Patient preferences for drug delivery- Machine Learning guided human efforts: A Synergistic Approach

U. Adiga

Department of Biochemistry, Apollo Institute of Medical Sciences and Research, Murukambattu - 517127, Chittoor, Andhra Pradesh, India
Email: ushachidu@yahoo.com

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Abstract

Pharmaceutical formulation and treatment process attributes, such as dose frequency and route of administration, can have an impact on quality of life, treatment adherence, and disease outcomes. The aim of this systematic review and meta-analysis is to examine studies on preferences for pharmaceutical treatment process attributes, focusing on research in diabetes, oncology, osteoporosis, autoimmune disorders and other non-communicable diseases using machine learning software tools in addition to researcher guided efforts. The literature search should be focusing on identifying studies reporting preferences for attributes of the pharmaceutical treatment process. Studies should be required to use formal quantitative preference assessment methods, such as utility valuation, conjoint analysis, or contingent valuation. Searches should be conducted using Medline, EMBASE, Cochrane Library, Health Economic Evaluation Database, and National Health Service Economic Evaluation Database. Data should be extracted by machine learning software tools as well. Quality of the obtained data should be checked by Down and black check list. The statistical analysis should be carried out using the software 'Comprehensive Meta-Analysis software, version 2.0' Despite heterogeneity in study methods and design, some general patterns of preference may clearly emerge. Overall, the results of this review may suggest that treatment process has a quantifiable impact on preference and willingness to pay for treatment, even in many situations where safety and efficacy are the primary concerns. Patient preferences for treatment process attributes can inform drug development decisions to better meet the needs of patients and deliver improved outcomes. Findings from this study may have direct relevance to researchers working in drug development because results can provide insight into the value that patients place on treatment process attributes. Results may also aid clinicians in selecting treatments with attributes that have the potential to enhance treatment adherence.

Keywords: pharmaceutical formulation; treatment process attributes; quality of life; treatment adherence; systematic review

Introduction

Most people would recognize that patient preferences have an important role to play in healthcare decision making, although it is only recently that decision makers have shown interest in quantitative methods for eliciting patient preferences. Previously, the patient's role in health policy development was mostly limited to representation on decision making committees (European Medicines Agency (EMA), 2014; Food and Drug Administration (FDA), 2015; Facey et al., 2010). Increasing recognition of the limitations of such an approach – focusing on the qualitative input of a small number of not necessarily representative patients, as only one voice in a large decision making group – has led to calls for the rigorous quantification of the patient voice (Weernink et al., 2014).

A significant effort is committed to the quantification of clinical and safety endpoints to inform healthcare decision making. This is completely appropriate if we are to make decisions that benefit patients and society more generally. Another important consideration, however, is that until recently, patients' preferences for these attributes have not received the same amount of attention. We are pleased to acknowledge changes in this attitude, and the increased quantification of patient preferences to inform decision making. While we have just started to determine precisely how patient preferences should be collected and incorporated into decision making, these are exciting developments, and we look forward to participating in a scientific discussion that will further advance these techniques. In the meantime, given decision makers' interest in patient preference data, manufacturers should be systematically considering the collection of such data in their evidence generation planning and getting expert input into the design and implementation of these studies. There is little data available to guide the decision makers in this regard, to the best of our knowledge.

Current Need assessment

The effectiveness of pharmaceutical treatments depends not only on the chemical properties of the medication, but also on how medication is formulated and administered. Differences in treatment regimen and treatment process can have a profound effect on how patients experience pharmaceutical therapy. For example, while some medications are administered orally as tablets or capsules, others require intravenous (IV) administration in a hospital setting. Furthermore, treatment regimens can vary in terms of dose frequency and dose flexibility, including whether medications need to be taken with meals. These pharmaceutical formulation and treatment process attributes (subsequently referred to as "process attributes") can impact patient adherence, and therefore indirectly affect the efficacy and safety of a medication (Hixson-Wallace et al., 2001; Morris & Schulz, 1993; Raue et al., 2009; Shikiar et al., 2002; Shikiar & Rentz, 2004). They can also have a direct effect on how patients experience treatment, which can impact health-related quality of life. One way to examine and quantify the importance that patients place on the treatment process attributes is to use formal preference assessment methods, such as health state utility valuation and discrete choice experiments.

These approaches permit quantitative comparison of the relative importance that patients place on a set of treatment attributes. While a substantial amount of research has documented the impact of efficacy and safety on patient preference for various medication options (Allan et al., 2001; Gelhorn et al., 2013; Johnson et al., 2007; Johnson et al., 2009).less is known about the importance of treatment process attributes. Still, a smaller growing body of research has consistently highlighted the importance of how medications are taken (Brennan & Dixon, 2013; Donaldson & Shackley, 1997; Swan et al., 2003). In addition, studies that include efficacy and/or safety attributes along with treatment process attributes can also quantify patients' willingness to accept a risk of adverse events or reduced treatment benefit for the sake of improved comfort or convenience.

Rationale

Little is known about patient preferences for participation in medication administration and hospital discharge planning. Individual patient understanding of and interest in participation in medication administration varies. In accordance with individual patient preferences, patients need to be included more effectively and consistently in their own medication management when in hospital.

For many tasks including but not limited to systematic reviews and meta-analyses the scientific literature needs to be checked systematically. Scholars and practitioners currently screen thousands of studies by hand to determine which studies to include in their review or meta-analysis. This is error prone and inefficient because of extremely imbalanced data: only a fraction of the screened studies is relevant. Hence we are attempting a machine learning guided systematic review and meta-analysis on patient preferences of drug delivery. The proposed systematic reviewing should be an interaction with machine learning algorithms to deal with the enormous increase of available text in addition to human efforts of screening.

Objective

This study aimed to systematically review as well as synthesize data by meta-analysis by screening the published papers that evaluate preferences of patients' non- monetary and monetary attributes of pharmaceutical treatment process attributes, by a team of researchers with the help of machine learning software tools.

Methods

Preference assessment methods to be included in the review

This review focuses on studies that have used a range of methodologies to assess and quantify preference for process attributes. Preference assessment methods can be grouped into two broad categories (table 1). Stated preferences are derived from surveys or interviews with an experimental design such as conjoint or contingent valuation studies. Stated preference methods allow researchers to focus on specific attributes, control the way preferences are elicited, and assess preferences for hypothetical products Table 1: Studies that should be screened based on the following methods

Category		Method
Indirect	Choice based	Discrete choice experiment
		Best-worst scaling
	Matching	Time-trade-off
		Standard gamble
Direct	Ranking	Simple Multi-Attribute Rating Technique Exploring ranks(SMARTER))
	Rating	Visual analogue scales (VAS)
		Point allocation
	Pairwise	Analytical Hierarchy Process(AHP)
		Measuring Attractiveness through a Categorical Based Evaluation (MACBETH)
	Swing weighting	Simple Multi-Attribute Rating Technique with Swings (SMARTS)
	Scoring rules	Bi-section method
		Difference method
	Threshold analysis	----

Literature search methods

Literature searches should be conducted in the following databases: PubMed, EMBASE, Cochrane Library, Health Economic Evaluation Database, and National Health Service Economic Evaluation Database. The list of search terms should be developed to identify articles that include the selected methods (ie, stated preference or utility assessment) and attributes related to treatment process. The following search terms (applied to article title and abstract) should be intended to identify studies using the relevant preference methods: stated preference(s), time trade-off, TTO, time trade off, standard gamble, conjoint, contingent valuation, discrete choice, discrete-choice, willingness to pay, and willingness-to-pay. Treatment process search terms should be intended to identify attributes related to route of administration, dose frequency, dose timing, dose size, convenience, and other process attributes. The search should be limited to studies published in English.Full-text primary articles should be eligible for inclusion. Articles should be included if they evaluated preferences for one or more treatment attributes through utility, conjoint, contingent valuation, and/or discrete choice. This review will include studies examining treatment preferences from the patient perspective (either from patients themselves or nurses as patient proxies) and from general population participants.

Exclusion criteria: Conference abstracts, editorials, and letters to the editor should be excluded. Articles should be considered for inclusion if they had both a preference methodology term and a process term. Articles should be excluded if they evaluated preferences for only efficacy and/or safety attributes (without assessment of preferences for treatment attributes, treatment processes, or treatment experience) or if they evaluated preferences through revealed preference rather than stated preference or utility methods.

Data extraction methods

Data extraction should be done in two parts;

(i) Manually by the research team

(ii) Machine learning guided data extraction

Manual data extraction

After articles are selected for inclusion, study characteristics should be extracted and organized into table shells so that findings could be examined and summarized across studies. For each article, the following characteristics should be captured in the data extraction tables: therapeutic area (diabetes, autoimmune disease, oncology, or osteoporosis), preference assessment method (conjoint, utility, contingent valuation, or multiple methods), respondent samples (patients, proxy, or general population), treatment process attribute results (route of administration, dose frequency, dose timing, dose size, treatment duration, and other), and comparison of treatment process attributes vs efficacy and safety. As much as possible, an effort was made to present results consistently across studies, including preference for levels within each attribute and relative importance across attributes. However, the level of detail and presentation of results in the source articles varied greatly, and therefore, it was not always possible to extract the same

quality or depth of information across studies.

Machine learning guided data extraction

Following softwares tools should be used for the machine learning(ML) guided data extraction;

Table 2: Software tools with URLs for data extraction

Software tool	URL
ASReview (ASReview Core Development Team, 2019	https://github.com/asreview/asreview
Colandr (Cheng et al., 2018)	https://github.com/datakind/permanent- colandr-back
FASTREAD (Yu et al., 2018;Yu & Menzies, 2019)	https://github.com/fastread/src
HAWC (Shapiro et al., 2018)	https://github.com/shapiromatron/hawc/tree/master
MeSHSIM (Lajeunesse, 2016)	https://github.com/JingZhou2015/MeSHSim
METAGEAR package for R(Bigendako & Syriani, 2020)	https://github.com/cran/metagear/
PARSIFAL	https://github.com/vitorfs/parsifal
ReLiS (Bigendako & Syriani, 2020)	https://github.com/geodes-sms/relis
REviewER	https://github.com/bfsc/reviewer
Revtools (Westgate, 2019	https://github.com/mjwestgate/revtools

Manual and ML guided data should be compared, additional data obtained by ML tool should be included, duplications should be deleted.

Quality check for the selected articles

In order to assess the methodological quality of the articles selected for final review. the Down and Black checklist should be used and scored accordingly. The Down and Black checklist consists of 27 items that are divided under 5 subscales i.e the Reporting of the study, External validity, Internal validity (Study bias/ Blinding), Internal validity (Confounding/ Selection bias) and power of the study. Each of these sub scales are scored as 11, 3,7,6 and 5 respectively. A score of 0 being the lowest and highest being 32. The articles whose results will not be consistent with the objectives mentioned for the study should be removed. The articles should be categorized as those with the Down and Black score ,<20 , 20-24 ,24-28 and 28-32 and should be reviewed separately.

PRISMA guidelines should be followed for the meta analysis. Methods of data analysis and statistical methods

Studies should be segregated objective wise and should be analysed further. Descriptive data should be summarized as numbers and percentages for categorical data and means or medians and standard deviations or ranges for continuous data.

The statistical analysis should be carried out using the software '**Comprehensive Meta- Analysis software, version 2.0'** applying the continuous measures test for meta-analysis.

Random effect models should be used to calculate proportion difference and standard error (SE) with a 95% confidence interval. Heterogeneity should be found out in the perception of the participants of the study. Random effect models should be used to calculate OR and CI. The significance of summary ORs should be determined with a Z test. Heterogeneity assumption should be checked by χ^2-based Q test. A p-value <0.05 for the Q test should be considered as significant heterogeneity among the studies. $p<0.1$ should be considered significant for heterogeneity assessment. Publication bias should be assessed by Egger's and Begg's test.

Expected outcomes

The current study is designed to identify stated preference studies and utility studies as these methods can provide a quantitative assessment of specific treatment process attributes. The meta-analysis will support quantitative estimation of the strength of end-user preferences for different attributes and how they are traded off against one another. In addition, it supports monetary valuation of different attribute combinations that produce estimates of the indirect benefits to end-users. By monetizing preferences, a comparison with the direct monetary costs of administering biologic drugs can be made. The predicted cost estimates plus preference valuations measured in this study may be considered in (bio) manufacturing decision-making. This is the kind of information manufacturers need in order to make patient friendly drugs that have low administration costs. The use of such evidence in pre-market R&D and manufacturing decisions should yield drug products with added value. Cost-effectiveness assessments, from a healthcare payer perspective, will capture the added value in terms of savings in drug administration costs.

The comfort of an improved mode of drug administration is seldom considered in evidence-based medicine and often seen as "luxury". The results of this study however may show the monetary value of intangible end-user benefits (what some may consider luxury that can be ignored) is significant. This finding is most relevant to (bio) pharmaceutical manufacturers as they are the translators of promising (biologic) drug candidates into medicines that offer positive direct health benefits relative to placebo or existing treatments. The pertinent issue here is whether healthcare payers recognize and are willing to pay for the indirect benefits to end-users, besides the direct health benefits. If they do, manufacturers should be faced with the right incentives to produce drugs that make significant contribution to patient care. If the mode of drug administration is simply a vehicle by which

the (incremental) health benefits provided by a drug are delivered to patients, then pharmaceutical manufacturers need to have some knowledge of end-user preferences for this vehicle if they are to produce patient-friendly medicines. The proposed review emphasizes on this fact.

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