves more slowly than clinical use.

A rapidly expanding literature ranging from case reports to prospective studies to review articles—including recent supplements to *The Journal of Clinical Psychiatry*—documents in some cases clear evidence for and in others possible utility of some or all atypical antipsychotics in numerous indications: acute mania[1–4]; mixed states[5,6]; maintenance therapy for bipolar disorder[7]; bipolar depression[8,9]; bipolar disorder with comorbid anxiety[10]; augmentation in unipolar depression[11–14]; treatment of selective serotonin reuptake inhibitor–induced apathy[15]; anxiety disorders including obsessive-compulsive disorder, posttraumatic stress disorder, social phobia, and generalized anxiety disorders[16–18]; and impulsivity in borderline personality disorder.[19,20] While augmentation therapy initially was most frequently described, monotherapy is also being reported on and investigated for several of these disorders.[21–23]

This widespread use in the community recently prompted another well-informed internist colleague to ask, only partly in jest, whether we were ready yet to simply treat everyone we saw with an atypical as first-line therapy. "If we could just deal with those metabolic side effects," he suggested, "an atypical for every disorder would certainly be simpler than making all of our complicated diagnostic distinctions and worrying about antidepressant induced manias, would it not?"

The efficacy of the atypicals may be specifically related to their serotonergic and other pharmacologic properties.[24] It is conceivable, however, that a portion of their reported utility is overoptimistic, a nonspecific mild benefit for the symptoms of anxiety, agitation, preoccupation, and psychic distress common to a number of psychiatric disorders. The unexpectedly strong performance of perphenazine in the well-publicized and often-discussed CATIE study[25] should make us reflect on how specific some atypicals' efficacy actually is.

Immediately after residency in the 1980s, I had the pleasure of working in an underserved rural clinic where a remarkably large percentage of patients were treated with typical antipsychotics as monotherapy. Many of those patients had for years carried some schizophrenia-spectrum diagnosis (to justify the use of antipsychotics?). Over the course of a year, dozens of patients who had been treated with antipsychotic monotherapy were rediagnosed as having bipolar disorder, recurrent psychotic or nonpsychotic depression, obsessive-compulsive disorder, panic disorder, and social phobia. Medication regimens were changed accordingly.

I believe the changes in those patients' treatment plans were generally for the better; certainly, many had suffered blunting, motoric effects and cognitive side effects from widespread use of typical antipsychotics that self-affirmingly made them "look schizophrenic." Yet what was so striking then, and what stays with me today, is that most of these patients did indeed have nonspecific but very real benefit from traditional antipsychotics that we little understood or wanted to consider at that time because of our dread of their side effects.[26–28]

It is possible that typical antipsychotics, even without the unique pharmacologic profiles of their second-generation descendents, conferred benefits, but their safety profile made us not fully evaluate those benefits. The "major tranquilizers" were certainly used for a wide variety of psychiatric complaints in the first decades of their use.[29]

Nothing should make psychiatrists feel better about the objectivity of our diagnostic algorithms than to watch 2 nuclear radiologists interpret a scan or 2 cardiologists read an echocardiogram. Yet, for all of our scientific rigor and remarkable advancements in the past 30 years, our field is one in which definitions are more subjective than in other fields, clinical alliance is key, and therapeutic success can be difficult to measure, document, or describe. Partly for those reasons, psychiatry is filled with well-known examples in which lack of toxicity has guided treatment decisions made in clinical practice more than demonstrated efficacy.

In 1982, 2 editorials accompanied Martin Keller's often-quoted article,[30] which documented undertreatment of depression and underdosing of antidepressants. Those editorials opined that practitioners were making reasonable risk-benefit analyses[31] in their choices of antidepressant treatment given that tricyclic antidepressants are toxic and that "benzodiazepines are among the safest drugs available."[32(p1879)] Similarly, prior to the introduction of fluoxetine, trazodone became one of the most widely prescribed antidepressants (irrespective of indication) in the United States.[33] In the 1990s, fluoxetine's safety profile encouraged likely overuse particularly by nonpsychiatrists for multiple symptoms and complaints, often without regard for diagnosis. Only recently, gabapentin was briefly widely hailed for its utility in bipolar disorder despite a paucity of supportive evidence.[34]

That atypical antipsychotics have been recognized to have potentially significant side effects may ultimately, ironically, be the main factor that spurs our judicious investigation and use of them. Their metabolic and other toxicities, both recognized and unrecognized, and the mandate to understand toxicities in special populations, such as children and adolescents, are likely to encourage investigators and clinicians to better define their indications and prescribe them thoughtfully.

Atypical antipsychotics, whatever that class and term may eventually come to encompass, appear rich in possibility and capable of threatening a number of paradigms. It took us 30 years of inquiry and refinement following the introduction of tricyclic antidepressants to come to understand how to use them—and we came to decide we understand them only because we moved on to other classes of drugs.

Clinical practice patterns and experience suggest, even more than the published literature, that atypicals are widely used, broadly efficacious, and, like tricyclics, similarly rich in potential. Unlike most of our previous classes of agents—tricyclics, benzodiazepines, typical antipsychotics, and serotonin reuptake inhibitors—atypicals appear heterogeneous as a class, differing one from another not only in side effects but in their therapeutic spectrum.

We have much to learn about how best to use the atypical antipsychotics, particularly for nonpsychotic indications. We don't yet know whether they may be widely underutilized or overutilized. We should humbly look forward to a decade or two of investigation that better defines our field and helps our patients.

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