

Anxiety About Antidepressants

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A recent front-page *New York Times* article (1) reframed a mental health success story into a conspiracy theory. The article, titled “Many People Taking Antidepressants Discover They Cannot Quit,” presents public health population-level data indicating that, indeed, many people are taking antidepressants. Many researchers interpret this as indicating progress in the successful diagnosis and treatment of depression—and in particular, compliance with quality guidelines that emphasize treatment trials of adequate duration. However, the article instead juxtaposes these population data with anecdotes and small descriptive studies of individuals who have had difficulty discontinuing treatment. The argument moves from ecological fallacy to conspiracy when it implies that the paucity of longer-term data is by design. Mostly unspoken in the article is the sense that it can’t be good for all of these people to be taking these medications long term ... can it?

Ironically, the *Times* article appeared only a week after a meta-analysis published by Cipriani and colleagues (2) demonstrated, once again, this time based on data on more than 100,000 individuals, that antidepressants are generally similar to one another in efficacy and are consistently superior to placebo. Yet media accounts still routinely treat antidepressant efficacy as an open question and toxicity as a near certainty.

Psychiatrists may therefore be forgiven for indulging the temptation to try to understand this societal ambivalence, notable throughout the article. We are told that antidepressants were originally considered “enough to get through a crisis, and no more.” We read that “every other person is depressed and on medication,” while patients maintained on antidepressants report “creeping unease” about “daily pill-popping.” None of these remarks will surprise clinicians—the same criticism of medication treatment of depression has been voiced for decades. The latent assumption is that pharmacotherapy represents a shortcut, an avoidance of doing real work. Our colleague Peter Kramer described it in 1993 as “pharmacological Calvinism” (a term he credits to Gerald Klerman, from two decades earlier), which represents “a general distrust of drugs used for non-therapeutic purposes and a conviction that if a drug makes you feel good it must be morally bad” (3).

The informative analogy might be treatment of type 2 diabetes. While diet and exercise have a substantial impact on disease course (notably, results far more compelling than those in depression), it is hard to envision front-page articles in the *New York Times* about the dangers of long-term

diabetes treatment. Instead, this article invites readers to make fallacious jumps connecting islands of truth in pursuit of a titillating, and stigma-perpetuating, theory: psychiatric disease and the suffering it brings are a failing of character best addressed through clean living or perhaps cleansed with redemptive suffering.

Factually, as the article acknowledges, withdrawal syndromes have been recognized from the beginning of the modern psychopharmacologic era. For this reason, slow, systematic tapers—when necessary, incorporating longer half-life antidepressants—represent a standard of care. And many clinicians will recognize in their practice some of the phenomena noted in the article, such as patients requiring very long tapers of medications. Clinicians will also recognize that in some cases, such symptoms actually represent recurrence of depressive, anxious, and somatic symptoms—the indication for treatment in the first place. That patients are able to *sustain* long-term treatment is testament to half a century of work on tolerability.

The article is also undeniably correct that we know far too little about long-term consequences of antidepressants—and nearly every medication in common use in medicine. That antidepressants are singled out may reflect a unique degree of discomfort with medications that affect the brain, but

the big picture reminds us that all medications have off-target or longer-term impact that cannot be captured in the regulatory approval process. Instead, this falls to the systems for postmarketing surveillance (in the United States, the Food and Drug Administration’s Adverse Event Reporting System), which in turn rely on voluntary reporting by clinicians. As such, each of us can help contribute to the knowledge we all need.

With the rise of large-scale electronic health records, health registries, and biobanks, we are better positioned than ever before to investigate long-term effects of antidepressants on health. While some surveillance efforts are already in place, they tend to focus on severe, shorter-term effects. More investment in understanding effects that may be more subtle and require more chronic exposure would be most welcome by patients, families, clinicians, and researchers. As

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used the Medicaid Analytic eXtract database, a large and valuable nationwide claims database that has increasingly been used to evaluate medication outcomes during pregnancy. While this database does not contain information pertaining to body weight or reliable ascertainment of obesity, precluding the ability to fully address this potential confounder, the authors conducted several well-conceived exploratory analyses to reasonably hypothesize that the effect of antipsychotic discontinuation (compared with continuation), rather than differences in obesity rates, was most likely responsible for the association of treatment condition with gestational diabetes.

One of the strengths of this study, compared with previous literature comparing users with nonusers, was the comparison of women who continued antipsychotic medication with women who discontinued, avoiding some of the major differences between users and nonusers that could confound the understanding of the risk for gestational diabetes. While there are substantial advantages to this approach, a discontinuation cohort may of course have some differences from those who remain on medication, beyond just the change in antipsychotic treatment status, and this study provides useful additional analyses that seek to address this potential confound. The comparison with discontinuers offers numerous advantages for relative risk estimates. However, regarding background risk, for the reader's reference it might be useful to understand the background rate of gestational diabetes in a non-antipsychotic-using cohort with, for example, a similar level of contact with the health care system.

While increased risk for diabetes during quetiapine treatment has not been consistently detected in the general adult population, even in analyses with much larger sample sizes (8), detection of this risk signal among pregnant women may be consistent with their more metabolically vulnerable state. In addition to the less robust results reported for quetiapine by Park et al., readers may note that the quetiapine cohort is different from the other cohorts in a couple of ways. The quetiapine sample size is larger, which likely reflects the wide-scale off-label use of low-dose quetiapine to promote sleep or as an anxiolytic, and the rate of prior occurrences of gestational diabetes was higher in this group, relevant to the risk for gestational diabetes during future pregnancies. While the authors conducted appropriate covariate and other analyses (e.g., restricting the cohorts to approved indications) to address these issues, they also appropriately concluded that the elevated relative risk of developing gestational diabetes with quetiapine observed in the primary analysis should be interpreted cautiously.

Overall, Park et al. provide a robust study design and analysis that offers a significant contribution to our understanding of antipsychotic medication-related metabolic risk during pregnancy. The results of this new report inform overall risk-benefit considerations for antipsychotic use during pregnancy. The results also represent another demonstration of the value of large observational databases like the Medicaid Analytic eXtract, whereby continued efforts to increase database content

and quality will likely contribute to additional public health insights. Antipsychotic medications are commonly used among pregnant women for the treatment of a variety of psychiatric disorders, but potential benefits should be carefully weighed against the risk for serious adverse events. Gestational diabetes is a serious pregnancy complication in the short-term and a known contributor to risk for postpartum development of type 2 diabetes mellitus, which in turn contributes to risk for cardiovascular disease and other conditions associated with premature morbidity and mortality in this vulnerable population.

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usual, the challenging question is who should pay for such studies. As psychiatrists, part of our responsibility is advocating on behalf of our patients. Here, this entails pushing for expanded data gathering so that we can better inform patients and families about both long-term benefits *and* long-term risks.

In short, the *New York Times* article buried the lead: the extent to which treatment of depression—whether pharmacologic, psychotherapeutic, or some combination—can truly change lives for the better. The increasing number of people receiving standard depression treatments in the United States represents the success of a substantial public health effort. Anything that stands in the way of people seeking treatment requires that we speak up and try to address both the cognitive and affective biases that may prevent effective treatment. We as psychiatrists do need more data, and we need to work harder to understand the reasons that depression treatments still provoke so much anxiety.

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