RESEARCH ARTICLE

Levodopa Dose Equivalency in Parkinson's Disease: Updated Systematic Review and Proposals

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ABSTRACT: Background: To compare drug regimens across clinical trials in Parkinson's disease (PD) conversion formulae between antiparkinsonian drugs have been developed. These are reported in relation to levodopa as the benchmark drug in PD pharmacotherapy as 'levodopa equivalent dose' (LED). Currently, the LED conversion formulae proposed in 2010 by Tomlinson et al. based on a systematic review are predominantly used. However, new drugs with established and novel mechanisms of action and novel formulations of longstanding drugs have been developed since 2010. Therefore, consensus proposals for updated LED conversion formulae are needed.
Objectives: To update LED conversion formulae based on a systematic review.
Methods: The MEDLINE, CENTRAL, and Embase databases were searched from January 2010 to July 2021. Additionally, in a standardized process according to the GRADE grid method, consensus proposals were issued for drugs with scarce data on levodopa dose equivalency.
Results: The systematic database search yielded 3076 articles of which 682 were eligible for inclusion in the systematic review. Based on these data and the standardized consensus process, we present proposals for LED conversion formulae for a wide range of drugs that are currently available for the pharmacotherapy of PD or are expected to be introduced soon.
Conclusions: The LED conversion formulae issued in this Position Paper will serve as a research tool to compare the equivalence of antiparkinsonian medication across PD study cohorts and facilitate research on the clinical efficacy of pharmacological and surgical treatments as well as other non-pharmacological interventions in PD. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: levodopa equivalent daily dose; levodopa equivalent dose; LEDD

Levodopa is the most effective and widely used drug for the treatment of Parkinson's disease (PD). However, in the advanced stages of PD, patients with higher dosages of levodopa are at risk of developing motor and non-motor complications, such as dyskinesia and motor/non-motor fluctuations, in a dose-dependent manner.[1] In response, a range of new drugs and delivery systems have been developed and introduced for PD treatment. The pharmacotherapeutic armamentarium in PD now includes traditional oral, transdermal, inhaled, sublingual, intrajejunal, and subcutaneous delivery routes of antiparkinsonian medication. Drug agents include levodopa, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, N-methyl-D-aspartate (NMDA)-type glutamate receptor antagonists, anticholinergics, and selective adenosine A_{2A} receptor antagonists. To compare the intensities of antiparkinsonian medication across different study cohorts, the concept of 'levodopa equivalent dose' (LED) was introduced. These are reported in relation to 100 mg of levodopa as the benchmark drug in PD pharmacotherapy. Adding up the LED of each drug provides a total LED that condenses the antiparkinsonian medication into a single number, which is artificial but still useful and, if implemented according to a standardized method, comparable across study populations. In 2010, Tomlinson et al. systematically reviewed studies including LED for a range of antiparkinsonian drugs and proposed LED conversion formulae.[2]

Since then, new antiparkinsonian drugs, with both established and novel mechanisms of action, such as safinamide, istradefylline, or opicapone, have been introduced, and novel formulations of longstanding drugs, such as inhaled levodopa, intrajejunal levodopa/carbidopa/entacapone, or sublingual apomorphine, have been developed. In addition, the original review did not include anticholinergics, which were available for the pharmacotherapy of PD at the time and are available, affordable, and still used frequently in many regions of the world.[3-8] Therefore, there is a need for revised and updated LED conversion formulae based on a fresh systematic review of the current literature.

Methods

Systematic Review

References for this Position Paper were identified by reviewing our personal files and systematically searching MEDLINE, CENTRAL, and Embase databases for manuscripts published in English and German between January 2010 and July 2021 on antiparkinsonian medication on the market or expected to be introduced soon (Q1/2023). In MEDLINE, we used the terms: "l-dopa equivalent" [all fields] OR "levodopa equivalent" [all fields] OR "l-dopa equivalency" [all fields] OR "levodopa equivalency" [all fields]. This search strategy was adapted in other electronic databases. The systematic review was registered in PROSPERO (CRD42021239664, July 2021). Following Cochrane recommendations,[9] we also handsearched reference lists of identified studies, previous reviews on the same topic, and GoogleScholar for relevant grey literature sources[10] (eg, web-calculators[11]). We recorded, which LED conversion formulae were used and screened references cited in the context of LED conversion formulae. We followed the PRISMA reporting guidelines. Following the methodology reported by Tomlinson et al.,[2] we recorded conversion formulae of all drugs in relation to immediate-release levodopa/dopa decarboxylase inhibitor 100/25 mg and calculated the arithmetic mean and mode for each drug (Tables S1–S6).

Standardized Consensus Process According to the GRADE Grid Methodology

The author panel of this Position Paper reviewed available clinical and pharmacological studies and reached a consensus for proposed LED conversion formulae using a standardized consensus process according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) grid methodology.[12] This method was preferred over others (eg, a Delphi panel or the nominal group technique) because the GRADE grid allows 'strong' and 'weak' recommendations. The panelists reviewed the evidence and rationale for the proposed LED conversion formulae for each drug as well as its practical implementation in example calculations before completing the form. The panelists voted anonymously to allow for free expression of views. One, non-voting investigator (H.S.D.) facilitated all steps of this process. The first round of GRADE grid ratings was polled within 7 days. The results of the previous round were summarized and fed back to the panelists by the facilitator within 24 hours. Panelists were asked to review these summary results and their own grading in the previous round and revise their answers within 3 days. The process terminated after a stability of results was reached. All steps were implemented electronically (voting, presentations of the summarized results, and revisions of specific proposals). Following the methodology of Jaeschke et al.,[12] we used predefined criteria for a recommendation of proposed LED conversion formulae for each specific drug (>50% of the votes in favor and < 20% against the specific proposal). A 'strong recommendation' of the proposed LED conversion formula for a specific drug required that >70% of the votes strongly recommend the proposal. A strong recommendation of a proposed LED conversion formula implies that the desirable effects of issuing the proposal outweigh the undesirable effects.

Results and Discussion

The systematic database search yielded 3076 articles (Fig. 1), of which 682 were eligible for inclusion in the systematic review (Table S8). These were assigned to one of three categories: (1) studies using the LED conversion formulae proposed by Tomlinson et al., (2) studies not providing information on the LED conversion method, and (3) studies using proposals by other authors (eg, Hobson et al.,[13] Lozano et al.,[14] Krack et al.,[15] Fine et al.,[16] Wenzelburger et al.,[17] Parkin et al.,[18] Thobois et al.,[19] Pahwa et al.,[20] Esselink et al.,[21] or Deuschl et al.[22]). Figure S1 illustrates that the Tomlinson et al. method is predominantly used for LED calculations. Furthermore, the handsearch revealed that >2600 peer-reviewed publications cited the proposals by Tomlinson et al., which is currently the most frequently cited peer-reviewed paper in PD research published since 2010, whereas the second most frequently cited publication in this context, Hobson et al.,[13] was cited by <100 peer-reviewed publications as a reference to LED conversion formulae.

Development Strategy for Updated Levodopa Equivalency Dose Conversion Formulae

The proposals by Tomlinson et al. were retained in our current proposals, mainly because of the lack of sufficient new data for longstanding drugs indicating a need for change (Tables S1–S6). Furthermore, the proposals by Tomlinson et al. were considered as 'good practice' as they were used in the overwhelming majority (>95%) and in a high number of peer-reviewed publications in the field of PD research. This was the case for controlled- and extended-release levodopa, intrajejunal levodopa/carbidopa infusion, entacapone, tolcapone, selegiline, rasagiline, all ergot- and non-ergot-derived dopamine agonists (except for sublingual apomorphine, which has been marketed only recently), and immediate-release amantadine.

In some cases, our systematic review identified randomized controlled trials (RCTs) or meta-analyses, which provide sufficient evidence of clinical efficacy of

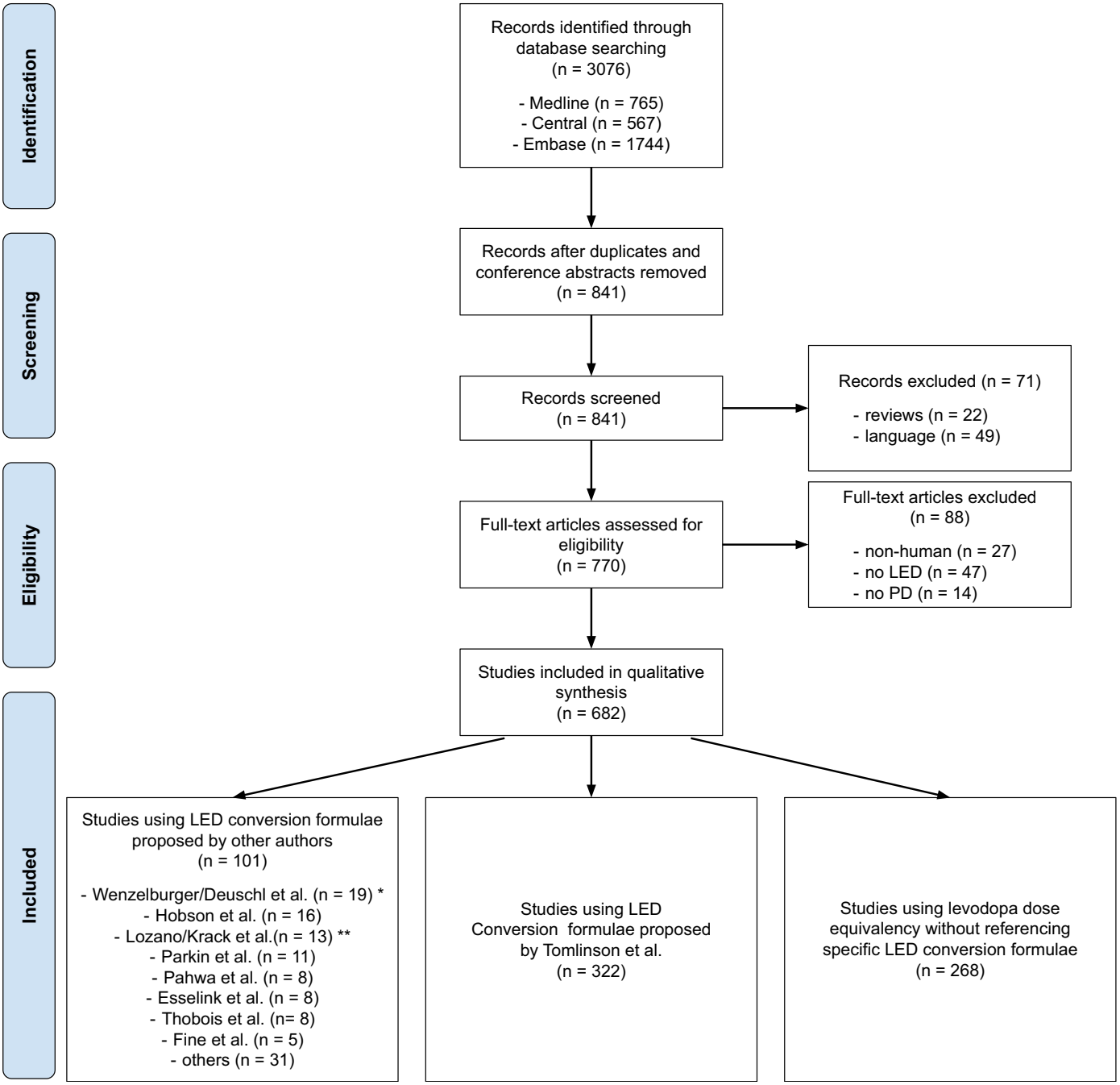

FIG. 1. Flowchart for systematic review of electronic databases. Multiple references to publications on levodopa equivalent dose (LED) conversion formulae were recorded in several cases: Nine studies included references to the method published by Tomlinson et al. and at least one other method and 18 studies included references to the LED conversion formulae proposed in two or more publications from other authors (Table S8). *The conversion factors proposed by Deuschl et al. include a minor adaption of the proposals by Wenzelburger et al. for controlled-release levodopa (LED < 10% smaller). **The conversion factors proposed by Krack et al. expand conversion factors to by Lozano et al. to include the drugs lisuride and apomorphine. Abbreviations: LED, levodopa equivalent dose; PD, Parkinson's disease. [Color figure can be viewed at wileyonlinelibrary.com]

specific antiparkinsonian medication for an improvement of total motor examination assessed with the (Movement Disorders Society) Unified Parkinson's Disease Rating Scale-Part III (UPDRS-III/MDS-UPDRS-III), but not sufficient data for an establishment of a dose-dependent relationship between this drug and immediate-release levodopa. In such cases, we therefore proposed a conversion for all doses of the specific drug, which improved total motor examination, to a specific dose of immediate-release levodopa.

For these and other drugs, for which the systematic review showed that data were scarce, panelists reviewed available clinical and pharmacological studies summarized below and reached a consensus on the proposals

for LED conversion formulae using a standardized consensus process according to the GRADE grid methodology.[12]

Proposals for Levodopa Equivalency Dose Conversion Formulae for Specific Antiparkinsonian Drugs with Scarce Data

In this section, we report in detail which specific studies and information provided by drug manufacturers and regulatory agencies (eg, the European Medical Agency or U.S. Food and Drug Administration) we considered in our deliberations during the standardized consensus process:

- Dual-release levodopa: We specifically considered a crossover study which reported a higher bioavailability (20%) and clinical efficacy on UPDRS-III total (11%) in dual-release compared to controlled-release levodopa.[23]
- Extended-release levodopa: Our critical appraisal included two studies[24,25] in which 530 patients switched from immediate- to extended-release levodopa (IPX066) with mean daily conversion ratios of 1:2.0–2.1.
- Inhaled levodopa: We specifically considered pharmacokinetic investigations of inhaled levodopa which reported that 84 mg capsules (50 mg fine particle dose) provide levodopa plasma levels (>400 ng/mL) needed to achieve meaningful improvement of OFF periods.[26] This study showed that incremental plasma levodopa concentrations exceeded 400 ng/mL within 10 minutes in 77% of subjects and reached maximum plasma concentration after approximately 15 minutes. However, approximately 45 minutes after levodopa inhalation, plasma levels fell below the 400 ng/mL threshold. Therefore, our proposed LED conversion formula for inhaled levodopa takes into account that an administration of a smaller second dose (60 mg capsules, 35 mg fine particle dose) may be required to counteract an early re-emergence of motor OFF state and thereby approximate the pharmacodynamic and clinical effects of a single dose of immediate-release levodopa 100 mg.
- Intrajejunal levodopa/carbidopa/entacapone infusion: We specifically took two studies into consideration that reported a 76% smaller levodopa maintenance dose requirement of intrajejunal levodopa/carbidopa/entacapone compared to intrajejunal levodopa/carbidopa infusion.[27,28]
- Subcutaneous foslevodopa/foscarbidopa infusion: We found no studies explicitly stating LED conversion formula for subcutaneous foslevodopa/foscarbidopa infusion. However, we appraised a pharmacokinetic study with crossover design which reported similar levodopa exposures after subcutaneous infusion of foslevodopa/foscarbidopa 700/35 mg compared to intrajejunal infusion of levodopa/carbidopa 350/87.5 mg followed by two doses of oral levodopa/carbidopa 100/25 mg.[29]
- Opicapone and other COMT inhibitors: The LED conversion formula for opicapone proposed here is in line with two previous publications.[30,31] A higher efficacy has been reported for opicapone compared to entacapone and, therefore, the LED conversion factor of opicapone is higher compared to entacapone (levodopa dose multiplied by 0.5 compared to 0.33, respectively).[31] We found no head-to-head studies on the clinical efficacy of opicapone and tolcapone that would support the superiority of one over the other. A network analysis by Song et al. compared changes in levodopa daily dose under entacapone, tolcapone, and opicapone without considering differences of study populations' PD severity (motor and non-motor symptoms total burden) or patient demographics, such as age, sex, and disease duration, in the statistical analysis.[32] The authors discuss that a reduction of levodopa daily dose observed only for tolcapone may result from the initial levodopa doses taken before tolcapone initiation and that more clinical trials and larger cohorts are needed to reach credible results.
  Of note, once daily opicapone intake reduces COMT activity and thereby increases the LED for all levodopa intakes during the whole day.[33] In contrast, the duration of effect of tolcapone and entacapone in substantially reducing COMT activity (<80%) is shorter: tolcapone 100 mg acts for 8 hours and entacapone 200 mg for 4 hours.[33,34] Therefore, we propose that an LED increase applies only to these durations immediately after intake of COMT inhibitors.
- Apomorphine hydrochloride sublingual: We found no studies reporting LED conversion formulae for sublingual apomorphine hydrochloride. Therefore, we assessed two studies that investigated the pharmacokinetics and comparative bioavailability of sublingual and subcutaneous apomorphine hydrochloride.[35,36] In these studies, a similar apomorphine exposure was observed at a ratio ranging between 6.0 and 7.5 for corresponding dosages of the two formulations (subcutaneous:sublingual 2:15, 3:20, 4:25, and 5:30).
- Immediate/extended-release amantadine: We found no studies reporting LED conversion formulae for immediate-/extended-release amantadine. The U.S. Food and Drug Administration has approved immediate-/extended-release amantadine (OS320) based on the bioequivalence of a once-daily regimen of 320 mg immediate-/extended-release amantadine hydrochloride to a twice-daily regimen of 160 mg amantadine hydrochloride syrup as the reference listed drug.[37] Therefore, we propose the same LED

conversion formula for both immediate-/extended- and immediate-release amantadine.

- Extended-release amantadine: We specifically assessed the following clinical and pharmacokinetic studies. First, in 32 patients switched from 275 mg/d immediate to 340 mg/d extended-release amantadine hydrochloride (ADS-5102), extended-release amantadine resulted in higher sustained daytime plasma concentrations than immediate-release amantadine and provided motor symptoms improvement.[38] Second, pharmacokinetic modelling has demonstrated that the intake of 340 mg/d extended-release amantadine hydrochloride once-daily at bedtime can provide a 1.4-fold higher daytime amantadine plasma concentration than three times daily intake of 100 mg/d immediate-release amantadine hydrochloride.[39] Therefore, the proposed LED conversion formula for extended-release amantadine considers this difference to immediate-release amantadine.
- Safinamide: We considered three studies including patients switched from other MAO-B inhibitors to safinamide and a consensus recommendation by Spanish PD specialists on a switch from rasagiline to safinamide.[40]

  The first study demonstrated that patients who switched from other MAO-B inhibitors to safinamide 50 mg/d experienced a median improvement of time spent in the motor OFF state from 60 to 30 minutes.[41] When patients who were switched from another MAO-B inhibitor to safinamide 50 mg/d and 100 mg/d were pooled, the levodopa daily dose was reduced from 716 to 649 mg (absolute reduction: 67 mg), whereas the LED of dopamine agonists and COMT inhibitors remained stable. The second study demonstrated that in patients switched from rasagiline 1 mg/d to safinamide 100 mg/d, patients' subjective symptoms of wearing off (Wearing-Off Questionnaire-19) improved.[42] The third study reported that 97 patients switched from rasagiline to safinamide noted a clinical benefit in motor (80%) and non-motor symptoms (33%) based on their self-assessments in the Clinical Global Impression of Change.[43] Reviewing this evidence, the Spanish consensus recommendation concluded that a switch from rasagiline to safinamide improves motor and non-motor symptoms.[40] We did not consider multiple treatment network comparison studies because for safinamide these are only based on the relative effects compared to placebo arms of different trials.[44,45] The interpretation of the results of these indirect comparisons is hampered by differences in the reference arms of included studies, such as motor and non-motor symptoms total burden, and patient demographics, such as age and sex. The information on the greater clinical efficacy of safinamide compared to rasagiline has only become available after Schade et al. proposed the same LED for rasagiline 1 mg/d and safinamide 50 mg/d or 100 mg/d.[31] In line with our clinical experience and the recently emerging data from switch studies outlined earlier, our proposed LED conversion formulae includes a higher LED for safinamide compared to other MAO-B inhibitors.

  Our systematic review found no evidence for a greater clinical efficacy of safinamide 100 mg/d compared to 50 mg/d on total motor examination, time spent in the motor OFF state, non-motor symptoms, and antiparkinsonian medication requirements. In line with the recommendations of the Spanish consensus on the use of safinamide in clinical practice,[40] the clinical experience of most of the panelists is that the higher safinamide dose may be useful for a reduction of dyskinesia in patients with new or worsening dyskinesia after initiation of safinamide 50 mg/d. However, given that the effect of safinamide on total motor examination is mostly mediated through its inhibition of MAO-B activity and 50 mg/d already achieve a full inhibition,[31] we propose a unified LED conversion for the safinamide doses 50 mg/d and 100 mg/d.
- Zonisamide: We considered four randomized, placebo-controlled trials that were included in a meta-analysis on the clinical efficacy of zonisamide in the treatment of PD.[46-50] These trials were conducted in Japan, where zonisamide 25 mg/d and 50 mg/d are approved for this indication. The meta-analysis provided evidence for an improvement of total motor examination (UPDRS-III) and wearing-off time in patients treated with approved doses of zonisamide. The mean levodopa dose of PD cohorts in Japan is lower than in Western study populations, possibly due to differences in physique, ethnicity, and diet, particularly lower animal protein intake,[51] and Japanese patients with PD develop side effects already at smaller levodopa daily doses.[46] In our systematic review, we found no studies reporting clinical efficacy and medication requirements in patients switched from other MAO-B inhibitors to zonisamide that would allow inferring an LED conversion formula by comparing their relative clinical efficacies. Furthermore, the relatively low baseline levodopa daily doses of Japanese patients with PD limit inferring an LED conversion formula from the reduction of levodopa after zonisamide initiation. Therefore, in view of a lack of data supporting a dose-dependent LED conversion formula for this drug, we propose a unified LED conversion for the zonisamide doses 25 mg/d and 50 mg/d.
- Trihexyphenidyl and other anticholinergics: In the Asia-Pacific region, anticholinergics are prescribed for PD pharmacotherapy more frequently than dopamine agonists (ie, second only to levodopa). In

TABLE 1 *Proposed conversion formulae for levodopa equivalency dose*

Drug class	Drug	Publications (patients) (n (n))	Conversion factor/ratio
Levodopa	Levodopa	–	DD × 1
	Dual-release levodopa*	0 (0)	DD × 0.85
	Controlled-release levodopa	27 (2320)	DD × 0.75
	Extended-release levodopa**	1 (0)	DD × 0.5
	Inhaled levodopa	0 (0)	DD × 0.69 (capsules)
	Intrajejunal levodopa/carbidopa infusion	1 (0)	DD × 1.11 (morning, maintenance, and extra doses)
	Intrajejunal levodopa/carbidopa/entacapone infusion	0 (0)	DD × 1.11 (morning dose) + DD × 1.46 (maintenance and extra doses)
	Subcutaneous foslevodopa/foscarbidopa	0 (0)	DD × 0.75
COMT inhibitors	Entacapone	10 (1038)	LD × 0.33[a]
	Tolcapone	7 (1038)	LD × 0.5[a]
	Opicapone	2 (0)	LD × 0.5[a]
Irreversible MAO-B inhibitors	Selegiline (oral)	9 (547)	DD × 10
	Selegiline (sublingual)	3 (366)	DD × 80
	Rasagiline	6 (450)	DD × 100
Non-ergot-derived dopamine agonists	Pramipexole (extended- or immediate-release)	23 (2155)	DD × 100 (salt) DD × 142.86 (base)
	Ropinirole	23 (2243)	DD × 20
	Rotigotine	4 (366)	DD × 30.3
	Piribedil	5 (404)	DD × 1
	Apomorphine hydrochloride (subcutaneous)	13 (963)	DD × 10
	Apomorphine hydrochloride (sublingual)	0 (0)	DD × 1.5
Ergot-derived dopamine agonists	Lisuride	10 (586)	DD × 100
	Bromocriptine	29 (2629)	DD × 10
	Pergolide	30 (2427)	DD × 100
	Cabergoline	12 (970)	DD × 66.67
	Dihydroergocryptine (DHEC)	4 (189)	DD × 5
Others	Amantadine hydrochloride (immediate-release)	6 (632)	DD × 1
	Amantadine hydrochloride (extended-release)***	0 (0)	DD × 1.25
	Amantadine hydrochloride (immediate-/extended-release)****	0 (0)	DD × 1
	Safinamide	1 (0)	LED = 150 mg[b]

(Continues)

TABLE 1 *Continued*

Drug class	Drug	Publications (patients) (n (n))	Conversion factor/ratio
	Zonisamide	0 (0)	LED = 100 mg[b]
	Trihexyphenidyl	0 (0)	LED = 100 mg[c]
	Istradefylline	0 (0)	LD × 0.2[d]

Note: Number of studies indicates the number of studies proposing LEDs in the database search.
Abbreviations: DD, daily dose of drug being converted to a levodopa equivalent dose; COMT, catechol-O-methyltransferase; LD, levodopa dose; MAO-B, monoamine oxidase B; LED, levodopa equivalent dose.
[a]COMT inhibitors: In patients treated with COMT inhibitors, the total LED is calculated in three steps: First, the LED of levodopa-containing medications is calculated. Second, this LED of levodopa-containing medications is multiplied by 0.33 (entacapone) or 0.5 (tolcapone or opicapone) to give the LED of the COMT inhibitor. Third, the LED of the COMT inhibitor is added to the LED of levodopa-containing medications and the subtotal LED of dopamine agonists, MAO-B inhibitors, and other antiparkinsonian medications to give the total LED. Of note, once daily opicapone intake reduces COMT activity and thereby increases the proposed LED of all levodopa intakes for the whole day. In contrast, the efficacy of tolcapone and entacapone on a substantial reduction of the COMT activity (<80%) is shorter: tolcapone 100 mg for 8 hours and entacapone 200 mg for 4 hours. Therefore, we propose that an LED increase applies only to these durations after intake of COMT inhibitors.
[b]Safinamide and zonisamide: We propose unified LED conversions for the zonisamide doses 25 mg/d and 50 mg/d to immediate-release levodopa 100 mg and for the safinamide doses 50 mg/d and 100 mg/d to immediate-release levodopa 150 mg. As there are no randomized controlled for zonisamide studies performed in other populations, the LED conversion formula should not be used outside Japan. [Correction added on 06 July 2023, after first online publication: The words 'for zonisamide' were added in the preceding sentence in this version.]
[c]Trihexyphenidyl and other anticholinergics, such as biperiden or benztropine: We propose a unified LED conversion formula for all doses of trihexyphenidyl that should be applied only to individual patients in whom the specific single dose of trihexyphenidyl provides a clinically important improvement of the Unified Parkinson's Disease Rating Scale-Part III (UPDRS-III) total by at least 5 points. In this clinical scenario, each clinically efficacious single dose of trihexyphenidyl is considered equivalent to a single dose of immediate-release levodopa 100 mg (eg, trihexyphenidyl 3 mg three times a day or, eg, trihexyphenidyl 4 mg three times a day would both result in an LED 300 mg). We propose to apply this rationale to other anticholinergics, such as biperiden and benztropine, when the same criterion of clinical efficacy on total motor examination assessed with the UPDRS-III total score is fulfilled.
[d]Istradefylline: The subtotal LED of levodopa-containing medications and COMT inhibitors is multiplied by 0.2 to give the LED of istradefylline, which is then added to the subtotal LED of levodopa-containing medications, COMT inhibitors, dopamine agonists, MAO-B inhibitors, and other antiparkinsonian medications to give the total LED.
*Madopar® dual-release (Madopar DR).
**IPX066 (Rytary®).
***ADS-5102 (Gocovri®).
****OS320 (Osmolex® ER).

studies from India,[5,52,53] New Zealand,[54] and Japan,[55] anticholinergics are prescribed to 24–40% of patients with PD.[56] Despite the frequent use in large populations of PD in this as well as other regions of the world,[3-8,57] we found no LED conversion formulae for anticholinergics, such as trihexyphenidyl, in our systematic review.

Therefore, we developed an LED conversion for this drug class taking the two following studies into consideration: First, a Cochrane systematic review of nine RCTs of anticholinergic drugs in PD reported that anticholinergics are more effective than placebo as monotherapy or as an adjunct to other antiparkinsonian drugs.[58] Second, a head-to-head study compared the clinical efficacy of single-dose administrations of 4 mg trihexyphenidyl and 200/50 mg levodopa/carbidopa on total motor examination (UPDRS-III).[59] In patients previously treated with trihexyphenidyl, a 4 mg dose of this drug improved the UPDRS-III total by 6.9 points, which exceeds the 5-point threshold for clinically important changes,[60] and improvements were observed for tremor, bradykinesia, rigidity, and axial subscores. Furthermore, levodopa 200 mg provided higher clinical efficacy than trihexyphenidyl 4 mg.[59]

Our systematic review did not find sufficient information to establish a dose-dependent LED conversion formula for trihexyphenidyl or other anticholinergics. Therefore, we propose a unified LED conversion formula for all doses of trihexyphenidyl, and this should be applied only to individual patients in whom the specific single dose of trihexyphenidyl provides a clinically important improvement in the UPDRS-III total. In this clinical scenario, clinically efficacious single doses of trihexyphenidyl are considered equivalent to a single dose of immediate-release levodopa 100 mg. We propose to apply this rationale to other anticholinergics when the same criterion of clinical efficacy on UPDRS-III total score is fulfilled.

- Istradefylline: Our systematic review found no publications on LED conversion formulae for istradefylline, which is approved as a non-dopaminergic adjunct to levodopa, not as a monotherapy. The levodopa daily dose reduction after istradefylline initiation will be investigated in the ISTRA ADJUST PD study.[61] Based on clinical experience from Japan and unpublished data, the expert medical advisory board of this study expects a 20% difference between the levodopa daily dose increase in patients treated with and without istradefylline at a 9-month follow-up.[61]

Table 1 presents the consensus proposals for LED conversion formulae developed in this Position Paper. Where available, our proposals took information from meta-analyses of clinical trials, relevant (pharmacological) studies, drug manufacturers, and regulatory

TABLE 2 *Proportion of votes cast by the panelists completing the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) assessment for proposed levodopa equivalent dose conversion factors (N = 27)*

Drug	Conversion factor/ratio	Strongly recommend proposal	Weakly recommend proposal	Neither recommend for or against proposal	Weakly recommend against proposal	Strongly recommend against proposal	Abstentions
Levodopa	DD x 1						
Dual-release levodopa*	DD x 0.85	**85.2**	14.8	0.0	0.0	0.0	0.0
Extended-release levodopa**	DD x 0.5	**88.9**	11.1	0.0	0.0	0.0	0.0
Inhaled levodopa	DD x 0.69 (capsules)	66.7	22.2	7.4	0.0	0.0	3.7
Intrajejunal levodopa/carbidopa/entacapone infusion	DD x 1.11 (morning dose) + DD x 1.46 (maintenance and extra doses)	**77.8**	18.5	3.7	0.0	0.0	0.0
Subcutaneous foslevodopa/foscarbidopa	DD x 0.75	63.0	33.3	0.0	0.0	0.0	3.7
Opicapone	LD x 0.5[a]	**96.3**	3.7	0.0	0.0	0.0	0.0
Apomorphine hydrochloride (sublingual)	DD x 1.5	**74.1**	18.5	3.7	0.0	0.0	3.7
Amantadine hydrochloride (extended-release)***	DD x 1.25	66.7	25.9	3.7	0.0	3.7	0.0
Amantadine hydrochloride (immediate-/extended-release)****	DD x 1	**77.8**	14.8	3.7	0.0	0.0	3.7
Safinamide	LED = 150 mg[b]	**70.4**	7.4	11.1	11.1	0.0	0.0
Zonisamide	LED = 100 mg[b]	51.9	25.9	18.5	0.0	0.0	3.7
Trihexyphenidyl	LED = 100 mg[c]	44.4	40.7	11.1	3.7	0.0	0.0
Istradefylline	LD x 0.2[d]	40.7	40.7	3.7	11.1	0.0	3.7

Note: See Table 1 legend for further information on the LED calculation of catechol-O-methyltransferase inhibitors, safinamide and zonisamide, trihexyphenidyl and other anticholinergics, and istradefylline.
Note: The proposed LED conversion formulae were recommended for all drugs.
Note: The recommendation rates for the proposed LED conversion formulae ranged between 77.8% (safinamide and zonisamide) and 100% (dual-release and extended-release levodopa, and opicapone) and the recommendation rates against the proposed LED conversion formulae were 14.8% (safinamide) or smaller.
Note: Strong recommendations are highlighted in bold type. Panelists 'strongly' recommended the proposed LED conversion formulae for dual-release levodopa, extended-release levodopa, intrajejunal levodopa/carbidopa/entacapone infusion, opicapone, sublingual apomorphine hydrochloride, immediate-/extended-release amantadine hydrochloride, and safinamide with 'strong recommendation' rates for the LED conversion formula of these drugs ranging between 70.4% (safinamide) and 92.6% (opicapone).
Abbreviations: DD, daily dose of drug being converted to a levodopa equivalent dose; LED, levodopa equivalent dose; LD, levodopa dose.
*Madopar® dual-release (Madopar DR).
**IPX066 (Rytary®).
***ADS-5102 (Gocovri®).
****OS320 (Osmolex® ER).

TABLE 3 *Protocol for levodopa equivalency conversions for antiparkinsonian drugs*

Drug	Conversion factor/ratio	Example	Calculated LED of the example
Levodopa	DD × 1	150 mg *D* qid	600 mg
Dual-release levodopa*	DD × 0.85	100 mg *D* bid	170 mg
Controlled-release levodopa	DD × 0.75	100 mg *D* qd	75 mg
Extended-release levodopa**	DD × 0.5	95 mg *D* bid	95 mg
Inhaled levodopa	DD × 0.69 (capsules)	84 mg *D* qd (capsules)	58 mg
Intrajejunal levodopa/carbidopa infusion	DD × 1.11 (morning, maintenance, and extra doses)	6 ml morning bolus +3.2 mL/h maintenance dose for 16 h = 1144 mg/d	133 mg morning bolus +1137 mg maintenance dose = 1270 mg
Intrajejunal levodopa/carbidopa/entacapone infusion	DD × 1.11 (morning dose) DD × 1.46 (maintenance and extra doses)	6 mL morning bolus +3.2 mL/h maintenance dose for 16 h = 1464 mg/d	133 mg morning bolus +1495 mg maintenance dose = 1628 mg
Subcutaneous foslevodopa/foscarbidopa	DD × 0.75	0.6 mL morning bolus +0.3 mL/h maintenance dose for 16 h = 1296 mg/day	108 mg morning dose +864 mg maintenance dose = 972 mg
Entacapone	LD × 0.33[a]	200 mg *D* tid + 100 mg levodopa tid	100 mg + 300 mg levodopa = 400 mg
Tolcapone	LD × 0.5[a]	100 mg *D* bid +150 mg levodopa tid	225 mg + 450 mg levodopa = 550 mg
Opicapone	LD × 0.5[a]	50 mg *D* qd + 150 mg levodopa qid	300 mg + 600 mg levodopa = 900 mg
Selegiline (oral)	DD × 10	10 mg *D* qd	100 mg
Selegiline (sublingual)	DD × 80	1.25 mg *D* qd	100 mg
Rasagiline	DD × 100	1 mg *D* qd	100 mg
Apomorphine hydrochloride (subcutaneous)	DD × 10	4 mg/h for 16 h = 64 mg/d	640 mg
Apomorphine hydrochloride (sublingual)	DD × 1.5	40 mg *D* bid	60 mg
Pramipexole (extended- or immediate-release)	DD × 100 (salt) DD × 142.86 (base)	1 mg (salt) *D* tid 2.1 mg (base) *D* qd	300 mg
Ropinirole	DD × 20	4 mg *D* qd	80 mg
Rotigotine	DD × 30	4 mg *D* qd	121 mg
Piribedil	DD × 1	50 mg *D* bid	100 mg
Lisuride	DD × 100	0.2 mg *D* tid	60 mg
Bromocriptine	DD × 10	5 mg *D* tid	150 mg
Pergolide	DD × 100	1 mg *D* bid	200 mg
Cabergoline	DD × 66.67	1 mg *D* tid	200 mg
Dihydroergocryptine (DHEC)	DD × 5	40 mg *D* tid	600 mg
Amantadine hydrochloride (immediate-release)	DD × 1	100 mg *D* qd	100 mg
Amantadine hydrochloride (extended-release)***	DD × 1.25	340 mg *D* qd	425 mg

(Continues)

TABLE 3 *Continued*

Drug	Conversion factor/ratio	Example	Calculated LED of the example
Amantadine hydrochloride (immediate-/extended-release)****	DD × 1	320 mg *D* qd	320 mg
Safinamide	LED = 150 mg[b]	50 mg *D* qd	150 mg
Zonisamide	LED = 100 mg[b]	50 mg *D* qd	100 mg
Trihexyphenidyl	LED = 100 mg [c]	4 mg *D* tid	300 mg
Istradefylline	LD × 0.2	20 mg *D* qd + 100 mg levodopa tid	60 mg + 300 mg levodopa = 360 mg

Note: See Table 1 legend for further information on the LED calculation of catechol-O-methyltransferase inhibitors, safinamide and zonisamide, trihexyphenidyl and other anticholinergics, and istradefylline.
Abbreviations: LED, levodopa equivalent dose; DD, daily dose of drug being converted to a levodopa equivalent dose; qid, four times a day; bid, twice a day; qd, once daily; LD, levodopa dose; tid, three time a day.
*Madopar® dual-release (Madopar DR).
**IPX066 (Rytary®).
***ADS-5102 (Gocovri®).
****OS320 (Osmolex® ER).

agencies into account. Table S7 grades the quality of evidence for proposed LED conversion formulae according to the modified GRADE system.[62-64] The consensus proposals incorporate the results of the standardized consensus process in which an agreement on a recommendation for the proposals of LED conversion formulae was established for all drugs (Table 2 and Supplementary Material page 1). Recommendation rates for these proposals ranged between 77.8% (safinamide and zonisamide) and 100% (dual-release and extended-release levodopa, and opicapone) and recommendation rates against these proposals were 11.1% (safinamide and istradefylline) or lower.

Strength and Limitations

A major limitation of our work is the present lack of sufficient data on the levodopa dose equivalency for a wide range of antiparkinsonian drugs. Particularly, trials with crossover designs and studies on drug-switching patterns can provide information on the LED conversion formulae for drugs with scarce data as described in the previous section. A critical discourse on the validity of LED and their implications for research is needed, specifically also to address the underlying rationale and methodology. COMT inhibitors increase plasma levodopa concentrations while MAO-B inhibitors increase synaptic dopamine levels in brain, whereas dopamine agonists bind to dopamine receptors, and other drugs, such as istradefylline, have non-dopaminergic mechanisms of action. [Correction added on 06 July 2023, after first online publication: The preceding sentence was updated in this version.] As discussed in previous publications on proposals for LED conversion formulae, due to the lack of sufficient data, the "proposals are neither objective, nor inherently scientific".[31] Therefore, this Position Paper does not represent an evidence-based medicine review as conducted by Seppi et al.[65] and Fox et al.[66] for the treatment of non-motor, and motor symptoms of PD, respectively, but a practical guide. The need for this Position Paper arises because, as outlined earlier, LED conversion formulae are a ubiquitously used research tool and, if implemented according to a standardized method, provide a means to compare pharmacological and surgical treatments in cohorts of patients with PD across study populations. A reason for the extensive use of LED conversions in the literature may be that a single number, which represents the total LED or the total antiparkinsonian medication requirements, provides statistical advantages over a list of medications. An alternative approach to presenting a single number for antiparkinsonian medication requirements may be providing a full list of individual medications.

Bearing in mind the conceptual and methodological limitations and shortcomings due to the scarcity and, in some cases, lack of data, the current proposals reflect LED conversion formulae to the best of our current knowledge and experience. We acknowledge that concepts, methods, and available data for LED conversion formulae are evolving, which will require future updates. The concept of LED conversion formulae could be broadened to include further pharmacological and non-pharmacological interventions in the future. It would be reasonable to add natural levodopa-containing supplements, such as mucuna pruriens or fava beans, and other treatments that are clinically efficacious and reduce antiparkinsonian medication requirements, such as subthalamic stimulation or magnetic resonance-guided high-frequency ultrasound. Therefore, LED conversion formulae proposals for these supplements could be added in future. A possible first step to bridge the knowledge gap resulting from the scarcity of comparative studies might be analyses using advanced statistical

TABLE 4 *Declaration of interests concerning antiparkinsonian drugs with scarce data on proposed levodopa equivalency dose conversion formulae*

Author	Dual-release levodopa	Extended-release levodopa	Inhaled levodopa	Intrajejunal levodopa/ carbidopa/entacapone infusion	Subcutaneous foslevodopa/ foscarbidopa	Opicapone	Apomorphine hydrochloride (sublingual)
	La Roche	Amneal Pharmaceutics	Acorda Therapeutics	Stada, Britannia, Lobsor	AbbVie, Neuroderm	Bial	Sunovion Pharmaceuticals
Jost							
Kaldenbach							
Antonini	x			x	x	x	
Martinez-Martin						x	
Timmermann					x		
Odin				x	x	x	
Katzenschlager			x	x	x	x	
Borgohain							
Fasano					x		x
Stocchi				x	x	x	x
Hattori					x		
Prashanth							
Rodriguez-Violante							
Falup-Pecurariu					x		
Schade							
Petry-Schmelzer							
Metta							
Weintraub							
Deuschl							
Espay		x	x		x		x
Tan							
Bhidayasiri				x			
Fung				x	x		
Cardoso							
Trenkwalder	x				x	x	

(Continues)

TABLE 4 *Continued*

Author	Dual-release levodopa	Extended-release levodopa	Inhaled levodopa	Intrajejunal levodopa/ carbidopa/entacapone infusion	Subcutaneous foslevodopa/ foscarbidopa	Opicapone	Apomorphine hydrochloride (sublingual)
Jenner	x				x	x	
Ray Chaudhuri	x			x	x	x	
Dafsari				x		x	
Sum	4	1	2	8	13	9	3
Recommendation rate for proposed LED conversion formula in GRADE grid voting	100%	100%	88.9%	96.3%	96.3%	100%	96.3%

Author	Amantadine hydrochloride Extended release	Amantadine hydrochloride immediate−/ extended-release	Safinamide	Zonisamide	Trihexyphenidyl	Istradefylline
	Supernus, Adamas (former: US WorldMeds)	Supernus, Adamas (former: US WorldMeds)	Newron, Eisai, Meiji, Zambon	Eisai (patent expired)	(patent expired)	Kyowa Kirin
Jost						
Kaldenbach						
Antonini			x			x
Martinez-Martin						
Timmermann						
Odin			x			
Katzenschlager			x			
Borgohain						
Fasano						
Stocchi			x			x
Hattori			x	x		x
Prashanth						
Rodriguez-Violante						

(Continues)

TABLE 4 *Continued*

Author	Amantadine hydrochloride Extended release	Amantadine hydrochloride immediate−/ extended-release	Safinamide	Zonisamide	Trihexyphenidyl	Istradefylline
Falup-Pecurariu						
Schade						
Petry-Schmelzer						
Metta						
Weintraub			x	x		
Deuschl						
Espay	x	x				x
Tan						
Bhidayasiri			x	x		
Fung						
Cardoso						
Trenkwalder						
Jenner			x	x		x
Ray Chaudhuri			x			
Dafsari						x
Sum	1	1	9	4	0	6
Recommendation rate for proposed LED conversion formula in GRADE grid voting	92.6%	96.3%	77.8%	81.5%	85.1%	81.4%

Abbreviations: LED, levodopa equivalent dose; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

methods applied to existing real-world datasets (eg, nonlinear automated problem solvers can be used to develop LED conversion formulae in specific clinical or study cohorts).[67] Furthermore, uncertainty and sensitivity analyses could account for, for example, body weight or the limited representation of PD populations with specific demographic and clinical parameters resulting from inclusion criteria of clinical trials.[68,69] Closely connected to this issue, particularly in the absence of RCTs directly comparing the efficacy of drugs, network analyses can provide a useful tool for indirect comparisons,[70] but only if they are methodologically conducted well, namely if they account for heterogeneity of study populations and use individual patient data,[71] include reference arm adjustments,[72] or identify populations-of-interest in addition to conducting rigorous sensitivity analyses.[73] To date, network analyses of treatments of PD have not implemented these best practice measures, which may explain why their main result that as monotherapy selegiline was found to be to be more effective than levodopa in a study by Zhuo et al.[74] and as adjunct therapy to levodopa in studies by Binde et al. and Yan et al. to be more effective than all other MAO-B inhibitors[44,75] and all dopamine agonists.[45] The clinical validity of these results is questionable, and these results contradict the recommendations of the MDS evidence-based medicine review on the treatment of motor symptoms of PD.[66] Furthermore, these network analyses are currently not considered in national guidelines, such as the American Academy of Neurology on the dopaminergic therapy of motor symptoms in early Parkinson disease.[76] However, network analyses including individual patient data from study populations and better statistical models may help to refine proposed LED conversion formulae.[71] In this context, we encourage a critical appraisal of the validity of the proposed LED conversion formulae issued here, in particular based on better network analyses and real-world datasets. In particular, we also acknowledge that LED conversion formulae are based primarily on study populations from Western countries, and the large proportion of Caucasian patients with PD in these studies may not be representative of study populations in other regions of the world. In this context, the systematic review could be extended to include publications in other languages such as Japanese, Chinese, French, Spanish, and more. To mitigate the risk of language bias we included a global panel of movement disorders experts in the standardized consensus process for this Position Paper. Nonetheless, the validity of our proposed LED conversion formulae needs confirmation in PD cohorts with different ethnicities.

Conclusions

This Position Paper presents the first consensus proposals for LED conversion formulae for 'novel' and longstanding antiparkinsonian drugs. To our knowledge, we incorporate the first updated systematic review on this topic published since 2010. Specifically, we report new consensus proposals for LED conversion formulae for a wide range of antiparkinsonian drugs, such as dual-release levodopa, inhaled levodopa, intrajejunal levodopa/carbidopa/entacapone infusion, subcutaneous foslevodopa/foscarbidopa infusion, extended-release and immediate-/extended-release amantadine, safinamide, zonisamide, trihexyphenidyl, and istradefylline. Table 3 presents a protocol for LED conversions for antiparkinsonian drugs. The Supplementary 'LED Calculator' provides an accessible and easy-to-use tool to apply our proposed LED conversion formulae.

In conclusion, the updated standardized LED conversion formulae proposed here provide a tool to compare the relative dose intensities of 'novel' and longstanding drugs used to treat PD in clinical studies. Moving forward, regular updates of consensus proposals for LED conversion formulae will be necessary. We advocate that the manufacturers of antiparkinsonian drugs should investigate the levodopa dose equivalency of drugs as one of the top priorities for phase IV trials. ■

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Data Availability Statement

The data used to support this study's findings are available from the corresponding author upon reasonable request.

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Supporting Data

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