Global Levodopa Dose Equivalency Calculator

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***Abstract*— In medical treatment of Parkinson's Disease, there is standard conversion formulas available between Levodopa and calculated equivalent dose amount of other antiparkinsonian drugs. Although there are calculation systems in the literature that include these formulas, the accuracy and stability of the currently available programs are highly questionable. For this reason, an interface was designed using the Python Tkinter library and an algorithm that included accepted formulations in the literature was designed to create the most accurate and stable calculator design. Aim of designed LED calculation program is to systematically reach the standard results by selecting the active ingredients of the drugs prescribed, both the commercial names and active pharmaceutical ingredient of the drugs. LED program can also be used in clinical research studies which can help to prevent Levodopa therapy calculation errors and provide efficient time management.**

Keywords*— *Levodopa, Levodopa Equivalent Dose, Dose Calculator, Python CustomTkinter GUI

I. Introduction

Parkinson's disease (PD) is a progressive neurological disorder characterized by a large number of motor and non-motor features (dementia, sleep disorders, and autonomic dysfunction) that can impact on function to a variable degree [1], [2]. Generally considered the cardinal signs of PD's are defined as bradykinesia, in combination with either rest tremor, rigidity or both [3].

Levodopa is one of the most effective medicinal treatments of PD motor symptoms [4]. Levodopa is absorbed in the proximal small intestine and metabolized by the aromatic L-amino acid decarboxylase (AADC) enzyme. Thus, L-DOPA and Carbidopa are formulated together to increase the fraction of L-DOPA transported to the brain for conversion to dopamine [5]. Other peripheral L-DOPA decarboxylase inhibitor is bensarazide in clinical use [6]. Additionally in pharmacological management of PD, L-DOPA formulation is used with other pharmacological agents for instance monoamine oxidase-B inhibitors (selegiline, rasagiline), dopamine agonists (rotigotine, bromocriptine, pergolide, lisuride), and catechol-O-methyltransferase inhibitors (entacapone, tolcapone) [7].

Generally, it is believed that a dopamine agonist to which Levodopa could be added lead to a lower incidence of motor fluctuations and dyskinesia for many years, but adverse effects such as hallucinations, somnolence, and edema were more common in the dopamine agonist group and parkinsonian motor features were more improved in the Levodopa therapy [8]. Previously L-DOPA was avoided in the early stages of the disease because of the fear of possible dyskinesia but now it is shown that patient with early PD starting treatment with low dose of L-DOPA do not differ from the ones who begin Levodopa 40 weeks later, in terms of prevalence of L-DOPA induced motor complications [9].

In clinical studies of PD conversion formulas between L-DOPA and antiparkinsonian drugs are being used to compare different drug formulations. These are reported in relation to Levodopa as the benchmark drug in PD pharmacotherapy as 'Levodopa Equivalent Dose' (LED) [10]. LED formula is calculated the equivalent dose of active pharmaceutical ingredient contained in Levodopa-like drugs.

In this study, a program which is mainly LED calculator is designed for the clinical and academical research. The main purpose of this attempt is to effectively track the patients' treatment, pursue the pharmacological and clinical research, and create a baseline for the academical research requiring validated and reliable LED calculation results.

II. Medthods and Materials

A. Software Design and Development

The LED calculation program was developed using Python's Tkinter and CustomTkinter library, which is a custom graphical user interface (GUI) toolkit. The software's design mainly focuses on user-friendly interaction, allowing neurologists and researchers to easily input patient name, medication data and calculate the total LED values and Levodopa dose per a day. The

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main window of the application is divided into subsections such as patient information, drug information and drug story displayment and calculation outcomes. The interface is structured with input fields for patient information (patient name/surname), entrance of medication information (drug name commonly used in Türkiye, hour to take medicine and drug dose), drug ingredient's information (name, dose and its drug type), buttons for adding drug ingredient entrance field, adding entered medicine data to calculation, calculating the LED value. All medication story is presented in table form at the bottom side of the application window and a display area for output results such as LED and total L-DOPA dose. Each subsection allows the user to input the dosage in milligrams (mg), depending on the medication type. Button "Calculate" triggers the LED calculation using the formulas embedded in the program's algorithm. Program has a "Report" button which exports all entrances with patient demographics. This allows clinicians or researchers to track patients' treatment and carry out pharmacological research.

B. LED Calculation Formulas

The software lies in the LED calculation algorithms, which are based on well established formulas in the literature [10]. In the literature, each formula is tailored to the specific medication type and its clinical equivalent dose to Levodopa.

These formulas were derived from clinical studies validated by academical research, which are widely accepted in the LED calculations [10]. In addition to this, the program permits for real-time calculation of LED displaying the total L-DOPA dose as soon as the user inputs the relevant medication dosages into related fields.

In the design of the software algorithm, the following formulas were used:

TABLE I. LIST OF DRUG TYPES WITH CORRESPONDING FORMULA

Drug Type[a]	Formula
Levodopa	((DD*1)+(LD*0.33))*T[b]
	(DD*1)*T
Extended-release Levodopa	(DD*0.5)*T
Rasagiline	(DD*100)*T
Apomorphine hydrochloride (subcutaneous)	(DD*10)*T
Pramipexole (extended/immediate-release)	(DD*100)*T
Ropinirole	(DD*20)*T
Piribedil	(DD*1)*T
Amantadine hydrochloride (immediate-release)	(DD*1)*T
Trihexyphenidyl	((DD*T)/4)*100
Zonisamide	((DD*T)/50)*100
Amantadine sulfate	(DD*1)*T

[a] Calculations for Intrajejunal Levodopa/Carbidopa Infusion are excluded
[b] DD: Daily Dose; LD: Levodopa Dose

C. Data Sources and Validation of LED Calculations

Designed to ensure accuracy of LED calculations, the program will be validated using patient data from Medipol University Parkinson's Disease and Movement Disorders Center (Medipol PARMER), experimental outcomes from the research articles and the results of existing programs. This data includes medication history and corresponding clinical LED calculations, providing a reliable basis to test the program's performance. Additionally, the software will be cross-referenced with existing online LED calculators (Parkinson's Measurement, PDMedCalc, EQUIDopa) to ensure reliability and consistency.

D. Software Design Testing and Validation

The software algorithm will undergo exhaustive testing procedures involving a variety of patient profiles and different medications to ensure its reliability and accuracy. The cases selected for the test category will include a range of drug combinations and dosages reflecting typical clinical scenarios encountered in the management of Parkinson's disease. The results produced by the designed program will then be compared with the results of manual calculations performed by neurologists during the clinical evaluation to test the accuracy of the LED calculations.

In addition to technical validation, application usability testing will be conducted with a group of neurologists and researchers. Feedback will be collected on interface design, ease of use, and clarity of system outputs to improve design, content, and user experience and the program design is optimized.

III. RESULTS

The design part of program was completed. Feedback on LED calculation results is regularly received from neurologists. Neurologists' first impressions of the program were that it is a time saving programme in daily practice while planning the daily Levodopa doses that the patient should use. In addition, it was reported by the data specialist and researchers at Medipol PARMER that it can also help to save time for data collection.

IV. DISCUSSION AND CONCLUSION

The main cause of Parkinson's disease and movement disorders is the deficiency of neurotransmitter called dopamine. Many dynamic (Deep Brain Stimulation) or static (pharmacological) methods are being tried to eliminate dopamine deficiency. In terms of neurology, pharmacological studies play an important role in the treatment of patients who are in the early stages aided other treatments or who are not suitable for surgery. Among today's treatment approaches, the most commonly used ones are Levodopa or Levodopa equivalent drugs, which are used to mimic the dopamine effect and try to change the course of the disease. In this context, it is essential to calculate the Levodopa equivalent dose in order to measure the healing effect of the drugs on the disease and, moreover, to keep the side effects on the patients under control.

In calculating the LED value, the equivalent dose of active ingredients (Levodopa, Entacapone, Ropinirole etc.) contained in Levodopa-like drugs is calculated. In order to perform the calculations, a literature review was conducted and the most generally accepted formulas in the literature were examined [10]. These formulas generally include two types of variables:

coefficient depending on the drug type category and daily drug usage dose. When the literature is examined, it is understood that there is no comprehensive program with a dynamic structure within itself among the LED calculation program designs and there are programs based on region, hospital, disease and doctor [11], [12]. In addition, there are many equivalents of drugs in the market. Therefore, from time to time, especially foreign patients experience difficulties in their treatment processes, and it takes a long time to find out which drug used in Türkiye corresponds to the active ingredients of the equivalent drug. When all these issues are evaluated, it is clearly seen that clinicians and clinical researchers in this field need an original and comprehensive LED calculation module.

In this project, an LED calculation module design is being made that meets the clinical need. The program includes patient demographics, patient drug information (time of use, frequency and dose), drug active ingredient name and dose addition (if the patient lives in a different country), presentation panel of drugs included in the LED calculation parameters (drug name, hour/frequency, dose, name of ingredients etc.), LED value and total Levodopa daily dose result parameters. The program design is currently being optimized for ease of use with the opinions of neurology specialists. The latest version of the program was shared with neurology specialists who are actively involved in Medipol PARMER and after the usage training, the program is tested for accuracy and stability measurement.

In clinical studies comparing the efficacy and safety of the investigational product in the treatment of Parkinson's disease, it is aimed to reach fast and error-free results in daily Levodopa equivalent dose calculations. Furthermore, with the mobile application version planned for the future, it is aimed to analyze the data related to the L-DOPA equivalent dose taken during on/off hours and to perform remote treatment management without the patient coming to the clinic, and it is anticipated that it will facilitate the visit management of international patients in the clinic. Additionally, this program is a calculation language development tool that can be used universally in other clinics, regardless of both ease of use and ongoing restrictions, and especially among neurology specialists, and that complies with certain standards.

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