Actual Versus Expected Doses of Half Tablets Containing Prescribed Psychoactive Substances:
A Systematic Review

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ABSTRACT

Objective: To assess through a systematic review of the literature if the practice of splitting tablets containing psychoactive/psychotropic medications for medical or economic reasons would result in the expected doses.

Data Sources: A MEDLINE and PsycInfo comprehensive search of English-language publications from January 1999 to December 2015 was conducted using the terms describing tablet splitting (*tablet splitting*, *split tablets*, *tablet subdivision*, *divided tablets*, and *half tablets*) and psychoactive substances (*psychoactive medicines*, *psychotropic medicines*, *antidepressants*, *anxiolytics*, *anticonvulsants*, *antipsychotics*, and *antiparkinsonian agents*). An additional supplementary search included the references from the articles found.

Study Selection/Data Extraction: Studies were included if splitting content was directly related to psychoactive medications and examined the effect of tablet splitting on drug uniformity, weight uniformity, and adherence of psychoactive drugs. Articles were systematically reviewed and examined regarding the study design, methodology, and results of the study. A total of 125 articles were screened, and 13 were selected.

Results: Tablet splitting implications are extensive, yet substantial deviations from the ideal weight, potency, and dose uniformity are more prone to be important to patient safety. The uneven division of tablets might result in the administration of different doses than what was prescribed, causing under- or overdosing, which might be relevant depending on the drug. In 55% of the cases, splitting psychoactive drugs was satisfactory.

Conclusions: It cannot be generalized that splitting psychoactive drugs compromises dose accuracy, thus tablet splitting might still be employed in cases in which the advantages outweigh the disadvantages. It is recommended that alternatives be adopted to prevent the disadvantages related to tablet splitting.

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Tablet splitting is a common practice among patients on oral pharmacotherapy.[1] The score line in the center of the tablet is designed to assist splitting,[2] allowing the administration of half or quarter tablets[3] according to the score line characteristics. Besides reducing the prescription cost, tablet splitting allows dose flexibility, facilitating dose titration and tapering,[4] which is especially important when considering individual patient differences, pediatric and geriatric communities, and that not all strengths are available in the market.[1]

The test of uniformity of dosage units described in the *United States Pharmacopeia and National Formulary*[5] is an important standard for the analysis of drugs. This test evaluates the consistency of dosage units; the units should have a drug content within a narrow range of the labeled dose.[5,6]

Tablet units may be evaluated by content uniformity or weight variation testing. Weight variation is based on the weight of individual units and might be applied for tablets containing ≥ 25 mg of the active drug consisting of ≥ 25% of the weight of the dosage unit. Content uniformity is based on the potency of the drug evaluated individually in a number of units and can be employed in all situations. Both tests are used to assess that individual content is within the established limits.[5] Both tests are applied in whole tablets; nevertheless, they are used in tablet-splitting research.

About 25% of tablets are split, even those that are unscored or not allowed to be split according to the package insert.[1,7] Splitting modified-release tablets may result in toxicity or therapeutic ineffectiveness due to uncontrolled active substance release or active substance degradation, respectively.[1] One study[8] found that approximately 37% of all tablets used in an elderly care home were split, and, of those, psychotropic drugs were split the most (around 36%).

The number of prescriptions of split tablets was compared to 600,000 dispensed tablet prescriptions in Sweden.[9] Split tablets were prescribed in 10% of the cases. Hypnotics (22%) and selective serotonin reuptake inhibitors (19%) were the most prescribed split tablets, while anxiolytics and neuroleptics constituted 14% and 2%, respectively. Substances studied included paroxetine, flunitrazepam, citalopram, sertraline, nitrazepam, diazepam, escitalopram, and alprazolam.[9]

The frequency of splitting narrow therapeutic index drugs was investigated in an outpatient setting in Taiwan.[10] Findings showed that the number of prescriptions involving splitting was 30% of the total prescriptions for carbamazepine, 4% for lithium, and 5% for phenytoin.[10]

Insurance companies recommend that many drugs be split for cost reasons, including psychoactive medications such as

Clinical Points

- Tablet splitting of psychoactive medicines allows dose flexibility and reduces treatment costs.
- Unsatisfactory splitting potentially compromises the efficacy and safety of the treatment.

sertraline, citalopram, gabapentin, and olanzapine.[11] Tablets may be split by hand, knife, scissors, or splitters. Studies[4,12,13] show that tablet splitters have better patient adherence because of convenience and cost benefit.

Although it is expected by patients and health care providers that the splitting of tablets will result in an accurate dose and desired therapeutic effect, while maintaining the quality of the medication,[14] different issues related to this practice have been raised such as difficulty to break, variation in weight and drug content uniformity, loss of mass, and drug stability of the split portions.[4]

This review aimed to assess if the practice of splitting tablets containing psychoactive/psychotropic medications for medical or economic reasons would result in the expected doses.

METHODS

Search Strategy

The structure of this review was based on PRISMA guidelines.[15] The MEDLINE and PsycInfo databases were searched, and literature published between January 1999 and December 2015 was reviewed. A comprehensive search was conducted to find literature relevant to psychoactive drug tablet splitting using the terms describing tablet splitting (*tablet splitting*, *split tablets*, *tablet subdivision*, *divided tablets*, and *half tablets*) and psychoactive substances (*psychoactive medicines*, *psychotropic medicines*, *antidepressants*, *anxiolytics*, *anticonvulsants*, *antipsychotics*, and *antiparkinsonian agents*). Searches were built using the Boolean operators "OR" and "AND" to obtain all possible relevant articles. An additional supplementary search included references from the identified articles.

Elegibility Criteria

Inclusion criteria consisted of splitting content directly related to psychoactive medications, English language, and date limit. We included research articles, reviews, and case reports that examined the effect of tablet splitting on drug uniformity, weight uniformity, and adherence to psychoactive drug prescription. Studies were excluded if they fell outside the scope of interest. Screening was performed by title and abstract and then full text.

Data Extraction and Synthesis

Articles were systematically reviewed and examined regarding the study design, methodology, and results of the study. Relevant information was compiled and organized. Figure 1 provides a flow diagram of references selected through the review process.

RESULTS

A total of 125 references were identified, and 13 studies[6,11,14,16–25] investigating tablet splitting of psychoactive medications were included, each focusing on different parameters. Many reasons are given for studying tablet splitting of psychoactive medications: these tablets are commonly split in health care networks and nursing homes, are often present in tablet-splitting programs of insurance companies, are high priced, may present a narrow therapeutic index, are used for long-term treatment, or require drug tapering.[11,16–20] A summary of the studies included in the review is presented in Table 1.

DISCUSSION

Tablet splitting is a common practice in the psychiatric and geriatric communities, aiming to adjust doses and

Figure 1. Flow Diagram of References Selected

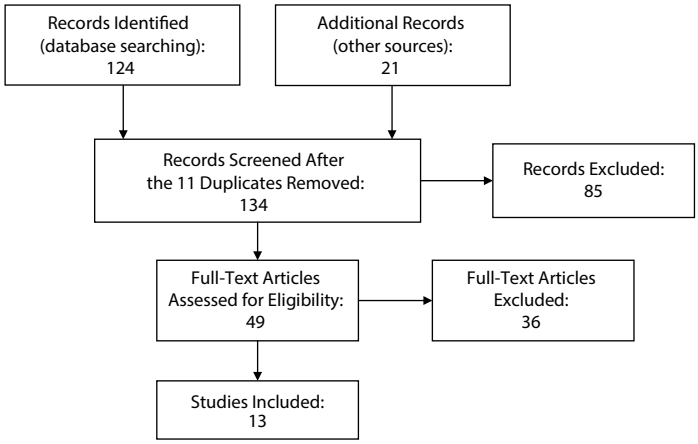

Table 1. Summary of Results From 13 Studies on Tablet Splitting

Drug	Dose	Criteria to Determine Quality of Split: Weight Uniformity	Criteria to Determine Quality of Split: Dosage Unit Uniformity	Study Population	Method of Splitting	Result of Splitting: Satisfactory	Result of Splitting: Unsatisfactory	Study
Antidepressants								
Citalopram	40 mg	85%–115%	…	Trained tester	Tablet splitter	×		Polli et al[16]
	40 mg	…	90%–110%	Pharmacy student	Tablet splitter		×	Hill et al[17]
Sertraline	100 mg	Comparison of half to whole tablet	…	Volunteers	Hand breaking or tablet splitter	×		Matuschka and Graves[21]
	100 mg	85%–115%	…	Trained tester	Tablet splitter	×		Polli et al[16]
	100 mg	85%–115%	…	Trained analyst	Razor blade	×		Teng et al[6]
	50 mg	90%–110%	90%–110%	Health professionals	Knife	×		Helmy[18]
	25 mg and 50 mg	85%–115% and RSD < 6%	…	Split previously in long-term care facilities	Tablet splitter		×	Rosenberg et al[22]
	50 mg	85%–115%	…	…	Tablet splitter		×	Horn et al[23]
Mirtazapine	30 mg	90%–110%	90%–110%	Health professionals	Knife	×		Helmy[18]
Paroxetine	40 mg	85%–115%	…	Trained tester	Tablet splitter	×		Polli et al[16]
	40 mg	85%–115%	…	Trained analyst	Razor blade	×		Teng et al[6]
	10 mg	85%–115% and RSD < 6%	…	Split previously in long-term care facilities	Tablet splitter	×		Rosenberg et al[22]
Trazodone	50 mg (supplier 1)	85%–115% and RSD < 6%	…	Split previously in long-term care facilities	Tablet splitter	×		Rosenberg et al[22]
	50 mg (supplier 2)	85%–115% and RSD < 6%	…	Split previously in long-term care facilities	Tablet splitter		×	Rosenberg et al[22]
Venlafaxine	50 mg	85%–115% and RSD < 6%	…	Split previously in long-term care facilities	Tablet splitter		×	Rosenberg et al[22]
Fluvoxamine	100 mg	85%–115% and RSD < 6%	…	Split previously in long-term care facilities	Tablet splitter	×		Rosenberg et al[22]
Anxiolytics								
Lorazepam	2.5 mg	85%–115% and 75%–125%	85%–115% and 75%–125%	…	…	×		Zaid et al[14]
Bromazepam	3 mg	90%–110%	90%–110%	Health professionals	Knife		×	Helmy[18]
Buspirone	10 mg	85%–115% and RSD < 6%	…	Split previously in long-term care facilities	Tablet splitter		×	Rosenberg et al[22]
Anticonvulsants								
Gabapentin	600 mg	stability[a]	stability[a]	…	Tablet splitter	×		Volpe et al[11]
Phenobarbital	60 mg	75%–125% and RSD < 6%	…	Laymen and nurses	Hand breaking, scissors, or knife		×	Elliott et al[24]
	30 mg	75%–125%	…	Pharmacy students	Knife		×	Tahaineh and Gharaibeh[19]
Carbamazepine	100 mg	85%–115%	…	…	Tablet splitter		×	Horn et al[23]
Oxcarbazepine	150 mg	90%–110%	90%–110%	Health professionals	Knife	×		Helmy[18]
Antipsychotics								
Risperidone	0.25 mg	85%–115% and RSD < 6%	…	Split previously in long-term care facilities	Tablet splitter	×		Rosenberg et al[22]
	1 mg	85%–115% and RSD < 6%	…	Split previously in long-term care facilities	Tablet splitter		×	Rosenberg et al[22]
	Variable	medication adherence[b]	medication adherence[b]	Patients	…	×		Weissman and Dellenbaugh[25]
Antiparkinsonian agents								
Carbidopa and levodopa	…	85%–115% and 75%–125%	…	Volunteers	Hand breaking, tablet splitter, or knife		×	Verrue et al[20]
Acetylcholinesterase inhibitor agents								
Donepezil	5 mg	85%–115% and RSD < 6%	…	Split previously in long-term care facilities	Tablet splitter		×	Rosenberg et al[22]

[a]Study used stability parameters as criteria to determine quality of split. [b]Study used medication adherence parameters as criteria to determine quality of split. Abbreviation: RSD = relative standard deviation.
Symbol: … = not reported.

Table 2. Characteristics of the Medications Evaluated in the Included Studies

Drug	Half-Life (h)	Narrow Therapeutic Index	Strengths Available in the Market (mg)
Antidepressants			
Citalopram	33	No	10, 20, 40
Sertraline	26	No	25, 50, 100
Mirtazapine	20–40	No	7.5, 15, 30, 45
Paroxetine	3–65	No	7.5, 10, 12.5, 20, 25, 30, 37.5, 40
Trazodone	10–12	No	50, 100, 150, 300
Venlafaxine	4	No	25, 37.5, 50, 75, 100, 150, 225
Fluvoxamine	15–26	No	25, 50, 100, 150
Anxiolytics			
Lorazepam	10–20	No	0.5, 1, 2
Bromazepam	11–22	No	3, 6
Buspirone	2.1	No	5, 7.5, 10, 15, 30
Anticonvulsants			
Gabapentin	5–7	Yes	100, 300, 400, 600, 800
Phenobarbital	48–144	Yes	15, 16, 16.2, 30, 32.4, 60, 64.8, 97.2, 100
Carbamazepine	18–65	Yes	100, 200, 300, 400
Oxcarbazepine	9	Yes	150, 300, 600
Antipsychotics			
Risperidone	20	No	0.25, 0.5, 1, 2, 3, 4
Antiparkinsonian agents			
Carbidopa/levodopa	1.5	No	10/100, 23.75/95, 25/100, 25/250, 36.25/145, 48.75/195, 50/200, 61.25/245
Acetylcholinesterase inhibitor agents			
Donepezil	70	No	5, 10, 23

reduce costs.[17] Prescription patterns of split tablets ordered by community pharmacies for patients residing in retirement homes were analyzed by repacking in unit-of-use pouch blisters.[26] Findings showed that 8.5% of the repacked tablets were split, mostly in half (around 88%). Of the 132 different drugs that were split, 50% were psycholeptics or psychoanaleptics. The drugs most often split were pipamperone (15.8%), levodopa/decarboxylase inhibitor (10.2%), quetiapine (6.5%), lorazepam (5.1%), mirtazapine (4.3%), torasemide (3.9%), zolpidem (3.2%), metoprolol (2.7%), citalopram (2.7%), and risperidone (2.6%).[26]

Individuals with dementia often present with behavioral disorders that require antipsychotic prescriptions. However, treatment of these behavioral symptoms often demands doses that are commercially unavailable.[27] Approximately 35% of patients with dementia versus 24% of patients without dementia in a geriatric outpatient setting were prescribed fractioned doses, indicating tablet splitting, and most of the patients with dementia who split tablets (around 73%) also did so with psychotropic drugs.[27]

In 55% of the cases,[6,11,14,16,18,21,22,25] splitting was satisfactory; however, the results varied according to the pharmacologic class of the medications evaluated. The best splitting results were obtained for most of the antidepressant (68.7%) and antipsychotic (66.7%) drugs evaluated compared to anticonvulsants (40.0%) and anxiolytics (33.3%). For medications used to treat Parkinson's and Alzheimer's diseases, splitting results were unsatisfactory, although only one medication in each category was analyzed. These results are relevant, especially for the geriatric population due to the high prevalence of splitting tablets of psychoactive drugs in this group.

There is no agreement on the best technique for splitting tablets. Comparison of splitting with a tablet splitter and breaking by hand showed that portions obtained with the splitter were more uniform with regard to weight and content variation than those broken by hand.[28] When comparing hand breaking to razor blade splitting, hand-broken tablets yielded cleaner splits with less crumbling. Nevertheless, tablets split by a razor blade were more uniform with regard to weight than hand-broken ones.[6] Splitting using a kitchen knife and a tablet splitter for cyclobenzaprine tablets yielded great weight variation, failing to meet the criteria used in these studies.[17,29] Nevertheless, 8 of 12 different medications had satisfactory weight uniformity when a tablet splitter was used.[16] Three techniques were compared for splitting a "best-case tablet" (round, flat, uncoated, break-marked): hand breaking, tablet splitter, and kitchen knife. Only hand-broken split portions were satisfactory according to the criteria used in the study.[30]

The uneven division of tablets may result in the administration of different doses than what was prescribed,[17] causing under- or overdosing, which might be relevant depending on the drug.[4] Another factor that contributes to inaccurate dosages is fragmentation during splitting. Multifragmentation or powdering leads to weight loss and, consequently, to drug waste,[19] which might decrease total drug availability in the body over time.[1,31] Additionally, the occasional loss of mass resulting from tablet splitting might put those who come into contact with the powder at risk, depending on the drug.[30]

Other parameters beyond weight and drug content uniformity were evaluated in 2 studies.[11,25] One study[11] evaluated the stability of gabapentin split tablets and obtained a satisfactory result. The other study[25] evaluated medication

adherence, service utilization, and clinical outcomes for patients with schizophrenia or related disorders when splitting risperidone tablets. Tablet splitting had no impact on clinical outcomes, although outpatient service utilization patterns and amount of medication dispensed increased, especially during the beginning of the study. This increase might be related to tablet splitting due to initial technical difficulties or communication problems regarding splitting instructions.[25]

Patients may not adhere to tablet-splitting instructions because of difficulties or confusion. Tablet scoring can also be misleading in some cases.[19] Quinzler and colleagues[1] pointed out that some tablets that should not be split are manufactured with score lines, giving patients and health professionals the impression that these tablets are appropriate for splitting. The authors[1] found that these tablets were actually frequently split.

Another important factor for assuring the administration of accurate and precise split doses is the high degree of correlation between weight and drug content. Even if the splitting procedure was performed satisfactorily, resulting in 2 halves with equal weights, if the active drug is not distributed homogeneously throughout the tablet, distinct doses would be obtained from the split portions.[14] This factor is especially important for tablets containing highly potent medications[14] in which unit doses usually comprise a very small amount of the active drug.

Pharmacokinetics appear to determine if clinical impacts on long-term outcomes would result from splitting.[17,18] Table 2 presents characteristics of the medications used in the splitting studies, such as drug half-life, drugs with a narrow therapeutic index, and availability of tablets in a suitable dose range on the market. Unsatisfactory splitting might have a negative impact on clinical outcomes of short half-life medications. Nevertheless, the long half-life of some medications might soften the impact of inaccurate splitting, working as a pharmacokinetic buffer. For narrow therapeutic index drugs, slight changes or fluctuations in daily doses might result in potentially significant adverse events and loss of efficacy due to inaccurate splitting.[18] As pharmacokinetics are altered by aging, elderly people usually present a higher risk of adverse effects due to dose fluctuation.[10]

Tablet splitting might be better suited for long half-life drugs with a broad therapeutic window and large-sized tablets that are scored, flat, oblong, or oval. Tablet splitting might be less suited for modified-release, small-sized, and easily crumbled tablets and drugs with a bitter taste and narrow therapeutic window.[18]

Some studies[4,32] report that splitting antidepressant drugs would not be harmful, since their therapeutic effects would be based on long-term alterations in neurotransmitter systems. Therefore, small dose fluctuations would not have a significant impact on clinical outcomes.[4,32] Patients' subjectivity also may affect daily efficacy measurements.[17]

Different suppliers of the same drug might affect tablet-splitting directions. One study[22] evaluated the splitting of tablets containing the same drug from different suppliers. Findings showed that trazodone split tablets were satisfactory from only one supplier.[22] Therefore, variation in tablet-splitting quality also depends on which drug manufacturer is evaluated; consequently, results may differ between products.

Although tablet splitting has many advantages, various issues have been raised regarding the efficacy and safety of the practice. Oral solutions and lower-strength tablets are alternatives to tablet splitting. Nevertheless, some studies[9,10,33] point out that even when these alternatives are available, tablet splitting still remains a frequent choice.

Tablet-splitting implications are extensive, yet substantial deviations from the ideal weight, potency, and dose uniformity are more prone to be significant with regard to patient safety.[16,22,24,34] A limitation of this review was that most of the included studies focused on physical and chemical parameters of the tablets; therefore, no conclusions can be drawn from these findings.

CONCLUSIONS

Tablet splitting is a routine practice in drug regimens for both medical and economic reasons. The accuracy of delivered doses of psychoactive substances after splitting is a concern with regard to the efficacy and safety of the pharmacotherapeutic treatment. While in some studies splitting psychoactive drugs resulted in inaccurate doses, others found splitting was satisfactory, resulting in the intended doses.

It cannot be generalized that splitting psychoactive drugs compromises dose accuracy, thus tablet splitting might still be employed in cases in which the advantages outweigh the disadvantages. Nevertheless, it is recommended that new strengths of existing medications in the form of tablets be introduced in the market or that liquid forms be adopted in order to prevent the disadvantages related to tablet splitting.

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