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To Split or Not to Split?
Systematically reviewing the evidence surrounding pill-splitting

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Abstract

Background: Tablet splitting can provide dose flexibility, and cost savings. However, pharmaceutical representatives typically discourage the practice.

Aim: To identify and summarize all published concerns related to tablet splitting and to present the experimental evidence that investigates those concerns.

Design and Setting: Systematic review and qualitative synthesis of pill-splitting concerns and evidence.

Methods: Medline and EMBASE were searched, over all years of publication, for articles in English discussing the splitting of tablets/pills. Eligible articles included original research, narrative reviews, systematic reviews, and expert opinion.

Results: After removing duplicates, 1,837 potentially relevant articles underwent dual review and 1612 articles were excluded based on title and abstract. After examination of 225 full texts, 138 articles were included (1 systematic, 4 narrative reviews, 101 original research articles, and 32 opinion articles). The described concerns included difficulty breaking tablets, loss of mass, weight variability, chemical instability, overly rapid dosing if sustained-release medications are split, noncompliance, and patient confusion resulting in medication errors. We found no

substantive evidence to support concerns regarding loss of mass, weight variability, chemical instability, or noncompliance. Evidence does support 1) some older adults struggling to split tablets without pill splitters, and 2) the inappropriateness of splitting sustained-release preparations given the potential for alteration of the rate of drug release for some products.

Conclusion: With the exception of slow release tablets, which should not be split, and excepting those elders who may struggle to split tablets based on physical limitations, there is little evidence to support pill-splitting concerns.

How this fits in

In our experience, pharmaceutical representatives commonly discourage the splitting of their products. In the literature, concerns have been raised about difficulty breaking tablets, losing tablet mass, unequal splitting, chemical instability, confusion leading to medication errors, and the mistaken splitting of slow release preparations. Although some older adults may struggle to split tablets without pill-splitters, we found little to justify tablet-splitting concerns other than the need to avoid splitting slow release preparations. With the exception of slow release medications, tablet splitting to facilitate lower medication doses, and lower medication cost, appears safe.

Introduction

Using the lowest effective dose of all medications is key to minimizing adverse drug effects in older adults, and in those with polypharmacy.^{1,2} Splitting tablets in half can help to achieve these lower doses, and often results in substantial cost savings for patients.³⁻⁵ However, manufacturers commonly discourage the splitting of their products, and this leads some health care providers to be reluctant to suggest it.⁶ In order to obtain more objective information on the safety of tablet splitting, we conducted a systematic review of the literature in which we gathered and synthesized 1) all arguments against tablet splitting, and 2) all original research which validated or refuted those concerns.

Methods

Review Process

Dual reviewers were employed to evaluate titles and abstracts. A single reviewer assessed full texts for inclusion and extracted information. Two authors discussed and synthesized the data. As we were primarily interested in gathering and synthesizing both opinion, and non-clinical trial research related to tablet splitting, the usual PRISMA processes for evaluating study quality (which focus on clinical trials) did not apply.

Databases and Search Criteria

On May 29, 2019 we searched Medline and EMBASE databases for eligible studies spanning all available years of publication. With the assistance of a medical librarian we developed searches (online supplement eMethods) centered on the concepts of tablet (tablet*, pill, pills, capsule) and splitting (split*, half, halv*, divid*, break*, cut, cutting). The search was expanded under the heading of exp Tablets/ad [Administration & Dosage] and limited to the English language.

Included Studies

We obtained and read all studies discussing pill-splitting. This included original research, expert opinion, narrative review, and systematic review. Studies were excluded if pill-splitting was not a major focus of the paper or if the papers were not written in the English language.

Results

The database search yielded a total of 2,425 articles, of which 588 were duplicates. We screened 1837 titles and abstracts for inclusion, and examined the full texts of 225 articles, of which 138 met our inclusion criteria and were included in our qualitative review (Fig 1). The characteristics of included publications is provided in Table 1. The list of included articles is available in the online supplement (eReferences), as is a table breaking each study down according to publication type and the concerns raised or addressed (Supplementary Table 1).

Key Concern#1: Difficulty Breaking Tablets

Concern that patients may struggle to split tablets was raised in 38 articles, and pertained to splitting both by hand, and using a pill-splitter. This concern focused on older adults potentially

being limited by diminished manual dexterity, visual or cognitive impairments.⁷⁻⁹ Authors assumed tablets are harder to split when smaller, harder, and asymmetric in shape,¹⁰ and that splitting is easier by pill splitter, than by hand. Score lines are expected to make splitting easier.⁷

Evidence

Manual Splitting: Of 120 elderly acute care patients admitted to a teaching hospital, 94 (78.3%) were unable to either break a scored tablet by hand unaided, or open a medication container manually.¹¹ Manual splitting was similarly self-reported as difficult by 29.7% of home-dwelling adults 70-years and older,¹² and 36% of home-dwelling adults over 75-years.¹³ Geometry and composition of the tablet matter. Diabetics over 70-years were unable to split generic glyburide tablets 80% of the time, but only 30% failed to split a non-generic tablet with an easier to split design.¹⁴ Younger adults split tablets by hand more successfully than older adults (78.2% vs 38.1%), but age didn't correlate with the accuracy of splitting tablets into equal halves when successfully split.⁷

Use of a Pill Splitter: Numerous studies support pill splitters making splitting easier.^{3,4,15} Of 233 respondents to a survey (73% response rate) of Californian Air Force medical center patients asked to split lovastatin tablets to reduce costs (mean age 65-years), only 6% felt the splitter wasn't easy to use.¹⁶ Similar results were reported for a convenience sample of 30 Dutch patients selected to have a wide variation in physical ability, and asked to split both a large and small round uncoated tablet. While 17% of all participants, and 42% of those 65-years and older, failed to split tablets by hand, all participants successfully split tablets using two types of splitters.¹⁷ In another convenience sample of 30 older adults (mean 64.9-years), all successfully split a variety

of tablets, although accurately splitting tablets into equal halves was better in those given instructions on splitter use.¹⁸ Overall, *evidence suggests splitting tablets by hand is challenging for some older adults, for whom pill-splitters, or assistance from pharmacists or family may be needed.*¹⁹

Key Concern #2: Loss of Mass

Concern that splitting could pulverise (turn to powder) a meaningful proportion of the tablet was raised in 29 articles. The resulting loss of mass could potentially lead to incorrect dosage, and contamination / health concerns for those unwittingly exposed to the residue.^{7,20,21} If tablets fragment to a large degree, they may even need to be discarded, leading to increased healthcare costs.²²

Evidence

Although losses of mass up to 14% have been observed for tablets split into quarters,²³ the average loss has been reported as 2.6% for round tablets, and “insignificant” when tablets are oblong (an elongated oval shape).²⁴ Multiple other studies describe loss of mass as acceptable or insignificant.^{4,25,26} Overall, *evidence suggests that loss of mass is negligible for the vast majority of medications.*

Key Concern #3: Chemical Instability

Concern that split tablets would chemically or physically degrade was raised in 19 articles. Concerns centered on increased friability of split tablets, and chemical reaction with air, water, or light once coatings are breached, or packaging is removed. Splitting drugs with an enteric

coating, used as a protective barrier against stomach acidity, can also increase the rate of degradation within the gut.^{22,27-30} Potential consequences could include patients experiencing more adverse effects, or receiving lower effective doses of the active substance.²⁵

Evidence

One study assessed chemical stability of 11 quartered cardiovascular medications stored in plastic containers without light exposure 30-45 days post-split. Three of these 11 medications demonstrated decreased active drug including digoxin (mean drug concentration 68% of expected), spironolactone (82% of expected), and both generic and brand name amlodipine (91% and 93% of expected). Only the drop in digoxin concentration was believed clinically important.³¹ Similarly, split tablets were considered chemically stable for levothyroxine (after 8 weeks at 25°C/60% relative humidity), aspirin (at 1 week of refrigeration), and gabapentin (9 weeks at room temperature).^{30,32,33} Another study found gabapentin, risperidone, and losartan to be chemically stable at 90 days (25°C ± 2°C/60% ± 5% relative humidity).³⁴

More evidence on chemical stability of specific split medications is needed. However, *of the 16 studied medications we identified, only digoxin degraded fast enough for chemical instability to be considered clinically important.* Where medications are known to degrade, or where there is uncertainty, splitting only one tablet at a time should mitigate this concern. We found no studies examining bioavailability after enteric coated tablets were split.

Key Concern #4: Weight/dose variability

Concern that tablets would split unequally, and hence vary in dosage, was raised in 93 articles.^{29,35-37} This could lead to under-dosing, or over-dosing, and was of particular concern for drugs with a narrow therapeutic index.^{19,38}

Evidence

Several studies evaluated split tablet weight variability.^{26,31,39-41} One study analyzed 560 pharmacy-dispensed split tablets of 22 drugs and found only 32 (5.7%) of 560 tablet halves to deviate more than 15% from the expected weight⁴². In contrast, 41.3% of 1752 hydrochlorothiazide tablets manually split (i.e. no pill splitter) by 94 healthy volunteers deviated from their expected weight by more than 10%.²⁶ Other studies reported less clinically significant weight variation upon splitting,^{25,43} including studies reporting the drug content of half-tablets of warfarin and salbutamol, split by tablet splitter, to fall within USP specification criteria^{15,44}. In a study of scored and unscored tablets of Risperdal, Paxil and Zoloft, split by tablet-splitter, all half-tablets produced uniform dosages.⁴⁵ Similarly, for 30 lorazepam half-tablets, drug content was within 75-125% of expected for every half portion.⁴¹

An argument against the clinical importance of weight variability, even where it does exist, is 1) average doses remain the same over time, 2) differences in body weight are likely to have greater influence on drug levels than the observed minor differences in tablet weight,⁴⁶ and 3) a 10% variation in a single dosage will not mean a 10% variation in steady state drug levels, especially for drugs with longer half-lives.^{47,48} In terms of efficacy, multiple studies found no significant changes in total or LDL-cholesterol levels after splitting statins.⁴⁹⁻⁵¹ Overall, *although minor weight variation is likely to occur to some extent, it is unlikely to be clinically important.*

Key Concern #5: Sustained-release medications

Concerns about splitting sustained-release medication was raised in 27 articles. Sustained-release of medications with short half-lives is commonly achieved either by slow-release external tablet coatings, or by embedding medication in a slowly degrading matrix. Splitting such preparations could compromise the release mechanism and result in overly rapid drug release, and potential harm from overdose.^{6,52,53}

Evidence

While sustained-release preparations are not intended for splitting, it has been explored in some studies. Altered drug release kinetics were reported post-split for sustained-release matrix tablets of diltiazem,⁵⁴ and aspirin,⁵³ but not melatonin – although further cutting into quarters or crushing melatonin matrix tablets did alter release kinetics.⁵⁵ Film-coated verapamil tablets also retained their release characteristics upon splitting.⁵⁶ Overall, while some extended-release medications may be safe to split, *the impracticality of providers trying to remember which products can be split and which cannot, and the potential harm of overly rapid drug release, supports the generalization against splitting all slow-release products.*⁵⁷

Key Concern #6: Confusion / Noncompliance

Concern that directions to split tablets add complications that might confuse patients, or lead to non-compliance, was raised in 24 articles.^{28,35,58} In particular, there was concern that patients could split the wrong medication, that splitting could lead to miscommunication with patients or

pharmacists (such as 1/2 tablet being misinterpreted to mean 1-2 tablets), or that the extra hurdle to use the medication could lead come to stop it altogether.

Evidence

Using pill counting, patient questionnaire, and tracking the patient refill history of 105 fosinopril users, there was no significant difference in compliance for those who split fosinopril tablets, and those who did not.⁵⁹ This is consistent with reporting from a tablet-splitting program, which reported no compliance problems.¹⁶ Another tablet-splitting program involving 2,019 patients reported only 7% of patients found tablet-splitting to influence their desire to take medication.⁵¹ We found no studies examining the frequency of errors being made by patients or pharmacists.

Overall, while evidence is needed to explore whether confusion or miscommunication can lead to medication errors, *available evidence suggests compliance does not suffer when tablets are split*. For patients where confusion may be more likely, this problem can likely be overcome by bubble-packing by pharmacists, or weekly dosette box preparation by caregivers.

Discussion

Summary of main findings

Concerns related to pill-splitting include difficulty breaking tablets, loss of mass, weight variability, chemical instability, disruption of slow-release mechanisms, confusion/medication error, and noncompliance. Of these, evidence supports only the concern that some frail elders may struggle to split tablets without a pill splitter, and the caution that slow-release tablets should not be split.

Strengths and limitations of the study

Our findings are strengthened by having reviewed the literature systematically, with the use of dual reviewers in the review of titles and abstracts. They are limited by the qualitative nature of our synthesis, and the observational nature of much of the evidence. While including essentially all article types is a strength so far as enabling a broad perspective of the topic, it is also a limitation, in that the tools and templates for reporting a study's methods, findings, quality, and bias do not lend themselves to a collection of included studies that range from opinion to basic science.

Comparison with existing literature

Taken together, the evidence we have gathered supports the experience of tablet splitting programs that describe splitting tablets as safe, effective, and readily accepted by patients and providers.^{5,51} Our findings are at odds with narrative reviews that caution against pill-splitting.⁶⁰

Implications for future research and clinical practice

Provided patients who would struggle to split tablets are assisted in doing so, and provided slow-release tablets are not targeted for splitting, tablet-splitting appears to be an effective tool for utilizing minimum effective doses, and reducing medication costs.

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Ethical Approval:

Not applicable

Competing Interest:

The authors have declared no competing interests.

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Table 1. Characteristics of included publications (n=138)

Publication Type	No. (%)
Original Research	101 (73.2)
Opinion	32 (23.2)
Narrative Review	4 (2.9)
Systematic Review	1 (0.7)
Splitting Advantages Raised	
Cost-savings	73 (52.9)
Dose flexibility/titration	66 (47.8)
Ease of swallowing	46 (33.3)
Splitting Concerns Raised	
Weight/dose variability	93 (67.4)
Difficulty breaking tablets	38 (27.5)
Loss of mass	29 (21.0)
Sustained-release tablets	27 (19.6)
Confusion/Noncompliance	24 (17.4)
Chemical instability	19 (13.8)
Primary Authors (1st and last)	
Pharmacist	128 (62.7)
Unknown	58 (28.4)
Specialist Physician	9 (4.4)
Non-clinician	6 (2.9)
Generalist Physician	3 (1.5)
Nurse	0 (0.0)
Location of 1st Author	
North America	67 (47.9)
Western Europe	27 (19.3)
Asia	17 (12.1)
Eastern Europe	12 (8.6)
South America	7 (5.0)
Africa	5 (3.6)
Australia	5 (3.6)