Three Clinically Important but Underutilized and Misunderstood Tools: Formulas to Estimate Creatinine Clearance, the Package Insert, and Therapeutic Drug Monitoring

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The impetus for this commentary stemmed from the request by the Journal for me to review a manuscript (now article) by Grünender et al. 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, Grünender et al 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, Grünender 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 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. 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 Grünender 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 Grünender 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 Grünender 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 cited and used by Grünender 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
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