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Does splitting a tablet obtain an accurate dose? A systematic reviewand meta- analysis

B. Akhila, P. Anil Kumar Yadav, Dr. N. Padmaja

Abstract

The requirement to divide tablets into two or more doses in order to optimize medication for specific patients has led to widespread tablet splitting. Problems may develop if a tablet is divided in an uneven manner.

The goal of the study was to provide a comprehensive review of the research on how tablet splitting affects dosage accuracy.

Study inclusion criteria were studies published before January 2020 that examined the impact of tablet splitting on dosage accuracy and were located using a search of MEDLINE, EMBASE, CINAHL, and Cochrane. Any medication study in which the pill was broken might be considered. The screening and data extraction were done by two separate reviewers. There have been meta-analyses done to see whether pill splitting affects how well a dosage works. (Project number: CRD42018106252 at PROSPERO) Of the 25 studies considered, 16 looked at how tablet splitting affected tablet weight, 1 looked at how it affected drug concentration, and 8 looked at both. The weight and drug content of split tablets were found to vary by just a little amount in a meta-analysis (0.87% and 0.24%, respectively, 95% confidence range 0.63%-1.11% and 95% confidence interval 0.06%-0.43%). There was considerable discrepancy across trials with regards to weight, but not with regards to drug content fluctuation (I2 =.50, vs.1%). Tablet features and the technique used to divide the tablets both had a role in determining how well they worked.

This investigation reveals that the weight and drug content variance is modest independent of the technique and tablet properties, even if tablet splitting may affect dosage accuracy. To further understand the function of tablet splitting on dosage accuracy, more research is required to measure medication plasma concentrations as well as the effect on patient health outcomes including blood pressure and cholesterol levels.

Keywords: tablet, dosage, precision, adjustment, evaluation.

INTRODUCTION

Tablet splitting is a widespread practice resulting from the need to alter doses into two or more parts and opti- mise medicine usage in individual patients. Almost a quarter of all drugs administered in primary care are split.[1] Subdividing a tablet is a common part of modern-day drug therapy. Patients may need to over- come dysphagia to facilitate swallowing large tablets.[2–4] This practice can be relatively unproblematic since it can bring the required amount to the patient. 5 However, complications may occur if a pill is broken and then portion of it is abandoned or consumed at a different time.

Dosage manipulation by splitting a tablet may be difficult because of the potential for ingestion of uneven pieces or loss of tablet weight, both of which might result in an inaccurate dose.

6,7 Drugs with different amounts of active ingredients or other ingredients may have different effects on the body. 8 This is particularly crucial for medications with a narrow therapeutic index and a short half-life, since their effects are highly dose-dependent. 9 The quality of stored pills may also decline with time. In order to meet the criteria for content or mass homogeneity, split pieces must be consistent. 10,11 Product that is exclusive to a certain brand To the extent that appropriate credit is given to the author(s), the work may be used for noncommercial purposes and distributed in any media, according to the provisions of the Creative Commons Attribution-NonCommercial-NoDerivs License.

Pharmaceutical Analysis

Dr.K.V. Subba Reddy Institute of Pharmacy

(Approved by AICTE,P.C.l New Delhi& Permanently Affiliated to JNTUA Anantapuramu

MOU with Government General Hospital &KMC, K urnool

The medicine package inserts may include information on whether or not a certain pill is suitable for splitting. This advice, however, is often disregarded. 12 Many hospitals also have their own medication information and medicine formularies that address tablet splitting. However, there is frequently a discrepancy between the information obtained from these many sources. Patients, doctors, pharmacists, and nurses might all become confused because of this, so it's important to pay attention. We need standardized documentation and data on tablet splitting. Although changing the dosage by dividing pills is common practice, there is little literature that summarizes the information on whether or not this really works. Previous analyses have narrowed their attention to a single group, medicine, or illness. 13,14 Despite the fact that the 2012 assessment didn't zero in on any one group of people, any one medicine, or any one ailment, it's clear that we need to do some updating. 15 This review aims to summarize the research on how tablet splitting affects dosage precision.

METHODS

The results of this systematic review are presented following the guidelines of the PRISMA declaration for 2020. PROSPERO is aware of the review and has registered it (Registration Number: CRD42 018106252). The procedures used to conduct this review have been previously documented and will only be briefly described here. 16

Procedure for Seeking

Together with a medical research librarian, we formulated a search strategy and compiled a list of relevant keywords.

All studies published in MEDLINE, EMBASE, CINAHL, and the Cochrane Library between their inceptions between 1946 and 2020 were considered for inclusion in the review. A search for citations in pivotal publications and a study of references in included research led to the discovery of additional studies. The following is an outline of the included keywords:

1.Intervention, (tablet* split*, (tablet* break*, (tablet* cut*, (tablet* manipulate*)).

Title, abstract, original title, name of substance, topic heading, floating subheading, keyword heading, protocol supplementary concept, rare illness supplementary concept, unique identifier, and synonyms are all examples of mp.

The primary effect is to (pill split, pill shatter, pill cut, pill manipulate).

title, abstract, original title, substance name word, topic heading word, floating subheading word, [keywords for headings, a secondary concept for a procedure, a secondary concept for a rare condition, a unique identifier, and some synonyms].

Study Selection

The eligibility of abstracts and full texts was determined by two researchers (KC, MK) working separately and using predefined inclusion and exclusion criteria. The senior author was brought in to address the differences of opinion between the two reviewers.

Eligibility Criteria

Eligible studies might have been conducted with any medicine, and it was not necessary that the pill be broken. Participant characteristics were not limited in any way. Any procedure that required the patient to manipulate tablets (but not capsules) for oral administration was considered. Tablets might be manipulated by slicing, chopping, or breaking them into manageable pieces. In this case, we had an entire, uncracked tablet to use as a reference point.

Outcomes

The major result was the weight or percentage of drug content retained after splitting the tablet, indicating how accurately the dosage was preserved. Evaluation of the effect of physical tablet properties, the impact of tablet splitting on health outcomes, patient satisfaction, and other secondary outcomes were also considered.

Data Extraction

Two researchers (KC, MK) used data from three of the included studies to prototype and iteratively optimize the data extraction form. 16 The data from all included studies were retrieved by a single researcher separately. A secondary researcher checked all of the study data to ensure its accuracy.

Analytical Statistics

To account for within-study variability, we used fixed-effects and random-effects models based on a binomial distribution in our meta-analyses of proportions. Confidence intervals (CIs) for the mean were computed using the Wilson Score technique, with a 0.5 continuity correction applied when the numerator was zero, and the CIs were limited by zero and one. We did subgroup meta-analyses based on splitting technique (manual vs. mechanical vs. sharp tool) and tablet characteristics (size, shape, and score line), and we presented the results

I2 measures the fraction of total variability that can be attributed to real world causes as opposed to random variation. Stata 15 (StataCorp, College Station, TX, USA) was used for all statistical analyses, and the metaprop tool was used to determine overall prevalence rates across all groups.

Judgment of Possible Bias

Two researchers independently used suitable risk of bias techniques to evaluate the potential for bias in the included studies.

Discussions between reviewers and the senior author resulted in a resolution of 16 disagreements. If a study satisfied all of the other inclusion criteria, we did not eliminate it because of a problem with its methodology.

RESULTS

The literature search identified 1259 potentially eligible articles. Of these articles, 1188 were excluded on title

and abstract screening. The remaining 71 underwent fulltext screening, and an additional 46 articles were excluded due to failure to meet inclusion criteria. The final analysis included 25 studies. Figure 1 shows the process of study selection.

Characteristics of Included Studies

The search for relevant literature yielded 1259 possible items. To be specific, 1188 articles were disqualified due to title issues. and screening in the abstract The remaining 71 were subjected to a thorough text screening, after which another 46 were disqualified for not meeting inclusion requirements. Twenty-five studies were included in the final tally. The procedure for choosing studies is shown in Figure 1.

Inclusion Criteria for Studies

There were no randomized controlled trials that matched the inclusion criteria, hence all research that were included were conducted in a lab. Six thousand six hundred and seventy pills containing a total of eleventy-six distinct medications were lost throughout the included trials. More over half (n = 63, 54%) of these 116 medications were cardiovascular aids; the remainder were either analgesics, anti-inflammatories, or psychotropics.

medications for epilepsy (n = 7), diabetes (n = 6), and other conditions (n = 17) make up 15% of the total. About a third (n = 9, 36%) of the included research took place in the United States, while the remaining 14 took place in other countries. Perspectives of fragmenting groupings antiepileptic (*n* = 7, 6%); diabetic (*n* = 6, 5%); and other (*n* = 17, 15%) drugs. From the 25 studies include, approximately a third were conducted in the United States (*n* = 9, 36%), with the rest in various different countries. The experience of groups engaged in splitting

iPad users varied from healthcare professionals (n = 15, 60%) to the general community (n = 4, 16%), but few research reported on the demographics of the splitters or their degree of expertise. Sixteen (64% of the total) of the studies cited American pharmacopoeias, five (20%) cited European pharmacopoeias, one (4%) cited British, one (4%) cited Indian, and two (8%) cited none.

Outcomes

Accuracy of dosing as determined by weight or medication content was the main endpoint (Table 1). Most studies used halved pills. Very few studies have attempted to divide tablets into thirds or halves; only one has even tried to divide a tablet into halves.

Precision of Dose Determined by Drug Mass and Concentration

Using the drug's weight, twenty-four trials determined the efficacy of the doses. If you were to divide a pill in half, the average weight difference would be 0.87 percent (95% CI 0.63 to 1.11 percent, I2 50%, Figure 2a). Dose accuracy was evaluated in nine investigations based on the percentage of active ingredients in tablets. Figure 2b shows that the average drug content variation of a split tablet was 0.24% (95% CI: 0.06-0.43%).

Dosage Accuracy Using a Table-Splitting Method

Different dose-splitting techniques produced varying degrees of dose precision (Table 2). There were three main types identified: I dividing pills by hand, (ii) using a dedicated tablet splitter, and (iii) using a sharp instrument such a razor or knife. Tablet splitters were employed in eight out of the ten investigations.

Table 1 General characteristics of included studies

Reference	Method of splitting	Dose accuracy	Pharmacopeia referenced	Outcome
Boogie (2004)[18]	Tablet cutter, hand	Weight	USP	Splitting of unscored valdecoxib tablets resulted in low mean weight variation
Cook, Edwards[19]	Tablet cutter, knife	Weight	USP	Split tablets varied considerably in weight
Dosti, Malaj[20]	Tablet cutter	Weight	EP	Weight deviation depended on presence of score line
Elliott, Mayxay[3]	Not specified	Weight	EP	10% of tablets deviated by more than 25%; coated and unscored tablets resulted in greater weight variation
Habib, Alanizi[21]	Tablet cutter, hand	Weight and drug content	USP	There was greater variation in weight when tablets were split by hand. Drug content variation appeared to be attributable to weight variation that occurred during the splitting process
Helmy (2015)[22]	Knife	Weight and drug content	USP	Approximately 15% of half-tablets fell outside USP specification of weight and drug content. The subsequent mean percentage weight loss was less than 1.5% for all drugs. Drug content variation was attributable to weight variation that occurred during splitting process
Hill (2009)[23]	Tablet cutter	Weight and drug content	USP	Almost a quarter of split tablets fell outside USP specification of drug content. Drug content variation in half-tablets appeared to be attributable primarily to weight variation due to splitting process
Kadi (2016)[24]	Tablet cutter	Weight and drug content	USP	Following splitting, approximately three quarters of split tablets fell outside USP specification of drug content; recommend not to split unscored tablets
McDevitt (1988)[25]	Tablet cutter, hand	Weight	USP	Less than an eighth of tablets split deviated in weight by more than 20%
Nidanapu (2016)[26]	not specified	Weight and drug content	IP	Splitting tablets resulted in suboptimal dosage and plasma concentrations
Nolly (2005)[27]	Tablet cutter	Weight	USP	Tablet splitting was acceptable, resulting in acceptable weight variations
Madathilethiu (2018)[28]	Tablet cutter	Weight and drug content	USP	Quartering 10 mg hydrocortisone tablets produced unacceptable dose variations
Polli (2003)[29]	Tablet cutter	Weight	USP	Two thirds of drugs passed the weight uniformity test, with remaining third generally within 20% of target weight range

separating tablets by hand, and by using a blade, by the count of nine. Two research failed to detail their partitioning techniques (Table 1). Using a pill splitter resulted in less weight variation (0.58%, 95% CI 0.35-0.82%), while using a sharp instrument resulted in more weight variation (1.43%, 95% CI 0.74-2.11%), although manually dividing the medicine had the least weight variation (0.44%, 95% CI 0.00-1.00%). When compared to using a sharp instrument (0.24, 95% CI 0.01-0.58%) or manually breaking the tablet (1.56, 95% CI 0.01-66.82%), the tablet splitter resulted in the least variance in drug content (0.13%, 95% CI 0.00-0.36%).

Features of Tablets That Affect How Well They Reconstitute After Being Split for Dosage

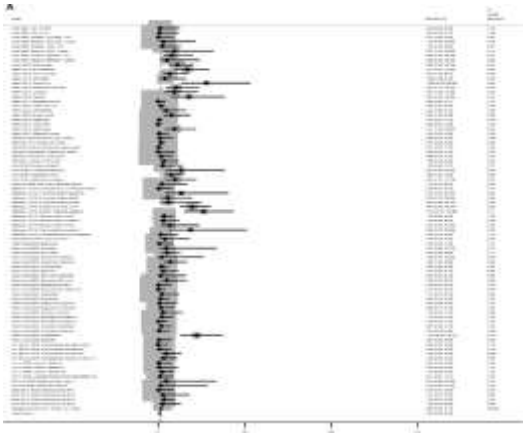
Scientists have reported on a variety of tablet features that might affect the split tablet's ability to deliver the correct amount (Table 2). From the total of 25 research, 23 (or 92%) mentioned whether or not a score line was used. Weight variation for scored tablets was 0.72 percent (95% confidence interval [CI] 0.45 percent to 0.98 percent) and drug content variation was 0.29 percent (CI 0.03 percent to 0.6 percent) lower than weight variation for unscored tablets (1.09 percent [CI] 1.09 to 1.09 percent).

Drug content fluctuation was 0.87 percent (95% confidence interval [CI]: 0.56 to 1.63 percent).

According to the studies (n = 16, 64%) that reported on tablet shape, the weight and drug content of oval-shaped tablets were more consistently distributed (weight variation: 0.54%, 95% CI: 0.25-0.83%; drug content variation: 0.48%, 95% CI: 0.51-1.48%) than those of round shape (weight variation: 0.99%, 95% CI: 0.45-1.52%; drug content variation: 2.36%, 95% CI: 0.66-4.06%).

Moreover, there was not much of a difference in the range of drug content variation between tablets with and without coating (1.61%, 95% CI 0.14% to 3.08%), as reported by 60% of the 25 investigations (n = 15). But there was more variance in weight among coated pills (1.15 percent, 95% CI 0.38 to 1.91 percent) than among uncoated tablets (0.65 percent, 95% CI 1.16 to 1.15 percent).

The Effects of Tablet Splitting on Health Outcomes and Patient Satisfaction



Almost three quarters of individuals in the research had plasma medication concentrations that were beyond the optimum range. 26 Patients' demographics were not discussed in any of the included studies.

whether taking the broken pill is a pleasant or bearable experience. No information was provided on tablet splitting's effect on taste or stickiness. But, according to one research

There was no mention of any health consequences from taking the broken pill in any of the studies we reviewed. Still, one

Figure 2 (Continued)

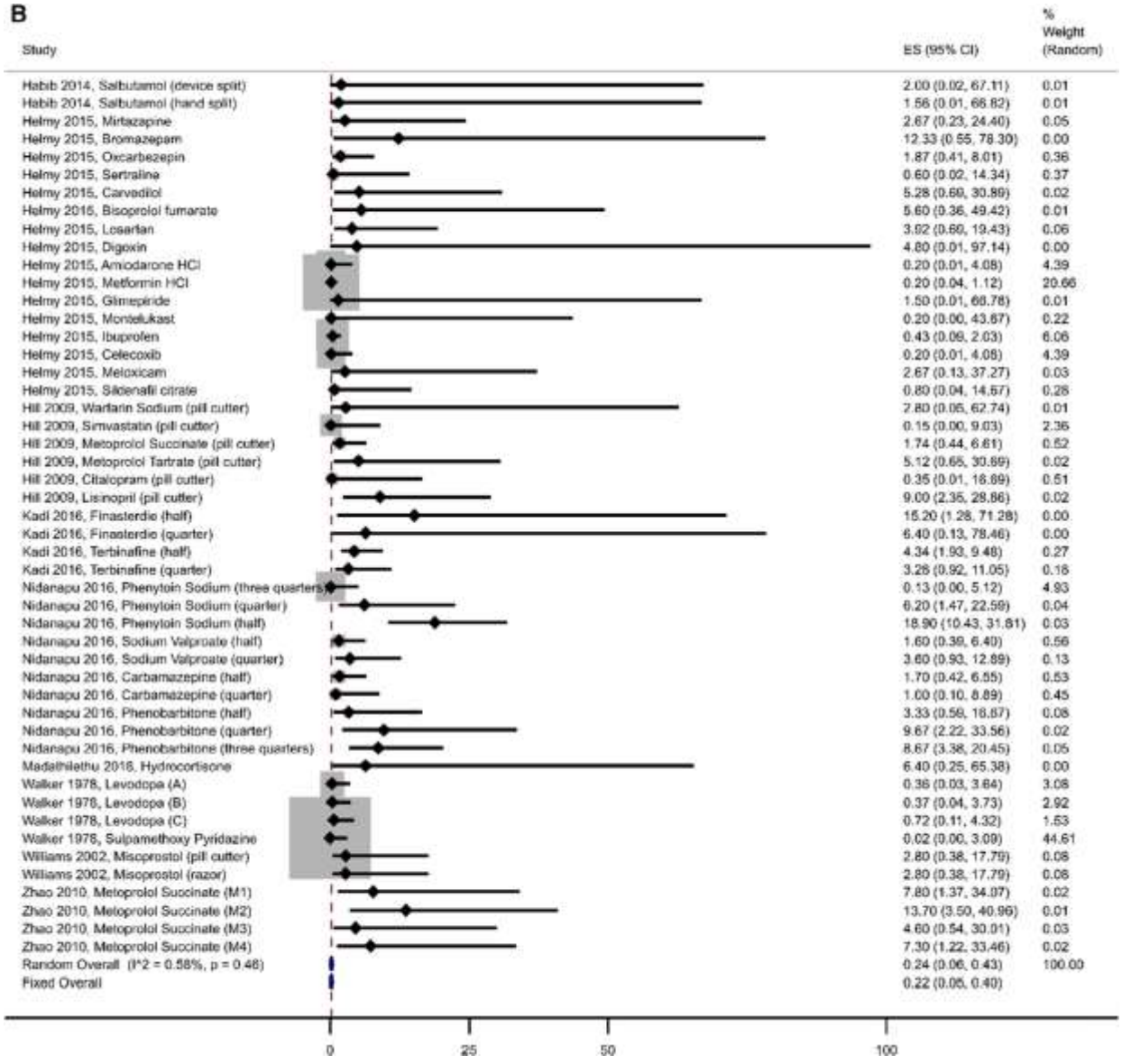


Figure 2 (a) Meta-analysis on mean weight variation on split tablet. (b) Meta-analysis on mean drug content variation on split tablet.

found that almost all participants (96.8%) would choose a lower dosage formulation over splitting a pill if given the option. Furthermore, over 80% of participants polled for this survey said they would pay more (with the median increase being 20%) for a lower dose strength. 26

Evaluation of the Quality of Studies

Figure 3 displays the results of the quality evaluation of the included studies. Studies used a combination of pills, and there were no randomized trials. Appropriate

Most research employed approaches intended to achieve their goals. More than half of the studies described their data collection methods and sample sizes for each medication. Studies also failed to account for the relative standard deviation of split tablets in their analyses. Many research attempted to accomplish their stated goals, but many failed to provide an adequate discussion of their findings.

DISCUSSION

Tablet splitting, according to previous studies,21 raises issues for drug and content variance.

Table 2 Weight and drug content variation of tablets within the studies

	Weight		Drug content	
Number of studies	24		9	
Variation overall	0.87%	(95%	0.24%	(95%
	CI	0.62–1.11%)	CI	0.06–0.43%)
Method of splitting				
Manual splitting	0.44%	(0.00–1.00%)	1.56%	(0.74–2.11%)
Tablet splitter	0.58%	(0.35–0.82%)	0.12%	(0.00–0.36%)
Sharp tool	1.43%	(0.74–2.11%)	0.24%	(0.01–0.58%)
Scoring				
Scored tablets	0.72%	(0.45–0.98%)	0.29%	(0.03–0.61%)
Unscored tablets	1.09%	(0.56–1.63%)	0.87%	(0.14–1.60%)
Shape				
Oval	0.54%	(0.25–0.83%)	0.48%	(0.51–1.48%)
Round	0.99%	(0.45–1.52%)	2.36%	(0.66–4.06%)
Coating				
Coated	1.15%	(0.38–1.91%)	1.61%	(0.14–3.08%)
Uncoated	0.65%	(1.16–1.15%)	1.61%	(0.20–3.03%)

and that this may have an effect on people's health. This meta-analysis is the first of its kind to systematically review the literature on the topic of pill splitting and its effect on dosage accuracy. Our objective was to learn more about how dividing pills affected dosage accuracy. Fortunately, this systematic review and meta-analysis indicated that the effects of dividing a tablet on its weight and pharmacological content were minimal.

The meta-analysis results indicated that the splitting procedure and tablet properties were

accurate dosing, albeit the variations were small. There was an improvement in accuracy while dividing scored pills compared to those that were not scored. The review indicated that the least amount of weight fluctuation occurred while breaking tablets manually, whereas the least amount of drug content variation occurred when using a pill splitter. Previous research has demonstrated that hefty tablets with deep score lines can be broken into pieces of the predicted weight. Alternatively, phenobarbital pills, which are tiny and lack a score line, produced subpar splitting results both in terms of precision and percentage content. 32 Small variations in dosage may result in sub- or supra-therapeutic levels, making such considerations clinically relevant for drugs like warfarin that have a narrow therapeutic index. 5 To ensure that patients are receiving consistent dosing of their medicine, it may be essential to reformulate such tablets into capsules providing the requisite therapeutic dosage.

Keep in mind that not all medications can be divided, notwithstanding the results of this article. Splitting extended-release pills, for instance, might cause toxicity owing to the fast and uncontrolled release of the drug's active component. Coated tablets were more consistent in their drug content after being split than uncoated tablets, however there was a significant weight difference between the two. Coated pills may attract water when broken, which might cause the medicine to become unstable and reduce its therapeutic benefits.

Different pill splitting techniques and their effects on dosage accuracy were evaluated in this overview.

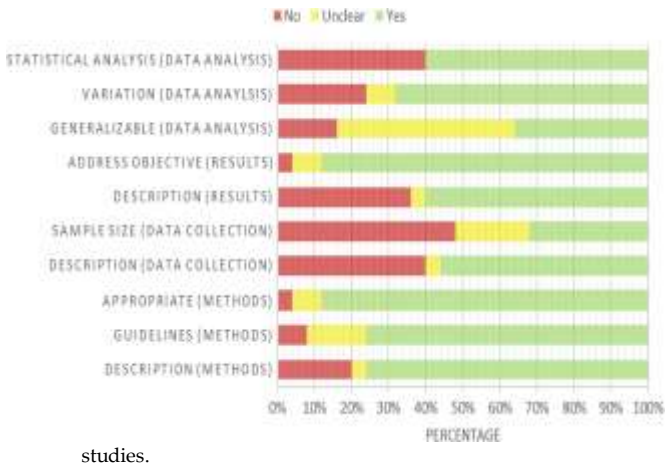


Figure 3 Review of authors' judgements about each risk of bias item, presented as percentages across all included studies.

a breakup. Confusion has arisen since there is no universally agreed-upon, standardized procedure for dividing pills or determining the efficacy of split dosages. Official sources do not provide any information on tablet splitting, as noted by Arnet and Hers- berger for the vast majority of scored tablets. 5

No research that were considered evaluated how patients felt after taking a split pill. Splitting a pill may be troublesome if it leads to people taking different amounts of the drug, and some research suggests that doing so may not affect health outcomes. 6 However, the split pills in this evaluation were so similar to one another in terms of weight and pharmacological content that serious clinical implications are very improbable. For certain medications, including warfarin, it is possible that little variations in drug content might affect results. In instances where extremely tiny dosage differences might have significant therapeutic implications, studies evaluating the dose accuracy of a split tablet and examining the impact of ingestion may be warranted.

In clinical settings, dividing tablets is routine. It is normal practice to divide a larger tablet into two smaller ones in order to save money. 1,6 Where the price per pill does not grow proportionately with increasing dosage strength, splitting has resulted in savings of up to 45 percent for medications used in primary care. 1 To meet the specific requirements of certain patients, tablets may be broken in half.

There were several caveats to our analysis. First, studies that might have affected secondary outcome findings may have been excluded since they did not provide the main outcome (dose accuracy by weight or drug content). Second, there may be unmeasured differences in dosage accuracy due to individual differences in splitting techniques and user experience. To reduce the potential for a systemic impact, subgroup analyses were performed. Thirdly, we were restricted by the low-quality of the available research; specifically, the absence of randomized trials, the failure to report on patient satisfaction results, and the small number of studies evaluating dosage accuracy based on drug content.

CONCLUSION

Based on the data presented here, it seems that splitting tablets may have an impact on dosage accuracy, but that the effects are modest in terms of differences in weight and drug content. Not all medications can be divided in half without risking serious side effects.

the indices, since the outcomes may be either beneficial or harmful. Splitting tablets with a slow-release coating may alter the formulation's underlying structure and therapeutic efficacy, therefore it's best to avoid doing so. There is a need for further research, particularly that which measures the correlation between medication plasma concentrations and clinical outcomes like blood pressure and cholesterol levels in patients.

— are necessary to fully comprehend the impact of tablet splitting on dosage precision. Therapeutic drug monitoring, pharmacokinetic and pharmacodynamic measurements, and specific stability studies are all necessary for medications having a limited therapeutic window.

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