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Three Clinically Important but Underutilized and Misunderstood Tools:

Formulas to Estimate Creatinine Clearance, the Package Insert, and Therapeutic Drug Monitoring

Sheldon H. Preskorn, MD[a,*]

The impetus for this commentary stemmed from the request by the *Journal* for me to review a manuscript (now article) by Gründer et al.[1] Initially, I thought the manuscript was solid but wondered if the findings deserved publication since they were initially included in the drug's package insert more than 20 years ago.

On further reflection, I concluded it merited publication for several reasons: First, replication—particularly in a clinical meaningful sample—was important. Second, the manuscript implicitly addressed 3 tools whose clinical importance is not understood and hence frequently not used by clinicians: (1) formulas that exist to estimate creatinine clearance, (2) the package insert, and (3) therapeutic drug monitoring (TDM). I address each of these points in this commentary.

In a large (n = 175) and clinically relevant sample, Gründer et al[1] demonstrated that renal function is an important determinant of the concentration of risperidone and its active metabolite, 9-hydroxyrisperidone (also known as paliperidone), achieved by administering a given dose of the drug to a specific patient. Parenthetically, risperidone and paliperidone are considered equally active, and thus the combination of their plasma drug levels is referred to as the plasma drug levels of the active moiety. On the basis of their findings, Gründer et al recommend reducing the risperidone dose by 50% in patients with a glomerular filtration rate below 60 mL/min.

That replicates the findings published by Snoeck et al[2] in a much smaller group of subjects: those who were young and healthy versus those who were elderly or had moderate-to-severe impairment in renal function. The work by Snoeck et al is representative of the studies required by regulatory agencies such as the US Food and Drug Administration (FDA) during the development of a drug so that such information can be included in the package insert for the drug. Parenthetically, the package insert is jointly written by the manufacturer and the regulatory agency and is the last step in the approval of a new drug for the market. The information by Snoeck et al appeared in the package insert for risperidone by or before July 2, 1999, and can be found through the FDA website .[3] The reader can use that website to find the package insert for any FDA-approved drug and its history of approval; thus, it is a tool that every clinician reading this commentary can utilize for any FDA-approved drug his or her patient is taking.

Why is the replication by Gründer et al important? For several reasons: the study by Snoeck et al was done in a research unit with paid volunteers, not patients, and was based on a single oral administration of a 1-mg dose of risperidone, which is generally not clinically relevant. In contrast, the Gründer et al study was done in a much larger sample of patients undergoing routine clinical care with risperidone at clinically relevant doses being administered on an ongoing daily basis. That the findings are so close provides reassurance to clinicians of the value of the package insert, which was developed based on the result of the drug development studies, like the one by Snoeck et al, and required by the FDA and other such regulatory entities to register a drug.

While not its primary focus, the Gründer et al article underscores the aforementioned 3 tools—how to estimate creatinine clearance, the package insert, and TDM—that are important to the optimum care of patients.

There are several mathematical formulas to estimate creatinine clearance based on knowing 4 facts about the patient: (1) age, to account for the age-related decline in renal function; (2) ideal lean body weight, to estimate the amount of creatinine generated by the patient per day; (3) sex, to adjust for the fact that women have a higher percentage of body fat even when at ideal lean body weight; and (4) serum creatinine, determined by the production of creatinine relative to its renal clearance. The reader can use the reference[4] cited and used by Gründer et al or can do an internet search for one of the other formulas. Such an estimate is of critical importance when dosing lithium and other drugs such as paliperidone that are principally dependent on renal clearance.

Why is the package insert important? In my experience, most clinicians do not appreciate the package insert as

[a]Department of Psychiatry and Behavioral Sciences, Kansas University School of Medicine, Wichita, Kansas

*Corresponding author: Sheldon H. Preskorn, MD, Department of Psychiatry, Kansas University School of Medicine, 1010 N Kansas, Wichita, KS 67214.

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being the most evidence-based piece of literature they will ever read about a drug, nor the fact that it is as close to an authoritative piece of literature on a drug as exists.[5] The package insert is the culmination of all of the drug development work required to get a drug approved and is the last step in the approval of a new drug. The reader should know that if he or she is ever sued over the alleged misuse of a drug, the plaintiff's attorney will almost undoubtedly submit the package insert for that drug into evidence. While using a drug in a manner not consistent with the package insert is not in and of itself evidence of malpractice, the clinician should have a good reason for the deviation from the package insert. That is why it is important that the reader know how to access the package insert for any drug the patient is taking and that it can be done with a few keystrokes on a computer.[3] The Gründer et al article underscores the importance and comprehensiveness of the package insert when one realizes that their finding replicates a finding contained in the package insert for risperidone 20 years earlier than their study.

Why is TDM important? In my experience, most clinicians are amazed to learn that they can measure the level of almost any psychiatric medication they prescribed and that there is well-founded guidance for what the results mean. Gründer et al come from the tradition and the group that has produced wonderful summaries of this literature: the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP), which is a group of German-speaking psychiatric researchers and psychiatrists who have published 3 successive versions of TDM expert group consensus guidelines, with the latest[6] summarizing the results of 1,358 articles in 3 major sections: (1) theoretical aspects of TDM, (2) the evidence underscoring the importance of plasma drug concentrations of specific drugs to guide their clinical use, and (3) practical aspects of TDM in psychiatry and neurology. (The full text of that article can be found via https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0043-116492 [accessed September 5, 2019].)

My simplistic approach to using TDM is that one can almost always find useful information by doing TDM for most drugs (as exceptions to this general rule, some drugs have quite short half-lives that make it technically difficult to do and rely on TDM). The reason why the information is almost always useful is that you are looking for something that should be there (ie, the drug you are prescribing and the patient is presumably taking). If the drug's level is nondetectable, that raises the question of adherence. If it is detectable, then, like in the story of Goldilocks, is the concentration unusually low or high for the dose you are prescribing, or is it just right? In essence, you—the prescriber—are measuring the ability of the patient to clear the drug. Parenthetically, clearance is dosing rate divided by plasma drug concentration. Also parenthetically, TDM today yields more actionable information for the prescriber of psychiatric medications than does genetic testing and measures the functional status of the patient at the time of the measurement. Genetic testing tells you what the patient is genetically capable of doing but not necessarily their current functional state due to a phenomenon known as phenoconversion.[7]

In summary, knowing the science and the tradition behind the article by Gründer et al involves all of the aforementioned factors, and your ability to use these tools will make you a better clinician.

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