Atypical Antipsychotics and Tardive Dyskinesia

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The approval and release of multiple atypical antipsychotics in the 1990s was met with much optimism and fanfare in the mental health community. Designed to exert unique pharmacological effects in the central nervous system (CNS) that resulted in superior efficacy and safety, the atypical agents have been widely embraced as first-line agents for the psychotic symptoms associated with schizophrenia, bipolar disorder, and dementia. In the United States, nearly $4 billion was spent on atypical agents during 2001. The atypical antipsychotics account for more than three-quarters of prescriptions for all antipsychotics and nearly 85% of total spending for antipsychotic agents in the U.S. To add perspective, the market leader, olanzapine, surpassed fluoxetine sales in the first quarter of 2001, with sales of $637.1 million versus $622.9 million.

While the popularity of atypical antipsychotics in North America can hardly be disputed, questions about therapeutic superiority persist. For example, in a large meta-analysis published in the British Medical Journal, researchers concluded that the purported benefits of atypical agents over conventional compounds could be attributed to the inappropriately high doses of comparator drug (i.e., haloperidol) used in the randomized controlled trials. Although the wisdom and utility of calculating an effect size from 52 different studies and patient populations has been questioned, the message was clear: If we are to continue investing so heavily in these newer compounds, unequivocal evidence of safety and efficacy must be demonstrated.

Of all the various and sundry claims attached to the atypical antipsychotics, perhaps the most appealing is the reduced risk (or total absence) of tardive dyskinesia. Defined as the delayed manifestation of abnormal irregular motor movements, tardive dyskinesia is widely regarded as the “worst case scenario” among patients on long-term antipsychotics. In severe cases, tardive dyskinesia can seize the trunk, limbs, or jaws of a person, preventing any purposeful movement. Even in mild cases, the symptoms can be embarrassing and relentless, resulting in additional social isolation and decreases in medication adherence.

Previous research efforts examining the potential association of atypical antipsychotics with tardive dyskinesia have generally been favorable, but the results are not yet definitive. Among the atypical agents, data supporting clozapine’s decreased risk of tardive dyskinesia is most impressive, but, as the clinical utility of clozapine is limited to treatment-resistant schizophrenia, the risk encountered with other atypical agents may be more pertinent. Studies with risperidone, olanzapine, andquetiapine have also reported a decrease in the incidence of new-onset tardive dyskinesia, but the majority of these investigations have been relatively brief in duration (i.e., less than a 12-month follow-up period) and often consist of data pooled from Phase III studies concluded prior to FDA approval. These data are certainly valuable and revealing, but readers should be reminded that these types of studies are conducted in a relatively contrived environment, where patient populations are generally young, lack significant medical comorbidities, and exhibit comparatively severe psychopathology. Evidence of long-term safety from the real-world setting is very limited.

In this issue of JMCP, Marshall et al. have attempted to examine the rates of tardive dyskinesia from actual clinical practice through a retrospective analysis of a VA Health Care System database. The authors chose a nested case-control study design for their investigation, measuring the influence of various demographic risk factors among patients diagnosed with tardive dyskinesia (i.e., cases) to a matched cohort of patients receiving antipsychotics who have not developed tardive dyskinesia. The patient population consisted of adults who had received at least two prescriptions for antipsychotics during the three-year study period. Cases (n=42) were defined as patients carrying a diagnosis for tardive dyskinesia in a hospital discharge summary or clinic visit note, and the control group (n=160) was randomly selected (prior to matching).

In the results, the authors report that they were unable to find a statistically significant difference between conventional and atypical antipsychotics in the incidence of tardive dyskinesia. After adjusting for various demographic factors, the authors found that patients receiving conventional compounds were only slightly more likely to carry a diagnosis of tardive dyskinesia (OR=1.02; 95% CI=0.0465–2.232). The strongest risk for tardive dyskinesia was associated with diagnosis, as patients with schizophrenia or schizoaffective disorder carried the greatest risk and those diagnosed with depression were least susceptible.

The authors should be commended for their efforts in analyzing a large and complex database to answer this important research question. The description of subject selection (and exclusion) was particularly thorough. There are, however, multiple confounding factors and other methodological limitations that might explain their findings. For instance, while the selection of a nested case-control design may permit researchers to calculate relative risk from a limited number of subjects, it also introduces the potential for a wide variety of selection bias. In this investigation,
it is quite possible that patients receiving atypical antipsychotics were overrepresented among the cases, since many clinicians would start patients with preexisting tardive dyskinesia on an atypical agent. Furthermore, many VA facilities have had prescribing guidelines for atypical agents that often mandated that patients fail multiple trials with conventional compounds prior to initiating the newer, more expensive antipsychotic. Under these circumstances, one would anticipate that patients receiving atypical agents would have a more extensive history of neuroleptic exposure and, therefore, be predisposed to the development of tardive dyskinesia. In fact, the lack of information about previous neuroleptic exposure (drug as well as dose and duration) is a strong confounding variable in this study overall.

The very nature of tardive dyskinesia makes it a difficult syndrome to study. It is generally believed that patients must be receiving antipsychotics continually for several months before the characteristic symptoms emerge. Any meaningful comparison between antipsychotics, therefore, would require at least 12 months of study follow-up. Longer studies are also necessary to rule out the appearance of transient withdrawal dyskinesias occurring when antipsychotic medications are switched (or doses significantly decreased). Additionally, tardive dyskinesia is not extremely common, carrying a cumulative annual incidence of 5%, and therefore requires a relatively large patient population to conduct a comparative analysis of sufficient statistical power.

In the future, it is hoped that further efforts will be made to objectively measure the incidence of new onset tardive dyskinesia among representative patient populations treated with atypical antipsychotics. Although the results of the study may have been compromised by confounding factors, the conceptual approach is noteworthy. Similar, more rigorous analyses are warranted. Future studies examining the incidence of tardive dyskinesia in special populations (e.g., children and adolescents, bipolar disorder) and the potential reversal of TD symptoms with long-term atypical agents would be appreciated as well.

As one prominent schizophrenia researcher recently noted, any discussion of tardive dyskinesia in the age of atypical antipsychotics may amount to nothing more than “an early requiem.”12 Similar to sentiments once expressed by Mark Twain, one hopes that reports of the demise of tardive dyskinesia are (not) greatly exaggerated.

REFERENCES
Gabapentin and Indications of Appropriate Use

In the dim past, medical care proceeded on emotion. For early shamans, medicine men, or their equivalents, there was no science. There was no formal measurement. There was need, response, and uncontrolled observation.

Then we began to measure. And, with reflection on measurement, we ushered in the potential for science. With refinement of measurement and refinement in the analysis of measurement, we created science. Yet, do we presume that today the era of emotion is over? Do we presume that all of medical care is now based on science? Do we presume that patients come to us with the hope and anticipation that physicians will dispense only rigorous science? America has a booming “health food” industry. Does it prosper because of the dispensation of rigorous science? Do patients buy based on science?

Most people of the world, including this author, believe in one or another perspective of “a life hereafter,” under the aegis of religion. What science makes this rational? Where is the double-blind, placebo-controlled study that demonstrates that spirits exist? Yet, while we have no such study, some surveys have indicated that only a small percentage of Americans, let alone people of the world, would consider themselves atheists.

Superstition is considered a routine human behavior. This causes black cats to fear for their lives at Halloween. People wear all manner of amulets or take nostrums to ward off evil spirits. People fear the dark. Children fear going to sleep without a light on. Movies about monsters are routine. Yet, has anyone ever seen and scientifically studied a true monster?

I believe that it is a false presumption to think that all human behavior is guided by the dictates of science. In the long view, we are, as a species, barely evolved “from the forest,” so to speak. Why then do we believe that medicine should be dispensed only rigorously? America has a booming “health food” industry. Does it prosper because of the dispensation of rigorous science? Do patients buy based on science?

We should—within reason and wisdom—try to move medical care toward science. From science comes organization, appropriate consistency, some kinds of wisdom, protection against the vicissitudes of self-interest, prognosis, and other benefits. Yet, the truly wise will know the limits of these endeavors. The limit of science in medical care is derived from variation. Human conditions present endless variations, rather than distinct subcategories. Humans are analog, rather than digital. Science and digital analysis would like to presume that humans will fit into a relatively small number of rigid and distinct subcategories, such as would be convenient for the computer (particularly an insurance company computer). Yet, humans present more variations than a digital model may comfortably handle. To presume that we can judge good medical care by applying a rigidly digital model is ultimately a fool’s errand. Science is good, wisdom is broader.

Hamer et al., in this issue of the Journal report what they describe as remarkable findings regarding the use of gabapentin for indications not approved by the FDA. The findings do, in fact, comport with what we suspect occurs with this drug in clinical practice. The authors fail, however, to delve into the practical reasons for their findings. Below the surface are some questions to ponder. The first question we must ask is “What are we to conclude from the very widespread use of gabapentin?” Is this simply a result of highly effective marketing? Or, are there other reasons?

Bearing on these questions, the authors conclude that the majority of use of this drug was “not beneficial.” However, they performed the study in a population served by a university cadre of physicians and observed wide use of the drug by these physicians. Are we to presume that these physicians are knowledgeable about the use of this drug or that they have a penchant for prescribing drugs that are ineffective?

The authors conclude that the drug was apparently ineffective, but they also point out that it was recurrently prescribed and taken in sufficient quantity to produce an average cost per patient of more than $1,000 during this relatively short study period. By this use, the patients seem to indicate considerable willingness to take this “ineffective” drug.

Actually, there is logic to the widespread use of this drug. However, the logic is not to be found simply in its use for seizures or its extreme effectiveness for controlling chronic pain conditions. Rather, the logic that drives this drug is (a) few major side-effects (including few serious side-effects that may garner malpractice suits), (b) few drug interactions (which is a particularly relevant issue in patients with affective disorders and chronic pain who are often on multiple drugs), (c) comparatively better tolerance in a population of patients who are particularly prone to complain of side-effects (chronic pain and mood-disordered patients), and (d) comparative ease of use (including less need for follow-up blood-level monitoring or toxicity tests). The drug is widely used because it may be effective for a variety of conditions (a revealing pursuit) and because it is relatively easy for a doctor to prescribe and a patient to take.

It is further erroneous to presume that prescribing drugs to patients with mood disorders and chronic pain is a rigorous science, free of emotion and placebo. Patients with mood disorders and chronic pain may report benefit from magnets, copper bracelets, being blessed, and myriad other treatments of questionable pathophysiologic efficacy. So, physicians soon learn that one of the goals of prescribing to these patients is to try not to harm them (ergo, use of a comparatively benign drug like gabapentin) while giving them something that might work.

The authors point out that amitriptyline might be as effective as gabapentin in this population, and at a much-reduced cost. Indeed, I would agree. I prescribe vastly more amitriptyline than gabapentin. But, I also know, in my own practice, that it takes
2 to 3 times as long to prescribe the amitriptyline because of issues such as settling the patient's fears of taking an “antidepressant,” gaining weight, of being “too tired,” and so forth. As insurance companies constantly ratchet down what they will pay for spending time with patients, the outcome should be obvious. Physicians are not, as a group, naive—they will do what they consider to be most effective in the least amount of time.

So, reconsideration should be given to the authors’ hypothesis that this cadre of university physicians is misguided. Gabapentin has risen to pharmacological stardom for specific reasons. These physicians probably understand this. The physicians who prescribe the drug and the patients who take it are both seeking to meet goals. If this drug is taken away, the parties will use other medications in the pursuit of those goals. Perhaps the next choice will be one with more side-effects, more secondary dysfunctions, more drug interactions, more malpractice suits. Will the costs be less? Maybe or maybe not. The equation is not simple.

What we may gain from this article is some insight into the real world of working with humans, as recipients and as providers. We may learn that both patients and providers may accept as “good” that which science would question. Yet, it is wrong to presume that this means the humans have the problem. All of medical care exists for humans. Medical care does not exist at the pleasure of science, but for the satisfaction of humans in need.

To make a “science” of the results of Hamer et al. requires understanding human behavior in the medical care arena. It requires understanding what motivations lead patients to consume and providers to provide. We can use the principles of science to begin to understand. But only if we recognize that much of what guides medicine is not easily measured in the laboratory and thus is not easily rendered subservient to the analysis of science. There is science to it, but much of this requires wisdom beyond the laboratory.

We must not abandon science in medical care. Yet, neither should we become slaves to its limitations. And, most assuredly, we should not use science as a weapon to bludgeon those who provide rational and honorable medical care that is guided by principles beyond that which science can prove. Wise use of science knows its strengths—and its limitations.

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**REFERENCE**  