TITLE:

Application of Quantitative Models to Systematically Evaluate Factors Impacting Swallowability of Tablets

AUTHORS:

Di Cui[1], Karen Li[1], Manar Al-Ghabeish[1], Meredith R. McGuire[1], Wei-Jhe Sun[1], Meng Hu[2], Liang Zhao[2], Myong-Jin Kim[1]

1. Division of Therapeutic Performance II, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA

2.Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA

PURPOSE:

Swallowability may be defined as the patient being able to take the drug without gagging or choking per the U.S. Food and Drug Administration (FDA)'s Guidance for Industry [1]. The usability of drug products is greatly impacted by its swallowability, since swallowing difficulties may lead to many issues such as the misuse risk from inappropriate manipulation of opioid tablets to make swallowing easier [2-4]. The U.S. FDA has also published a guidance on tablet size to help reduce swallowing difficulties [4]. Many research studies including some clinical studies have been conducted on assessing factors that impact swallowability. However, most of the reported results were based on a single clinical study for a certain group of subjects and used conventional statistical methods, like a chi-test for analysis [5-8]. In this abstract, we reviewed study designs used for clinical swallowing evaluation that were submitted to FDA, collected data from eight completed studies and conducted a systematic evaluation on factors affecting swallowability based on machine learning models.

METHODS:

This work first established a dataset by collecting individual subject data from eight clinical studies with swallowability assessment submitted to the FDA. Data were standardized/integrated from these eight clinical studies retaining individual level swallowability data. In the standardized database, 1028 records from 667 subjects were collected in total (with 352 of these subjects having two or three records of swallowing one drug product with different formulations). Each record had an outcome variable indicating the tablet swallowability from the subject, five subject-specific factors (i.e., "age", "sex", "height", "weight", and "healthy status"), and four product-specific factors (i.e., "drugCoating" indicating whether the product is coated, "drugMaxDimension" indicating the product maximum physical dimension, "drugColor" indicating the product physical color, and "drugShape" indicating the product physical shape).

With the constructed dataset, exploratory analysis (e.g., correlation analysis) and modeling approaches (e.g., logistic regression and machine learning model - Conditional Decision Tree) were conducted to assess the impact of these variables on swallowability of drug products.

RESULTS:

The correlation analysis found that "height" and "weight" were highly correlated with "age", and "drugShape" was correlated with "drugMaxDimension". Thus, we used "body mass index (i.e., BMI = Weight/Height)" to replace "height" and "weight" and filtered out "drugShape". We then applied the Conditional Decision Tree to the remaining seven independent factors including "age", "sex", "BMI", "healthy status", "drugCoating", "drugMaxDimension" and "drugColor" to assess their impact on swallowability. The generated conditional decision tree (Fig. 1) split the database into seven bins. The results show two subgroups of bins based on the subject's ability to swallow the drug product. The "Able" subgroup with 75% or more of subjects able to swallow consisted of Bins III, IV, VI and VII, and the "Unable" subgroup with 25% or less of subjects able to swallow consisted of Bins I, II, and IV. By examining the decision paths of these two subgroups, we observed the following results: "age" and "drugMaxDimension" were two main factors that affect swallowability. Specifically, subjects younger than 6 years of age tended to have difficulty swallowing generally all types of tablets (tree splitting 1→2). Subjects aged 6-11 years tended to have swallowability problems when the size of tablets is larger than 15mm (tree splitting 1→5→9→Node 10, comparing with tree splitting 1→5→6). Lastly, subjects older than 11 years of age in general have no swallowability issue (tree splitting 1→5→9→11).

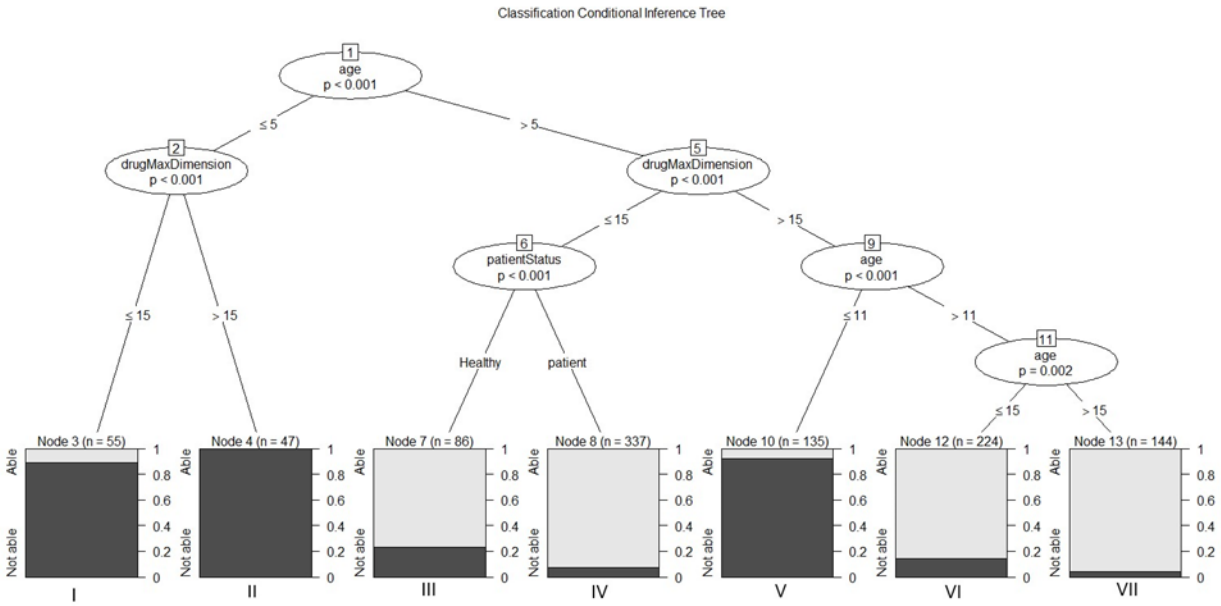
CONCLUSIONS:

This research work complements the existing swallowability literature by applying a quantitative model across multiple clinical studies. The findings identified age and the maximum dimension as primary factors affecting swallowability which is consistent with previous literature. Considering that the Conditional Decision Tree is a machine learning model for pattern recognition, this work offers a great potential for future research in predicting swallowability of specific tablets and its target subject groups.

DISCLOSURES:

This abstract reflects the views of the authors and should not be construed to represent FDA's views or policies.

IMAGE:



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