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Quickest way to less headache days: an operational research model and its implementation for chronic migraine

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Abstract

Objective Choosing migraine prevention medications often involves trial and error. Operations research methodologies, however, allow us to derive a mathematically optimum way to conduct such trial and error processes.

Background Given probability of success (defined as 50% reduction in headache days) and adverse events as a function of time, we seek to develop and solve an operations research model, applicable to any arbitrary patient, minimizing time until discovery of an effective migraine prevention medication. We then seek to apply our model to real life data for chronic migraine prevention.

Methods An operations research model is developed and then solved for the optimum solution, taking into account the likelihood of reaching 50% headache day reduction as a function of time. We then estimate key variables using FORWARD study by Rothrock et al. as well as erenumab data published by Barbanti et al. at International Headache Congress 2019.

Results The solution for our model is to order the medications in decreasing order by probability of efficacy per unit time. This result can be generalized through calculation of Gittins index. In the case of chronic migraine the optimum sequence of chronic migraine prevention medication is a trial of erenumab for 12 weeks, followed by a trial of onabotulinumtoxinA for 32 weeks, followed by a trial of topiramate for 32 weeks.

Conclusions We propose an optimal sequence for preventive medication trial for patients with chronic migraine. Since our model makes limited assumptions on the characteristics of disease, it can be readily applied also to episodic migraine, given the appropriate data as input. Indeed, our model can be applied to other scenarios so long as probability of success/adverse event as a function of time can be estimated. As such, we believe our model may have implications beyond our sub-specialty.

Keywords Headaches, Migraine, Operations research, Medication selection, Migraine prevention

Background

Migraine has an approximate global prevalence of 14.7% [1]. Unfortunately, finding an effective prevention therapy for patients often involve trial and error [2, 3]. Medication trial failures cause frustrations and helplessness among migraine sufferers [3, 4]. An expedient way of determining effective prevention therapy can significantly benefit our patients.

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Operations research (OR) is the study of optimal decision-making using mathematical models. In healthcare, OR models have been used to propose selections of chemotherapy combinations, to identify optimal criteria for screening, and to inform clinicians on when to initiate medications or to perform surgical interventions [5–12]. To the best of our knowledge, OR methods have not been applied to medication selection in headache.

The aim of this paper is to propose an OR model for migraine medication selection. We assume that for any randomly selected patient one can estimate the probability of success for individual prevention medications as a function of time. We then derive the optimal sequence of medication trial, minimizing time for the discovery of an effective treatment. As a proof of concept, we utilize published data to demonstrate that this model can be implemented for real world decision-making purposes in chronic migraine.

Methodology

Although we outline our operations research model for the clinician and layperson in the methodology section, we include an in depth technical methodological portion in Supplementary Material.

For modeling purposes, we define successful/effective treatment response as 50% improvement in monthly headache days. (Monthly headache days is defined as the number of days with headaches in a single month.) This value is not intrinsic to our model but to the input data. We assume that given any two medications, their respective probabilities of success are statistical independence. We assume that any intolerable adverse event would be discovered before observing 50% improvement in headache days. Finally, only one medication is allowed to be tried at a time.

The model

Given a set D of preventive medications, for drug i in D, we describe the likelihood of reaching 50% headache day reduction over the course of time, $(t_{i,1} \leq t_{i,2} \leq \dots)$ by probability $(p_{i,1} \leq p_{i,2} \leq \dots)$. We similarly describe the likelihood of discovering an adverse event over the course of time $(t_{i,1} \leq t_{i,2} \leq \cdots)$ by probability $(q_{i,1} \leq q_{i,2} \leq \dots)$. We consider the space of policies that stop administering a drug when an intolerable adverse event is discovered, and solve for a sequence of prescription trials that minimizes the expected time until an effective drug is identified.

Topiramate, onabotulinumtoxinA, and CGRP antagonists are the only medications widely accepted to have evidenced based efficacy in chronic migraine prevention [13, 14]. We use published 50% responder rates for week 12 and week 32 as well as adverse event rates from the FORWARD study as estimates for $(p_{i,1} \leq p_{i,2} \leq \dots)$ and $(q_{i,1} \leq q_{i,2} \leq \dots)$ for topiramate and onabotulinumtoxinA [15]. We use 50% responder rates from Barbanti and colleagues' retrospective study to estimate probability of real world efficacy as a function of time for erenumab [16]. We estimate adverse event for erenumab based on package insert [17]. Our input data for the model is summarized in Table 1.

(A note on notations: The set D in our case represents the set of onabotulinumtoxinA, topiramate, and erenumab. The first subscript i represents one of these medications. The second subscript k, represents the epoch of time under consideration. P(x) and E(x) represent the probability and expected value of x, respectively. An asteroid (*) next to a variable denotes optimum solution.)

Notice that in the FORWARD study, the 32 week probability for both OnabotulinumtoxinA and topiramate is lower than that during week 12. Although this reflects real life circumstances in the FORWARD study itself – in this case, intolerability of topiramate – this is unrealistic for our purpose. Therefore, in our modeling we have modified the 32 week topiramate/onabotulinumtoxin A probability to be equal to that in week 12 for modeling purposes.

Theoretical results

Our model is a case of the multi-armed bandit problem in operations research. Solutions to this class of problem can be solved through calculation and identification of a ratio called the Gittins Index at every decision point [23]. In other words, index ratios are calculated for all possible choices at every decision point; one then identifies the next optimum decision by picking the decision with the highest index. We denote the calculation of these indices as functions $\sigma_i : \{t_{i,1}, \dots\} \to \mathbb{R}_+$ for each drug i. We denote the Gittins index as σ_i^*

The solution for our model is to order medications by probability of efficacy per unit time. Consider a simplified scenario: When the efficacy of each drug i is known only for one period t_i, then the optimum sequence is to administer drug i for t_i periods in decreasing order of p_i/t_i. For example, suppose a hypothetical antiepileptic has a 90% probability of being effective (let's call this p_{AED}) only by the end of 3 months (t_{AED}) whereas a hypothetical CGRP mab has a probability of 50% (p_{CGRP}) only by the end of 1 month (t_{CGRP}). The optimal solution is to try the hypothetical CGRP first for 1 month followed by trying the antiepileptic for 3 months. Note that in this scenario we assume no observable intermediate benefit can be appreciated until the end of either month 1 for CGRP or month 3 or the antiepileptic.

Table 1 Input data for our model based on FORWARD study and Barbanti et al

OnabotulinumtoxinA	
Time (weeks)	Probability of Success (i.e. reaching 50% reduction in headache frequency.)
12	.407 to .456
32	0.4
Topiramate	
Time (weeks)	Probability
12	0.225 to .294
32	0.12
Erenumab (i.e. Aimovig)	
Time(weeks)	Probability
4	0.612
8	0.667
12	0.875
Adverse event OnabotulinumtoxinA leading to discontinuation	
Time (weeks)	
4	0.013636364
Adverse event Topiramate leading to discontinuation	
Time(weeks)	
4	0.422535211
Adverse event aimovig, per package insert	
Time(weeks)	
4	0.03

A more realistic generalized solution to the above can be derived: the optimum sequence is to administer drug i for t_i^* periods, where

$$\sigma_i(t) = \frac{\text{P(efficacy with no adverse effects if administered until time}t)}{\text{E(time administered if administered at most until time } t)} = \frac{\sum_{j:t_{i,j}\le t}(p_{i,j}-p_{i,j-1})(1-q_{i,j})}{\sum_{j:t_{i,j}\le t}(t_{i,j}-t_{i,j-1})(1-p_{i,j-1})(1-q_{i,j-1})}$$

is the probability of efficacy per unit time if the drug were administered until time t, and

$$t_i^* = argmax_{t\in\{t_{i,1},\dots\}}\sigma_i(t)$$

is the time period that maximizes the efficacy per unit time of drug. Then, in order to determine which drug to try next, the indices for the trialed drug i need to be recalculated after trying it for time t_{i,k^*}. (Proof of both of the above results are included in Supplementary Material 2).

In other words, $\sigma_i(t)$ represents a generalized version of p_i/t_i. The numerator of $\sigma_i(t)$ represents the probability of the drug efficacy if administered until time t, assuming that the drug is no longer administered if an adverse event is discovered. The denominator of $\sigma_i(t)$ represents the time the drug is administered to the patient before time t, taking into account that this time may be shorter than t if the drug is successful earlier in the process or if there are adverse effects.

Application of model to chronic migraine data

Based on FORWARD as well as Barbanti study data, we calculated the above indices for the first iteration and present the results in Table 2. (Here, σ_{ik} represents the index for each medication at specific time k for drug.)

Inputs are adjusted to ensure probabilities are increasing over time by taking the maximum probability of efficacy up to each specific time frame.

Using the input data, the first drug to trial is erenumab, for at least 4 weeks. We then calculated the above indices for the second iteration and present the results in Table 3. Using the input data, the next step is to continue the trial of erenumab for a total of 12 weeks.

Using the input data, an optimal sequence is:

1) A trial of erenumab for 12 weeks

Table 2 Calculations of indexes for first iteration based on input data

	σ_{i1}	σ_{i2}	σ_{i3}	$\sigma(t_i^*)$
OnabotulinumtoxinA lower bound	0	0.033761086	0.017018394	0.033761086
OnabotulinumtoxinA upper bound	0	0.037825688	0.019882016	0.037825688
Topiramate lower bound	0	0.015073529	0.00739479	0.015073529
Topiramate upper bound	0	0.019696078	0.010121587	0.019696078
Erenumab	0.14841	0.117518309	0.124862449	0.14841

Note: Input adjusted to ensure probabilities are increasing over time. σ_{ik} represents the index for each medication at specific time k for drug i

Table 3 Calculations of indexes for second iteration based on input data

	σ_{i1}	σ_{i2}	σ_{i3}	$\sigma(t_i^*)$
OnabotulinumtoxinA lower bound	0	0.03376108562	0.01701839441	0.03376108562
OnabotulinumtoxinA upper bound	0	0.03782568807	0.01988201633	0.03782568807
Topiramate lower bound	0	0.011710568	0.00739479	0.011710568
Topiramate upper bound	0	0.015871804	0.01012158667	0.01587180365
Erenumab		0.071686204	0.09119278779	0.091192788

Note: Input adjusted to ensure probabilities are increasing over time. σ_{ik} represents the index for each medication at specific time k for drug i

2) If the above fails, then proceed with onabotulinumtoxinA for 32 weeks
3) If the above fails, then proceed with topiramate for 32 weeks.

Since estimates for OnabotulinumtoxinA and topiramate are based on a lower and upper bound in our input data, it is possible that the following alternative sequence is also optimal:

1) A trial of erenumab for 12 weeks
2) If the above fails, then proceed with onabotulinumtoxinA for 12 weeks
3) If the above fails, then proceed with topiramate for 12 weeks
4) If the above fails, switch back to onabotulinumtoxinA for 20 weeks
5) If the above fails, switch back to topiramate for 20 weeks.

This alternative optimal solution is logistically difficult, clinically peculiar, and is therefore only theoretical.

Our model is not a simulation. All of our calculations are conducted through Microsoft Excel.

Discussion

In this proof of concept study, we frame the process of migraine preventive medication selection as an OR problem. We outline a methodology for the construction and real life implementation of such an OR model. We believe such a perspective will be invaluable to clinical practice.

Applications of OR to medical decision making/clinical trial design have relied mostly on Markov Decision Process (MDP) [18, 19]. Traditionally, medical decision-making MDP models are personalized, computationally demanding, require large amount of data and are often difficult to interpret for practitioners [9–12]. These limitations have prevented widespread use of personalized MDP models clinically [10, 20]. As an alternative, our paper utilizes a multi-armed bandit process, a special case of MDP well studied in OR which utilizes an "index" method [5, 6]. We are unable to find a prior instance of utilization of this method in clinical decision-making for medication selection.

Our model allows for a clinically intuitive way of understanding medication optimization: we can estimate optimal sequence for prevention medication selection with the index p_i/t_i – prioritizing and select medications that maximizes probability of efficacy per unit of time. This index should be re-evaluated in real time and on each follow up visits to offer continual guidance for the next medication choice.

Although the focus of this paper is chronic migraine, we believe that OR models for medication selection should not be limited to our subspecialty. Given that we make no assumption on the underlying disease process, our model and its solution may be directly applicable to a wide range of clinical medicine scenarios outside our discipline.

Strength and limitations

We want to be very clear: our model is not intended to be utilized to the exclusion of all other patient centered concerns such as medication overuse headaches, patient comorbidities, or drug-drug interactions. Indeed,

mathematical modeling is not a substitute for good doctoring and is not a panacea for addressing all clinical decision making considerations.

Our model's assumptions are its limitations: First, we assume mono-therapy in medication selection. While we believe this to be a reasonable assumption, we acknowledge that this is not often true in the real world. Challenging our paradigm of monotherapy, for example, is the open question of whether synergism exists between onabotulinumtoxinA and CGRP antagonists.

Closely related to the question of synergism is our assumption of independence of efficacies in our model: that is, responding to one medication cannot help us predict response to another medication. Indeed, data from large real life observational studies appears to suggest that independence may not be the case among CGRP antagonists and onabotulinumtoxinA where the failure of the former may imply a higher chance of ineffectivness of the latter [24]. Addressing this problem is a potential future direction in improving our model.

Our model also does not take into account ways in which patient-specific factors affects efficacies of individual medications. This is, in part, due to the lack of data for patient-specific factors for various medications as a function of time. However, recent artificial intelligence models have shown promise in being able to predict patient-specific efficacies for CGRP antagonists [24–26]. These advances in precision medicine may be readily used in our model for the development of personalized optimal medication choices in migraine.

Our most significant limitation is the scarcity of available data for our model. Firstly, as a proof of concept paper we are not wedded to the idea of using only FORWARD nor Barbanti data for our model; the primary purpose of this paper is a methodological one after all. Indeed, we have to account for study specific peculiarities in our model. Namely, that the percentage of responders for both onabotulinumtoxinA and topiramate during week 12 of the FORWARD study is lower than that during week 32. While this is possible during clinical trials, it becomes problematic in mathematical modeling. Furthermore, the reason for this discontinuation is attributed to intolerability of patients for whom topiramate reached 50% reduction, i.e. success in terms of migraine treatment. While our implementation of the FORWARD model does consider the probability of an adverse event within the first 4 weeks, it does not consider this sort of failure (although it can be modified to do so). This is due to the fact that side effect as a function of time is not included in the FORWARD study. We forsee that with better input data our model may be more accurate in the future.

Secondly, we have decided to only include real-life data based on the critique that clinical trial responder rates may not translate directly to real word settings. This methodological concern is especially regrettable in regards to CGRP data: A number of authors were able to estimate 50% response rates of erenumab and galcanezumab as a function of time; yet these study were extrapolated from clinical trial, therefore limiting their application to this paper [21, 22].

Finally, we modeled adverse effects of medications as an observable entity. This may fail to take into account potential side effects that are not observable. Specifically, topiramate has been well-recognized as teratogenic and some have argued for its exclusion as a prevention therapy in female migraine sufferers [27].

The strength of our model lies in its conformity with real life perspectives of contemporary migraine treatment paradigm. Firstly, the American Headache Society recently support CGRP as a first-line treatment for migraine prevention [28]. Secondly, our optimal sequence of medication selection conforms to the principal of *primum non nocere* in medication selection: intolerabilities of topiramate have well documented in the literature, from high discontinuation rates to higher frequency of adverse effects when compared to CGRP and onabotulinumtoxinA [29–31]. Our model reflects the logical approach of using CGRP and onabotulinumtoxinA prior to topiramate.

Future directions

In order to apply our solution to real life decision-making, we require real life data in the form of responder rate as a function of time. We hope that this paper will alert future researchers to the importance of real-world data, allowing for improvement in implementation of our method.

Conclusions

An OR model can be constructed for optimal medication decision-making in headache prophylaxis. We outline the methodology for such an OR model and its empirical implementation. Although our model supports the sequence of erenumab, followed by OnabotulinumtoxinA, followed by topiramate, more data is needed to support this sequence as being optimal. We believe a similar approach can be applied to other specialties.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04124-5.

Supplementary Material 1

Supplementary Material 2

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IL and PZ contributed to the design of the study. IL implemented the study. All author contributed equally in drafting, editing, and approving the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
N/A.

Consent for publication
N/A.

Competing interests
IL has no financial conflict of interest. PZ: He has received honorarium from Alder Biopharmaceuticals, Board Vitals, and Fieve Clinical Research. He collaborates with Headache Science Incorporated without receiving financial support. He had ownership interest in Cymbeline LLC. He works as a consultant for Acumen LLC.

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