

Weight Uniformity of Split Tablets Required by a Veterans Affairs Policy

JAMES E. POLLI, PhD; SHARON KIM, BA; and BRIAN R. MARTIN, PharmD

ABSTRACT

OBJECTIVE: To split several tablet products relevant to the Veterans Affairs (VA) Maryland Healthcare System and assess whether the resulting half tablets provide equal doses.

METHODS: From a VA list of products that are required to be split, 7 products were evaluated, along with 5 other commonly split tablet products. A trained pharmacy student split tablets using a tablet splitter provided by the VA. Half tablets were assessed for weight uniformity.

RESULTS: Of the 12 products subjected to splitting, 8 products (atorvastatin, citalopram, furosemide, glipizide, metoprolol, paroxetine, sertraline, and warfarin) yielded half tablets that passed the weight-uniformity test. The 4 failing products were lisinopril, lovastatin, rofecoxib, and simvastatin. Unusual tablet shape and high tablet hardness predisposed products to failing the weight-uniformity test. The 4 failing products resulted in half tablets that were generally within 20% of their target weight range, suggesting that splitting these specific products would not result in adverse therapeutic effects due to dose variation created by tablet-splitting.

CONCLUSION: Split-tablet results were relatively favorable and generally support a VA practice to split specific tablets. Public quality standards for half tablets, including their content uniformity, are needed to better delineate the policies for acceptable tablet splitting.

KEYWORDS: Tablet splitting, Weight uniformity, Tablet-weight uniformity, Veterans Affairs

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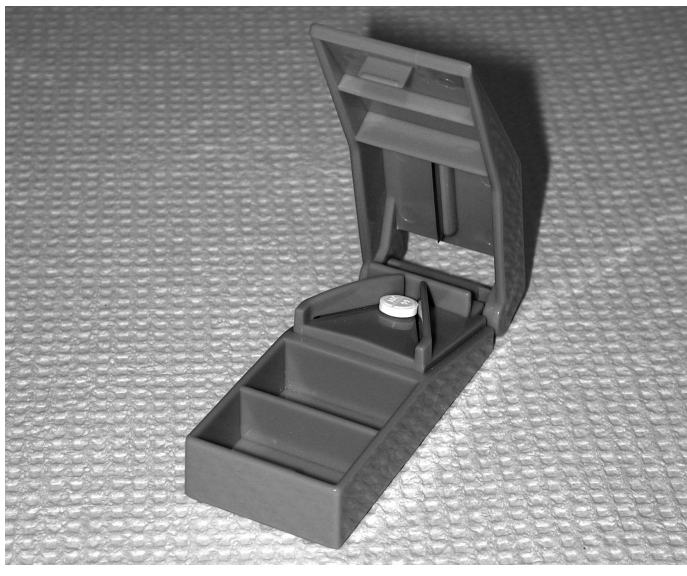
In recent years, the U.S. Department of Veterans Affairs (VA) has been faced with escalating pharmacy costs. These increased costs are the result of increased enrollment, an aging patient population that requires more prescription medicines, and increased acquisition costs of prescription medicines. The VA has turned to tablet-splitting programs as one approach to contain costs. Several pharmaco-economic studies have indicated that splitting certain tablets can produce significant cost savings.¹⁻⁵

A tablet-splitting program was implemented 2 years ago at the VA Maryland Health Care System, which is part of the Veterans Integrated Service Network 5 (VISN 5) region. VISN 5 provides care for veterans in Maryland; Washington, D.C; eastern West Virginia; Northern Virginia; and south central Pennsylvania.

Candidate drugs were considered for this tablet-splitting initiative if they had a relatively high cost, tablet splitting was not considered to be detrimental to drug release, and the tablets were easily split with a standard tablet-splitting device. VISN 5 now mandates tablet splitting of 8 tablet products for outpatients: atorvastatin, citalopram, lovastatin, paroxetine, rofecoxib, sertraline, sildenafil, and simvastatin. New prescriptions for these products are filled with a tablet that contains twice the prescribed dose, and patients are instructed to take 1 half tablet. A standard tablet-splitting device is also dispensed with the prescriptions. A patient may opt out of the tablet-splitting program if the splitting of tablets proves to be difficult. Also, several other tablets are frequently split, due to cost and therapeutic reasons. Between May 2001 and April 2002, the tablet-splitting initiative directly saved the VA Maryland Healthcare System about \$560,000; approximately 41,000 patients received pharmacy services from the health care system during this time.

Equal splitting is presumably necessary for weight uniformity from half tablet to half tablet. We previously found that several commonly split tablets, when split by a razor blade or by hand, usually did not produce evenly split tablet halves.⁶ We observed that no visible tablet features (e.g., tablet scoring) predisposed a product's half tablets from passing or failing the uniformity test. Rosenberg et al. found tablet splitting to yield half tablets that generally did not meet an expectation for dose uniformity.⁷ They determined the weights and weight uniformity of tablet halves dispensed by pharmacists. Rosenberg et al. found that only 7 of the 22 dispensed prescriptions met an expectation of accurate tablet halves (defined as less than 15% error) with acceptable weight uniformity (i.e., less than 6% relative standard deviation).

FIGURE 1 Photograph of Tablet Splitter



From these recent studies, we hypothesized that tablet splitting following practices of the VA Maryland Health Care System would result in half tablets that generally fail to provide acceptable dose uniformity. Specifically, the objective of our study was to split several tablet products relevant to the VA Maryland Healthcare System and assess whether the resulting half tablets provided equal weights. Seven of the 8 mandatory split products in the VISN 5 region (all but sildenafil) were evaluated, along with furosemide, glipizide, lisinopril, metoprolol, and warfarin, which are commonly split at the VA Maryland Healthcare System. Although not mandatory, splitting of these latter 5 products is permissible, at the discretion of the prescriber. Splitting tablets allows for more precise dosage adjustment and greater patient convenience, for example, by eliminating the need for 2 separate prescriptions to achieve a desired dose. For instance, a patient prescribed lisinopril 30 mg daily can take a 20 mg and a 10 mg tablet, which would require 2 copayments since a 30 mg tablet is not commercially available. Alternatively, the patient could be prescribed one and one-half 20 mg tablets daily, which requires only 1 prescription and only 1 copayment.

Methods

The following products were donated by either the VA Maryland Healthcare System or the University of Maryland School of Pharmacy: atorvastatin 40 mg (Lipitor, Pfizer, Lot #053X0V), citalopram 40 mg (Celexa, Forest, Lot #M0114M), furosemide 40 mg (Geneva, Lot #114028), glipizide 10 mg (Geneva, Lot #126255), lisinopril 40mg (Prinivil, Merck, Lot #L4686; generic lisinopril was not available at the time of this study but is now purchased by the VA), lovastatin 40 mg (Mevacor, Merck, Lot #L1143; generic lovastatin was not available at the time of this

study but is now purchased by the VA), metoprolol tartrate 50 mg (Caraco, Lot #1333A), paroxetine (Paxil, GlaxoSmithKline, Lot #400019B13), rofecoxib 25 mg (Vioxx, Merck, Lot #L3103), sertraline 100 mg (Zoloft, Pfizer, Lot #9JP018A), simvastatin 20 mg (Zocor, Merck, Lot #L1016), and warfarin 5 mg (Coumadin, DuPont Pharmaceuticals, Lot #SP094A).

The previously described tablet-splitting method and acceptance criteria were followed,⁶ with the exception that a tablet splitter (ACE-LIFE Pill Splitter model PS12E; Health Enterprises Inc., North Attleboro, MA) was used. This tablet splitter consists of upper and lower platforms, which are connected by a hinge. The lower platform provides for the placement of the tablet within a V-shaped region. A razor blade is centered on the upper platform. A tablet is split by pressing the upper platform onto the lower platform (Figure 1). This model of tablet splitter is distributed to VA patients who are instructed to split tablets. For this study, one trained, supervised pharmacy student (tester) performed all tablet splitting in a controlled laboratory environment. This study design did not employ patients; rather, it employed a trained tester to split tablets, since individual patients are known to vary in their ability to split tablets. In evaluating the hypothesis that tablet splitting would result in half tablets that generally fail to provide acceptable dose uniformity, our methodology represents a best-case approach.

Each tablet was carefully placed in the designed split area of the splitter; in all cases, the aim was to obtain evenly split tablet halves. The tester split Zestril 40 mg tablets to affirm the ability of the tester to obtain the favorable tablet-splitting results reported previously (i.e., weight uniformity that passes the acceptance criteria).⁶ If a tablet was scored, the tablet was situated in the splitter such that the blade would cut within the score groove. However, for warfarin and furosemide, splits were also performed when the tablet was randomly placed in the splitter (i.e., random orientation of the tablet score relative to the blade). Also, because of its trapezoid shape, lisinopril (Prinivil) could be placed into the splitter with 2 different orientations; both orientations were evaluated.

The previously applied criteria were followed in assessing whether the resulting half tablets split uniformly.⁶ The criteria were adapted from the U.S. Pharmacopeia's (USP) <905> "Uniformity of Dosage Units" test for whole tablets.⁸ Briefly, the test entailed subjecting 30 tablets of each product to the following:

- 30 tablets were weighed. The mean weight per tablet was calculated. The acceptable 85% to 115% range for a perfectly split tablet was determined from this mean weight. All weight measures employed a Mettler AE 100 analytical balance (Mettler Toledo, Inc., Columbus, OH).
- 10 of the 30 tablets were individually weighed. Each tablet was split, resulting in 20 half tablets. Each half tablet was weighed.
- From the 20 half tablets, the number of tablet halves outside the 85% to 115% range was counted. The number outside the 75% to 125% range was also counted. The relative standard

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TABLE 1 Performance of Tablets That Split Successfully

Product	Percent Outliers Beyond 85%-115% (and Beyond 75%-125%)	Percent RSD	Percent Dose Loss (\leq Max)	Observations	Scored (Y/N)	Flat (Y/N)	Tablet Shape
Celexa 40 mg	0 (0)	6.1	0.2 (0.4)	Dramatic score; appears to facilitate accurate splitting	Yes	No	Oval
Coumadin 5 mg (orientation 1)	0 (0)	3.3	0.00 (0.18)	Tablet situated such that blade would split tablet along the score	Yes	No	Round
Coumadin 5 mg (orientation 2)	0 (0)	6.2	0.5 (1.4)	Tablet situated such that score was randomly oriented relative to blade	Yes	No	Round
Furosemide 40 mg (orientation 1)	0 (0)	3.9	0.8 (1.7)	Tablet situated such that blade would split tablet along the score	Yes	Yes	Round
Furosemide 40 mg (orientation 2)	0 (0)	7.8	1.3 (7.3)	Tablet situated such that score was randomly oriented relative to blade	Yes	Yes	Round
Glipizide 10 mg	0 (0)	6.1	0.08 (0.95)	Tablet situated such that blade would split tablet along the score	Yes	No	Round
Lipitor 40 mg	0 (0)	5.5	0.1 (0.4)	Tablet situated such that blade would split tablet where a score would be; difficult to position in the splitter	No	No	Oval
Metoprolol 50 mg	0 (0)	5.4	0.1 (0.4)	Tablet situated such that blade would split tablet along the score but the most difficult to position in the splitter since the tablet is oblong	Yes	No	Oblong
Paxil 40 mg	0 (0)	3.5	0.56 (1.00)	Tablet situated such that blade would split tablet where a score would be	No	No	Oval
Zoloft 100 mg	0 (0)	3.3	0.1 (0.3)	Tablet situated such that blade would split tablet along the score	Yes	No	Oblong

deviation (RSD) of the half-tablet weights was calculated. If, at most, 1 half tablet was outside the 85% to 115% range, but within the 75% to 125% range, and if the RSD was $\leq 10.0\%$, the half tablets passed this uniformity test.

- If 2 half tablets were outside the 85% to 115% range (but within 75% to 125% range) or if RSD $> 10.0\%$, the additional 20 tablets were split. To pass, none of the additional 40 half tablets could be outside the 85% to 115% range, and the RSD for all 60 half tablets needed to be $\leq 10.0\%$.
- If 3 or more of the 20 half tablets were outside the 85% to 15% range, the half tablets failed this uniform test. Also, if any half tablets were outside the 75% to 125% range, the half tablets failed this uniformity test.

Hence, like the USP "Uniformity of Dosage Units" test for whole tablets, half tablets could fail because of too many half tablets outside the 85% to 115% range, too many half tablets outside the 75% to 125% range, or too high an RSD. However, the criteria applied here are more liberal than the USP test for whole tablets, since the USP test allows an RSD of a maximum 6%. Also, half-tablet weight, rather than chemical assay of actual drug, was evaluated. These 2 aspects facilitate tablet halves to pass the uniformity test. The percent-dose loss due to the splitting process was also monitored. The percent-dose loss was the relative difference between the weight of the original tablet and the combined weight of its 2 half tablets.

Results

Of the 12 products subjected to splitting, 8 products (67%) yielded half tablets that passed the weight uniformity test. These results generally contrast with previous results where 8 of 11

razor-blade-split products provided half tablets that failed.⁶ Tables 1 and 2 list the products that passed and failed, respectively. Using a tablet splitter in this study, all 6 scored tablets passed, while most unscored tablets failed (4 of 6 failed). This tendency conflicts with a previous observation that no visible tablet features (e.g., tablet scoring, tablet shape) predisposed a product's half tablets from passing or failing the uniformity test.⁶ Among the 3 products included in both our previous and the present study, paroxetine and sertraline each passed in both studies, while atorvastatin failed previously but passed here.

Warfarin and furosemide passed, regardless of how the tablet score was oriented relative to the splitter's blade (Table 1). For each of these products, results from the random orientation were slightly less desirable than the results from the nonrandom orientation. Lisinopril failed, regardless of how the tablet score was oriented relative to the splitter's blade (Table 2).

Rofecoxib and simvastatin (Table 2) failed the uniformity test for every reason: too many half tablets outside the 85% to 115% range, too many half tablets outside the 75% to 125% range, and too high an RSD. Lovastatin and lisinopril in one orientation (i.e., the orientation that provided a more stable fit of the Prinivil tablet within the tablet splitter) failed for 2 of these 3 reasons. Lisinopril in the other orientation (i.e., the orientation that provided a poor fit of the tablet within the tablet splitter) failed for all 3 reasons.

Discussion

Favorable Tablet-Split Results

The objective of this report was to split several tablet products relevant to the VA Maryland Healthcare System and assess

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TABLE 2 Performance of Tablets That Did Not Split Successfully

Product	Percent Outliers Beyond 85%-115% (and Beyond 75%-125%)	Percent RSD	Percent Dose Loss (\leq Max)	Observations	Scored (Y/N)	Flat (Y/N)	Tablet Shape
Mevacor 40 mg	15 (0)	10.4	0.9 (3.2)	Failed by a small margin	No	Yes	Octagon; thick
Prinivil 40 mg (orientation 1)	20 (0)	13.4	1.5 (7.2)	This orientation provided a good fit of the tablet within the tablet splitter	No	Yes	Trapezoid (but not a square); top of the tablet was inserted toward the blade of the tablet splitter
Prinivil 40 mg (orientation 2)	40 (10)	15.8	0.6 (1.0)	This orientation provided a poor fit of the tablet within the tablet splitter	No	Yes	Trapezoid (but not a square); bottom corner of the tablet was inserted toward the blade of the tablet splitter
Vioxx 25 mg	50 (20)	21.1	1.9 (6.2)	Thick and hard tablet; most difficult to split since the blade is able to move tablet during splitting	No	No	Round; the tablet is almost spherical, due to its small tablet diameter, round shape, and convex (nonflat) surface
Zocor 20 mg	20 (10)	15.0	0.00 (1.30)	Difficult to position the tablet in the splitter	No	No	Shield-like; the tablet's sharpest point was inserted toward the blade of the tablet splitter

whether the resulting half tablets provided equal doses. Our findings here are surprisingly favorable. Using the same criteria applied here, our previous observations from razor-blade splitting showed that a majority of tablets did not split evenly and visible tablet features did not predict a product's half tablets from passing or failing the uniformity test.⁶ Using similar criteria, Rosenberg et al. also observed tablet splitting that resulted in half tablets that generally did not exhibit half-tablet uniformity.⁷

Hence, our expectations for this study were low. However, the results are relatively favorable and generally support the mandatory tablet-split policy of the VISN 5 region. Of the 12 products subjected to splitting, 8 products yielded half tablets that passed the weight-uniformity test. For these 8 products, including warfarin, it would appear that motivated and capable patients, under the direction of a pharmacist, would not experience any adverse therapeutic effects due to dose variation from tablet splitting. This conclusion is based on the half tablets of these 8 products exhibiting weight uniformity to whole tablets.

One possible explanation for the differences between this study, where a majority of tablets passed, and our previous results, where a majority of tablets failed, is that the use of a specific model of tablet splitter provided better tablet splitting. However, Sedrati et al. identified several tablet products that, when split using a tablet splitter, resulted in half tablets with doses outside a 85% to 115% range of the target half-tablet dose.⁹ Similarly, Horn et al. found several products used in pediatric patients to not split equally.¹⁰ Another possibility is that the VA was selective in identifying tablet products for splitting (i.e., preferentially selected tablets that split evenly). The VA has previously indicated that sertraline tablets split accurately.¹¹

Possible Role of Tablet Shape and Hardness in Less-Favorable Tablet-Split Results

The 4 products that failed the weight-uniformity standard were lovastatin, lisinopril, rofecoxib, and simvastatin. In contrast to our previous observations that scoring, or any other visible characteristic, could not predict uniformity test results,⁶ a tablet score here tended to explain whether a tablet passed or failed the uniformity test. However, we suspect that shape and tablet hardness, and not scoring, were perhaps the true determinants of acceptable uniformity. Relative to the products that split evenly (Table 1), 3 of the 4 failed products (Table 2) have unusual shapes. Lisinopril (Prinivil) is trapezoidal in shape, with no central axis that could provide an even split. Additionally, lisinopril, in either orientation, did not sit well within the tablet splitter; the tablet did not match the angle of the tablet splitter and rocked as the blade cut through the tablet, particularly for the second orientation (Table 2). Simvastatin's positioning within the splitter was unstable because of the tablet's shield shape. In contrast to the unusual shapes of lisinopril and simvastatin, the roundness of glipizide facilitated its favorable positioning within the tablet splitter.

The hardness and spherical shape of rofecoxib resulted in difficult, unreliable splitting. (Tablet hardness was assessed by the tester's perception of the force required to split the tablets; rofecoxib tablets were deemed the hardest tablets.) Rofecoxib's extreme hardness required that the tablet-splitter's blade be firmly pressed into the tablet. Subsequently, this great force caused the tablet to uncontrollably rock as the tablet was cut. Rofecoxib also lost the most tablet residue (i.e., "crumbs"), because of the need to press hard on the tablet splitter.

Lovastatin did not exhibit any apparent shape or hardness difficulties, but it marginally failed. Lovastatin is a relatively thick tablet for its small size.

Interestingly, all 4 products from Merck failed, and all non-Merck products passed. These Merck products—lisinopril, lovastatin, rofecoxib, and simvastatin—do not appear to share any one common physical characteristic, except that each has an unusual shape to some extent.

Lovastatin and Lisinopril: Clinical Considerations

For lovastatin, 15% of the half tablets exhibited weights greater than $\pm 15\%$ of target. For one orientation of lisinopril within the tablet splitter (i.e., orientation 1, where the top of this trapezoidal-shaped tablet was placed toward the splitter's blade), 20% of the half tablets exhibited weights greater than $\pm 15\%$ of target. The percent RSD for lovastatin and lisinopril half-tablet weights was just over 10%. A similar degree of failure was previously observed with several other products.⁶ Cohen has indicated that this degree in half-tablet weight variability is acceptable since therapeutic outcomes would likely be unchanged.⁵

Given the wide therapeutic index of lovastatin^{12,13} and lisinopril,¹⁴ it would appear that splitting these 2 products is acceptable. Gee et al. found that splitting HMG Co-A reductase inhibitors such as lovastatin had no negative effect on lipid panels or liver enzyme tests.¹⁵ Laboratory lipid and liver enzyme tests were conducted before and after 512 patients were enrolled in an HMG Co-A reductase inhibitor tablet-splitting program. Among the patients, 85% of the patients were treated with simvastatin, 15% were taking lovastatin, and 1 patient was administered atorvastatin. Patients were maintained on the same HMG Co-A reductase inhibitor and dose before and after implementation of the program. Laboratory results comparing whole- and half-tablet performance from all 512 patients indicated that there was no change in total cholesterol and triglycerides. Statistically, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) changed favorably, and liver enzymes AST and ALT each increased, although these changes were apparently not clinically significant. These results suggest that a split-tablet program had no effect of HMG (e.g., lovastatin) clinical outcomes.

Rindone found that splitting lisinopril did not change control of stable hypertension.¹⁶ Rindone randomized 28 patients with hypertension, who were on stable doses of lisinopril, into a crossover clinical trial. Patient blood pressures were measured when they were taking whole tablets and split tablets. No statistically significant differences in systolic or diastolic blood pressures were observed between whole-tablet and split-tablet groups.

Simvastatin: Clinical Considerations

Relative to lovastatin and lisinopril, tablet-splitting results for simvastatin were less satisfactory (Table 2). Twenty percent of the half tablets fell outside the $\pm 15\%$ target weight range, with

half of those half tablets falling outside the $\pm 25\%$ target weight range. However, 3 studies have assessed the clinical performance of split simvastatin tablets and found favorable results. Using retrospective chart review, Duncan et al. evaluated the effect of splitting simvastatin on patient LDL cholesterol and total cholesterol.¹⁷ Patients were taking simvastatin whole tablets and obtained regular lipid management and cholesterol measurements. Patients were converted to split tablets and maintained the same milligram-per-day dose. There was no statistically significant increase in either LDL or total cholesterol after conversion to split tablets; in fact, each laboratory value decreased. Duncan et al. conclude that half-tablet dosing of simvastatin was as effective as whole-tablet dosing. They also found similar findings for atorvastatin.

In a similar study, Rindone and Arriola converted hyperlipidemic patients from fluvastatin to simvastatin, where patients were instructed to use a tablet splitter to split simvastatin tablets in half.¹⁸ In the 56 patients who completed the study, total cholesterol, triglycerides, and high-density lipoprotein were unchanged, with LDL statistically decreasing. Rindone and Arriola indicate that this substantial cost-savings approach, which, in part, relied on splitting simvastatin tablets, exhibited lipid control in the majority of patients. Most recently, Gee et al. measured laboratory lipids and liver enzyme levels in 512 patients who were enrolled in a HMG Co-A reductase inhibitor tablet-splitting program, where 85% of the patients were treated with simvastatin, as described above.¹⁵ These 3 studies, along with the present split-tablet results and wide therapeutic index of simvastatin,¹⁹ support the mandatory tablet-split policy for simvastatin.

Rofecoxib and Sildenafil: Clinical Considerations

Rofecoxib tablets provided the least desirable half tablets. Fifty percent of the half tablets fell outside the $\pm 15\%$ target weight range, 40% of those half tablets fell outside the $\pm 25\%$ target weight range. Since rofecoxib has a high therapeutic index,^{20,21} we anticipate that these rofecoxib dose variations will not result in adverse clinical outcomes. The effective daily dose of rofecoxib ranges from 12.5 mg to 50 mg, but the drug is not particularly sensitive to dose. Further, when healthy volunteers were administered up to 5 times the maximum recommended dose for a period of 14 days, no serious toxicities were observed²¹; hence, dose variations from rofecoxib half tablets do not present a toxicity problem.

While sildenafil tablets were not split here and are on the VISN 5 mandatory split list, a clinical study supporting VA policy by Orrico et al. found that the dose of sildenafil citrate could be titrated to the lowest effective dose while incorporating tablet splitting as a method to reduce drug cost.²² In 96 patients, 58% responded to 50 mg (half tablet) of the drug.

Further Managed Care Considerations

To date, the mandatory tablet-splitting program continues to

offer a substantial costs savings to the VA, both on a local and a national level. Results here support this program, as weight uniformity was generally acceptable for these products. Tablet-splitting initiatives offer the VA, and potentially other managed care organizations, an attractive cost benefit, while maintaining quality health care for health plan members.

As demonstrated here with the several nonmandatory split products tested, other prescription medications may be suitable for a tablet splitting program. For a product to be an appropriate candidate for splitting, several factors should be considered.¹ Sustained-release, enteric-coated, and other dosage forms where tablet splitting would compromise the product's intended release mechanism should not be considered. The product should be relatively flat-priced across dose or have an acquisition cost to the organization that would offer a savings by splitting the higher doses. To maximize savings, tablet splitting should be preferentially considered for more expensive medications. Using these criteria, VA and other health care organizations may prospectively identify prescription medications where mandated tablet splitting will reduce prescription costs while not compromising patient care.

It should be noted that the VA tablet-splitting program is cost-neutral to patients. The patient copayment is \$7 for a 30-day supply, although some patients are exempt from providing a copayment because of financial status or service-connected disabilities. Since copayments are based on days of therapy and not drug costs, VA patients do not have a financial motivation to split tablets. However, patients in other health care systems, particularly those patients who pay out-of-pocket for medications, would likely have a greater incentive to utilize tablet splitting. This motivation would be most pertinent to those products that are flat-priced, enabling patients to purchase twice the drug supply for a given cost.

Limitations

The results of this study generally support the mandatory tablet-splitting policy of the VISN 5 region but are subject to limitations. One limitation is that there are no publicly defined acceptance criteria for half-tablet weight uniformity. Hence, alternative criteria can be considered and applied to our results. In our consideration of the data, we applied criteria that we have used previously.⁶ These criteria are more liberal than the USP test for whole tablets, in part since the USP test allows only an initial RSD of no more than 6%, while the criteria that we applied allowed 10% RSD. If an initial 6% RSD limit were applied, several of the products in Table 1 that we found to pass would require further evaluation (i.e., "Stage 2" testing) and could possibly fail. Additionally, half tablets were assessed for dose uniformity immediately after being split; half tablets were not placed back into a prescription vial, where they may be subjected to attrition. At this time, we know of no specific evidence to favor any particular acceptance criteria for weight uni-

formity of half tablets. It has been suggested that patients, caregivers, and health systems would benefit from public quality standards for half tablets.^{6,7}

A second potential limitation of this study is the use of a trained pharmacy student to perform the tablet splitting. It is possible, and even likely, that different outcomes would result, depending on who performed the splitting. It would be perhaps desirable to evaluate the ability of various individuals and patients to split tablets and to elucidate the individual patient factors that contribute to successful tablet splitting. Given the positive results of our study, further research would be desirable to determine if VA patients can obtain similar favorable weight uniformity to better replicate the real-world environment. Other studies have assessed the ability of patients to split tablets. McDevitt et al. evaluated the ability of healthy volunteers to split hydrochlorothiazide tablets by hand.²³ Gender, age, education, or tablet-splitting experience were not found to be predictive of the ability of individuals to split tablets. Peek et al. evaluated the ability of patients to split simvastatin, metoprolol, warfarin, and lisinopril tablets.²⁴ Individual patients were assigned to one of 4 groups that differed in brand of tablet splitter and whether patients were instructed in the method of tablet splitting. Peek et al. found that both the brand of the tablet-splitting device and instruction improved tablet-splitting accuracy. Patient experience also resulted in more accurate splitting of warfarin tablets.

A third potential limitation was our use of a specific device to split tablets. Peek et al. found that one splitter performed better than another splitter.²⁴ The suggestion that different tablet-splitting devices can yield markedly different uniformity results reflects our previous anecdotal experience with a tablet-splitting device different from the device used in the present study. In our previous experience, the commercially available tablet splitter appeared to be of lower quality and poor design; a razor blade was simply glued onto a plastic housing at an angle not perpendicular with the plastic housing, resulting, commonly, in properly centered tablets splitting into approximately one third/two third "halves." The poor design and performance of this earlier device caused us to abandon the use of a tablet splitter and rely on splitting tablets with a simple razor blade, by hand.⁶ Hence, we suspect that the quality of the tablet splitter can directly affect half-tablet weight uniformity, and our results using the ACE-LIFE Pill Splitter model PS12E may not be applicable to all tablet-splitting devices.

We also did not measure patient outcomes. Tablet splitting could have an adverse effect on patient compliance. Several studies have examined the influence of patient tablet splitting on compliance and generally indicate that most patients accept tablet splitting. For example, Carr-Lopez et al. studied 233 patients, aged 35 to 87 years, who were prescribed 40 mg tablets of lovastatin and instructed to split them into two 20 mg doses.²⁵ Most patients reported that the tablet splitter was easy

to use and did not affect their compliance. However, 6% reported that the tablet splitter was difficult to use, and they would not split tablets even to save money. Mendez et al. found similar results for patients taking half tablets of simvastatin, although 40% of patients believed that splitting would influence compliance.²⁶ Fawell et al. studied the relationship of tablet splitting and compliance, drug acquisition cost, and patient acceptance for fosinopril sodium.²⁷ Patients accepted tablet splitting, and the splitting of fosinopril sodium tablets reduced the drug acquisition costs in the health system without affecting patient compliance.

Another potential limitation is the unknown clinical significance of dose variability in half tablets. The focus of our work was on products relevant to the VISN 5 region. Other products of interest may include drugs with a narrower therapeutic index. Dose variability is expected to be of greater potential importance for drugs with a narrow therapeutic index. Warfarin was evaluated here and is considered a narrow therapeutic index drug. Given the small dose variations observed here for warfarin half tablets and the lack of evidence to suggest any adverse clinical effects of such small dose variations, we anticipate tablet splitting of warfarin to have no clinical consequence.

Conclusion

Previous observations from experience with razor blade tablet splitting showed that a majority of tablets did not split evenly and that visible tablet features did not predict success or failure of the half tablets to pass the weight-uniformity test. However, our results for weight uniformity in the current study were favorable and generally support the mandatory tablet-splitting policy of the VISN 5 region. We interpret our results to indicate that a tablet-splitting policy is a viable approach to provide patients with dosage forms with acceptable weight uniformity. There is, however, a need for quality standards for half tablets to permit health care providers to better delineate the acceptability of tablet-splitting policies.

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DISCLOSURES

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