Levodopa equivalent dose conversion factors – an updated proposal including opicapone and safinamide

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There has been a steadily growing armamentarium of drugs for the symptomatic treatment of Parkinson's disease (PD). Consequently, as various pharmaceutical agents are used, it has become more difficult to perform and compare clinical trials with different medication regimens. Since levodopa remains the gold standard treatment, conversion factors have been proposed to calculate levodopa equivalent doses (LED) for each drug to facilitate comparison of medication regimens. Adding up LEDs of each drug lead to a daily total LED that is artificial but feasible and—if used as a standard scheme—comparable internationally. Since the last widely accepted proposal of LEDs for PD drugs by Tomlinson et al. (2010)[1], there has been no update.

We hereby propose LED conversion factors for opicapone and safinamide, which are currently missing but urgently needed in ongoing clinical trials and observational studies.

Opicapone is a new peripheral COMT-Inhibitor. Tomlinson et al. (2010) have proposed a conversion ratio, rather than a conversion factor for inhibitors of COMT activity, by considering the mode of action of these drugs in terms of prolongation of the duration of the co-administered levodopa treatment. The suggested ratio for entacapone is 0.33 X LD (co-administered levodopa dose); the suggested ratio for tolcapone is LD X 0.5, respectively[1]. For opicapone, we suggest a ratio higher than for entacapone, since our literature search (see Supplemental Material S1) and clinical experience suggest that opicapone is slightly more efficacious than entacapone[2]. However, there are no intriguing data suggesting that opicapone might be more efficient than tolcapone,[3] we, therefore, propose using the same ratio for calculating the LED of opicapone as is used for tolcapone (LD X 0.5).

Safinamide is mainly a reversible MAO-B-inhibitor. Other proposed mechanisms likely play no relevant additional role concerning levodopa equivalence. For safinamide, we propose an LED of 100 mg, independently of the actual administered dose, since full reversible inhibition of MAO-B activity is already reached in the lowest commercially available preparations of safinamide[4]. In the previous scheme[1], this would make safinamide equivalent to 1mg rasagiline and 10mg oral selegiline.

All existing LED proposals (including our current additions), are based on clinical experience and empirical approaches. They pooled together studies by individual researchers, which provided sparse and inconsistent data. Consequently, these proposals are neither objective nor inherently scientific. To the best of our knowledge, there has not been a thorough evaluation so far. There needs to be a critical retrospective discussion on whether calculating LED reflects what we ought to measure and if conclusions drawn from these calculations are valid. This pseudo-validity remains the major limitation of calculating LEDs.

In conclusion, we believe that our proposed conversions fit reasonably well into the previous scheme of conversion factors (Table 1) and still sufficiently reflect the potential of both drugs. However, they follow the same limitations as the previous proposals[1]. Prospectively, the LED conversion factor scheme needs a global reassessment with an attempt to use more objective measurements (using validated rating scales, adjusting for placebo, etc.) and thereby allowing the inclusion of new agents.

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Authors' roles

1) Research project: A. Conception, B. Organization, C. Execution
2) Manuscript: A. Writing of the first draft, B. Review and Critique

SS: 1A, 1B, 1C, 2A, 2B
BM: 1C, 2B
CT: 1A, 2B

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CT has received honoraria for consultancy from Britannia and Roche and for educational lectures from UCB. She has received research grants from the Michael J. Fox Foundation for Parkinson's Research and the EU (Horizon2020). She holds patents for the treatment of dyskinesia in PD with oxycodone/naloxone and the PDSS-2 Scale as well as publishing royalties for a book for PD patients published in Schattauer Verlag, Germany, 2015.

Ethical Compliance Statement

The authors confirm that the approval of an institutional review board or patient consent was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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TABLE 1

TABLE 1 Conversion factors for calculating total levodopa equivalent dose (LED) for commonly used agents				
Drug class	Drug (*D*)	Conversion factor/ratio	Example	Calculated LED of the example
L-Dopa	IR L-Dopa	DD x 1	100 mg *D* tid	300 mg
	CR L-Dopa	DD x 0.75	100 mg *D* qd	75 mg
	ER L-Dopa	DD x 0.5[†]	200 mg *D* tid	300 mg
	Duodopa	DD x 1.11	7 ml bolus + 4.7 ml/h for 16 h = 1640 mg/day	1820 mg
COMT inhibitors	Entacapone	LD x 0.33*	200 mg *D* tid in combination with 100 mg levodopa tid	100 mg (+300 mg LD)
	Tolcapone	LD x 0.5*	100 mg *D* tid in combination with 100 mg levodopa qid	200 mg (+400 mg LD)
	Opicapone	LD x 0.5*	50 mg *D* tid in combination with 100 mg levodopa qid	200 mg (+400 mg LD)
MAO-B inhibitors	Selegiline oral	DD x 10	10 mg *D* qd	100 mg
	Selegiline sublingual	DD x 80	1.25 mg *D* qd	100 mg
	Rasagiline	DD x 100	1 mg *D* qd	100 mg
	Safinamide	LED = 100mg	50 or 100 mg *D* qd	100 mg
Nonergot-derived Dopamine receptor agonists[§]	Apomorphine	DD x 10	5 mg/h for 16 h = 80 mg/day	1820 mg
	Piribedil	DD x 1	50 mg *D* tid	150 mg
	Pramipexole, ER/IR	DD x 100	2,1 mg *D* ER *qd*	210 mg
	Ropinirole, ER/IR	DD x 20	4 mg *D* tid	240 mg
	Rotigotine	DD x 30	8 mg *D* qd	240 mg
Other	Amantadine	DD x 1	100 mg *D* tid	300 mg

D drug; LED levodopa equivalent dose; IR immediate release; CR controlled release; ER extended release; DD daily dose; LD levodopa dose; qd once a daily; tid three timed a day; qid four timed a day; COMT catechol-O-methyl transferase; MAO-B monoamine oxidase type-B

* The result is then added to the total daily L-Dopa dose.
§ For information on ergot-derived dopamine agonists refer to Table 1 in Tomlinson et al. (2010)[1]
† As proposed by Espay et al. (2017)[5]
Note: Adapted and modified from Tomlinson et al. (2010)[1]