The improvement of MAO-B inhibitors in Parkinson’s disease is clinically irrelevant: a review

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Introduction: The purpose of this review is to examine the clinical relevance of the statistically significant effects of monoamine oxidase-B inhibitors (MAO-B) inhibitors in Parkinson’s disease (PD).

Methods and Results: We applied the Minimal Clinically Important Difference (MCID) as a way to evaluate results as clinically significant and make a reference to the studies that calculated MCID for PD. The calculated MCID values were applied to the large-scale studies of the MAO-B inhibitors Selegiline, Rasagiline and Safinamide to evaluate the clinical importance of Unified Parkinson’s Disease Rating Scale (UPDRS) Part III and Total mean changes. Only the PRESTO and LARGO studies for Rasagiline manage to exceed both UPDRS III and UPDRS Total MCID. In a similar manner, we applied the MCID to the large-scale studies of MAO-B inhibitors to evaluate OFF-time reduction mean changes. No study manages to exceed the OFF-time MCID. Finally, we compared the clinical outcome of Rasagiline with the Substantial Clinical Difference and with that of Levodopa and the Dopamine Agonist Pramipexole.

Conclusion: Even if statistically significant, the MAO-B inhibitors’ clinical efficacy is at least marginal and controversial, especially in comparison with that of Dopamine Agonists or Levodopa.

Keywords: Minimal clinically important difference, Parkinson's disease, Monoamine oxidase-B inhibitors
Introduction

The monoamine oxidase-B inhibitors (MAO-B) have a prominent place in the treatment of Parkinson's disease (PD), especially in the early stages of the disease, both for their contribution to the delay of Levodopa (LD) treatment initiation, and for their much talked neuroprotective role [1-3]. However, questions have been raised for their effectiveness as antiparkinsonian medication [4]. Although several studies demonstrate statistically significant effects of MAO-B inhibitors [5-17], whether they have clinical significance remains to be seen, as a clinical trial may identify a small but statistically significant change in an outcome measure that may have little or no relevance to whether a patient actually feels improved. Thus, concern arises from the question: what is the magnitude of improvement that can be recognized as such by the clinician and/or, most importantly, by the patient as such? In the current study, we used the Minimal Clinically Important Difference (MCID) as a measurable size for evaluation of an outcome as clinically significant and applied it to the results of some of the largest studies with the most widely used MAO-B inhibitors, Rasagiline, Selegiline and Safinamide. Finally, we compared the results of the MAO-B inhibitors with those of Dopamine Agonists (DA) and LD.

Studies which calculate the Minimal Clinically Important Difference (MCID)

The most widely accepted method of assessment of the clinical signs and symptoms of PD patients is the Unified Parkinson's Disease Rating Scale (UPDRS) [18-20]. More specifically, UPDRS Part III (Motor Examination Part) is used to evaluate the antiparkinsonian effect of the intervention on the patients' motor abilities, which are, after all, the most important aspect of their everyday lives affected by the disease. Alternatively, in LD-treated, advanced disease patients, OFF-time reduction during 24h can be used as a measure [21, 22].

According to Jaeschke et al. [23] MCID is defined as the minimum change that can be recognized and appreciated by the clinician, while it is also important for the patient. The methods of MCID calculation are the anchor- and distribution-based approaches [24, 25].

The anchor-based approach requires an external standard that is simultaneously independent, interpretable and has a clinical relevance and correlation with the object being surveyed [21]. The most widely accepted anchor for PD patients for MCID determination is the Clinician-rated Global Impression of Improvement (CGI-I) scale (1=very much improved; 2=much improved; 3=minimally improved; 4=unchanged; 5=minimally worsened; 6=much worsened; 7=very much worsened) [21, 22, 26-28]. Determining the MCID done either by calculating mean change on the UPDRS among patients with score 4 (unchanged) and 3 (minimally improved) on the CGI-I scale or by Receiver Operating Characteristic (ROC) curve analysis were developed, where cutoff values for UPDRS and OFF-time changes best distinguished minimally improvement patients from those with no change [22, 29], estimated as the point on the ROC curve closest to (0,1), calculated as the minimum value of the square root of (1 - sensitivity)2 + (1 - specificity)2. Distribution-based approach is based on the distribution of the measure in the study population, but is mainly used to calculate the effect size [26, 28].

The challenges arising from determining the MCID are not few. First, these methods can give different MCID, even on the same sample, while, conversely, the same method can give different MCIDs in different samples [22, 29]. Furthermore, Hauser et al. [21, 22] pointed out the importance of the placebo effect in the MCID, while highlighting that the MCID varies from drug to drug, as studies using drugs with larger efficacy tend to calculate larger MCIDs.

Schrag et al. [27] used two double-blind clinical trials comparing DA Ropinirole with LD and Bromocryptine, respectively. The study concluded on a Clinically Important Difference of -8.0 points of mean change in the UPDRS Total score and -5.0 in the UPDRS Part III. However, neither those trials were placebo-controlled, nor the drugs' doses were stable over time.

Shulman et al. [28] performed a cross-sectional observational study of patients and concluded to an MCID of -4.1 to -4.5 for UPDRS Total and -2.3 to -2.7 for UPDRS Part III. Nevertheless, whether these results can be applied on clinical trials remains to be seen.

Rascol et al. [30] based on a double-blind, randomized Rasagiline study calculated an MCID of -1.52 for the UPDRS Part III. Nonetheless, these results were extracted by evaluation of both Rasagiline and Placebo groups.

Horvath et al. [26] estimated the MCID for UPDRS Part III up of -3.25 based on within-patients score method and -3.5 based on ROC analysis. The study included all disease severity degrees, all kinds of medications but no placebo.

The studies by Hauser et al. [21, 22] are the most relevant for our discussion, since their data are derived from clinical trials that include a placebo control group, include patients in early PD as well, evaluate an intervention that is mildly efficacious, utilize also subject-rated impression of change and, finally, used data from two double-blind, randomized Rasagiline studies. According to Hauser’s anchor-based analysis (using both mean change within patients and ROC curve analysis) the lower limit for the MCID is -2.0 for UPDRS Part III, -3.8 for UPDRS Total and -1.0 hours (h) for reduction in OFF-time [21].

Moreover, Hauser et al. [22] using data from two randomized, double-blind, placebo controlled-trials comparing DA Pramipexole (PPX), either extended (ER) or immediate (IR) release in either advanced or early PD patients suggest that data derived using patient-rated self-impression of change as in Patient-rated Global Impression of Improvement (PGI-I; 1=very much better;
2=much better; 3=a little better; 4=unchanged; 5=a little worse; 6=much worse; 7=very much worse) are more relevant than data derived using clinician-rated impression of change (CGI-I), because we are interested in whether subjects themselves actually feel improved. Furthermore, they suggest the MCID to be calculated as the change in the outcome measure in active treatment group subjects who rate themselves “a little better” minus the mean change in placebo-treated subjects who rate themselves as unchanged [MCID = (UPDRS active drug "little better") - (UPDRS placebo "unchanged")].

These results, however, refer to Pramipexole and, thus, they avoid recommending them for MAO-B inhibitors. Finally, they recommend the former MCID they determined [21] as lower limit of MCID for antiparkinsonian medication.

All taken into account, we conclude that the best measure to evaluate the clinical efficacy of MAO-B inhibitors are the MCIDs suggested by Hauser et al. 2011 (UPDRS Total = -3.8, UPDRS Part III = -2.0, reduction in OFF-time = -1.0 h).

**MCID application in UPDRS Part III and UPDRS Total mean changes in MAO-B inhibitors’ studies**

**Selegiline studies**
Selegiline is a selective, irreversible MAO-B inhibitor, among the first ever used as antiparkinsonian medication. The results of the studies examined are demonstrated on Table 1.

The DATATOP [5] study, a double-blind, randomized, placebo-controlled trial, recruited 889 patients with early PD and assigned them to one of four treatment groups: Selegiline 10mg/d (mg/d) plus Tocopherol placebo, Selegiline placebo plus Tocopherol 2000IU/day (IU/d), Selegiline 10mg/d plus Tocopherol 2000IU/d and Selegiline placebo plus Tocopherol placebo. The results demonstrated on two cumulative groups, Group A (n=401), patients who did not receive Selegiline, and Group B (n=399), patients who received Selegiline. Practically, with Tocopherol not implying any statistically significant antiparkinsonian effect whatsoever, this can be considered a Selegiline monotherapy treatment. After 3 months of treatment the UPDRS Part III changed by 1.0 and -0.8, while UPDRS Total changed by 1.6 and -1.4 for treatment Groups A and B from baseline, respectively, far from at least satisfying, according to the MCID of -2.0 for Part III, and -3.8 for Total UPDRS, as suggested by Hauser et al. [21, 22].

Furthermore, data extracted from the DATATOP extension study [6] showed that, at the same time, the initial first group (Selegiline 10mg/d plus Tocopherol placebo) changed by -0.9 and -1.5, while the fourth group (Selegiline placebo plus Tocopherol placebo) changed by 0.7 and 1.3 in UPDRS Part III and Total from baseline, respectively (Selegiline vs placebo = -1.6 and -2.8, respectively). Neither of these results meet the MCID criteria by Hauser et al. [21, 22].

Larsen et al. [7] enrolled 163 early PD patients in a double-blind, placebo-controlled study, randomizing them to receive either Selegiline (10mg/d) or placebo, in addition to LD/Benserazide. After 3 months of treatment, the Selegiline group (n=73) changed by -13.1 and -18.4 and the Placebo group (n=81) by -10.9 and -15.1 from baseline in UPDRS Part III and Total, respectively (Selegiline vs Placebo = -2.2 and -3.3, respectively), with only the Selegiline vs. Placebo score for Part III slightly exceeding the 2.0 limit, the sample size being, however, relatively small. Noted, the massive impact of LD treatment compared to Selegiline, to which we are going to refer more thoroughly later.

**Table 1. Mean changes of Selegiline groups vs. matching placebo groups.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (months)</th>
<th>Selegiline (mg/day)</th>
<th>UPDRS Part III</th>
<th>UPDRS Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DATATOP [5]</td>
<td>3</td>
<td>10</td>
<td>-1.6</td>
<td>-2.8</td>
</tr>
<tr>
<td>Larsen et al [7]</td>
<td>3</td>
<td>10</td>
<td>-2.2</td>
<td>-3.3</td>
</tr>
<tr>
<td>MCID</td>
<td>-2.0</td>
<td>-3.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Rasagiline studies**
Rasagiline is another selective, irreversible MAO-B inhibitor, more recently used than Selegiline in treatment of PD. The examined studies’ results are demonstrated on Table 2.

The TEMPO study [8], a double-blind, placebo-controlled study (n=404) recruited early PD patients and randomly assigned them into three groups, with the first receiving (n=138) Placebo, the second (n=134) receiving Rasagiline monotherapy 1mg/d and the third (n=132) receiving Rasagiline monotherapy 2mg/d. After 26 weeks of treatment, the difference from baseline between the Rasagiline 1mg group vs the Placebo group was -2.71 and -4.2

**Table 2. Mean changes of Rasagiline groups vs. matching placebo groups.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (weeks)</th>
<th>Rasagiline (mg/day)</th>
<th>UPDRS Part III</th>
<th>UPDRS Total/Part II+III</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMPO [8]</td>
<td>26</td>
<td>1</td>
<td>-2.71</td>
<td>-4.20</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.68</td>
<td>-3.56</td>
<td></td>
</tr>
<tr>
<td>ADAGIO [10]</td>
<td>36</td>
<td>1</td>
<td>-1.88</td>
<td>-3.03</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.28</td>
<td>-3.19</td>
<td></td>
</tr>
<tr>
<td>PRESTO [12]</td>
<td>26</td>
<td>0.5</td>
<td>-2.91</td>
<td>-4.11</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2.87</td>
<td>-4.21</td>
<td></td>
</tr>
<tr>
<td>MCID</td>
<td>2.0</td>
<td>-3.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

UPDRS = Unified Parkinson’s Disease Rating Scale; MCID = Minimal Clinically Important Difference
for UPDRS Part III and Total, respectively, whilst the difference from baseline between the Rasagiline 2mg group vs the Placebo group was -1.68 and -3.56 for UPDRS Part III and Total, respectively. Though the Rasagiline 1mg group exceeds the MCID, it should be noticed that these results refer to no actual clinical improvement in the UPDRS, but to just deceleration of clinical signs and symptoms’ deterioration (unadjusted mean differences equal to 0.1, 0.7 and 3.9 from baseline in UPDRS Total for Rasagiline 1mg, 2mg and Placebo groups, respectively).

During the extension study, [9] patients in the placebo group were treated with 2mg Rasagiline for 6 months, whilst the dosages in the other two groups remained unchanged. Thus, after 1 year, the mean differences between the Rasagiline 1mg vs. the Rasagiline 2mg delayed treatment group were -1.06 and -1.82 for UPDRS Part III and Total, respectively and the mean differences between the Rasagiline 2mg vs the Rasagiline mg delayed treatment group were -0.99 and -2.29 for UPDRS Part III and Total, respectively. More interestingly, as referred in the article, an analysis based only on the 249 patients who completed the extension study showed similar but not statistically significant results.

Similar to TEMPO [8] is the ADAGIO [10] study. In this double-blind, randomized, placebo-controlled trial, 1176 patients early PD patients were initially assigned to Rasagiline monotherapy 1mg/d (n=288), Rasagiline monotherapy 2mg/d (n=300) or matching Placebo (n=588) for 36 weeks. The mean differences from baseline at week 36 were 0.50 and 1.22 for Rasagiline 1mg/d, 0.20 and 1.06 for Rasagiline 2mg/d and 2.38 and 4.25 for matching Placebo, for UPDRS Part III and Total, respectively. More interestingly, as referred in the article, an analysis based only on the 249 patients who completed the extension study showed similar but not statistically significant results.

During the ADAGIO post-hoc analysis, [11] patients in the placebo group were randomly assigned to 1mg or 2mg Rasagiline for 36 weeks, whilst the dosages in the other two groups remained stable. Thus, after 72 weeks the mean differences from baseline were 1.45 and 2.82 for Rasagiline 1mg early treatment group, 2.21 and 4.50 for the Rasagiline 1mg delayed treatment group, 1.94 and 3.47 for Rasagiline 2mg early treatment group, 1.59 and 3.11 for the Rasagiline 2mg delayed treatment group for UPDRS Part III and Total, respectively. More interestingly, as referred in the article, an analysis based only on the 249 patients who completed the extension study showed similar but not statistically significant results.

During the extension study, [9] patients in the placebo group were treated with 2mg Rasagiline for 6 months, whilst the dosages in the other two groups remained unchanged. Thus, after 1 year, the mean differences between the Rasagiline 1mg vs. the Rasagiline 2mg delayed treatment group were -1.06 and -1.82 for UPDRS Part III and Total, respectively and the mean differences between the Rasagiline 2mg vs the Rasagiline mg delayed treatment group were -0.99 and -2.29 for UPDRS Part III and Total, respectively.

The LARGO [13] study, a double-blind, randomized, placebo-controlled trial, recruited 687 PD patients already receiving LD treatment. The patients were randomly assigned to Rasagiline 1mg/d (n=231), Entacapone 200mg/d (n=227) or Placebo (n=229) as add-on to LD treatment for 18 weeks. The mean differences between Rasagiline 1mg and Placebo were -2.94 and -3.24 for UPDRS Part III and Total, respectively. As a result, only the UPDRS Part III exceeds the MCID.

Safinamide studies

Lastly, we present Safinamide, an a-aminoadipic derivative, initially developed as antiepileptic drug, but also seemed to inhibit MAO-A and -B receptors [31-33]. It has completed the Phase III development program as add-on therapy to DAs and to LD in patients with early and mid-to-late stage PD [34]. The results of the studies examined are presented on Table 3.

Borgohain et al. [14,15] recruited 669 PD patients, already on LD treatment, to a double-blind trial and randomly assigned them to Safinamide 100mg/d (n=224),...
Safinamide 50mg/d (n=223) or matching Placebo (n=222) for 24 weeks. The mean differences from baseline for the UPDRS Part III were -6.9, -6.1 and -4.3 for each group, respectively. The mean differences between the Safinamide 100mg/d vs Placebo group were -2.6 and -3.6 for UPDRS Part III and Total, respectively. The mean differences between the Safinamide 50mg/d vs Placebo group were -1.8 and -2.3 for UPDRS Part III and Total, respectively. Only the mean difference between the Safinamide 100mg/d vs Placebo group for the UPDRS Part III manages to exceed the MCID. Dyskinesias, however, were more frequent among the Safinamide 100mg/d group and the Safinamide 50mg/d group than the Placebo group (18.3%, 21.1% and 12.6%, respectively).

Stocchi et al. [16] recruited 270 early PD patients, already on a single DA, in a double-blind trial and randomized them to one of the following groups: Safinamide 200mg/d (n=89), Safinamide 100mg/d (n=90) or matching Placebo. At the end of the 24-week period, the mean changes from baseline were -3.9, -6.0 and -3.6 for the UPDRS Part III, respectively (Safinamide 200mg/d vs placebo= -0.3 and Safinamide 100mg/d vs placebo= -2.4). The cumulative mean change between Safinamide 200mg/d group vs placebo group for UPDRS Parts II and III is -0.5, while the corresponding change for the Safinamide 100mg group is -3.4. Once again, only the mean change between Safinamide 100mg/d vs. placebo manages to exceed MCID.

### MCID application in OFF-time reduction mean changes

As mentioned before, an important aspect of the antiparkinsonian medication is their effect on OFF-time reduction in moderate or advanced PD patients. Before we proceed, we shall remind that the MCID for OFF-time by Hauser et al. [21, 22] is -1.0 hours per day. The results are presented on Table 4.

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (weeks)</th>
<th>MAO-B inhibitor (mg/day)</th>
<th>OFF-time reduction (hours/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lew et al [17]</td>
<td>52</td>
<td>Selegiline 1.25-2.5</td>
<td>-0.40</td>
</tr>
<tr>
<td>PRESTO [12]</td>
<td>26</td>
<td>Rasagiline 0.5</td>
<td>-0.49</td>
</tr>
<tr>
<td>LARGO [13]</td>
<td>18</td>
<td>Rasagiline 1.0</td>
<td>-0.94</td>
</tr>
<tr>
<td>Borgohain et al [14]</td>
<td>24</td>
<td>Safinamide 100</td>
<td>-0.60</td>
</tr>
<tr>
<td>MCIDb</td>
<td>-1.00</td>
<td>Safinamide 50</td>
<td>-0.60</td>
</tr>
</tbody>
</table>

MAO-B = Monoamine oxidase-b inhibitor; MCID = Minimal Clinically Important Difference

Lew et al. [17] studied the efficacy of orally disintegrating (ODT) Selegiline. This open-label, placebo-controlled extension study, included 254 mid-to-late PD patients, already receiving LD and assigned them to Selegiline ODT 1.25mg for 6 months, followed by Selegiline ODT 2.5mg for another 6 months (n=171) or matching placebo for 12 months (n=83). The mean change in OFF-time reduction was -1.6h and -1.2h for the two groups, respectively (Selegiline ODT 1.25-2.5 vs Placebo= -0.4h), far below the MCID.

In the PRESTO [12] study, initially designed to evaluate OFF-time reduction, the mean changes were -1.41, -1.85 and -0.91 for Rasagiline 0.5mg, Rasagiline 1mg and Placebo groups, respectively (Rasagiline 0.5mg vs Placebo= -0.49h, Rasagiline 1mg vs Placebo= -0.94h). Similarly, in the LARGO [13] study, the mean changes were -1.18h and -0.40h for Rasagiline 1mg and Placebo groups, respectively (Rasagiline 1mg vs Placebo= -0.78h). Neither these results manage to exceed the MCID.

Finally, Borgohain et al. [14, 15] demonstrated unsatisfactory results for OFF-time reduction, with mean changes of -1.3h, -1.3h and -0.7h for Safinamide 100mg, Safinamide 50 mg and Placebo groups, respectively (Safinamide 100mg vs Placebo= -0.6h, Safinamide 50mg vs Placebo= -0.6h).

### Rasagiline versus Levodopa, Pramipexole and the Substantial Clinical Difference

MCID implies that, while the results of Selegiline, Rasagiline and Safinamide for the UPDRS are at least controversial, those for the OFF-time reduction are undoubtedly inadequate. Noted, the MCIDs calculated by Hauser et al. [21] are among the lowest proposed by the MCID studies mentioned in the current review. One could claim that what the MAO-B inhibitors may lack in efficacy, they replenish it thanks to their so-called neuroprotective role in PD. However, strong disagreement seems to be put against that theory [4], whilst every antiparkinsonian medication, including DAs and even LD, seems to possess neuroprotective properties, at least at the early stages of the disease [35-37]. Thus, until a certain biochemical pathway that verifies the drugs’ neuroprotection without question is discovered, the only way to quantify their effect on the patient’s clinical improvement will be the changes in UPDRS and OFF-time reduction and the most efficient way to evaluate them will be the MCID.

Besides, beyond quantification, with the importance of putting the patient before the numbers taken for granted, one rhetorical question arises: is the minimal clinical effect what we demand from a treatment? Is just a minimal change, barely recognizable, what the patient is expecting from the clinician? Therefore, Hauser et al. [22] calculates the Substantial Clinical Difference (SCD), defined as "the mean change in the outcome measure in active treatment group subjects who rated themselves much better minus the mean change in placebo-treated subjects who rated themselves as unchanged", [22, p5] based on the PGI-I.
scale. The SCD calculated for the PPX IR Early PD group, the one with the lowest difference, is -7.1.

Taken into account that these results are based on Pramipexole (PPX) and PGI-I scale, they nevertheless more than overwhelm any improvement in UPDRS III, Total or OFF-time ever recorded by any MAO-B inhibitor in the studies presented in the current review. Figure 1 compares SCD for UPDRS Part III calculated for the PPX IR Early PD group by Hauser et al. (33 weeks), to the mean change of UPDRS Part III in the Rasagiline 2mg group from the ADAGIO [10] study (36 weeks).

Moreover, as previously explained, due to MCID’s specifics, every drug may yield different MCIDs. Hence, every different drug is, unavoidably, compared mainly to itself. Consequently, another intriguing question arises: how would a MAO-B inhibitor’s clinical effect stand in direct comparison with that of another antiparkinsonian medication’s, such as DAs or LD?

Poewe et al. [38] in their double-blind study from which Hauser et al. [22] extracted their results, recruited 539 early PD patients and randomly assigned them to Placebo (n=103), Pramipexole Extended Release (ER: n= 223) and Pramipexole Immediate Release (IR: n=213). After 33 weeks of treatment the mean changes from baseline were -1.1 and -1.3 for the Placebo group, -6.1 and -8.3 for the ER group, and -6.4 and -8.8 for the IR group for UPDRS Part III and UPDRS Total, respectively (ER vs Placebo= -5.0 and -7.0, IR vs Placebo group= -5.3 and -7.5 for UPDRS Part III and Total, respectively).

Pahwa et al. [39] evaluated the clinical efficacy of IPX066 (an extended release Levodopa/Carbidopa formulation) in a randomized, double-blind, placebo-controlled, 30-week study. 381 early PD patients were randomized into four groups: placebo (n=90), 145mg thrice daily, 245mg thrice daily (TID) and 390mg thrice daily. The mean changes from baseline for the placebo group were -0.7 and -0.4 and for the 390mg TID were -11.0 and -15.2 for UPDRS Part III and UPDRS Total, respectively (390mg TID vs Placebo= -10.3 and -14.8 for UPDRS Part III and UPDRS Total, respectively).

The results of the IPX066 390mg TID group (IPX) and the Pramipexole Immediate Release group (PPX-IR) are demonstrated on Figures 2 (vs matching placebo) and 3 (from baseline), together with the Rasagiline 2mg group from the ADAGIO [10] study. The results refer to 30, 33 and 36 weeks of treatment, respectively, and demonstrate the points of improvement in the UPDRS. In contrast with any MAO-B inhibitor, not only do these results clearly exceed the MCID multiple times, but they also refer to actual, substantial improvement, not just deceleration of disease progression.

**Conclusion**

In conclusion, our review implies that what may be statistically significant is not necessarily significant for the
clinician and, most importantly, for the patient. The present review, using MCID calculations shows that MAO-B inhibitors’ clinical efficacy seems to be quite questionable, particularly in comparison with that of LD or DAs. One could argue for the occurrence of more frequent and severe adverse events with these drugs, but the main reason for their side effects is their actual clinical effect. Nevertheless, MCID’s specifics prove to be its largest weaknesses. Thus, further investigation to manifest a global, reliable MCID for all antiparkinsonian medications is needed. To our concern, PD is a devastating disease and, given the lack of an actual cure, the patients deserve at least treatments that substantially improve their symptoms in a clinically recognizable manner.

Abbreviations

CGI-I: Clinician-rated Global Impression of Improvement; DA: Dopamine agonists; ER: Extended release; LD: Levodopa; MAO-B: Monoamine oxidase-B inhibitors; MCID: Minimal Clinically Important Difference; PD: Parkinson’s disease; PGI-I: Patient-rated Global Impression of Improvement; PPX: Pramipexole; ODT: Orally disintegrating; ROC: Receiver Operating Characteristic; SCD: Substantial Clinical Difference; UPDRS: Unified Parkinson’s Disease Rating Scale

Competing interests

Yiannakis A: the author declares no conflict of interest. Konitsiotis S: travel grants and speaker’s honoraria from Abbvie, Boehringer, Glaxo-SmithKline, Novartis, Pfizer, TEVA, UCB.

References


