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Development of a predictive model for urgency urinary incontinence☆

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ABSTRACT

The ability to set realistic expectations of treatment response in patients with overactive bladder (OAB) can have an impact on patient engagement and adherence to study medication. In order to help set treatment expectations for OAB, a Physician Predictive Tool has been developed based on predictive modelling. Models have been developed utilizing data from eight Phase 3 and 4 fesoterodine clinical trials and these models enable the prediction of individual treatment response in subjects with OAB, based on various baseline characteristics. The data utilized and covariates that were hypothesized to influence treatment response are described. The model selection and development process are also outlined, and the final model and some example results utilizing this model are presented. Finally, we discuss the potential benefits and limitations of such a predictive tool.

1. Introduction

Fesoterodine, a competitive muscarinic receptor antagonist, is indicated for the treatment of overactive bladder (OAB) in adults with symptoms of urgency, urgency urinary incontinence (UUI), and frequency [1]. Recently, there have been several published systematic reviews and meta-analyses to assess the effect of antimuscarinic (AM) drugs in clinical trials in subjects with OAB. These have confirmed the efficacy and safety of AMs, with improvements in OAB symptoms and health-related quality of life (HRQL) [2–5]. However, it has been found that treatment response in individual patients can vary, and extrapolating clinical trial outcomes as described for a study population to an individual patient remains challenging.

Because of this variability in response, a major gap in the current treatment of patients with OAB has been the ability to set realistic expectations and to retain patient engagement [6]. Previous studies have shown that persistence rates for AM medications is generally low [7], and both efficacy and tolerability play a key role in patients' satisfaction and adherence with their treatment [6,8]. Because of the unmet need and the availability of extensive clinical data, a Physician Predictive Tool was developed for use by prescribing physicians and other healthcare professionals, who often want to know how clinical trial data can be applied to the individuals they are treating. The aim of this work was to provide a simple tool that used available trial data to help prescribers set reasonable expectations of treatment outcomes for their patients. The predictive model could also potentially help locate the sub population who will benefit the most from treatment.

Fesoterodine was launched for the treatment of OAB in 2008, and there is a wealth of individual subject data from the clinical trial program that can be utilized to gain an understanding of how patients respond to fesoterodine and which clinical factors influence their response to treatment. This predictive model is a tool that physicians can use when diagnosing and explaining to their patients the potential outcome of using fesoterodine to manage their OAB symptoms. The tool developed offers healthcare professionals a simple way of characterizing patients based on baseline symptoms and, through the use of quantitative statistical techniques, enables an estimate of predicted treatment outcomes.

Abbreviations: AM, antimuscarinic; BMI, body mass index; BPH, benign prostatic hyperplasia; CART, classification and regression trees; DB, double-blind; ER, extended release; HRQL, health-related quality of life; LS, least squares; MARS, multivariate adaptive regression splines; OAB, overactive bladder; OAB-q, Overactive Bladder Questionnaire; OL, open-label; PPBC, Patient Perception of Bladder Condition; USS, Urinary Sensation Scale; UUI, urgency urinary incontinence.

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2. Materials and methods

2.1. Datasets and variables

We assessed the characteristics of all recently conducted fesoterodine studies to determine which were sufficiently consistent in their design to warrant inclusion. The following characteristics were required for inclusion into our model: 12 weeks treatment duration and included both 4 mg and 8 mg dosages, as either fixed or flexible treatment regimens.

The most common primary endpoint in the trials was the number of UUI episodes per 24 h. This is both a clinically relevant outcome – as it is recognized as typically one of the most bothersome symptoms and one that is likely to lead to patients seeking treatment [9]. Therefore, change from baseline in UUI was chosen as the outcome measure to predict, and subjects with >0 and <15 UUI episodes per 24 h at baseline and treated with fesoterodine were included in the model. This included the majority of subjects studied, and also meant that any results obtained would not be skewed by a few severe subjects. Table 1 presents the characteristics of the studies included in the analysis [10–20].

The following variables were initially included in the integrated dataset, as these were baseline characteristics or prognostic factors that were hypothesized to have an influence on treatment response (either due to biological plausibility or based on findings from prior analyses):

- Baseline UUI frequency, micturition frequency, urgency frequency
- Baseline Patient Perception of Urgency Scale, baseline PPBC, baseline Overactive Bladder Questionnaire (OAB-q) HRQL, baseline OAB-q symptom bother
- Gender, age, body mass index (BMI), hormonal status, previous number of pregnancies, smoking history, childbearing potential, diabetes, benign prostatic hyperplasia (BPH), prior OAB treatment

2.2. Model development

Once a basic group of studies and datasets were available to use, several possible models to fit were investigated. The first two models to be examined were: Multivariate adaptive regression splines (MARS) and classification and regression trees (CART). MARS is a nonparametric regression spline-based method and makes no assumptions about the underlying functional relationship between the dependent and independent variables. Polynomial splines are used as approximating functions for data fitting and statistical analysis [22]. MARS also searches for interactions between variables, allowing any degree of interaction to be considered as long as the built model can better fit the data. CART is also a non-parametric method of optimally partitioning the response variable into separate 'branches' based on the dependent variables. This continues until each branch reaches a terminal node, and at this point each observation of the response variable is uniquely categorized at the terminal node, by a unique 'rule' [23]. These are similar modelling techniques; however, each has their advantages and disadvantages. We assessed both methods by comparing the results from fitting each model to the same datasets. It became clear that there were differences in the results observed for the two types of models and the reasons for these differences were further investigated. One approach to investigate the differences in results was to manually fit several linear regression models to replicate the MARS procedure. However, the results from this approach were not robust as there were too few observations for some subgroups. As both MARS and CART artificially split the data into many subgroups and create model predictions for each of these, these models may not perform well when there are sparse data for a particular subgroup. Therefore, in order to overcome this issue, an overall linear regression model (see below) was fitted to all of the data.

2.3. Linear regression model

A linear regression model is a more practical and accurate approach since predictions can be made individually. This method also has the following advantages:

- Easily translates into a tool a physician could use
- Provides individual prediction of treatment response for a patient
- Can assess the influence of various covariates
- Deals with sparse data for more severe patients
- Easily determines how well the predicted responses compare to actual responses
- A stepwise selection procedure could be used to test significance of covariates
- An analogous logistic regression model could be used to assess the probability of becoming dry for an individual (or any other binary outcome)

The main disadvantage of a linear regression model is that it assumes a linear response. Therefore, any non-linearity in the treatment response will not be taken account of (unless a transformation of the response variable or covariates is applied), and is therefore also more sensitive to outliers.

Initial results demonstrated that a linear regression model was a good predictor based on baseline UUI and there was good agreement with the CART model. The extensive training and test datasets randomly created from the pool of studies included in the modelling replicated the results and baseline UUI was overwhelmingly the most significant covariate. A decision was made to continue developing the linear regression model, as this could easily provide an individual prediction of change in UUI.

The model building process investigated the influence of various covariates, and the parameter estimate obtained for each covariate was utilized to construct the final predictive model from which individual outcomes for treatment response, based on change from baseline in UUI, could be estimated.

2.4. Logistic regression model

In parallel to the linear regression model development, logistic regression models were also developed based on the same set of covariates. The aim of the logistic regression models was to enable predictions of the binary outcomes to be estimated: for example, to estimate the probability of a 50% reduction from baseline in UUI (taking a value of Yes or No). Similar logistic regression models for the probability of a 100% reduction (i.e., OAB 'diary dry' at the end of treatment) and the probability of an 80% reduction from baseline in UUI were also developed. These can be used to determine predicted probabilities of the event occurring based on values of all of the covariates. It also allows for the odds ratios of a particular binary event (e.g., becoming 'diary dry' at the end of treatment or not) to be estimated, based on the values of different factors or covariates.

The predicted value from a binary logistic regression model is the estimated probability of a patient being 'diary dry' or having an 80% (or 50%) reduction from baseline in UUI, whereas the predicted value from the linear regression model is the predicted change from baseline in UUI. So for any particular set of patient characteristics, the set of linear and logistic regression models could predict both the continuous and binary outcomes.

Once all the predictive models had been developed, the parameter estimates obtained were used to build the predictive tool within a spreadsheet format. Baseline characteristics could be easily inputted to then predict outcomes for change from baseline in UUI, and the probability of a 100%, 80%, and 50% reduction from baseline in UUI.