Technology Assessment Program

Office of Patient Care Services

UPDATED INFORMATION FOR VA TECHNOLOGY ASSESSMENT PROGRAM (VATAP) REPORTS

In June 2000, VATAP was relocated within the Veterans Health Administration from the Office of Research & Development to the Office of Patient Care Services. The following report was produced prior to the relocation of VATAP.

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VA TECHNOLOGY ASSESSMENT PROGRAM
SHORT REPORT – *Tablet Splitting*

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Executive Summary

Tablet splitting has received media, policy, and research attention for several reasons:

- As tablets of all doses for some drugs are sold for the same price, if a physician prescribes tablets for twice the dose needed by a patient and advises splitting the tablets, costs for drug acquisition may be substantially reduced.

- The need for dose titration, should tablets in low enough doses not be available (Therapeutics Initiative, 1995).

VA's Chief Patient Care Services (PCS) Officer requested that the MDRC Technology Assessment Program (TAP) provide a bibliography and overview of any empiric literature available on the safety and effectiveness of splitting drug tablets. While tablet splitting may have cost benefits, the Chief Patient Care Services Officer was concerned that the safety of the practice be documented before it became institutionalized as VA policy.

His specific concern was*:*

"Is there any evidence for increased risk or reduced safety from splitting, or is this just a remote, unlikely, and purely hypothetical concern?"

Literature database searches and consultation with VA pharmacists identified 35 citations from peer-reviewed journals or conference proceedings. Of these, 9 (25.7%) met inclusion criteria for this review.

The limited available literature indicates that:

- Tablet splitting, either manually or with devices designed for the purpose, does not routinely produce equal halves.

- Depending on the dose-response curve and therapeutic window for a particular drug, this inequality of split may be associated with clinically important outcomes or risks. However, currently available studies do not provide evidence that potential clinically important outcomes or adverse events have actually occurred or been observed.

- Splitting may negate the effects of specific tablet formulations such as enteric coatings or other sustained release mechanisms. Accordingly, oral dosage forms that should not be crushed, split, or chewed include sublingual or buccal products, enteric-coated products, and extended-release products. In some cases, liquid dosage forms or capsules whose contents may be substituted are available for patients who have difficulty swallowing whole tablets.

- VA's Tablet Splitting Committee [within the Pharmacy Benefit Management (PBM) Strategic Healthcare Group] concurs that splitting of sustained release preparations should not be recommended.

Since patients cannot obtain double strength tablets of prescription drugs without a prescription, physician and pharmacist supervision of tablet splitting is built into existing regulatory systems for drug distribution.

An additional component of physician and pharmacist supervision could include monitoring the ability of patients to split tablets with acceptable accuracy. Monitoring may be particularly helpful for patients with impaired vision, or for those with compromised function of arms and hands.

Before the request to the TAP, VA's Pharmacy Benefit Management (PBM) Strategic Healthcare Group had conducted its own literature review and drafted a summary document as a possible basis for future policy

PBM reported to TAP that its primary concern in the draft was protection of patient safety. The draft lists tablets that cannot be divided as: non-scored sustained release preparations; enteric-coated tablets; and tablets that crumble easily. The draft further recommends that adverse events associated with divided tablets be reported through the local Pharmacy and Therapeutics Committee to the VISN formulary and therapeutics body and thence to the VA PBM Strategic Healthcare

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Group. The PBM draft is accompanied by procedures and written patient education materials. However, tablet splitting is not currently supported by VA national policy.

Background

VA's Chief Patient Care Services (PCS) Officer requested that the MDRC Technology Assessment Program (TAP) provide an overview of any empiric literature available on the safety and effectiveness of splitting drug tablets. His specific concern was*:*

"Is there any evidence for increased risk or reduced safety from splitting, or is this just a remote, unlikely, and purely hypothetical concern?"

According to the Chief PCS Officer and the literature (3 published studies meeting inclusion criteria for this report were conducted within VA) splitting of tablets is practiced within VA at a number of facilities. He asked that TAP provide a bibliography. The remainder of this short report will provide context for that bibliography (the "References" section) and the literature that it represents.

Assessment Methods

To identify published studies, TAP conducted searches of the following databases on January 12 and 25, 2000: MEDLINE®, HealthSTAR®, International Pharmaceutical Abstracts®, and EMBASE®. Search terms included variations on pill, tablet, or medication, and splitting, divided, halved, cut, or sliced. VA pharmacists and the PBM Strategic Healthcare Group supplied additional references.

Abstracts retrieved from these databases were reviewed, and articles were selected for inclusion in this report from the abstracts using the following criteria:

- Publication in an English-language peer-reviewed journal, (or acceptance for presentation at a peer-reviewed meeting and represented by an abstract with sufficient detail to judge research question, study, design, data analyses, and results);

- Presentation of research or analysis of split tablet drug safety or efficacy in adult human patients with quantitative results.

In cases where abstracts were the only available information (e.g., abstracts of presentations in meeting proceedings) and the abstract supplied inadequate detail for this report, authors were approached directly for further detail on their studies. Those who complied with TAP requests are listed under "Acknowledgements" (page 9).

Other published articles are referenced if they provide useful background material.

Other information sources
To obtain additional citations or information on policies and practices regarding tablet splitting, the TAP posted requests to electronic mail exchanges maintained for the International Network of Agencies for Health Technology Assessment (INAHTA) and evidence-based medicine communities.

Results

TAP database searches and other sources yielded 35 citations. Of these, 9 (25.7%) met inclusion criteria. Frequencies of the various categories of published reports are listed in Table 1. Articles meeting inclusion criteria (corresponding to the first row in Table 1) are further detailed in Table 2.

Table 1. Overview of the Literature – frequencies of article types in database searches and other sources

Category of published article(number of articles in subcategories)	Frequency
*Safety, efficacy, costs, or dose titration of split tablets	9
Descriptive article lacking research question, data, or results (including editorial, opinion, or letter)	4
Pediatric patients	1
Language other than English (one each in French, German, and Japanese)	3
Laboratory or *in vitro* analyses: • Contribution of inert ingredients or manufacturing processes to splitting properties (7) • Pharmacokinetic or dissolution properties of whole versus split tablets (9) • Accuracy or reproducibility of manual or device splitting • Letters with some research data [but not complete research report] (2)	18
Total number of citations identified through all sources	35

***** Articles represented by this row met inclusion criteria.

Table 2. Abstracted information from articles meeting inclusion criteria (first row in Table 1), organized by drug class

Reference, drug class (VA studies in bold)	Methods	Results
Cholesterol-lowering agents		
Mendez, 1999; *Simvastatin*	**Setting:** Teaching hospital, VAMC in Puerto Rico **Design:** Quasi-experimental (pre- and post-LDL levels), with satisfaction survey administered 2-3 weeks after study enrollment **Subjects:** 2 cohorts of patients coming to pharmacy with new prescription for *Simvastatin:* those provided with tablet splitter and those not so provided	In progress, due for completion 9/99, but not published at time of TAP searches for this report Details here were provided by the authors' transparencies for a presentation **Costs:** Tablet splitting saved $100,000 annually for all patients using *Simvastatin* at San Juan VAMC **Clinical outcomes**: Unavailable (only 25% of either cohort had final LDL evaluation) **Satisfaction:** • 62% survey response • 92% found splitter easy to use and takes < 1 minute • 60 % believed that splitting would not influence compliance • 52% found that pharmacist had adequately demonstrated splitting • 44% found that directions for splitting had been adequately discussed

Reference, drug class (VA studies in bold)	Methods	Results
Rindone and Arriola, 1998; various statins	**Setting:** VAMC, Arizona **Design:** case series **Subjects:** 60 patients with hyperlipidemia **Methods:** • *Simvastatin* tablets split (except for 2 patients who could not use splitter); split • *Simvastatin* substituted for *Fluvastatin* at 8:1 dose ratio; before and after substitution lipid profiles assessed; • 60 patients entered study, 56 completed protocol; outpatients selected from those who had received constant dose of *Fluvastatin* for at least 6 weeks	**Clinical results:** • The only change in lipid components was a NS decrease in LDL with *Simvastatin* • 41% achieved LDL goals with *Simvastatin* versus 30% with *Fluvastatin* (significant) **Withdrawals from study:** • 2 failures to complete protocol • 2 due to side effects of *Simvastatin* • None due to lack of ability or desire to split tablets **Conclusions:** • *Simvastatin* can be substituted for *Fluvastatin* in majority of patients without loss of lipid control • In many patients, LDL may decrease significantly with substitution • Use of 8:1 dose ratio and tablet splitting results in cost savings ($120/patient-year of therapy, $11,000 annually at VAMC) **Comments:** • Statins have broad therapeutic windows, making absolute accuracy in splitting non-essential; *Simvastatin* is not approved for splitting by manufacturer, but study patients were willing and able to use splitter
Carr-Lopez, 1995; *Lovastatin*	**Setting:** Air Force medical center, northern CA **Design:** survey **Subjects:** 318 patients, 233 usable survey responses (73%) **Methods:** patients selected from prescription records by cross-referencing *Lovastatin* and tablet splitter	• Most respondents found splitter easy to use and did not believe that it would influence compliance or waste medication • 6% thought splitter difficult to use and would not use it, even if splitting saved money. These respondents felt that splitting would influence compliance • Concern most frequently cited: splitting did not consistently produce equal doses
Other classes of drugs		
Valdez, 1999; SSRI	**Setting:** Medicare risk contract **Design:** retrospective review of medical records **Subjects:** 342 patients identified from HMO pharmacy claims database, 90 of these randomly selected for chart review	**Costs:** For Drug acquisition, MD office visits, dose adjustment, concomitant anxiolytic or hypnotic use calculated using commercial (drug company) software package • Highest for *fluoxetine* (not available as tablet and can't be split) • Similar for *paroxetine* • Reduced for *sertraline* by tablet splitting **Dose adjustment:** Required by 31% of all patients after beginning therapy
Rindone, 2000; Antihypertensive (*Lisinopril)*	**Setting:** VAMC, Arizona, clinical pharmacy department **Design:** retrospective medical record review **Subjects:** 29 (26 male) with hypertension and on stable dose of *Lisinopril*, selected at random from computer-generated lists of patients taking the drug **Methods:** • Baseline BP before cross-over randomization to full tablet versus split tablet for 2 weeks, followed by sitting BP measurement	**Systolic/diastolic BP:** NS difference **Patients' opinions:** • Mixed results on convenience and ability to split tablets • 89% willing to split tablets if cost savings to themselves resulted • 97% willing if cost savings to facility resulted **Conclusion:** splitting *Lisinopril* tablets does not result in changes in BP for patients with stable hypertension.

Reference, drug class (VA studies in bold)	Methods	Results
Orrico, 1998; Sildenafil (*Viagra*)	**Setting:** ambulatory care **Design:** case series **Subjects:** 547 patients referred by physicians for pharmacist consultations (FU completed for 110) **Methods:** sildenafil dose titrated to lowest effective dose, incorporating tablet splitting	**Response rates:** 85% overall: • 58% responded to 50 mg • 37% (3% partial response) responded to 100 mg • 1% responded to 75 mg **Side effects:** Side effects (in 20% of patients) included upset stomach, headache, skin flushing, lightheadedness, nasal congestion, groin pain
McDevitt, 1998; hydrochlorothiazide	**Setting:** NA **Design:** descriptive assessment of accuracy of manual tablet splitting **Subjects:** • 94 healthy volunteers recruited from suburban Philadelphia via newspaper announcement • Excluded if visually impaired, missing arms or fingers or with disabling arrthritis	**Deviation of tablet halves from ideal weight:** • 41% deviated by > 10% • 12% deviated by > 20% • Approximately 1% of weight lost to powdering or fragmenting when split **Predictors of results:** • Deviations not predicted by gender, age**,** or tablet splitting experience • 97% of subjects expressed preference for commercially available lower dose tablets, and 77% willing to pay median of 20% more than original prescription for them • Use of tablet splitting device did not improve accuracy **Conclusion:** If drugs with steep dose-response curves or narrow therapeutic window are split, the inaccuracies recorded could be clinically relevant.
Hixson-Wallace, 1998; anticoagulants (*Coumadin*)	**Setting:** pharmacist-managed anticoagulation clinic **Design, methods:** retrospective chart review and satisfaction survey to assess effect of regimen complexity (split versus whole tablets) on compliance, INR values, patient satisfaction **Subjects:** • 476 patients at pharmacist-managed anticoagulation clinic • Patients identified through chart review for all active patients at clinic • 100 patients then randomly selected for interview	• Most commonly prescribed dose was 5 mg for all clinic patients. • Compliant patients are more likely to have therapeutic INR values and to be taking non-alternating doses • Patients generally very satisfied with services at pharmacist-run clinic • Cost of whole-tablet regimen significantly higher than other regimens (with split tablets)
Fawell, 1999; angiotensin converting –enzyme inhibitor (*Fosinopril*)	**Setting:** VAMC, California **Design:** cohort comparison of compliance and costs in patients using device-split versus those using single whole tablets: • 971 patients split tablets and took one half tablet once daily • 646 took one whole tablet once daily	**Groups:** • Differed significantly in age • Did not differ significantly in number of medications, educational level, presence of caregiver, physical limitations, or copayment requirement • Median percent compliance not significantly different between groups • Splitting associated with 50% reduction in median annual acquisition costs

Abbreviations:
SSRI: selective serotonin reuptake inhibitors
INR: International Normalized Ratio = patient's prothrombin time/ mean normal prothrombin time
NA: not applicable
N: number of subjects in study
FU: follow-up

As indicated in Table 1 the highest frequency category of articles in the literature was *in vitro* studies of dissolution properties of split tablets, usually with comparison to whole tablets. Table 2 further details the 9 studies that met inclusion criteria. These and the *in vitro* dissolution studies provide only weak or indirect evidence on the safety of splitting drug tablets:

- Tablet splitting, either manually or with devices designed for the purpose, does not automatically or routinely produce equal halves.

- Depending on the dose-response curve and therapeutic window for a particular drug, this inequality of split may produce clinically important outcomes or risks of adverse effects.

- The effects of specific tablet formulations (enteric coatings or other sustained release mechanisms) may be negated by splitting.

- Finally, Pharmacists recognize cautions and concerns regarding tablet splitting. The widely circulated journal *Hospital Pharmacy* periodically features a section called "Oral dosage forms that should not be crushed." The 1998 update (Mitchell, 1998) lists the forms as sublingual or buccal products, enteric-coated products, and extended-release products. Mitchell also urges caution and consultation with a pharmacist before crushing or chewing drugs that irritate the oral mucosa, are extremely bitter, or contain dyes that could stain teeth and mucosa.

Information from INAHTA and the evidence-based medicine community

The findings from the limited available literature reported above were confirmed by respondents to the TAP's request for information from electronic mail lists.

Electronic mail lists did not yield any citations to published research that were not also identified in TAP searches.

Summary, Discussion, Conclusions

The published literature is limited with respect to both volume and quality of individual patient-based studies directly addressing the assessment question. While there are some indirect indications that the safety of tablet splitting could be a concern, the TAP was unable to identify published studies that directly document increased risks or decreased safety associated with splitting drug tablets. Reports from the international technology assessment or evidence-based medicine communities also failed to identify such evidence.

Common sense and the limited available literature both argue for caution in tablet splitting and for routine supervision of the practice by physicians and pharmacists. Supervision is built into regulatory systems for drug distribution, which would require a physician to prescribe double strength tablets before a patient could split them. (i.e., patients cannot obtain double strength prescription tablets without a physician's assistance.)

References

Citations reviewed for this report are listed below. Published studies meeting inclusion criteria are indicated by *.

Biron C, Licznar P, Hansel S, Schved JF. Oral anticoagulant drugs: Do not cut tablets in quarters [letter]. *Thrombosis and Haemostasis* 1999; 82(3):1201.

Canale B, Glosner SE, Henning T, Pitcherella R. Review of antidepressants in a Veterans Administration facility. *ASHP Midyear Clinical Meeting* 1998; 33(Dec):P-112E.

*Carr-Lopez SM, Mallett MS, Morse T. Tablet splitter: barrier to compliance or cost-saving instrument? *American Journal of Health-System Pharmacy* 1995; 52(Dec):2707-2708.

Casahoursat L, Lemagnen G, Larrouture D. Use of stress relaxation trials to characterize tablet capping. *Drug Development & Industrial Pharmacy* 1988; 14(15-17):2179-2199.

de Blaey CJ, Weekers-Andersen AB, Polderman J. [Compression of pharmaceuticals. V. Formulation development of a new compound with the aid of quantitative force displacement measurements (German)]. *Pharmaceutisch Weekblad* 1971; 106(Dec 3):893-903.

Elliott WJ. The costs of treating hypertension: what are the long-term realities of cost containment and pharmacoeconomics? *Postgraduate Medicine* 1996; 99(4):241-248, 251-242.

Erramouspe J, Jarvi EJ. Effect on dissolution from halving methylphenidate extended-release tablets. *Annals of Pharmacotherapy* 1997; 31(10):1123-1126.

Fagerstrom PO. Pharmacokinetics of whole and half Theo-Dur tablets. *European Journal of Respiratory Diseases* 1980; 61(109):62-66.

*Fawell NG, Cookson TL, Scranton SS. Relationship between tablet splitting and compliance, drug acquisition cost, and patient acceptance. *American Journal of Health-System Pharmacy* 1999; 56(24):2542-2545.

Francon D, Jean P, Inchauspe M, Calderon A, Dubouloz F. [Failure of gastric lavage in severe drug poisoning. Value of esophagogastric fibroscopy (French)]. *Annales Francaises d'Anesthesie et de Reanimation* 1987; 6(2):122-124.

Gabka J, Schwietzer CH. [Intensification of effect using a combination of analgesic drugs in a split-tablet (German)]. *Therapie der Gegenwart* 1974; 113(11):1898-1910.

Gibson SH, Rowe RC, White EF. Mechanical properties of pigmented tablet coating formulations and their resistance to cracking. Part 1. Static mechanical measurement. *International Journal of Pharmaceutics* 1988; 48(Dec):63-77.

Gupta P, K. G. Broken tablets: does the sum of the parts equal the whole? [Letter]. *American Journal of Hospital Pharmacy* 1988; 45(7):1498.

Herman J, Remon JP. Modified starches as hydrophilic matrices for controlled oral delivery. Part 2. In vitro drug release evaluation of thermally modified starches. *International Journal of Pharmaceutics* 1989; 56(1):65-70.

*Hixson-Wallace JA, Dotson JB. Effect of regimen complexity on compliance and cost of warfarin therapy. *ASHP Midyear Clinical Meeting* 1998; 33(Dec):CR-8.

Horn LW, Kuhn RJ, Kanga J. Evaluation of the reproducibility of tablet splitting in the pediatric patient. *ASHP Midyear Clinical Meeting* 1994; 29(Dec):P-448(R).

Kobayashi F, Ueno A, Nakagawa T, Adachi I, et al. [Release of morphine in splitting MS Contin tablet in half (Japanese)]. *Journal of Japanese Society of Hospital Pharmacy* 1994; 30(May):595-597.

Mandal TK. Effect of tablet integrity on the dissolution rate of sustained-release preparations. *Journal of Clinical Pharmacy and Therapeutics* 1996; 21(3):155-157.

McCormick EM. Making it easier to swallow. *Pharmacy Times* 1991; 57(Oct):94-95.

*McDevitt JT, Gurst AH, Chen Y. Accuracy of tablet splitting. *Pharmacotherapy* 1998; 18(1):193-197.

McEwen J, Durnin C, McMurdo MET, Moreland TA. Sustained-release verapamil: Multiple-dose pharmacokinetic comparison of 120-mg and 240-mg tablets and the effect of halving a 240-mg tablet. *Journal of Cardiovascular Pharmacology* 1989; 13(SUPPL. 4):S57-S59.

*Mendez CA, Lai L, Rivera G. Clinical and economic effect of providing patients with tablet splitters. *ASHP Midyear Clinical Meeting* 1999; 34(Dec):INTL-69.

Mitchell JF. Oral dosage forms that should not be crushed: 1998 update. *Hospital Pharmacy* 1998; 33(4):399-415.

Moreland TA, McMurdo MET, McEwen J. Multiple dose comparison of a whole 240 mg verapamil sustained-release tablet with two half tablets. *Biopharmaceutics and Drug Disposition* 1989; 10(3):311-319.

Okhamafe AO, York P. Stress crack resistance of some pigmented and unpigmented tablet film coating systems. *Journal of Pharmacy & Pharmacology* 1985; 37(Jul):449-454.

*Orrico KB, Veridiano RM, Wohl LB. Sildenafil dose titration program. *ASHP Midyear Clinical Meeting* 1998; 33(Dec):P-135E.

Primrose WR, Clee MD, Moody JP, Hockings N. Alteration of pharmacokinetics after halving a slow-release theophylline tablet. *Pharmacotherapeutica* 1983; 3(6):429-432.

Pritchard B, Senders H. Patient compliance aids. *On Continuing Practice* 1989; 16(July):25-29.

*Rindone, JP. Evaluation of tablet-splitting in patients taking Lisinopril for hypertension. *Journal of Clinical Outcomes Management.* 2000;7(4):22-4.

*Rindone JP, Arriola G. Conversion from fluvastatin to simvastatin therapy at a dose ratio of 8 to 1: effect on serum lipid levels and cost. *Clinical Therapeutics* 1998; 20(2):340-346.

Sedrati M, Arnaud P, Fontan JE, Brion F. Splitting tablets in half [Letter]. *American Journal of Hospital Pharmacy* 1994; 51(4):548, 550.

Shah VP, Yamamoto LA, Schuirman D, Elkins J, Skelly JP. Analysis of in vitro dissolution of whole vs half controlled-release theophylline tablets. *Pharmaceutical Research* 1987; 4(5):416-419.

Simons KJ, Frith EM, Simons FER. Dissolution and bioavailability studies of whole and halved sustained-release theophylline tablets. *Journal of Pharmaceutical Sciences* 1982; 71(May):505-511.

Therapeutics Initiative. Therapeutics Letter, Issue 10. ***Dose titration: minimize to maximize***. University of British Columbia. [Web Newsletter]. Accessed: January 13, 2000. Available: December 28, 1995. http://www.ti.ubc.ca/pages/letter10.html.

*Valdez C, Grier D. Determining the most economical SSRI for a Medicare risk contract. *American Journal of Health-System Pharmacy* 1999; 56(Jan):23-24.

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