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Pharmacists have been splitting scored tablets to individualize and titrate dosages since the end of the pill-rolling era. We have generally accepted that scored tablets may be evenly divided, resulting in 2 half-tablets containing one-half of the whole tablet strength. Slight powdering is unavoidable, but it is generally accepted that loss of a few molecules of active drug is not likely to be clinically significant. However, even when tablets are split by pharmacists, 1 study found significant weight deviations in almost 10% of half-tablets. We do not know if this weight variation correlates with active drug in each tablet half, or more importantly, if this variation will jeopardize clinical outcomes or safety.

In some instances, there may be no other way to satisfy the prescribed dose other than tablet splitting. In any case, we rationalize that the patient receives the necessary dose during the course of chronic therapy because the patient eventually consumes all tablet halves as prescribed—1 half-tablet at a time. Assuming a 10% weight deviation, if one half-tablet provides 90%, and the next contributes 110%, on average, the patient receives 100% of the dose over 2 doses. Presumably pharmacists rely on pharmacokinetics and pharmacodynamics when selecting opportunities for tablet splitting and pass on those drugs for which fluctuations may be a concern; one wonders if physicians share such concerns when nonstandard doses are prescribed. Pharmacists must be involved and vigilant when advising individual patients and participating in population-based tablet-splitting programs.

We have made assumptions and selected appropriate drugs to be halved based on our understanding of pathophysiology, pharmacology, and pharmacodynamics. We assume homogenous distribution of active drug in whole tablets, and thus, an equal distribution of active drug in the half-tablets. Some variation is expected, and the U.S. Food and Drug Administration (FDA) bioequivalence standards permit variance of plus or minus 20%. So, even with whole tablets, the actual dose ingested may fluctuate from whole tablet to whole tablet.

Past tablet-splitting research has assessed the half-tablet weight, uniformity, and even the clinical outcome of split tablets, including the work of Gee et al. (2002), which assessed clinical, service, and cost outcomes associated with tablet splitting. In this issue of JMCP, Hill et al. offer an unprecedented analysis of the accuracy and precision of tablet splitting by measuring the active drug component in tablet halves. This use of assay is an important step in assessing half-tablet weight variations.

Half-Tablet Variations—Do They Have Clinical or Practical Meaning?

As pharmacists, we presume that if the dose of an angiotensin-converting enzyme (ACE) inhibitor, statin, analgesic, or antidepressant fluctuates by a few molecules more or less than the prescribed dose, surely this fluctuation would not jeopardize effectiveness or safety, as these drugs are titrated in approximate milligram increments even with whole tablets. However, warfarin is typically not included in half-tablet programs. Controversy surrounding the narrow therapeutic index of this drug, its relatively low cost, and the often short-term nature of dosing associated with acute events such as orthopedic surgery for hip or knee replacement probably contribute to the absence of warfarin from formal tablet-splitting programs. For example, UnitedHealthcare’s Half Tablet Program in June 2007 listed only 15 drugs in 4 categories: 3 ACE inhibitors, 5 angiotensin receptor blockers (ARBs), 4 antidepressants, and 4 statins.

While most health plans do not promote splitting of warfarin tablets, Hill et al. included warfarin in their research because it was among the drugs “commonly split” in 1 Department of Veterans Affairs (VA) health care system. It is important to note that Hill et al. used an arbitrary standard for warfarin individual tablet variation (95%-105%), which is more narrow than the variation standard that they used for other drugs (90%-110%) and more narrow than the standard used by the United States Pharmacopeia (USP; 85%-115%) for weight and content uniformity of individual tablets. The standards used by Hill et al. are “typically applied to samples of 20 [tablets] or greater.”

Also curious are inconsistencies in Hill et al.’s recommendations regarding splitting warfarin tablets. The authors include a warning that “caution should be taken when splitting warfarin sodium due to the potential for significant adverse events with minimal change in daily dose.” However, the authors seem to negate their concerns by stating that “daily variation of international normalized ratio (INR) values…can result from food interactions, drug interactions, and variations in daily dose. For this reason, it cannot be stated that the minor differences in warfarin sodium half-tablet drug content will predict clinical outcomes.” While splitting of warfarin tablets presents a theoretically realistic concern in a population-based program, apparently the VA, the setting for the Hill et al. study, splits warfarin, presumably without problems.

Another point of confusion surrounds lisinopril half-tablet fluctuations. Hill et al. report that drug content variation for half-tablets “was greatest with lisinopril, which had tablet halves ranging from 81.15% to 125.72% of the target drug content for half-tablets. Thus, when tablet splitting is performed for this lot of lisinopril, patients may receive daily doses that vary by as much as 45%.” This admonition is somewhat inconsistent with Hill et al.’s later statement that “daily fluctuations in dose [of antihypertensives] would be expected to affect
blood pressure measurements and side effects and have no effect on long-term clinical end points."

This confusion over the clinical significance of variation in warfarin and lisinopril half-tablets creates negative sound bites that may cast an unjustified pall over tablet splitting in general for the hasty or uninformed reader who researches the topic no further.

**Tablet Splitting as a Managed Care Issue**

We acknowledge and accept that dispensing pharmacists split tablets— with fingers, a counting knife, device, or a blade—to accommodate prescribed doses not available in whole tablets. But why did tablet splitting migrate from solely a professional practice issue to a sometimes controversial managed care concern?

The reason is that tablet splitting both satisfies and challenges the raison d’être of managed care pharmacy: to deliver a value-based pharmacy benefit. The value equation puts the drug benefit in the numerator and cost in the denominator. In this equation, value increases with a greater benefit and/or a lower cost, and decreases with a lower benefit and/or higher cost. Tablet splitting delivers the same clinical outcomes at a lower cost. From this perspective, managed care can embrace tablet splitting.

For example, the generic lisinopril 40 mg cash price is about $18.00 for 30 tablets, and lisinopril 20 mg is about $14.00 for 30 tablets. If a patient is prescribed 20 mg daily, and the pharmacist splits fifteen 40 mg tablets to dispense 30 half-tablets (20 mg per half-tablet), the cost would be $9.00 for a 30-day supply, rather than $13.99, a savings of 36% without jeopardizing patient care. This is a tantalizing opportunity for pharmacy benefit plans and for patients, who typically experience a copayment savings of about 50% when participating in a half-tablet program.

In their study, Hill et al. cite other sources, including the VA, claiming success and forecasting significant cost savings from dividing certain drugs when a half-tablet of a larger strength is less expensive than a whole tablet of the half-strength. One source identified annual savings of approximately $342,000 through tablet-splitting in a plan with $10 million in annual pharmacy benefit expenditures. In 2004, the VA announced that splitting simvastatin tablets saved $46.5 million systemwide in fiscal year 2003. In another VA study, Gee et al. (2002) found that splitting statins produced savings of approximately $68 per patient per year without compromising lipid reduction.

**Concerns About Unintended Consequences Overstated?**

Detractors and concerned patient advocates have voiced concern about tablet splitting, challenging that tablet halves may not provide exactly one-half of the dose of the whole tablet; patients may be confused by one-half tablets and take an erroneous (double) dose, or splitting an extended-release tablet may jeopardize the rate of absorption; and any 1 of these occurrences may jeopardize clinical outcomes including patient safety. For example:

- The Institute for Safe Medication Practices advises patients to split tablets “only if you ‘half’ to” although the practice may be necessary for dosage titration or to reduce drug costs; the institute also acknowledges potential risks and admonishes prescribers to select the proper patient candidate for tablet splitting.

- In 2004, the American Pharmacists Association stated that tablet splitting can be effective for certain drugs and certain patients but should not be automatic or mandatory.

- A 2006 article in the *Journal of Family Practice* acknowledged the potential cost savings from tablet splitting but provided guidelines on what dosage forms or patients may or may not be appropriate candidates for tablet splitting. Also, the article pointed out that certain tablet-splitting devices may be more effective than others in creating mirror halves.

- Is there room for misinterpretation and a pharmaceutical misadventure if a patient is dispensed one-half tablets (split by the pharmacist) and the instructions read “take one-half tablet”? Might the patient further split the half-tablet and take one-quarter-tablet?

- Might a busy pharmacy dispense a whole tablet with the instructions reading ‘take one-half tablet’ and expect the patient to split the tablet? Can patients be expected to accurately and precisely split tablets themselves? Should they be given a tablet splitter by their managed care organization (MCO)? (Some MCOs have provided splitters to patients.)

Perhaps it is not tablet splitting per se that is objectionable, but the regimented splitting that may appear forced upon patients by managed care. As a sound bite headline, “a mandatory tablet-splitting program” sounds Orwellian; without more specific definition, it may erroneously be perceived to apply to all drugs and all patients.

In reality, the pharmacy directors at the MCOs and VA centers that recommend tablet splitting for some drugs are well aware of these and other concerns and, as a result, carefully select drugs to be split without potential for hazard. They generally avoid drugs for which slightly fluctuating blood levels may compromise outcomes or safety (so-called narrow therapeutic index drugs); drugs that are frequently titrated or monitored with lab assays; and, in general, drugs requiring accurate and precise dosage adjustments on a chronic basis to maintain desired effectiveness and safety outcomes, particularly in frail or otherwise fragile patients. Similarly, patients physically unable to split tablets are excused from this requirement.

**Is Current Splitting Practice a Non-Issue?**

In preparing this commentary I spoke with pharmacy directors of several large MCOs—open-panel as well as closed-panel plans with clinic pharmacies—who had instituted mandatory tablet splitting confined to a limited number of specific brand name drugs. Most acknowledged that the tablet-splitting programs reduced drug costs. However, many have abandoned their tablet-splitting programs because the target drugs have become
available as generics—instituting a maximum allowable cost program is an easier way to achieve cost savings.

Some MCOs and VA centers, however, continue to achieve cost savings with tablet splitting for select drugs. Others may once again embrace tablet splitting as new brand tablets are launched that satisfy desired criteria, particularly flat pricing among strengths of the same drugs. For all plans that do, Hill et al. have advanced our scientific understanding by showing that drug content was uniformly distributed for all medications analyzed, and half-tablet weight seems to be directly correlated with half-tablet drug content. However, they also cautioned that a potential for half-tablet dose variation may occur with warfarin sodium, metoprolol succinate, and lisinopril. Warfarin may be a concern; lisinopril perhaps not so much, despite the varied opinions presented in Hill et al.’s paper. Pharmacy directors will use these new data to help design and execute tablet-splitting programs with value for patients and health plans.

In their penultimate paragraph, Hill et al. state that unless performed by a device, tablet splitting, even by pharmacists and especially by patients, will likely result in significant tablet weight variations, and they further opine that “therefore, equal daily doses will be determined by the ability of patients to split tablets perfectly in half.” While we all agree that certain patients with challenges in cognition or dexterity are not appropriate candidates, the authors confirm by their research that most split tablets are within accepted ranges, and even those that are not may not result in negative clinical outcomes due to the gross dosages used. Hill et al. did not measure clinical outcomes, and the takeaway message is that there is reasonable content and weight uniformity among most tablet halves that result from tablet splitting. An opportunity to improve efficiency without jeopardizing patient safety, tablet splitting has been endorsed in a professional practice advisory from the Academy of Managed Care Pharmacy. Likewise, tablet splitting may be increasingly important from the consumer’s perspective; in a February 2009 Kaiser Health Tracking Poll, 15% of respondents reported that they had either split tablets or skipped medication doses to save on prescription drug costs in the previous year. Tablet splitting may be an effective method to individualize dosages and/or reduce costs when performed under the guidance of pharmacists, for informed and competent patients, and for appropriate drugs.

DISCLOSURES
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