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Highlights

1. We developed data-driven and expert-driven computer-based DSS models for medication change of Parkinson's disease patients
2. The DSS models cover the whole space of input attributes' values, i.e., any combination of motor and non-motor symptoms, and any epidemiologic characterization of a patient
3. Expert-driven DSS model resembles well the decisions made by physicians and outperforms the data-driven model in terms of accuracy.
4. The accuracy results indicate that the constructed models are sufficiently adequate and fit for the purpose of making suggestions to DSS users.

Decision Support for Medication Change of Parkinson's Disease Patients

Biljana Mileva Boshkoska [1, 2], Dragana Miljković [1], Anita Valmarska [1], Dimitrios Gatsios [3, 4], George Rigas [3], Spyridon Konitsiotis [4], Kostas M. Tsiouris [3,5], Dimitrios Fotiadis [3,6], Marko Bohanec [1]

[1]Department of knowledge technologies, Jožef Stefan Institute, Ljubljana, Slovenia

[2]Faculty of information studies in Novo mesto, Slovenia

[3]Unit of Medical Technology and Intelligent Information Systems, Dept. of Material Science and Engineering, University of Ioannina, Ioannina, Greece

[4]Department of Neurology, Medical School, University of Ioannina, Ioannina, Greece

[5]Biomedical Engineering Laboratory, School of Electrical and Computer Engineering, National Technical University of Athens, Athens, Greece

[6]Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, Ioannina, Greece

[biljana.mileva, dragana.miljkovic, anita.valmarska]@ijs.si, dgatsios@cc.uoi.gr, george.a.rigas@gmail.com, skonitso@gmail.com, tsiourisk@biomed.ntua.gr, fotiadis@cc.uoi.gr, marko.bohanec@ijs.si

Background and Objective: Parkinson's disease (PD) is a degenerative disorder of the central nervous system for which currently there is no cure. Its treatment requires long-term, interdisciplinary disease management, and usage of typical medications, including levodopa, dopamine agonists, and enzymes, such as MAO-B inhibitors. The key goal of disease management is to prolong patients' independence and keep their quality of life. Due to the different combinations of motor and non-motor symptoms from which PD patients suffer, in addition to existing comorbidities, the change of medications and their combinations is difficult and patient-specific. To help physicians, we developed two decision support models for PD management, which suggest how to change the medication treatment.

Methods: The models were developed using DEX methodology, which integrates the qualitative multi-criteria decision modelling with rule-based expert systems. The two DEX models differ in the way the decision rules were defined. In the first model, the decision rules are based on the interviews with neurologists (DEX expert model), and in the second model, they are formed from a database of past medication change decisions (DEX data model). We assessed both models on the Parkinson's Progression Markers Initiative (PPMI) and on a questionnaire answered by 17 neurologists from 4 European countries using accuracy measure and the Jaccard index.

Results: Both models include 15 sub-models that address possible medication treatment changes based on the given patients' current state. In particular, the models incorporate current state changes in patients' motor symptoms (dyskinesia intensity, dyskinesia duration, OFF duration), mental problems (impulsivity, cognition, hallucinations and paranoia), epidemiologic data (patient's age, activity level) and comorbidities (cardiovascular problems, hypertension and low blood pressure). The highest accuracy of the developed sub-models for 15 medication treatment changes ranges from 69.31 to 99.06 %.

Conclusions: Results show that the DEX expert model is superior to the DEX data model. The results indicate that the constructed models are sufficiently adequate and thus fit for the purpose of making "second-opinion" suggestions to decision support users.

Keywords: Parkinson's disease, medication change, decision support model

1 Introduction

Parkinson's disease (PD) is a complicated, degenerative disorder of the central nervous system which is manifested in each patient individually and for which there is currently no cure (Parkinson's disease. Diagnosis and treatment., 2018). The cause of the disease is connected with the reduced amount of a chemical called dopamine which is produced in the part of the brain called the substantia nigra. PD requires long-term, interdisciplinary disease management, which typically includes pharmaceutical treatment with levodopa (LD), dopamine agonist (DA), and enzymes, such as MAO-B inhibitor, as indicated in (Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care, 2006). Currently, there are as yet no treatments beyond symptomatic relief to slow down the neurodegenerative decline. Due to the different combinations of motor and mental symptoms from which PD patients suffer, the decision to change medications and their combinations are difficult and patient-specific (Gatsios, et al., 2016).

There are several official guidelines for the PD treatment. Detailed recommendations for the treatment of PD patients (Oertel, et al., 2010), (Oertel, et al., 2010a) were made available online by the European Academy of Neurology (EAN) and the European Federation of Neurological Societies (EFNS). A summary of the 2010 EFNS/MDS-ES evidence-based treatment recommendations for the management of Parkinson's disease (PD), including both early and late PD, is provided by (Ferreira, et al., 2013). The Movement Disorder Society (MDS) task force summarized the efficacy of treatments of specific non-motor (Seppi, et al., 2011) and motor PD symptoms (Fox, et al., 2011). One of the most systematic guidelines for the treatment of PD is presented in (Olanow, Watts, & Koller, 2001).

Guidelines are used to support the physicians' decisions in the treatment of PD patients, usually by creating decision trees, which is widely used method in medicine (Patela, Kaufmana, & Arochab, 2002). In the study of (Nguyen, Kunz, Taylor, & Acosta, 2018) decision trees were used for pharmacotherapy management of PD patients to answer two specific questions: whether the PD patient needs pharmacotherapy and whether that therapy is effective. In their study, Iskedjian and Einarson (2003) used the decision trees to examine whether the reduction of dyskinesia by using dopamine agonist instead of levodopa in newly diagnosed PD patients will have an economic impact. Their model, along with seven other models based on differential equations and Markov chains, were reviewed by Siebert et al. (2004). These models were focused on evaluating pharmaceutical and surgical treatments in terms of efficacy of one drug over another.

To the best of our knowledge, none of the existing models answers the question *how to change the medication*. Hence, the problem addressed in this paper was to develop a decision support model for suggesting medication change to physicians based on data about the patient's motor and non-motor symptoms. In particular, the physicians stay informed of their patients' status by conducting consultations, either by phone or in person. According to the Parkinson's Progression Markers Initiative (PPMI) study (Marek, et al., 2011), the physicians meet with their respective patients regularly at least 2-4 times annually. During these consultations, using standardized questionnaires, the physicians are informed of the patient's status, i.e., the severity of symptoms and the overall quality of the patient's life. Consultations are usually short, so the feedback to patients needs to be quick and integrated into the daily working routine of the health professionals. The quality of consultations can be improved with a decision support system (DSS) for modifications in PD medication management, which would be of great help for clinicians especially at the stage in which PD patients' response to medications becomes unpredictable, and clinicians have to make decisions about making changes in the disease management.

An initial framework for developing such a DSS was provided by the EU Horizon 2020 project called PD_manager (PD_manager: m-Health platform for Parkinson's disease management., 2015). Overall, PD_manager was aimed at developing and evaluating an m-Health platform for PD management (Gatsios, et al., 2016). The PD_manager DSS makes suggestions to the treating neurologists, who calibrate them and make final decisions (Tsiouris, et al., 2017).

This paper describes the process and results of developing a decision support model for medication change in PD patients. In particular, we provide expert-driven and data-driven computer-based models that suggest how to change the medication plan, i.e., by changing the dosage of the current medication or changing one medication with another. The models are open in the sense that they contain decision rules that can be inspected and verified by specialists. The models are guaranteed to be complete (covering all possible combinations of observed symptoms) and to obey the principle of dominance (the more severe the symptoms, the more need for medication change). The models are useful at providing "second-opinion" suggestions to medical users of the DSS. Based on the comparison of expert- and data-based models, we also show that the expert knowledge is invaluable compared to data driven knowledge when designing medication change models. To the knowledge of the authors this is the first time that models, implemented in a software program, are used for supporting the decision of neurologists in the process of medication change of PD patients.

In the following, we formulate the addressed problem (section 2) and describe the main methodological steps of the study (section 3). We present the produced models in terms of their structure and contents and assess and discuss their quality (section 4). The paper ends with a summary of achievements and contributions.

2 Problem formulation

The problem addressed in this study was to develop a decision support model for suggesting medication change to physicians. Based on the data about an individual patient, the aim is to identify and improve situations in which the current medication therapy is not sufficient and has to be changed. This should be carried out using the data that is available in the PD_manager DSS for each patient (Tsiouris, et al., 2017).

In general, there are two possible types of suggestions: (1) a yes/no (or change/no-change) suggestion, which only identifies the need for medication change, but leaves the decision of how to change the therapy to the physician and (2) a suggestion of how to change the medication, for instance, to replace some medication with another or change the dosage of the current medication given the patients' current symptoms and medication intake. The first, *yes/no* models were already presented in (Bohanec, et al., 2018). In this paper, we focus on the more complex decision-support model that suggests *how* to change the medication.

The functionality of the decision-support model is defined as follows:

- Given the *current medication treatment* of the patient and the patient's *present symptoms* and *epidemiologic factors*, the DSS should determine whether the current medical treatment is effective or not. The DSS should suggest one or more alternative changes of medications that are expected to reduce the manifestation of symptoms to the lowest possible level. The suggestions are presented to the treating neurologist who is responsible for making the final decision.
- The model addresses medication treatments consisting of any possible combination of a dopamine agonist (DA), levodopa (LD), and MAO-B inhibitors (MAOI).
- The model addresses the following medication change transitions:
    - *decrease/increase* the medication *dosage* or *intake* (for DA and LD)
    - *include/exclude* medication (DA, LD and MAOI);
    - change the medication from *current* to *new* (e.g., DA to LD)
- The model takes into account the following data about the patient:
    - *Motor symptoms*: bradykinesia, tremor (tremor at rest, action tremor and postural tremor), rigidity, dyskinesia (OFF duration, intensity and duration);

- *Non-motor symptoms*: mental problems (impulsivity, cognitive disorder, psychosis such as hallucinations and paranoia), presence of comorbidities (cardiovascular problems, low blood pressure and hypertension);
- *Epidemiologic characteristics*: age and activity of the patient.

- Given the scope of our study, which was restricted to patients treated with at least one medication, the *choice of initial therapy* is excluded from the model. Therefore, the transitions from no medication intake to some medication intake are not covered by the model.

Also, the DSS has to provide evidence (justification, explanation) to support the suggestions. The model is also expected to have the following properties (Bohanec, et al., 2018):

- *Robustness and completeness*: working on all possible inputs, including missing data.
- *Consistency*: free of logical errors and obeying the principle of dominance: the more severe the symptoms, the more imperative the change of medication.
- *Transparency and comprehensibility*: easy to understand the model and the way it works.
- *Accuracy and validity*: providing "right" suggestions for given situations, which are following clinical guidelines and medical practice.

3 Methods

We schematically present the methodology for developing the medication change model in Figure 1.

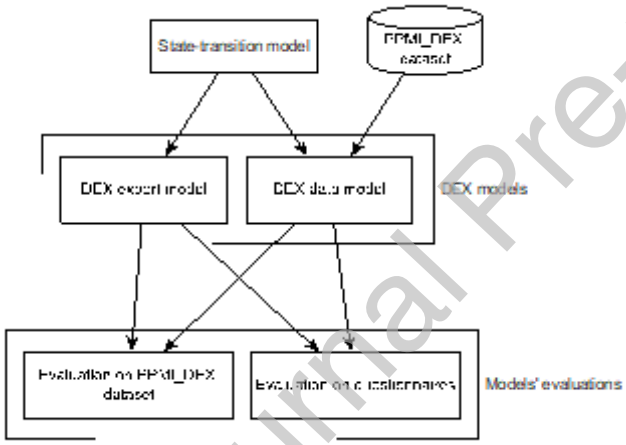

Figure 1 Schematic representation of the methodology.

Initially, we created a state-transition model which identifies all possible combinations of used medications and meaningful medication changes (transitions). The state-transition model was developed during the conducted interviews with a neurologist. Next, we expanded the state-transition model to a decision support model, which incorporates expert rules under which a specific medication change is performed, given the patients' current medication treatments. In particular, we used DEX methodology (Bohanec, Rajkovič, Bratko, Zupan, & Žnidaršič, 2013), which integrates qualitative multi-criteria decision modelling with rule-based expert systems. The DEX methodology is described in detail in section 3.2. We used two approaches to define expert rules in DEX, which resulted in two models:

1. *DEX expert model*, in which decision rules were defined by neurologists, and
2. *DEX data model*, where decision rules were developed using a dataset of real-life medication-change decisions (the PPMI_DEX dataset, see section 3.2).

Finally, both models were evaluated on:

1. 2420 instances from the PPMI_DEX dataset (Marek, et al., 2011),

2. 17 assessments, obtained by a questionnaire from neurologists from 4 different EU countries (United Kingdom, Italy, Greece and Slovenia).

The models' evaluations were also compared to *a-priori* accuracy on both datasets, which represents an accuracy of the model that provides all answers as "no medication change required".

3.1 State-transition model

State-transition (ST) modelling is an intuitive and transparent approach used in computer-based decision modelling. It is also one of the most widespread modelling techniques in clinical decision analysis (Siebert, et al., 2012). It can represent terms as a set of states and transitions among these states.

In our case, the states represent patients' current medication intakes and the transitions represent medication change. Specifically, each state represents a particular combination of the dopamine agonist (DA), levodopa (LD), and MAO-B inhibitors (MAOI). There are eight possible combinations (Figure 2), ranging from the combination labelled "O" (no medication intake) to "LD+DA+MAOI" (taking all three medications). The transition of one state to another is represented by arrows and, in general, there are multiple transitions possible to and from a given state. Notice that in Figure 2 there are no arrows to and from the state "O", which has been explicitly excluded from consideration in our study.

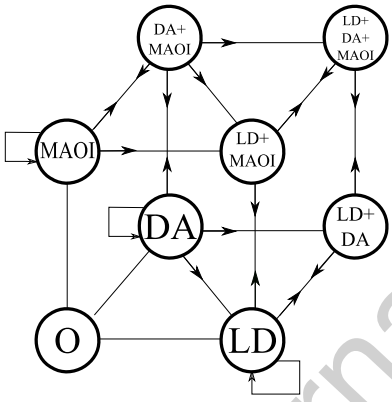

Figure 2 State-transition model.

This ST model serves as a framework in which the arrows are further accompanied by decision rules that describe under which conditions and how the corresponding transitions happen. The decision rules in the ST model may be given in different formats, such as decision tables, *"if-then"* rules or probabilistic distributions. We used a qualitative multi-attribute DEX methodology to model the states and transitions among states using *"if-then"* decision rules, which are commonly used in clinical medicine.

To formulate the decision rules for medication change and represent them in operational decision models, an inital workshop was organised at the Medical School of the University of Ioannina in Greece. Before the inital workshop, one neurologist and his assistant prepared use cases for medication change. The discussion of the use cases with decision analysts lead to the formulation and representation of decision rules as a DEX model. Several workshops, on-line meetings, and email exchanges with the neurologist followed, which served to define, discuss, correct, change and improve the proposed decision rules. The final decision rules are presented in section 3.2.

3.2 DEX models

The ST model given in Figure 2 shows the patients' medication treatments as states and transitions among states. The transitions represent medication change, which is usually required due to changes in patients' motor symptoms (dyskinesia intensity, dyskinesia duration, OFF duration), mental problems

(impulsivity, cognition, hallucinations and paranoia), epidemiologic data (patient's age, activity level) and comorbidities (cardiovascular problems, hypertension and low blood pressure). Hence, to model a transition, we need to evaluate the patient's symptoms and determine if the current medication treatment is successful or whether there are reasons to change the therapy and propose a corresponding change. Therefore, we need to identify and choose the best transition from the current state to a new one based on the knowledge of several medical and epidemiologic indicators. In this way, the problem of medication change represents a multi-criteria decision problem that can be approached using multi-criteria decision modelling (MCDM) methods.

MCDM is concerned with structuring and solving decision and planning problems involving multiple criteria (Greco, Ehrgott, & Figueira, 2016), (Bouyssou, Marchant, Pirlot, Tsoukiàs, & Vincke, 2006). Usually, MCDM proceeds by identifying and evaluating decision alternatives. The evaluation is carried out by some kind of a multi-criteria model, which involves multiple, possibly conflicting, criteria. Based on evaluation results, the decision alternatives are ranked and/or the best one is chosen for implementation. There is a multitude of MCDM methods (Greco, Ehrgott, & Figueira, 2016), (Watrobski, Jankowski, Ziemba, Karczmarczyk, & Ziolo, 2019), which largely differ in the ways of how they represent criteria and their structure, which evaluation and criteria-aggregation principles they use, how they acquire preference knowledge of decision makers, and to which extent they are supported by model-development software (Ishizaka & Nemery, 2013).

For the purpose of this study, we chose the method called DEX (Decision EXpert) (Bohanec, Rajkovič, Bratko, Zupan, & Žnidaršič, 2013), (Trdin & Bohanec, 2018). DEX is characterized as a qualitative, hierarchical and rule-based MCDM method, and all these characteristics are essential for addressing the medication change problem, which involves qualitative variables (e.g., patient's symptoms), multi-level dependencies between patient's states (see Figure 3 and section 4.2) and transition rules. A DEX model is composed of a hierarchical structure of qualitative (discrete) variables, called attributes. The evaluation of decision alternatives is carried out according to decision rules, defined by the model developer. DEX is supported by DEXi (Bohanec M. , 2015), a freely available software that supports both the development of DEX models and their application for the evaluation and analysis of decision alternatives. DEXi provides methods for acquiring expert knowledge, maintaining the consistency and completeness of models, and carrying out exploratory analysis of the decision alternatives and their consequences. DEX has been successfully used in previous projects for implementation of decision support models in healthcare (Bohanec, Zupan, & Rajkovič, 2000), (Šušteršič, Rajkovič, Dinevski, Jereb, & Rajkovič, 2009), (Bohanec, et al., 2017).

An example of a DEX model is presented in Figure 3. Actually, a part of the whole medication-change model (section 4.2) is shown that addresses the transition of changing the patients' medications from the current state of using dopamine agonist (DA) to a new medication treatment state where MAOI is added to DA (denoted as DA+MAOI). The top-level attribute in Figure 3, *ChangeDAtoDA+MAOI*, can take two values (*yes*, *no*) and represents the final recommendation of whether or not to change the medication from DA to DA+MAOI. This transition is assessed on the basis of the patient's current state, which is represented by three attributes: *usingDA* (whether or not the patient already uses DA), *cardiovascular* (if the patient suffers from cardiovascular comorbidities), and *MotorSymptoms* (if the patient has motor symptoms). The first two attributes are called *basic* as they represent model inputs, which are for each patient provided directly from a corresponding data base or through a user interface. The attribute *MotorSymptoms* is an *aggregated* one, i.e., it depends on other lower-level attributes; its value is determined according to the patients' symptoms: *rigidity*, *bradykinesia* and/or *tremor*. Similarly, the aggregated attribute *"Tremor"* is assessed according to three tremor-related input attributes: *tremor at rest*, *action tremor* and *postural tremor*.

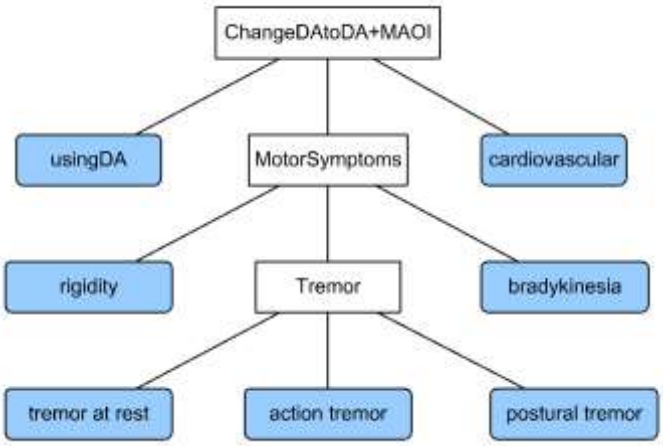

Figure 3 A hierarchical structure of a DEX sub-model for adding an MAOI to the current medication treatment with a dopamine agonist (DA).

In addition to a hierarchical structure of attributes, such as the one in Figure 3, a DEX model consists of decision rules. For each aggregate attribute (such as *Tremor*, *MotorSymptoms* and *ChangeDAtoDA+MAOI* in Figure 3), a decision table is defined that governs the bottom-up aggregation of the attribute values. Each row in the table is interpreted as an *if-then* decision rule. Figure 4 (left) displays a snapshot of the model structure in the DEXi software, and Figure 4 (right) displays the decision rules for the aggregated attribute "*ChangeDAtoDA+MAOI*".

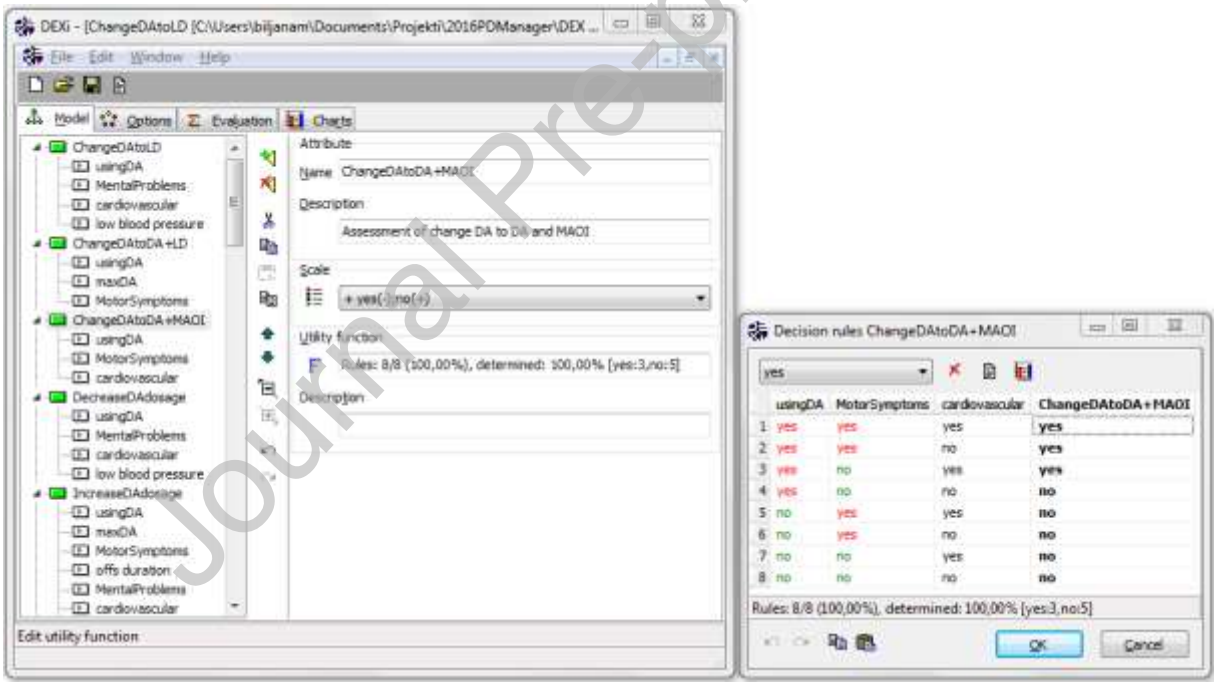

Figure 4 DEXi: Tree of attributes (left) and decision rules for the aggregated attribute "ChangeDAtoDA+MAOI" (right).

Translating a state-transition diagram to a DEX model is carried out as follows. For each two connected states in the state-transition diagram, given in Figure 2, one creates an aggregated attribute. For example, for the state change from *DA* to *DA+MAOI*, one creates an attribute named *ChangeDAtoDA+MAOI*. Then, one defines the *if-then* rules that govern the corresponding transition in a tabular format (as shown in Figure 4). In this study, decision rules were constructed using two different approaches, presented in section 3.4.

3.3 PPMI_DEX dataset

To develop and verify the medication change decision model, we used real clinical data of patients from the Parkinson's Progression Markers Initiative (PPMI) (http://www.ppmi-info.org/). PPMI is a

comprehensive observational study, using advanced clinical and behavioural assessments to identify biomarkers of PD progression. The PPMI data collection consists of datasets describing different aspects of the patients' daily living.

In PPMI, the condition and quality of life of a patient suffering from PD are determined using the Movement Disorder Society (MDS) questionnaire which is sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz, et al., 2008). The Montreal Cognitive Assessment (MoCA) (Nasreddine, et al., 2005), (Weintraub, et al., 2012) is used for rapid screening of mild cognitive dysfunction designed to assess different cognitive domains and the Modified Schwab and England Activities of Daily Living (ADL) Scale (Modified Schwab and England Activities of Daily Living Scale, 2018) is used for assessment of patient's level of functional independence. PPMI datasets are periodically updated, thus allowing clinicians to monitor patients' disease development through time.

In addition to the patients' symptoms data, the PPMI study also records all the concomitant medications the patients use during their involvement in the study. These records are described by the name of the medication, the medical condition it is prescribed for, and when the patient has started and/or ended the therapy with each particular medication. In this work, we focused solely on the patients receiving antiparkinson medications therapy. We were interested in the combinations of antiparkinson medications that patients have received between each of the time points when the MDS-UPDRS test and the MoCA test have been administered. Patients' therapies can be modified during the visits when the questionnaires are administered, as well as any time between these visits. The clinicians often perform phone call-ups to stay informed of the patients' status. The main families of drugs used for treating motor symptoms are levodopa, dopamine agonists, and MAO-B inhibitors. Patients' daily medication therapies can be converted into Levodopa Equivalent Daily Dosage (LEDD) (Parkinson`s Disease Measurement: PwP, surveys, trials, analysis, 2018), allowing comparison between different types of therapies.

In this paper we used the PPMI data as of June, 2016. We created a relevant data subset of the PPMI data collection, called PPMI_DEX, which contains input attributes used in the developed medication change models, associated with medication changes that were suggested by the clinician after each patient's visit. PPMI_DEX was extracted from the PPMI data collection, and it is aimed at: (1) defining decision rules in the DEX data model and (2) assessing the medication change models. For this reason, PPMI_DEX consists of a single flat data table that contains *the same* data items (attributes) as input attributes of the DEX expert model (section 3.2). Furthermore, PPMI_DEX attributes have the same value scales as the corresponding input attributes in DEX models. The matching between PPMI_DEX and the developed medication change models has been achieved by pre-processing of data from the PPMI data collection, which mainly consisted of:

- selection of attributes from the PPMI, so that only attributes that have corresponding counterparts in the models appear in PPMI_DEX,
- transformation of the PPMI data items into value scales that are used in the DEX models.

Some data records in the PPMI are incompletely defined, i.e., there are some missing data. In the data pre-processing, we opted not to discard the missing data from the analysis, but to replace the missing items with the lowest (least problematic) value of the corresponding DEX attribute (such as "*normal*" or "*mild*" for attributes representing symptoms). In this way, we did not lose information that is present in partially defined records of PPMI, therefore keeping the number of PPMI_DEX instances as high as possible. When some data item about a patient is unknown in PPMI, it is reasonable to assume that the item could not have been used as an indication for changing the medical therapy. This is equivalent to using *normal* or *mild* values in the DEX models, which never trigger, by themselves, the change of medication.

For each PD patient p_i involved in the PPMI study, and for each of their visits v_{ij} to the clinician, the values of the selected attributes were collected. Data instances were formed as pairs of patients and their visits (p_i, v_{ij}), where attributes' values in v_{ij} describe the status of the patient p_i at the time of the visit v_{ij}.

In PPMI, symptoms are measured using the MDS-UPDRS 0–4 scale (Goetz, et al., 2008), where 0 represents a non-present symptom, and 4 the most severe manifestation of the symptom. For the purpose of DEX modelling, and according to the requirement from the contributing physicians to help them in the quick assessment of whether a symptom exists or does not exist, MDS-UPDRS values were mapped into a two-valued attribute scale {*yes, no*} as follows:

- For motor symptoms: symptom severity of 0 or 1 to *no*; symptom severity of 2 – 4 to *yes*.
- For hallucinations: symptom severity of 0 or 1 to *no*; symptom severity of 2 – 4 to *yes*.
- For paranoia: symptom severity of 0 – 3 to *no*; symptom severity of 4 to *yes*.
- For all other symptoms: symptom severity of 0 or 1 to *no*; symptom severity of 2 – 4 to *yes*.

Epidemiologic attributes were discretized, too, as follows:

- Age: younger than 65 years ("lt65"), 65–75, 75 years or older ("gt75").
- Activity: *no, yes*; this assessment may be subjective (is the patient active or not?), or determined from the Modified Schwab and England Activities of Daily Living Scale (2018), so that <60% is interpreted as a no (the patient *is not* active), and ≥ 60% as a yes (the patient *is* active).

Details of the quantization schema, applied on all attributes that are used in the medication change models, are given in Appendix A.

3.4 DEX model development

In this study, we developed two DEX models: the *DEX expert model* and the *DEX data model*. In the former, we defined the decision rules based on experts' interviews. In the later, we extracted the decision rules from the PPMI_DEX dataset. To extract the decision rules, we employed the method of (Bohanec & Delibašić, 2015) in which DEX decision rules are developed gradually and interactively by taking into account the statistical properties of the learning dataset on medication change of real patients, i.e., from PPMI_DEX. Decision tables are formulated iteratively by observing conditional class probabilities of the given input attributes' values in the PPMI_DEX dataset, and by applying the principle of dominance on the partly constructed decision rules. The principle of dominance in decision theory states that a decision rule dominates another if the result of the former is sometimes better, and never worse than that of the latter (Bouyssou, Marchant, Pirlot, Tsoukiàs, & Vincke, 2006). The method follows a three-step approach:

1. Data Analysis, which consists of calculation of the conditional class frequencies for all combinations of attributes in the models.
2. Heuristic assignment of DEX class based on the class frequencies.
3. Expert modelling, which consists of an assessment of unassigned class values (if any) by systematically applying the principles of completeness and consistency.

3.5 Evaluation metrics

We evaluated the accuracy of the models on the following two datasets:

- a dataset obtained from physicians using a questionnaire, and
- the PPMI_DEX dataset.

In particular, we conducted a questionnaire to systematically test all sub-models that comprise the two medication change models. The questionnaire (presented in Appendix B) contains 25 hypothetical patients' scenarios drawn uniformly and directly from all subtrees in the medication change models. Each scenario in the questionnaire contains hypothetical data about the current medication treatment of the patient and data about the current state of motor symptoms (dyskinesia intensity, dyskinesia duration, OFF duration, as well as rigidity, tremor at rest, action tremor, postural tremor, bradykinesia), mental problems (impulsivity, cognition, hallucinations and paranoia), epidemiologic data (patient's age, activity) and comorbidities (cardiovascular problems, hypertension and low blood

pressure). The scenarios were evaluated by both medication models and by 17 neurologists (one from United Kingdom, seven from Italy, eight from Greece, and one from Slovenia).

The level of agreement between the DEX models' and the experts' medication change suggestions was for each question q assessed using the Jaccard index:

$$a_{r,q} = \frac{|E_{r,q} \cap M_q|}{|E_{r,q} \cup M_q|}$$

where r denotes the expert, $E_{r,q}$ the set medication changes suggested by the expert and M_q the set of medication changes suggested by the DEX model M. For all $n = 17$ experts, the average level of agreement was obtained as:

$$A_q = \frac{1}{n}\sum_{i=1}^{n} a_{i,q}$$

The assessed agreement between the DEX models' (DEX expert and DEX data model) and the experts' medication change suggestions is presented in

Table 8 in Appendix B.

The evaluation of both DEX models on the PPMI_DEX dataset was performed by using the accuracy measure. For each DEX model and each of its sub-models that represent medication change, the accuracy is defined as the proportion of correctly matched data between the DEX model suggestions and the data provided in the PPMI_DEX dataset.

4 Results

The medication change model consists of a state-transition model and decision rules. Two types of decision rules are defined, leading to two models: (1) DEX expert model, where decision rules have been defined by a neurologist, and (2) DEX data model, where the decision rules were extracted from the PPMI_DEX dataset.

4.1 State-transition model

The state-transition model defines all possible medication treatments of a patient (states) and medication changes (transitions among states). As shown in Figure 2, states are represented by circles and transitions (changes of medication treatment) by a directed arc (Mileva Boshkoska, et al., 2017). Each state corresponds to the set of medications that constitute the current treatment. The set can be empty (symbol O), which denotes no medication therapy, or it can consist of any combination of DA, LD and MAO-B inhibitor (MAOI). For example, the state DA+MAOI means that the patient is currently treated with a dopamine agonist (DA) and MAOI. From this state, there are four possible state changes depending on the combinations of patient's symptoms: add LD to the treatment (state marked as LD+DA+MAOI), remove DA from the current treatment (state marked as MAOI), remove MAOI and use only DA (state marked as DA), and replace DA with LD (LD+MAOI).

All transitions among states are presented in Figure 5. Each transition represents a change of at least one medication. The absence of a directed arc between two states means that a particular change of medication treatment is not addressed in the model, either because it has been deliberately excluded

(transitions from and to state O), or it is rarely or not at all used in practice. A reflexive arc means increasing/decreasing of the medication (dosage or intake) (Bohanec, et al., 2017).

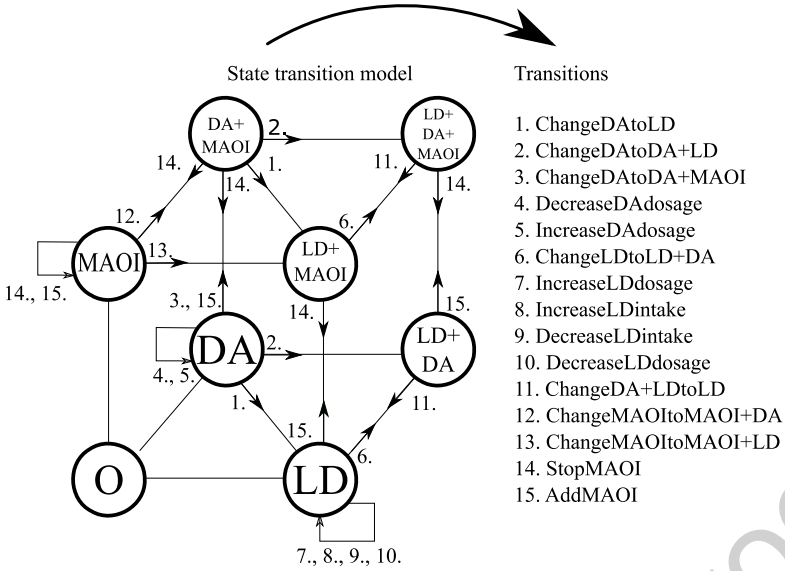

Figure 5 A state-transition model for medication change among levodopa (L), a dopamine agonist (DA), MAO-B inhibitors (MAOI) and their combinations (left); transitions among states represent medication changes (right). Symbol O represents the state where a patient has not been treated with medications.

Notice that Figure 5 contains some duplicate arc labels. For instance, the transitions from DA to LD and DA+MAOI to LD+MAOI are both labelled with number 1. This is because both transitions involve changing of dopamine agonist with levodopa, which is governed by the same decision rules. Also, note that some transitions have several labels indicating several possible transitions. For example, there are four labels next to the reflexive arc of the state LD indicating there are four possible transitions defined as *IncreaseLDintake*, *IncreaseLDdosage*, *DecreaseLDintake* or *DecreaseLDdosage*. Each of the transitions is defined with different decision rules.

When suggesting some medication change, it is essential to detect conditions that indicate a possible need to allow a transition from some state to another. Thus, each arc in the state-transition model has an associated set of rules that determine whether the transition is desired or not. We model the transitions among states and the accompanying decision rules in the DEX models, which are described in Section 4.2.

4.2 Structure of the decision-support model for medication change

The decision-support model provides rules for the patient's medication changes based on the current medication therapy and the current changes in motor symptoms, mental problems, epidemiologic data and comorbidities. In particular, all transitions given in Figure 5 are modelled using decision rules that are implemented in DEXi. Figure 6 presents the structure of the decision-support model for medication change. It consists of 15 sub-models (aggregated attributes), which correspond to the transitions given in Figure 5, and additional 6 sub-models that represent common concepts, related to the change of patient's motor symptoms (rigidity, tremor, and bradykinesia), mental problems (impulsivity, cognition, hallucinations, and paranoia), comorbidities (cardiovascular, low blood pressure, and hypertension), dyskinesia (OFF duration, intensity, and duration), personal characteristics (patient's age and activity level) and patient's current therapy (DA, LD, MAOI, and whether or not the maximum dosages of DA and LD have been reached). The purpose of the last 6 sub-models is to aggregate several specific symptoms into common indicators, which are used as inputs to the corresponding sub-model for a particular transition. For instance, *Dyskinesia* is a standard indicator that is determined from *OFF duration*, *dyskinesia intensity*, and *dyskinesia duration*.

Table 1 lists and explains the function of the 15 sub-models that correspond to the transitions in the state-transition model.

Table 1 Sub-models for 15 medication treatment changes that comprise the decision-support model for medication change

	Sub-models	Purpose
1	*ChangeDAtoLD*	Change therapy from dopamine agonist to levodopa
2	*ChangeDAtoDA+LD*	Change therapy from dopamine agonist to dopamine agonist and levodopa
3	*ChangeDAtoDA+MAOI*	Change therapy from dopamine agonist to dopamine agonist and MAO-B inhibitors
4	*DecreaseDAdosage*	Decrease the dosage of dopamine agonist
5	*IncreaseDAdosage*	Increase the dosage of dopamine agonist
6	*ChangeLDtoLD+DA*	Change therapy from levodopa to levodopa and dopamine agonist
7.	*IncreaseLDdosage*	Increase the dosage of levodopa
8	*IncreaseLDintake*	Increase intake of levodopa
9	*DecreaseLDintake*	Decrease of levodopa intakes
10	*DecreaseLDdosage*	Decrease the dosage of levodopa
11	*ChangeDA+LDtoLD*	Change therapy from dopamine agonist and levodopa to levodopa
12	*ChangeMAOItoMAOI+DA*	Change therapy from MAO-B inhibitors to MAO-B inhibitors and dopamine agonist
13	*ChangeMAOItoMAOI*+LD	Change therapy from MAO-B inhibitors to MAO-B inhibitors and levodopa
14	*StopMAOI*	Stop using MAO-B inhibitors
15	*AddMAOI*	Add MAO-B inhibitors

Figure 6 also presents the value scales for all input and aggregated attributes. Note that most attributes are binary, each taking one of the two corresponding values: *yes* or *no*. Coloured values indicate that the corresponding attribute is ordered so that the leftmost (**red**) value indicates a problematic, and the rightmost (***green***) a non-problematic patient's condition. The red/left values generally indicate a problem that must be addressed by medication change. Unordered attribute values are given in black colour.

Attribute	Scale
ChangeDAtoLD	**yes; *no***
├ *usingDA*	**yes; *no***
├ *usingLD*	**yes; *no***
├ *MentalProblems*	**yes; *no***
├ *cardiovascular*	yes; no
└ *low blood pressure*	yes; no
ChangeDAtoDA+LD	**yes; *no***
├ *usingDA*	**yes; *no***
├ *maxDA*	yes; no
└ *MotorSymptoms*	**yes; *no***
ChangeDAtoDA+MAOI	**yes; *no***
├ *usingDA*	**yes; *no***
├ *MotorSymptoms*	**yes; *no***
└ *cardiovascular*	yes; no
DecreaseDAdosage	**yes; *no***
├ *usingDA*	**yes; *no***
├ *MentalProblems*	**yes; *no***
├ *cardiovascular*	yes; no
└ *low blood pressure*	yes; no
IncreaseDAdosage	**yes; *no***
├ *usingDA*	**yes; *no***
├ *maxDA*	yes; no
├ *MotorSymptoms*	**yes; *no***
├ *OFF duration*	yes; no
├ *MentalProblems*	**yes; *no***
├ *cardiovascular*	yes; no
├ *age*	lt65; lt65; 65-75
└ *activity*	yes; no
ChangeLDtoLD+DA	**yes; *no***
├ *usingLD*	**yes; *no***
├ *MotorSymptoms*	**yes; *no***
├ *OFF duration*	yes; no
├ *MentalProblems*	**yes; *no***
└ *age*	lt65; lt65; 65-75
IncreaseLDdosage	**yes; *no***
├ *usingLD*	**yes; *no***
├ *maxLD*	yes; no
├ *MotorSymptoms*	**yes; *no***
├ *MentalProblems*	**yes; *no***
├ *dyskinesia duration*	**yes; *no***
├ *dyskinesia intensity*	**yes; *no***
└ *OFF duration*	yes; no
DecreaseLDdosage	**yes; *no***
├ *usingLD*	**yes; *no***
├ *MotorSymptoms*	**yes; *no***
├ *MentalProblems*	**yes; *no***
├ *dyskinesia intensity*	**yes; *no***
├ *dyskinesia duration*	**yes; *no***
└ *OFF duration*	yes; no
IncreaseLDintake	**yes; *no***
├ *usingLD*	**yes; *no***
├ *maxLD*	yes; no
├ *MotorSymptoms*	**yes; *no***
├ *MentalProblems*	**yes; *no***
├ *dyskinesia intensity*	**yes; *no***
├ *dyskinesia duration*	**yes; *no***
└ *OFF duration*	yes; no
DecreaseLDintake	**yes; *no***
├ *usingLD*	**yes; *no***
├ *MotorSymptoms*	**yes; *no***
├ *MentalProblems*	**yes; *no***
├ *dyskinesia intensity*	**yes; *no***
├ *dyskinesia duration*	**yes; *no***
└ *OFF duration*	yes; no

Attribute	Scale
ChangeDA+LDtoLD	**yes; *no***
├ *usingDA*	**yes; *no***
├ *usingLD*	**yes; *no***
├ *MentalProblems*	**yes; *no***
└ *cardiovascular*	yes; no
ChangeMAOItoMAOI+DA	**yes; *no***
├ *usingMAOI*	**yes; *no***
├ *MotorSymptoms*	**yes; *no***
└ *MentalProblems*	**yes; *no***
ChangeMAOItoMAOI+LD	**yes; *no***
├ *usingMAOI*	**yes; *no***
└ *MotorSymptoms*	**yes; *no***
StopMAOI	**yes; *no***
├ *usingMAOI*	**yes; *no***
├ *usingDA*	**yes; *no***
├ *Dyskinesia*	**yes; *no***
├ *MentalProblems*	**yes; *no***
└ *hypertension*	yes; no
AddMAOI	**yes; *no***
├ *usingMAOI*	**yes; *no***
├ *usingDA*	**yes; *no***
├ *usingLD*	**yes; *no***
├ *OFF duration*	yes; no
└ *MotorSymptoms*	**yes; *no***
MotorSymptoms	**yes; *no***
├ rigidity	**yes; *no***
├ **Tremor**	**yes; *no***
│ ├ tremor at rest	**yes; *no***
│ ├ action tremor	**yes; *no***
│ └ postural tremor	**yes; *no***
└ bradykinesia	**yes; *no***
MentalProblems	**yes; *no***
├ impulsivity	**yes; *no***
├ cognition	**yes; *no***
└ **Psychosis**	**yes; *no***
├ hallucinations	**yes; *no***
└ paranoia	**yes; *no***
Comorbidities	**yes; *no***
├ cardiovascular	yes; no
├ low blood pressure	yes; no
└ hypertension	yes; no
Dyskinesia	**yes; *no***
├ OFF duration	yes; no
├ dyskinesia intensity	**yes; *no***
└ dyskinesia duration	**yes; *no***
PersonalCharacteristics	**inactive; *active***
├ age	lt65; lt65; 65-75
└ activity	yes; no
CurrentTherapy	max; **yes; *no***
├ usingMAOI	**yes; *no***
├ usingDA	**yes; *no***
├ usingLD	**yes; *no***
├ maxDA	yes; no
└ maxLD	yes; no

Figure 6 Structure of decision-support model for medication change, attributes and their value scales.

4.3 DEX expert model

Each aggregated attribute in the DEX model is accompanied by decision rules presented in a tabular form. An illustrative example of decision rules for the change of medication treatment from dopamine agonist to levodopa (*ChangeDAtoLD*) is shown in

Table 2. The attribute *ChangeDAtoLD* aggregates the attributes *usingDA, MentalProblems, cardiovascular* and *low blood pressure*. The symbol "*" in

Table 2 denotes any value that may appear at that position. For instance, in connection with an attribute that may take one of the two values, for example, *yes* and *no*, the "*" stands for "*yes* or *no*".

*Table 2 Decision rules for change of medication treatment from dopamine agonist to levodopa (***red** *value indicates a problematic and the* ***green*** *a non-problematic patient's condition).*

	usingDA	**Mental-Problems**	**cardiovascular**	**low blood pressure**	**ChangeDAtoLD (aggregated attribute)**
1	**yes**	**yes**	*	*	**yes**
2	**yes**	*	yes	*	**yes**
3	**yes**	*	*	yes	**yes**
4	*	***no***	no	no	***no***
5	***no***	*	*	*	***no***

According to the rules defined in

Table 2, the change of medication treatment from DA to LD can happen only when the patient already takes DA. The change may take place in three different cases: the patient has mental problems, cardiovascular problems, or low blood pressure. Otherwise, the change to LD should not happen. Such decision tables are defined for all sub-models and are presented in the supplementary material.

To illustrate the usage of DEX expert model rules, consider three hypothetical patients denoted as P1, P2 and P3, given in Figure 7. The description of the patients, their current medication treatment (state) as well as their newly developed symptoms, are the following:

P1 Patient P1 uses DA; however, P1 experiences two problematic motor symptoms: rigidity and bradykinesia. P1 is active and younger than 65 years.

P2 Patient P2 uses LD and does not have any mental problems. However, P2 experiences OFF and dyskinesia durations. The patient is younger than 65 years and has an inactive lifestyle.

P3 Patient P3 uses the maximal prescribed dosage of DA, does not have any mental problems, but experiences one problematic motor symptom: rigidity. P3 is in the 65–75 age group and not active.

Figure 7 shows the results of the evaluation of each of the three patients with the DEX expert model. The recommendations, generated from the topmost aggregated attributes in each of the sub-models in Figure 7, are summarised as follows:

P1 For P1, there are three possible medication changes, all due to motor symptoms: (1) Change DA to DA+MAOI, (2) Increase DA dosage, and/or (3) Add MAOI.

Evaluation results

Attribute	P1	P2	P3
ChangeDAtoLD	no	no	no
usingDA	yes	no	yes
usingLD	no	yes	no
MentalProblems	no	no	no
cardiovascular	no	no	no
low blood pressure	no	no	no
ChangeDAtoDA+LD	no	no	yes
usingDA	yes	no	yes
maxDA	no	no	yes
MotorSymptoms	yes	no	yes
ChangeDAtoDA+MAOI	yes	no	yes
usingDA	yes	no	yes
MotorSymptoms	yes	no	yes
cardiovascular	no	no	no
DecreaseDAdosage	no	no	no
usingDA	yes	no	yes
MentalProblems	no	no	no
cardiovascular	no	no	no
low blood pressure	no	no	no
IncreaseDAdosage	yes	no	no
usingDA	yes	no	yes
maxDA	no	no	yes
MotorSymptoms	yes	no	yes
OFF duration	no	yes	no
MentalProblems	no	no	no
cardiovascular	no	no	no
age	lt65	lt65	65-75
activity	yes	no	no
ChangeLDtoLD+DA	no	yes	no
usingLD	no	yes	no
MotorSymptoms	yes	no	yes
OFF duration	no	yes	no
MentalProblems	no	no	no
age	lt65	lt65	65-75
IncreaseLDdosage	no	no	no
usingLD	no	yes	no
maxLD	no	no	no
MotorSymptoms	yes	no	yes
MentalProblems	no	no	no
dyskinesia duration	no	yes	no
dyskinesia intensity	no	no	no
OFF duration	no	yes	no
DecreaseLDdosage	no	no	no
usingLD	no	yes	no
MotorSymptoms	yes	no	yes
MentalProblems	no	no	no
dyskinesia intensity	no	no	no
dyskinesia duration	no	yes	no
OFF duration	no	yes	no
IncreaseLDintake	no	yes	no
usingLD	no	yes	no
maxLD	no	no	no
MotorSymptoms	yes	no	yes
MentalProblems	no	no	no
dyskinesia intensity	no	no	no
dyskinesia duration	no	yes	no
OFF duration	no	yes	no
DecreaseLDintake	no	no	no
usingLD	no	yes	no
MotorSymptoms	yes	no	yes
MentalProblems	no	no	no
dyskinesia intensity	no	no	no
dyskinesia duration	no	yes	no
OFF duration	no	yes	no

Attribute	P1	P2	P3
ChangeDA+LDtoLD	no	no	no
usingDA	yes	no	yes
usingLD	no	yes	no
MentalProblems	no	no	no
cardiovascular	no	no	no
ChangeMAOItoMAOI+DA	no	no	no
usingMAOI	no	no	no
MotorSymptoms	yes	no	yes
MentalProblems	no	no	no
ChangeMAOItoMAOI+LD	no	no	no
usingMAOI	no	no	no
MotorSymptoms	yes	no	yes
StopMAOI	no	no	no
usingMAOI	no	no	no
usingDA	yes	no	yes
Dyskinesia	no	yes	no
MentalProblems	no	no	no
hypertension	no	no	no
AddMAOI	yes	yes	yes
usingMAOI	no	no	no
usingDA	yes	no	yes
usingLD	no	yes	no
OFF duration	no	yes	no
MotorSymptoms	yes	no	yes
MotorSymptoms	yes	no	yes
rigidity	yes	no	yes
Tremor	no	no	no
tremor at rest	no	no	no
action tremor	no	no	no
postural tremor	no	no	no
bradykinesia	yes	no	no
MentalProblems	no	no	no
impulsivity	no	no	no
cognition	no	no	no
Psychosis	no	no	no
hallucinations	no	no	no
paranoia	no	no	no
Comorbidities	no	no	no
cardiovascular	no	no	no
low blood pressure	no	no	no
hypertension	no	no	no
Dyskinesia	no	yes	no
OFF duration	no	yes	no
dyskinesia intensity	no	no	no
dyskinesia duration	no	yes	no
PersonalCharacteristics	active	inactive	inactive
age	lt65	lt65	65-75
activity	yes	no	no
CurrentTherapy	*	*	*
usingMAOI	no	no	no
usingDA	yes	no	yes
usingLD	no	yes	no
maxDA	no	no	yes
maxLD	no	no	no

Figure 7 Illustration of the usage of the DEX expert model rules implemented into the structure of the decision-support model for medication change on three hypothetical patients' scenarios

P2 For P2, there are three options, which are all supported by OFF duration = *yes*: (1) Change LD to LD+DA, (2) Increase LD intake, (3) Add MAOI. The second suggestion is additionally supported by dyskinesia duration = *yes*.

P3 For P3, the model suggests three possibilities, all due to motor symptoms: (1) Change DA to DA+LD, (2) Change DA to DA+MAOI, or (3) Add MAOI.

The physician might decide to choose any (one or more) of the suggestions offered by the medication change model.

4.4 DEX data model

The DEX data model was developed with two questions in mind. First, we wanted to know if it is possible to extract decision rules for the DEX model solely from the PPMI_DEX dataset (Section 3.3). Second, we wanted to find out which model performs better in terms of accuracy: the DEX data model or the DEX expert model. We present the DEX data model in this section, and the results of comparison in section 4.5.

The DEX data model was obtained by using PPMI_DEX dataset to extract the decision rules, in particular, the class assignments for each of the sub-models given in Figure 6. It should be disclaimed that the decision rules have been developed by a decision analyst only by observing and analysing data in PPMI_DEX dataset, without any additional guidelines or interpretations given by medical experts. In this way we obtained decision rules that seem to be followed by clinicians when making decisions recorded in the PPMI data collection.

We employed the method of (Bohanec & Delibašić, 2015) which follows a general three-step approach, presented in section 3.4. Those three steps were applied for all 15 sub-models. Hereafter, we illustrate the process on the sub-model *ChangeDAtoDA+MAOI*, which involved the construction of decision rules as presented in

Table 3:

1. Conditional class frequencies were calculated for all combinations of attributes in the sub-model *ChangeDAtoDA+MAOI*. For all combination of attributes' values, two frequencies are given in

Table 3 under *Class frequencies*: the frequency of suggesting and not suggesting a change of DA to DA+MAOI, respectively.

Table 3 An example of a class assignment step for the sub-model ChangeDAtoDA+MAOI based on PPMI_DEX dataset (seventh column). The last column presents the class assignment obtained with DEX expert model. Differences in-class assignments are given in bold in the last two columns.

	Input attributes			Class frequencies of *ChangeMAOItoMAOI+DA*		*Assigned class in the DEX models*	
	usingMAOI	*Motor-Symptoms*	*Mental-Problems*	Class = *Yes*	Class = *No*	*DEX data model*	*DEX expert model*
1	yes	yes	yes	0	0.0256	no	No
2	yes	yes	no	0.8182	0.3297	yes	Yes
3	yes	no	yes	0	0.0101	no	No

4	yes	no	no	0.1818	0.0746	**yes**	**No**
5	no	yes	yes	0	0.0612	no	No
6	no	yes	no	0	0.4068	no	No
7	no	no	yes	0	0.0075	no	No
8	no	no	no	0	0.0846	no	No

2. Assigning a DEX class to each row in

Table 3. The assignments are based on the class frequencies in

Table 3. The DEX class was estimated using the following heuristic rule:

$$DEXclass = \begin{Bmatrix} yes, if\ f(ChangeDAtoDA + MAOI = \text{yes}) > f(ChangeDAtoDA + MAOI = \text{no}) \\ no, if\ f(ChangeDAtoDA + MAOI = \text{yes}) < f(ChangeDAtoDA + MAOI = \text{no}) \\ N/A\ , if\ f(ChangeDAtoDA + MAOI = \text{yes}) = f(ChangeDAtoDA + MAOI = \text{no}) \end{Bmatrix}$$

where N/A stands for not assigned and *f* for frequency. In

Table 3, the class assignment in DEX data model is presented in the seventh column.

3. Assignment of the class values, for cases for which the dataset does not provide enough data, and which are assessed by applying the principles of completeness and consistency.

For comparison purposes, we provide the assigned class according to DEX expert model as the last column in

Table 3. We notice one difference in class assignments in the fourth rule in

Table 3.

It is essential to mention that although the PPMI_DEX dataset consists of 2420 instances, the number of medication changes for the different sub-models in the PPMI_DEX dataset is generally small.

Table 4 shows the number of medication changes (column 2) and their proportion in the 2420 total data items in PPMI_DEX (column 3). There, the highest proportions of medication changes are observed with IncreaseLDdosage (about 16 %) and IncreaseDAdosage (about 12%), and all the other proportions are substantially lower. Such small numbers make it difficult to develop an accurate medication change model and calls for a larger representative dataset.

Table 4 Number of medication changes for all sub-models in PPMI_DEX dataset

Sub-model	Number (#) of medication changes for the sub-models in PPMI_DEX	Per cent (%) of medication changes for the sub-models in PPMI_DEX
ChangeDAtoLD	8	0.33
ChangeDAtoDA+LD	25	1.03
ChangeDAtoDA+MAOI	22	0.9
DecreaseDAdosage	120	4.95
IncreaseDAdosage	290	11.98
ChangeLDtoLD+DA	17	0.7
IncreaseLDdosage	385	15.91
DecreaseLDdosage	102	3.88
IncreaseLDintake	3	0.12
DecreaseLDintake	1	0.04
ChangeDA+LDtoLD	10	0.41
ChangeMAOItoMAOI+DA	33	1.36
ChangeMAOItoMAOI+LD	16	0.66
StopMAOI	39	1.61
AddMAOI	61	2.52

4.5 Evaluation of models

The evaluation results of the two models, the DEX expert model and the DEX data model, on the two datasets, PPMI_DEX and physicians' assessments, as well as the *a-priori* accuracies, are presented in Table 5. The third to fifth columns in Table 5 presents the accuracy of the medication change models and *a-priori* accuracy on the questionnaire data. The last three columns show the accuracy of the medication change models and the *a-priori* accuracy measured on the PPMI_DEX dataset. Bold values in Table 5 represent the best accuracy value obtained on the questionnaire data (columns 3–5) and on the PPMI_DEX data (column 6–8). Green values represent accuracies that exceed the *a-priori* one.

Table 5 Evaluation of models accuracies on the questionnaire dataset (third-fifth columns) and PPMI_DEX dataset (sixth-eight columns). Bold values represent the best accuracy values (among the columns 3–5 and 6–8). Green values present values higher than the a-priori.

		Accuracy on the questionnaire data [%]			*Accuracy on the PPMI_DEX dataset [%]*		
	Proposed medication change	DEX expert model	DEX data model	A-priori	DEX expert model	DEX data model	A-priori

1	*ChangeDAtoLD*	**81.65**	41.18	80.00	95.08	46.32	**99.67**
2	*ChangeDAtoDA+LD*	90.12	89.41	**96.00**	97.98	65.66	**98.97**
3	*ChangeDAtoDA+MAOI*	**76.94**	62.82	76.00	65.29	57.23	**99.09**
4	*DecreaseDAdosage*	**85.41**	53.65	80.00	91.13	51.28	**95.04**
5	*IncreaseDAdosage*	**90.82**	87.58	84.00	74.05	69.62	**88.02**
6	*ChangeLDtoLD+DA*	**91.29**	85.59	88.00	84.50	70.17	**99.30**
7	*IncreaseLDdosage*	87.76	65.40	**88.00**	68.43	59.50	**84.09**
8	*DecreaseLDdosage*	**78.59**	65.05	72.00	94.01	53.84	**96.12**
9	*IncreaseLDintake*	73.41	**91.00**	68.00	91.36	**100.00**	99.88
10	*DecreaseLDintake*	89.18	**98.27**	88.00	98.10	**99.96**	99.96
11	*ChangeDA+LDtoLD*	**95.53**	72.47	92.00	97.40	60.24	**99.59**
12	*ChangeMAOItoMAOI+DA*	**99.06**	95.06	92.00	67.23	60.12	**98.64**
13	*ChangeMAOItoMAOI+LD*	**93.65**	**93.65**	92.00	64.42	64.42	**99.34**
14	*StopMAOI*	**89.18**	41.91	84.00	89.46	58.84	**98.39**
15	*AddMAOI*	55.29	**69.31**	48.00	53.80	59.34	**97.48**
	Average	**85.19**	74.16	81.87	82.15	65.10	**96.90**

5 Discussion

The paper demonstrates two decision-support computer-based DEX models that may support users in the process of medication change of PD patients. Table 5 summarizes the results from the evaluation of both models accuracies on the questionnaire dataset (third-fifth columns) and PPMI_DEX dataset (sixth-eight columns).

Looking at the accuracies measured on the PPMI_DEX dataset, one can see that all *a-priori* accuracies are very high, mostly in the 90–100% range. The accuracies of both models are in most cases lower than the *a-priori* accuracy, which in principle indicates a poor performance. There are only two cases in which the DEX expert model exceeded (row 9 in Table 5) or matched (row 10 in Table 5) the *a-priori* accuracy. Comparing the two models, the DEX expert model substantially outperformed the DEX data model. In particular, the average accuracy of DEX expert model was 82.15%, which was higher compared to the 65.10% accuracy of the DEX data model. In addition, the average accuracy of the DEX expert sub-models is closer to the *a-priori* accuracy; however, it is smaller. This is because the majority of cases in PPMI_DEX did not involve any medication change after the patient's visit, which leads to a highly imbalanced distribution of the class attribute in the PPMI_DEX dataset (for example for the sub-model *ChangeMAOItoMAOI+DA*, from 2420 instances, 2387 instances have the class value of *"no"* and only 33 are classified as *"yes"*). Consequently, assuming the "*no*" answer by default is already highly accurate and difficult to outperform.

On the other hand, the measurements on the questionnaire data indicate a good performance of the DEX models. The average accuracy of the DEX Expert models is 85.19%, while the DEX data model had a lower accuracy of 74.16%. The DEX expert model was on average superior to the a-priori accuracy, which was 81.87% on average. The maximum accuracy of DEX Expert sum-models is 99.06% and it is obtained for *ChangeMAOItoMAOI+DA* sub-model. The minimum accuracy is 55.29% and it is obtained for *AddMAOI* sub-model. In this case, the *a-priori* accuracies are generally

lower due to fewer "*no*" medication suggestions in the questionnaires. Most of the sub-models in the DEX expert model have a higher accuracy when measured on the questionnaire dataset than the *a-priori* one, except in two cases where sub-models *ChangeDAtoDA+LD* and *IncreaseLDdosage* have very close however smaller accuracy than the *a-priori*. Again, the DEX expert model outperforms the DEX data model, whose accuracy exceeds the *a-priori* in 6 of 15 cases. In summary, the decision rules defined in the DEX expert model seem to closely reflect the practice of neurologists, captured through the questionnaires.

Finally, we assessed the average level of agreement between the DEX models and the answers of the 17 neurologists on the questionnaire using the Jaccard index. The results are presented in

Table 8 in Appendix A and show that the Jaccard index is high ranging from 0.68-0.95 for the DEX Expert model and from 0.65-0.89 for the DEX Data model.

These results show that the DEX expert model is superior to the DEX data model. The DEX expert model includes decision rules that represent normative medical knowledge consistently. The rules were formulated and verified by medical experts; the models are transparent and can be thus inspected, reviewed and changed if necessary. The DEX data model proved that it is possible to extract decision rules gradually and interactively. The DEX data model is a baseline showcase of a model developed entirely from data without consulting an expert. Results in Table 5 show that such a model is inferior in capturing the real patterns both in the PPMI_DEX dataset and on the developed questionnaires in comparison to the DEX expert model. By employing experts' knowledge, a generally better model was built. In summary, the results indicate that the constructed models are adequate and thus fit for the purpose of making "second-opinion" suggestions to DSS users.

6 Conclusion

This paper describes the construction of two decision-support models for the PD medication treatment changes. Based on the analysis of how the medication change is performed by physicians in four European countries, the available literature on medication change, and by following guidelines that were within the scope of our study, we formalized the relevant knowledge, and in cooperation with neurologists and decision analysts, we developed two decision-support models for medication change of PD patients. The assessment of the developed models was conducted only in the countries from which we obtained approvals from ethical committees, which is only from the countries where there were project partners, in the H2020 PD_manager project: Italy, Slovenia, United Kingdom and Greece. We limited our study on the data that we had available from the PPMI data set and from the questionnaire answered by 17 neurologists.

The models were developed using two approaches, (a) based on knowledge and (b) based on data, respectively. Both begun in a group consisting of medical experts and decision analysts, who formulated medication treatment changes in terms of a state-transition model, which counted in total 8 states and 15 possible transitions. This model was translated into a hierarchical structure of qualitative attributes according to the DEX method. The decision rules were defined in two ways leading to two decision-support models: DEX expert model (neurologist knowledge was used for defining the decision rules) and DEX data model (rules were extracted from the PPMI_DEX dataset).

Given the current medication treatment of the patient, present motor and non-motor symptoms and epidemiologic factors, the models determine whether the current medical treatment is effective or not and suggest one or more alternative changes of medications that are expected to reduce the manifestation of symptoms to the lowest possible level. Under medication treatments, we considered any possible combination of major anti-Parkinson drugs: dopamine agonist (DA), levodopa (LD), and MAO-B inhibitors (MAOI). The models include the following medication change transitions: decrease/increase the medication dosage or intake (for DA and LD), include/exclude medication (DA, LD and MAOI) and change the medication from current to new (e.g., DA to LD). The models do not address the choice of initial treatment nor patients with comorbidities.

This is the first time that such decision support models reach to a point to suggest change of PD treatment. Hence we anticipate the presented models as baseline models for change of medication in PD. In future studies the models may serve for comparison purposes in particular for improving or development of models for medication changes of PD patients who were not considered in our study.

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Appendix A Quantization scheme for the medication change models

Table 6 Quantization scheme for the medication change models.

Attribute	Dataset	Item	Interval of *Yes* values	Interval of *No* values
OFF duration	MDS-UPDRS Part IV	4.3	0-1	2-4
impulsivity	MDS-UPDRS Part I	1.6	0-1	2-4
cognition	MDS-UPDRS Part I	1.1	0-1	2-4
hallucinations	MDS-UPDRS Part I	1.2	0-1	2-4
paranoia	MDS-UPDRS Part I	1.2	0-3	4
rigidity	MDS-UPDRS Part III	Maximal value of 3.3a, 3.3b, 3.3c, 3.3d, 3.3e	0-1	2-4
tremor at rest	MDS-UPDRS Part III	Maximal value of 3.17a and 3.17b	0-1	2-4
action tremor	MDS-UPDRS Part III	Maximal value of 3.16a and 3.16b	0-1	2-4
postural tremor	MDS-UPDRS Part III	Maximal value of 3.15a and 3.15b	0-1	2-4
bradykinesia	MDS-UPDRS Part III	3.14	0-1	2-4
cardiovascular	Concomitant medications log	Cardiovascular medications	A patient takes medications for cardiovascular problems	A patient does not take medications for cardiovascular problems
low blood pressure	Concomitant medications log	Hypotension medications	A patient takes medications for hypotension problems	A patient does not take medications for hypotension problems
hypertension	Concomitant medications log	Hypertension medications	A patient takes medications for hypertension problems	A patient does not take medications for hypertension problems
activity	Modified Schwab & England ADL	Overall estimation (MSEADLG)	> 60	<=60

dyskinesia intensity	MDS-UPDRS Part IV	4.2	0-1	2-4
dyskinesia duration	MDS-UPDRS Part IV	4.1	0-1	2-4
usingMAOI	Concomitant medications log	MAOI medications	A patient takes MAOI medications	A patient does not take MAOI medications
usingDA	Concomitant medications log	Dopamine agonists (DA)	A patient takes dopamine agonists	A patient does not take dopamine agonists
usingLD	Concomitant medications log	Levodopa medications (LD)	A patient takes levodopa medications	A patient does not take levodopa medications
maxDA[1]	Concomitant medications log	Dopamine agonists (DA)	LEDD >= 480 mg/day	LEDD < 480 mg/day
maxLD	Concomitant medications log	Levodopa medications (LD)	LEDD >= 1000 mg/day	LEDD < 1000 mg/day
ChangeDAtoLD	Concomitant medications log	DA and LD	Patient's therapy has changed from DA to LD	Patient's therapy has not changed from DA to LD
ChangeDAtoDA+LD	Concomitant medications log	DA and LD	Patient's therapy has changed from DA to DA and LD	Patient's therapy has not changed from DA to DA and LD
ChangeDAtoDA+MAOI	Concomitant medications log	DA and MAOI	Patient's therapy has changed from DA to MAOI	Patient's therapy has not changed from DA to MAOI
DecreaseDAdosage	Concomitant medications log	DA	Patient's DA LEDD dosage has decreased	Patient's DA LEDD dosage has not decreased
IncreaseDAdosage	Concomitant medications log	DA	Patient's DA LEDD dosage has increased	Patient's DA LEDD dosage has not increased
ChangeLDtoLD+DA	Concomitant medications log	LD and DA	Patient's therapy has changed from LD to LD and DA	Patient's therapy has not changed from LD to LD and DA
IncreaseLDdosage	Concomitant medications log	LD	Patient's LD LEDD dosage has increased	Patient's LD LEDD dosage has not increased

[1] Maximal dosage for dopamine agonist is set separately. For medications not covered in http://www.toolkit.parkinson.org/node/139, we set the ceiling LEDD value to 480 mg/day.

DecreaseLDdosage	Concomitant medications log	LD	Patient's DA LEDD dosage has decreased	Patient's DA LEDD dosage has not decreased
IncreaseLDintake	Concomitant medications log	LD	Patient's DA LEDD dosage has increased and patient experiences dyskinesia	Patient's DA LEDD dosage has not increased and patient experiences dyskinesia
DecreaseLDintake	Concomitant medications log	LD	Patient's DA LEDD dosage has decreased and patient experiences dyskinesia	Patient's DA LEDD dosage has not decreased and patient experiences dyskinesia
ChangeDA+LDtoLD	Concomitant medications log	DA and LD	Patient's therapy has changed from DA and LD to LD	Patient's therapy has not changed from DA and LD to LD
ChangeMAOItoMAOI+DA	Concomitant medications log	MAOI and DA	Patient's therapy has changed from MAOI to MAOI and DA	Patient's therapy has not changed from MAOI to MAOI and DA
ChangeMAOItoMAOI+LD	Concomitant medications log	MAOI and LD	Patient's therapy has changed from MAOI to MAOI and LD	Patient's therapy has not changed from MAOI to MAOI and LD
StopMAOI	Concomitant medications log	MAOI	Patient's therapy has stopped taking MAOI	Patient's therapy has not stopped taking MAOI
AddMAOI	Concomitant medications log	MAOI	Patient's therapy has started taking MAOI	Patient's therapy has not started taking MAOI
ChangeDA+MAOItoLD+MAOI	Concomitant medications log	LD, DA, MAOI	Patient's therapy has changed from DA and MAOI to LD and MAOI	Patient's therapy has not changed from DA and MAOI to LD and MAOI
ChangeLD+MAOItoDA+MAOI	Concomitant medications log	LD, DA, MAOI	Patient's therapy has changed from LD and MAOI to DA and MAOI	Patient's therapy has not changed from LD and MAOI to DA and MAOI

Appendix B Evaluation of medication change models: Questionnaire and results

Figure 8 shows a questionnaire that was employed to systematically test all DEX sub-models that comprise the two medication change models. The questionnaire contains 25 hypothetical patients' scenarios, represented by data about the current medication treatment of the patient, data about the current state of motor symptoms (dyskinesia intensity, dyskinesia duration, OFF duration, as well as rigidity, tremor at rest, action tremor, postural tremor, bradykinesia), mental problems (impulsivity, cognition, hallucinations and paranoia), epidemiologic data (patient's age, activity) and comorbidities (cardiovascular problems, hypertension and low blood pressure). For each case, the experts could provide up to three suggestions.

Test examples for Model How

Questionnaire answered by: please enter your name
Date: enter date

Number	rigidity	tremor at rest	action tremor	postural tremor	brady-kinesia	impulsivity	cognition	hallucin-ations	paranoia	cardio-vascular	low blood pressure	hyper-tension	OFF duration	dyskinesia intensity	dyskinesia duration	age	activity	current medication treatmen
1	no	no	no	no	no	no	no	***yes***	***yes***	no	no	no	no	no	no	gt75	no	**LD**
2	no	no	no	no	***yes***	no	no	no	no	no	no	no	no	no	no	lt65	no	**MAOI**
3	no	no	no	no	no	no	no	no	no	no	no	no	***yes***	no	no	lt65	no	**LD**
4	***yes***	no	no	no	no	no	no	no	no	no	no	no	no	no	no	lt65	no	**MAOI**
5	no	no	no	no	no	no	***yes***	***yes***	no	no	***yes***	no	no	no	no	65-75	no	**DA**
6	no	no	no	*no*	no	no	no	no	no	no	no	no	***yes***	no	***yes***	gt75	no	**LD**
7	no	no	no	no	no	***yes***	no	*no*	no	no	no	no	yes	no	***yes***	lt65	no	**LD**
8	***yes***	no	no	no	no	no	no	no	no	no	no	no	no	no	no	lt65	***yes***	**DA**
9	no	no	no	no	no	no	no	*no*	no	no	no	***yes***	no	no	no	65-75	no	**DA + MAOI**
10	no	***yes***	***yes***	no	no	no	no	no	no	no	no	no	*yes*	no	no	lt65	***yes***	**DA**
11	no	no	no	no	***yes***	no	no	*no*	no	no	no	no	yes	no	no	lt65	no	**LD**
12	no	no	no	no	no	no	no	no	no	no	no	no	no	***yes***	no	gt75	no	**DA + MAOI**
13	no	no	no	no	no	no	***yes***	*no*	no	no	no	***yes***	no	***yes***	***yes***	lt65	no	**DA + MAOI**
14	no	no	no	no	no	no	no	***yes***	no	no	no	no	***yes***	***yes***	no	65-75	no	**LD**
15	no	***yes***	no	***yes***	no	no	no	no	no	no	no	no	yes	no	***yes***	65-75	no	**LD**
16	no	no	no	no	no	no	no	no	no	no	no	no	no	***yes***	no	lt65	no	**LD**
17	***yes***	no	no	no	no	no	no	no	***yes***	no	no	no	no	no	yes	65-75	no	**LD**
18	***yes***	no	no	no	***yes***	no	no	no	no	no	no	no	no	no	no	65-75	***yes***	**DA**
19	no	no	no	no	no	no	no	no	no	no	no	no	***yes***	***yes***	no	lt65	no	**LD**
20	no	no	no	no	no	no	no	no	no	no	no	no	***yes***	no	no	65-75	***yes***	**DA**
21	***yes***	no	no	no	***yes***	no	no	no	no	no	no	no	no	no	no	gt75	no	**DA, maximum dosage**
22	no	no	no	no	no	no	no	no	***yes***	***yes***	no	no	no	no	no	lt65	no	**DA + LD**
23	no	no	no	no	no	no	no	no	***yes***	no	no	***yes***	no	no	no	lt65	no	**DA + MAOI**
24	no	no	no	no	no	no	no	no	no	***yes***	no	no	no	no	no	gt75	no	**DA + LD**
25	no	no	no	no	no	no	no	no	no	no	no	no	no	no	***yes***	65-75	no	**LD**

Description of attributes and scales

activity	is subjective assessment of patient's activity or is determined from the UPDRS section IV, the Schwab and England Activities of Daily Living Scale, so that <60% is interpreted as "no", and 60% as "yes"
age	age is discretized in three groups: less than 65 years "lt65", between 65 and 75 years "65-75", greater than 75 years "gt75"
paranoia	is UPDRS item so that: "no" is UPDRS 0 to 3, and "yes" is UPDRS 4
cardiovascular	according to the concomitment log those patients that take medications for cardiovascular problems are interpreted as "yes", otherwise as "no"
low blood pressure	according to the concomitment log those patients that take medications for hypotension problems are interpreted as "yes", otherwise as "no"
hypertension	according to the concomitment log those patients that take medications for hypertension problems are interpreted as "yes", otherwise as "no"
all others	are UPDRS items so that: "no" is UPDRS 0 or 1, and "yes" is UPDRS 2 to 4
DA	dopamine agonist
LD	levodopa
MAOI	MAO-B inhibitors

Figure 8 Questionnaire

Table 7 shows DEX expert model suggestions for the cases in Figure 8. These suggestions were compared with neurologists' answers (

Table 8), using the Jaccard index that assesses the level of agreement between the two sets of answers.

Table 7 DEX expert model suggestions for the questionnaire use-cases.

DEX expert models' suggestions					
1	2	3	4	5	6
Decrease LD dosage	Decrease LD intake				
Change MAOI to MAOI+DA	Change MAOI to MAOI+LD				
Change LD to LD+DA	Increase LD dosage	Add MAOI			
Change MAOI to MAOI+DA	Change MAOI to MAOI+LD				
Change DA to LD	Decrease DA dosage				
Increase LD intake	Add MAOI				
Decrease LD dosage	Increase LD intake	Add MAOI			
Increase DA dosage	Add MAOI	Change DA to DA+MAOI			
Stop MAOI					
Increase DA dosage	Change DA to DA+MAOI	Add MAOI			

Change LD to LD+DA	Increase LD dosage	Increase LD intake	Add MAOI		
Stop MAOI					
Decrease DA dosage	Stop MAOI	Change DA to LD			
Decrease LD dosage	Increase LD intake	Add MAOI			
Increase LD dosage	Increase LD intake	Add MAOI			
Decrease LD dosage	Increase LD intake				
Decrease LD dosage	Increase LD intake	Add MAOI			
Increase DA dosage	Add MAOI	Change DA to DA+MAOI			
Change LD to LD+DA	Decrease LD dosage	Increase LD intake	Add MAOI		
Increase DA dosage	Add MAOI				
Add MAOI	Change DA to DA+MAOI	Change DA to DA+LD			
Decrease DA dosage	Decrease LD dosage	Decrease LD intake	Change DA+LD to LD	Change DA to DA+MAOI	Change DA to LD
Decrease DA dosage	Stop MAOI	Change DA to LD			
Decrease DA dosage	Change DA+LD to LD	Change DA to LD	Change DA to DA+MAOI		
Decrease LD intake					

The DEX expert medication model suggests up to six answers for all 25 hypothetical use-cases as given in Table 7

In

Table 8, the number of neurologists' answers for all scenarios is given in columns titled "Cumulative Physicians' answers". There, columns 1–6 refer to the same answers as those of the DEX expert model in Table 7. The next two columns tell the number of neurologists who suggested to keep on with the same medication treatment and the number of neurologists who suggest a different medication change than the DEX expert model. The last two columns give the mean Jaccard index (the average level of agreement between the DEX models and the 17 neurologists).

Table 8 The average level of agreement between DEX models and neurologists answers on questionnaires expressed as mean Jaccard index.

	Cumulative Physicians' answers							Mean Jaccard index	
Use case number	1	2	3	4	5	6	Nothing: use the same medication	Suggest other medication treatment	DEX Expert model	DEX Data model
1	11	4					2	1	0.92	0.69
2	14	4					0	1	0.94	0.81
3	7	5	7				0	4	0.87	0.73
4	16	5					0	0	0.95	0.83
5	9	10					0	1	0.94	0.80
6	6	3					4	8	0.86	0.65
7	5	2	6				2	4	0.84	0.81
8	10	2	2				1	6	0.84	0.80
9	4						10	4	0.90	0.71
10	8	3					0	9	0.82	0.89
11	10	7		3			0	1	0.82	0.72
12	6						3	13	0.90	0.85

13	8	8	4				3	2	0.87	0.78
14	6	8	1				3	1	0.85	0.81
15	3	2	3				1	10	0.80	0.71
16	11	4					3	4	0.90	0.68
17	4	3	2				5	4	0.81	0.78
18	5	1	2				0	12	0.80	0.68
19	7	4	6	3			0	0	0.82	0.66
20	8	2					0	13	0.86	0.82
21	1	1	10				0	8	0.83	0.76
22	7			9			2	0	0.68	0.81
23	7	5	5				3	2	0.86	0.78
24	4	6					6	0	0.76	0.75
25	5						2	12	0.90	0.81

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: