

TITLE: Pill Splitting: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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CONTEXT AND POLICY ISSUES

Breaking drug tablets is a common practice referred to as pill splitting, or tablet splitting.¹ A 2012 review article reported that 15% of Americans engage in pill splitting.² The modification of an oral medication by pill splitting serves a number of purposes. For example, pills might be split to ease administration (e.g., fragments of a tablet are easier to swallow than the whole tablet), or to obtain an intermediate dose not available as a marketed strength.^{1,3} Pill splitting may be of particular relevance to achieve appropriate dosing titrations for children, older adults, or persons of low body weight.⁴ When the cost of differing tablets strengths is the same, pills may be split to save money.^{1,3,4} For patients, if cost is a barrier, pill splitting may also increase patient adherence to treatment regimens by making medication more affordable.²

However, there are some concerns with tablet splitting. Splitting tablets into fragments raises issues of content uniformity and weight uniformity between segments.⁴ It has been suggested that pills that are extended-release or enteric-coated formulas not be split as there are concerns surrounding the changed properties of the tablets when split.^{1,4} Also, combination medications, with more than one active ingredient, where one ingredient dose may differ between pill sizes, but the other does not, may not be suitable for fragmenting.¹ There are also concerns of adverse reactions due to inhalation or dermal contact with pill fragments.⁴

Pill properties, such as size and shape,^{1,4} as well as fragility and the presence of scoremarks,¹ can affect the ability of a pill to be split. Pills that crumble easily or are known to fragment into unequal segments may not be appropriate for splitting.⁴ Also, the results of splitting may depend on the splitter's physical strength, precision, cognitive ability, and visual perception.¹ Out of hospital, patients may not be able to split pills if they have poor memory, or are fearful of inaccurate dosing.² Results of pill splitting may also depend on the tools used to split the tablets, which can include pill splitters, knives, hard surfaces, or manual splitting.³

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The purpose of this review is to assess evidence on the clinical effectiveness, cost-effectiveness, and evidence-based guidelines regarding pill splitting for patients in a hospital setting.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of pill splitting (oral medications) for patients in a hospital setting?
2. What is the cost-effectiveness of pill splitting (oral medications) for patients in a hospital setting?
3. What are the evidence-based guidelines regarding pill splitting (oral medications) for patients in a hospital setting?

KEY FINDINGS

No literature was identified regarding the clinical effectiveness or cost-effectiveness of pill splitting for patients in a hospital setting. One evidence-based guideline was identified regarding pill splitting for neonates or pediatric patients in a hospital setting. The following recommendations were made: tablet splitting is preferable to dispersing or crushing tablets and giving a proportion of the tablet; to split tablets, use a tablet splitter, which should be cleaned and replaced following manufacturer and local specifications; tablets should be split along the scoreline; if the tablet is not scored, consult a pharmacist prior to splitting; tablets should not be split into less than quarter segments, unless according to manufacturer specifications; tablets should be assessed visually to ensure segments appear equal in size; storing tablet segments should be in accordance with local policies.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including Ovid MEDLINE, Ovid Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and May 5, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients in hospital (all age groups)
Intervention	Oral medication in the form of pill, tablet, or caplet being split to accommodate a medication order for a lower dosage than what is available in solid form (i.e., pill splitting or tablet splitting)
Comparator	Oral liquid medication or alternate dosage forms
Outcomes	Q1: Clinical effectiveness; safety Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010.

Critical Appraisal of Individual Studies

The included guideline was assessed with the AGREE II instrument.⁵ Summary scores were not calculated for the included guideline; rather, the strengths and limitations of the guideline are described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 185 citations were identified in the literature search. Following screening of titles and abstracts, 155 citations were excluded and 30 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 31 publications were excluded for various reasons, while one publication met the inclusion criteria and was included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Details of the study characteristics are located in Appendix 2.

Study Design and Country of Origin

The included guideline⁶ was commissioned by the Patient Benefit Programme of the National Institute for Health Research out of the United Kingdom, and developed by contributions from Alder Hey Children’s National Health Services (NHS) Foundation Trust, Liverpool John Moores University, and Liverpool Women’s NHS Foundation Trust. The development of the guideline and its recommendations was based on a systematic review of the literature. The systematic review identified 42 relevant studies, where pills had been split, crushed, or dispersed. Of the 42 included studies, 38 were specific to split tablets. The studies were not limited by drug type, setting, or patient age. In addition to the systematic review, an observational study was

performed to observe the occurrence of drug manipulations, including tablet splitting, in two pediatric hospitals and one neonatal unit. Additionally, a quantitative review of all prescriptions, from the aforementioned clinical areas, was performed over a period of five days. Pediatric nurses in the United Kingdom were also surveyed regarding drug manipulations in pediatric practice.⁶

Patient Population

The identified guideline⁶ was focused on neonatal and pediatric in-patients. This included persons from birth, up to 18 years of age.

Interventions and Comparators

The guideline⁶ provides recommendations regarding oral drug manipulations, including pill splitting. The manipulations of interest are for the purposes of obtaining a required dose for use in neonatal and pediatric populations. Not included in this guideline are manipulations performed for ease of drug administration (e.g., pills split to assist swallowing). The guideline does not address any specific drug class or tablet type, nor does it address any specific patient indication.

Outcomes

The systematic review portion of the evidence collection reported on outcomes related to: bioavailability of split modified-release pills; weight and drug content uniformity of split pills; methods of pill splitting; outcomes related to effectiveness, patient adherence, and taste.⁶

Summary of Critical Appraisal

Details of the critical appraisal are located in Appendix 3.

Strengths of the included guideline⁶ include clearly stated objectives, patient population, target users, and recommendations. The guideline development group included persons from various professional groups, and a parent representative, which likely contributed to various perspectives being considered when developing recommendations. The authors of the guideline performed an observational study and a survey of pediatric nurses, in addition to a systematic review of the literature as the basis for their recommendations. This provided context and an understanding of drug manipulation in clinical practice. Generalized links between the evidence and the recommendations were also provided, adding a level of transparency to the development of recommendations. Also, the risks of drug manipulation were considered when developing guidelines, and a statement emphasizing foremost the wellbeing of the patient was included.

Despite the aforementioned strengths of the included guideline,⁶ there were some limitations. For the systematic literature review, the databases searched were listed, but specific search strings were not included, and neither were the specific inclusion and exclusion criteria for the included studies. The guideline provided some grading for the individual studies included in the literature review, however, the level of evidence for each recommendation was not graded. For example, there was no differentiation for recommendations based on limited or low quality evidence, or those based on high quality evidence. This presents some uncertainty regarding the specific recommendations. It was also uncertain if the guideline went through an external

review and validation process. Additionally, the guideline did not detail the costs and barriers to guideline implementation, or a procedure for updating the guideline.

Summary of Findings

Details of the study findings are located in Appendix 4.

What is the clinical effectiveness of pill splitting (oral medications) for patients in a hospital setting?

No literature was identified regarding the clinical effectiveness of pill splitting for patients in a hospital setting; therefore, no summary can be provided.

What is the cost-effectiveness of pill splitting (oral medications) for patients in a hospital setting?

No literature was identified regarding the cost-effectiveness of pill splitting for patients in a hospital setting; therefore, no summary can be provided.

What are the evidence-based guidelines regarding pill splitting (oral medications) for patients in a hospital setting?

One evidence-based guideline⁶ was identified regarding pill splitting for patients in a hospital setting. The systematic review that informed the guideline was not limited by drug type, or patient age or setting. For bioavailability, the systematic review included six studies where sustained-release tablets were split. Two of these studies found that patients administered split pills had higher peak plasma concentrations, compared to whole pills. There were no significant changes in bioavailability outcomes for the remaining four studies.⁶

Weight and drug content uniformity varied for the studies included in the systematic review. For example, there was one study reporting approximately 13% of halves outside of the accepted weight specification, and another reporting 100% of halves not meeting specifications. This depended on the products being studied, such as tablet shape, size, and whether the tablets were scored or not. There were also three studies that found a higher percentage of quarter segments not meeting specifications, compared to half segments.⁶

The studies included in the systematic review portion of the guideline regarding methods of pill splitting general found pill splitters to be more accurate than other methods (e.g., manually, kitchen knives, and scissors).⁶

Based on the findings of the literature review, the guideline provided recommendations on pill splitting for use by health care professionals for the manipulation of drugs for neonatal and pediatric in-patients. The following recommendations were made:

- tablet splitting is preferable to dispersing or crushing tablets and giving a proportion of the tablet
- to split tablets, use a tablet splitter, which should be cleaned and replaced following manufacturer and local specifications
- tablets should be split along the scoreline
- if the tablet is not scored, consult a pharmacist prior to splitting

- tablets should not be split into less than quarter segments, unless according to manufacturer specifications
- tablets should be assessed visually to ensure segments appear equal in size
- storing tablet segments should be in accordance with local policies.⁶

In regards to other outcomes, the guideline reported that for the included studies in the systematic review, patients did not find it difficult to split pills, and that pill splitting had no impact on adherence or compliance with medications.⁶

Limitations

This review has several limitations, especially with regard to a lack of relevant literature. No relevant literature was identified regarding the clinical effectiveness or cost-effectiveness of pill splitting for patients in a hospital setting. This precludes this review from providing any summary of patient outcomes or cost-effectiveness regarding pill splitting. The one identified guideline⁶ is specific to neonatal and pediatric populations in the United Kingdom. This may limit the generalizability of the recommendations to other patient populations, or to a Canadian context. Additionally, the guideline was developed specifically for a pediatric population, yet the literature base it draws from includes studies conducted in adults. This may raise questions the appropriateness of drawing recommendations for pediatric patients based on findings in adults. Due to these limitations, the findings of this review would be likely to change if new, relevant literature were to become available.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Limited literature was identified regarding pill splitting for patients in a hospital setting. Due to the lack of literature, few conclusions can be drawn regarding the clinical effectiveness and cost-effectiveness of pill splitting for patients in a hospital setting. One evidence-based guideline⁶ was identified, which provided several recommendations regarding pill splitting for neonatal and pediatric in-patients. These recommendations included using a pill splitter and maintaining it according to manufacturer specifications, refraining from splitting pills into segments less than one quarter, splitting pills along a scoreline if possible, and consulting with a pharmacist before splitting unscored pills.⁶ Overall, the guideline was clearly written, with specific recommendations, it considered risks of recommendations, and relevant professionals and a parent representative were involved in guideline development. Criticisms of the guideline include a lack of detailed search strategy, uncertain review and validation, as well as a lack of implications for guideline implementation.

The clinical effectiveness and cost-effectiveness of pill splitting for patients in a hospital setting remains unclear. There are guidelines regarding pill splitting for patients in a hospital setting and these provide a source of guidance for those determining if pills should be split, how they should be split, and the administration of split pills to patients.

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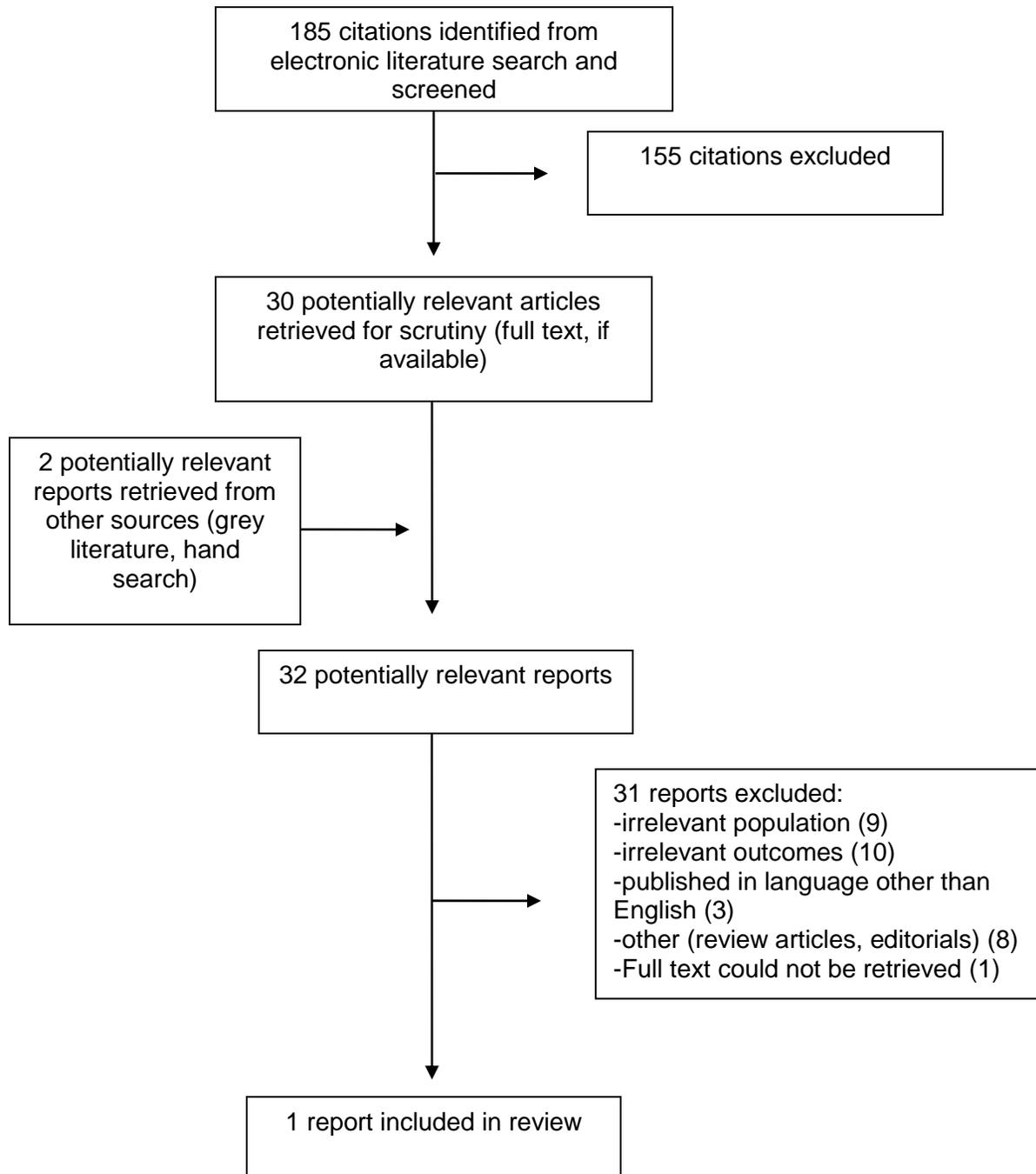
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Guidelines

Objectives			Methodology		
Intended users/ Target population	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, Selection and Synthesis	Evidence Quality and Strength	Recommendations development and Evaluation
Alder Hey Children's NHS Foundation Trust, 2013 ⁶					
Health care professionals in pediatric and neonatal settings in the UK	Manipulation of drugs, including tablet splitting, required in pediatric and neonatal care	Drug manipulations to obtain required doses used in pediatric and neonatal clinical practice	Systematic literature review, observational study to identify manipulations, quantitative review of prescriptions, survey of pediatric nurses, risk consideration	Based on quality assessment checklists, criteria specified by MORDIC study	Recommendations developed by guideline development group

NHS = National Health Services; MORDIC = Manipulation of Drugs Required in Children; UK = United Kingdom

APPENDIX 3: Critical Appraisal of Included Publications

Table A2: Strengths and Limitations of Guidelines using AGREE II⁵	
Strengths	Limitations
Alder Hey Children’s NHS Foundation Trust, 2013⁶	
<ul style="list-style-type: none"> • The objectives, patient population, and target users of the guideline are clearly stated • Recommendations are clearly stated • Guideline development group included parent representative, as well as other relevant professionals • Risks were considered when developing the recommendations • General links between evidence and recommendations is provided 	<ul style="list-style-type: none"> • Cost and barriers to guideline implementation are not discussed • A procedure for updating the guideline is not provided • It is uncertain whether the guideline was externally reviewed before publication • Criteria for the inclusion and exclusion of the evidence is not provided • Strengths and limitations of the evidence are generally rated without justification provided • Specific literature search strings are not provided

APPENDIX 4: Main Study Findings and Author’s Conclusions

Table A3: Summary of Findings of Included Studies
Recommendations
Alder Hey Children’s NHS Foundation Trust, 2013 ⁶
“Tablets should be split in preference to dispersing or crushing tablets and taking a proportion” (pg. 26)
“Split tablets using a tablet splitter” (pg. 26)
“Clean and replace tablet splitters according to manufacturer and local recommendations” (pg. 26)
“Scored tablets should be split along the scoreline, with the scoreline uppermost” (pg. 26)
“Consult a pharmacist prior to splitting unscored tablets” (pg. 26)
“Do no split tablets into less than ¼ segments, unless specified by manufacturer” (pg. 26)
“Visually assess the tablet segments to establish if they appear equal in size prior to administration” (pg. 26)
“Remaining segments of the tablet should be managed in accordance with local policy” (pg. 26)