Reproductive Pharmacovigilance and Best Practices

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In this issue, Pacilio et al[1] sought to characterize real-world practices around ketamine treatment and pregnancy testing, consent processes, and contraception use. They used online surveys to ascertain routines for pregnancy testing across ketamine clinics in the United States. They also performed a retrospective medical record review at an academic medical center to investigate the frequency of pregnancy testing and documentation of contraceptive use. Lastly, they reviewed publicly available informed consent documents for ketamine treatment to assess whether information on pregnancy exposure was included. The results are sobering. Fewer than half of clinics that responded reported that they discuss risks related to pregnancy exposures with patients, and only 20% required baseline pregnancy tests prior to treatment initiation, and even fewer conducted subsequent testing during ongoing treatment. A minority of clinics reported that they routinely recommend or require contraceptive use during ketamine treatment. At the academic medical center, retrospective chart review did show weekly pregnancy testing, yet only half of patients had documented use of contraception.

The authors are commended for addressing this topic. The findings should give us pause. It is noteworthy that in the United States and globally, unplanned pregnancies represent about 50% of all pregnancies. Major depressive disorder (MDD) is a condition that commonly affects women of reproductive age.

With the increasing use of ketamine and US FDA approval of esketamine for MDD, this is a highly relevant topic. More broadly, most new medications are launched to market with sparse pregnancy safety data. There are usually modest data for animals, with questionable application to humans. Women of reproductive potential who participate in clinical trials are usually required to use a reliable method of contraception, and pregnancy tests at baseline and throughout a trial are standard practice. Trials still rarely are designed to include pregnant women.[2] Therefore, we lack knowledge about the risks and benefits of newer medications in pregnancy. This affects women who need to make informed treatment decisions for chronic or recurrent conditions during pregnancy and those who have inadvertent exposures before they know they are pregnant.

There are preliminary animal data to suggest that ketamine may carry an increased risk of major malformations with early pregnancy exposure and for neurodevelopmental insults with exposure throughout pregnancy.[3–5] Avoidance of ketamine is recommended during pregnancy. Therefore, this study is timely and critically important. Notably, ketamine is not FDA approved for use for depression, yet many patients increasingly seek and receive care with it, and systematic protocols around informed consent about pregnancy risks and pregnancy testing are generally not in place.

It is imperative that best practices for women of reproductive age for the use of ketamine and esketamine are determined and utilized. This is even more clinically fitting due to the variable and dynamic state of access to legal abortion in the United States. In fact, even the documentation of pregnancy test results might represent a legal risk for some women. The implications of abortion restrictions have been described as pertains to clinical research and may also apply to clinical care.[6]

Ketamine and esketamine have been especially effective for many individuals with serious treatment-refractory psychiatric disorders and act with a more rapid response than standard antidepressants. For women who are trying to weigh the risks and benefits of the use of ketamine or esketamine during pregnancy, or to understand the risk of early exposure, human data are lacking. Animal studies fail to take into account the many confounding variables that occur with humans who are using medications. We know that untreated MDD and associated factors may affect obstetrical and neonatal outcomes and neurodevelopment.

For full disclosure and to share a resource, I am a coinvestigator for the Massachusetts General Hospital (MGH) National Pregnancy Registry for Psychiatric Medications.[7] Over the last 15 years, over 3,600 women to date have enrolled in this prospective pharmacovigilance research program. We have been able to provide new data for medications that are widely used and for which pregnancy risks were unknown or only meagerly studied.[8–10]

It is with our great appreciation that the authors cite the MGH National Pregnancy Registry for Psychiatric Medications in their discussion. Patients with any first-trimester exposure to ketamine, esketamine, or any newer antidepressant are eligible to enroll and provide precious data to inform the field about the reproductive safety of medications for which we now have little to none. Participation is completely remote, and it consists of up to 3 phone interviews: a baseline interview, typically in the first trimester; a follow-up interview at around

28 weeks' pregnant; and a final interview at around 3 months postpartum. The Registry enrolls pregnant people who have a history of psychiatric illness and/or take psychiatric medication at any point during pregnancy. During these interviews, information is gathered regarding demographics, medication use, social habits, medical and psychiatric history, and delivery outcomes. Outcome data are also obtained through a rigorous medical record review process. The primary outcome of the Registry is the presence of a major malformation identified within 6 months of birth. Other outcomes focus on infant and child neurodevelopment, which is especially relevant to ketamine exposures.

The authors have highlighted an area in psychiatry that needs our attention. As individual providers, we need to appreciate potential pregnancy exposures of treatments in women of reproductive age. Our health care systems should make this easier. Our federal agencies and pharmaceutical companies would serve the public by supporting rigorous ascertainment of pregnancy outcomes after pregnancy exposures so that women can make personalized informed decisions.

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