

# Levodopa use in Australia: an analysis of Pharmaceutical Benefits Scheme 10% data

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## ABSTRACT

**Background** Levodopa remains the mainstay of treatment of Parkinson's disease, however, over time motor fluctuations and levodopa-induced dyskinesia develop, requiring add-on therapies to control emerging symptoms. To date, however, there is no clear consensus in Australia, or elsewhere, at which dose of levodopa that add-on therapies should be considered.

**Objectives** The purpose of this study was to examine the treatment patterns of patients with Parkinson's disease in Australia, with particular focus on levodopa doses at the time of first add-on.

**Methods** This was a retrospective, observational, non-interventional study of patients with Parkinson's disease within the Australian Department of Human Services Pharmaceutical Benefits Scheme (PBS) 10% sample. Data on all reimbursed prescriptions (both general and concession), prescriber type and item code were extracted for patients who were dispensed at least three PBS reimbursed prescriptions for levodopa in the previous 12 months prescription from 1 January 2007 to 31 December 2021.

**Results** 154 850 unique patients were included, of whom 42 330 (27%) commenced add-on therapy during the period. In the 12 months prior to add-on therapy, levodopa doses ranged from 100 mg/day to 1000 mg/day. The majority of patients were prescribed add-on therapy by a neurologist and approximately 40% of patients were prescribed levodopa doses of 600 mg/day or more prior to the first add-on therapy being initiated.

**Conclusions** A large proportion of patients in Australia are managed with levodopa monotherapy doses that are considered high and many of these patients may benefit from the addition of add-on therapy to their regimen.

## INTRODUCTION

Levodopa remains the mainstay of treatment of Parkinson's disease (PD) but with long-term use, motor fluctuations (including wearing-off symptoms) and levodopa-induced dyskinesia develop.<sup>1</sup> These motor response complications can be accompanied by a range of non-motor symptomatology including pain and compulsive behaviours such as

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Levodopa is a cornerstone therapy for Parkinson's disease, with some patients requiring add-on therapies to manage disabling motor response fluctuations.

## WHAT THIS STUDY ADDS

⇒ We present real-life data showing that up to 40% of patients will start their first add-on therapy when the daily dose of levodopa reaches 600 mg or more.  
 ⇒ Add-on therapies tended to be used earlier by neurologists and earlier in younger patients and women.  
 ⇒ Dopamine agonists were common add-ons for lower levodopa doses, while monoamine oxidase type B inhibitors increased with higher levodopa doses.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings spotlight the significant role of neurologists in prescribing and suggest a need for tailored therapeutic strategies based on age and gender.

punding<sup>2</sup> and have a significant impact on functionality and quality of life (QoL). Proper recognition and management are important in optimising QoL and in so doing clinicians must balance the need to ensure improvement of PD symptoms in the short term while reducing the impact of these levodopa-induced complications.<sup>2</sup>

The most important risk factors for motor complications of levodopa include disease progression (with increasing loss of nigrostriatal dopamine), disease severity, higher individual doses of levodopa, peripheral pharmacokinetic factors affecting absorption of levodopa<sup>3 4</sup> and possibly genetic risk factors.<sup>4 5</sup> In the early stages of levodopa treatment, there is usually good response and patients are not aware of any re-emergence of parkinsonism, for example, if they are late taking a dose or miss a dose. Over time, on average 2–5 years of chronic use of levodopa, patients



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**Table 1** Patient demographics

| Demographic  | All patients commencing levodopa<br>N=154 850 | Patients on levodopa who commence<br>add-on therapy<br>N=42 330 |
|--|---|---|
| Age in years, mean (SD)  | 74 (14)                                       | 72 (11)   |
| Age in years   |   |   |
| <55  | 15 620 (10%)                                  | 2970 (7%)   |
| 55–69  | 36 580 (24%)                                  | 12 020 (28%)  |
| ≥70  | 102 850 (66%)                                 | 27 340 (66%)  |
| Sex  |   |   |
| Male   | 71 450 (46%)                                  | 24 590 (58%)  |
| Female   | 83 400 (54%)                                  | 17 740 (42%)  |
| Prescriber   |   |   |
| GP   | 79 100 (51%)                                  | 9120 (22%)  |
| Neurologist  | 60 690 (39%)                                  | 28 510 (67%)  |
| General medicine specialist  | 5430 (4%)                                     | 1740 (4%)   |
| Geriatrician   | 9630 (6%)                                     | 2960 (7%)   |
| Year of first PD claim   |   |   |
| 2007–2008  | 21 050 (14%)                                  | 6260 (15%)  |
| 2009–2010  | 20 590 (13%)                                  | 6640 (16%)  |
| 2011–2012  | 19 750 (13%)                                  | 6040 (14%)  |
| 2013–2014  | 19 880 (13%)                                  | 6680 (16%)  |
| 2015–2016  | 20 730 (13%)                                  | 6440 (15%)  |
| 2017–2018  | 21 710 (14%)                                  | 5730 (14%)  |
| 2019–2020  | 20 290 (13%)                                  | 3850 (9%)   |
| 2021   | 10 390 (7%)                                   | 690 (2%)  |
| Length of follow-up in years, median (minimum, maximum)  | 12 months (0–180 months)                      | 19 months (1–171 months)  |
| Percentages may not add to 100% due to rounding error.<br>GP, general practitioner; PD, Parkinson's disease. |   |   |

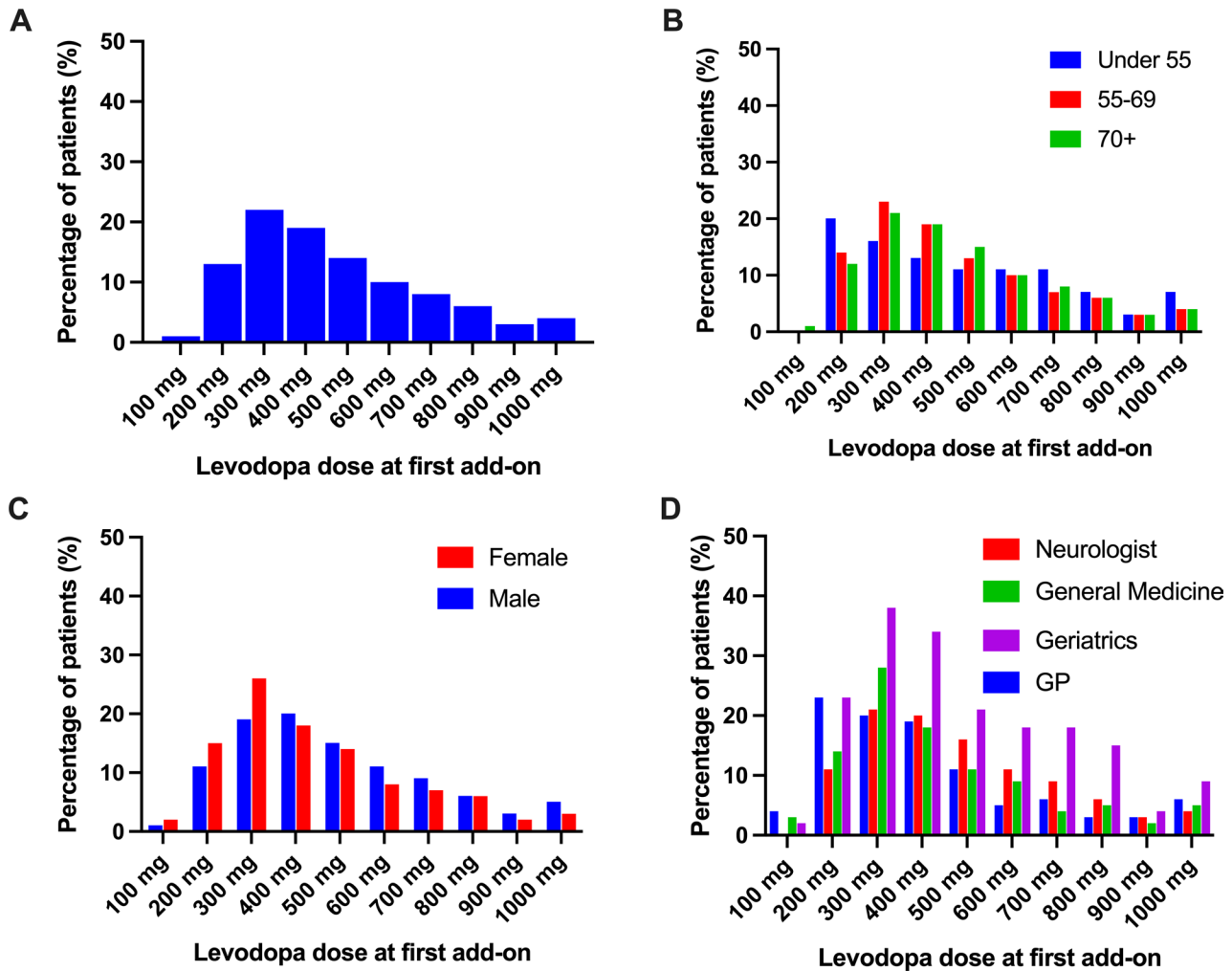
begin to become aware of fluctuations in the effects of medications.<sup>6</sup>

When administered orally, levodopa is absorbed mainly in the duodenum and the proximal small bowel. Peak serum levels are reached at 30–60 min and the half-life of levodopa is approximately 90 min.<sup>3</sup> Fluctuating levels of levodopa are further aggravated by factors such as slowed rates of gastric emptying, erratic jejunal absorption, gut microbiota, competition with dietary amino acids at absorption sites as well as across the blood-brain barrier.<sup>3 6</sup> Generally, when motor complications develop, clinicians add in an additional drug to maintain QoL and delay the introduction of advanced therapies. To date, there is no clear consensus in Australia, or elsewhere, at which dose of levodopa should add-on therapies be considered.<sup>1 7</sup> Potential add-on therapies available in Australia include dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors and catechol-O-methyltransferase inhibitors (COMT) inhibitors, anticholinergic drugs and amantadine.<sup>8</sup>

The purpose of this study was to examine the treatment patterns of patients with PD in Australia, with a particular focus on levodopa doses at the time of first add-on therapy.

## METHODS

This was a retrospective, observational, non-interventional study of patients with PD within the Australian Department of Human Services Pharmaceutical Benefits Scheme (PBS) 10% sample. The PBS subsidises medicines in Australia, at a cost of approximately \$A42.50 per prescription for general patients and \$A6.80 per prescription for concessional patients. All existing PD treatments are included on the PBS schedule unless they fall below the patient contribution threshold. The dataset is made available to researchers and data custodians to answer specific research questions.<sup>9</sup> The PBS 10% sample is a de-identified systematic random sample of medication dispensed under the PBS for a subset of 10% of the



**Figure 1** Levodopa dose at add-on. (A) Overall; (B) by age; (C) by sex; (D) by prescriber. Percentage of patients per levodopa add-on dose range overall (A), and by age (B), gender (C) and prescriber (D). Prior to first add-on, approximately 40% of patients were prescribed levodopa doses of 600 mg/day or more (A). GP, general practitioner.

Australian population. The PBS provides reimbursed access to medications in Australia.

### Participants

Patients who were dispensed at least three PBS reimbursed prescriptions for levodopa in a 12-month period during 1 January 2007 until 31 December 2021 are included (see online supplemental file 1 for a list of PBS item codes included). Patients were excluded if they had been prescribed levodopa for a period of <12 months.

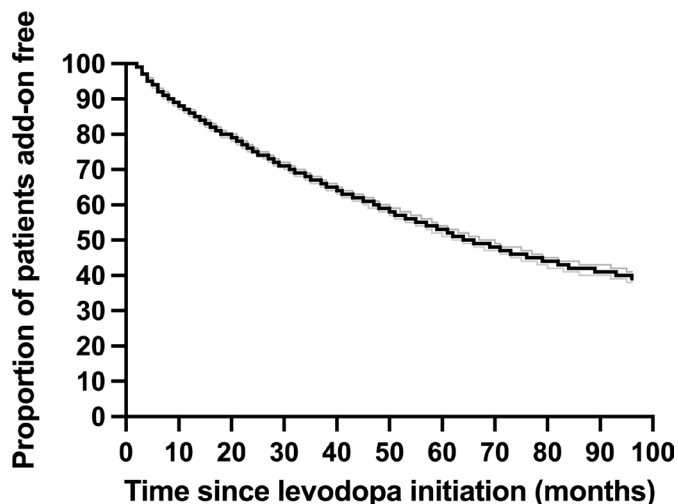
### Data

Data on all reimbursed prescriptions (both general and concession), prescriber type and item code were extracted. Prescribed drug names, quantity dispensed and class (dopamine agonists, MAO-Bs, anticholinergic drugs, amantadine, COMT entacapone or device-assisted therapies) were extracted. Doses of prescribed drugs were calculated as the average dose of a prescribed drug over a 12-month period, calculated as the number of doses dispensed

multiplied by the strength of each dose and divided by 365, and reported in days. For the purposes of this analysis, levodopa administered with benserazide or carbidopa is considered ‘monotherapy’. Two cohorts were defined: all patients commencing levodopa who met the inclusion and none of the exclusion criteria (‘total cohort’) and the subset that commenced add-on therapy (‘add-on cohort’).

### Statistical methods

No formal sample size calculation was conducted with respect to this study. All available data from the 10% PBS sample were included. Data are summarised descriptively. The managing prescriber is defined as the specialist prescriber type for each patient. This is the prescriber who has written the most levodopa scripts for that patient over the period. Where a patient has never seen a specialist, their managing prescriber is considered the general practitioner. The time to add-on therapy was defined as the time, in consecutive days, from the date of the first prescription of



**Figure 2** Time to add-on therapy. Percentage of patients per number of months between levodopa initiation therapy and levodopa add-on therapy. Median time to add-on therapy was 64 months (95% CI 49 months to 52 months).

levodopa monotherapy, to the date of the first add-on therapy. The time to add-on therapy was estimated using Kaplan-Meier methods. Patients were censored if they ceased therapy or the follow-up period ended. All analyses were conducted using Tableau (Tableau Software, Seattle, Washington, USA).

#### DATA SHARING

The data that support the findings of this study are available from Services Australia. Restrictions apply to the availability of these data, which were used under license for this study. Data are available at <https://www.service-australia.gov.au/organisations/about-us/reports-and-statistics/statistical-information-and-data#request> with the permission of Services Australia's External Request Evaluation Committee.

#### RESULTS

Data from 154850 unique patients who were prescribed levodopa were extracted from the 10% PBS sample. Demographics of included patients are reported in [table 1](#). The majority of patients were being managed by a neurologist, with much smaller numbers managed by a general practitioner, general medicine specialist or geriatrician. At treatment initiation (ie, naïve initiations across the period 2007–2021), the majority of patients prescribed levodopa were initiated on levodopa monotherapy (112 520/154 850 initiations, 73%). In the first-line setting, patients were commonly prescribed levodopa by the general practitioner (51%) or neurologist (39%). Prescriptions from general medicine specialists or geriatricians were less common (4% and 6%, respectively).

#### Levodopa doses at first add-on therapy

In the 12 months prior to adding-on to levodopa, doses of levodopa ranged from 100 mg/day to 1000 mg/day.

The median dose of levodopa in the 12 months prior to add-on was 438 mg/day. Approximately 40% of patients were prescribed levodopa doses of 600 mg/day or more prior to first add-on ([figure 1A](#)). There was a tendency to add-on additional therapies for PD at lower levodopa doses in younger patients, and in women ([figure 1B,C](#)).

#### Time to add-on therapy

Add-on therapy was initiated within 12 months in 14% of patients, within 24 months in 25%, within 36 months in 33%, within 48 months in 41%, within 60 months in 47%, within 72 months in 53%, within 84 months in 58% and within 96 months in 61%. The median time to add-on therapy was 64 months (95% CI 49 months to 52 months; [figure 2](#)).

#### Type of add-on therapy

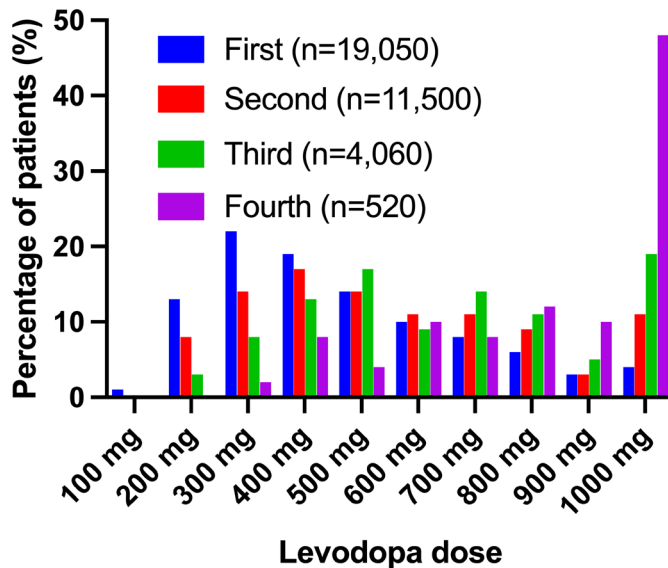
Add-on therapy included dopamine agonists (17%), MAO-B (7%), COMT (4%) and device-assisted therapies (<0.1%). The remainder did not receive add-on therapy (73%). Of the patients who received add-on therapy, dopamine agonists were added on more frequently at lower levodopa doses, while COMT inhibitors were added in at a similar rate across all levodopa doses. MAO-B inhibitors were prescribed more frequently as the levodopa dose increased ([figure 3](#)).

#### Levodopa doses at subsequent add-ons

Patients received second and third add-on therapies at higher levodopa doses ([figure 4](#)).

#### DISCUSSION

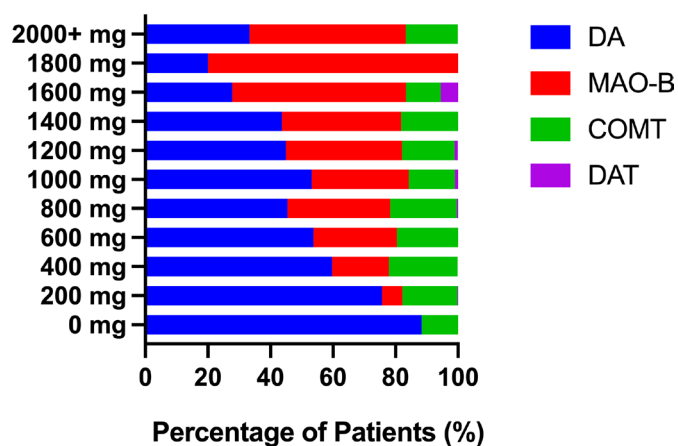
In our analysis of levodopa use in the Australian setting, first add-on therapy is frequently prescribed when levodopa doses are >600 mg/day. Add-on therapy is indicated for treatment of motor response complications such as wearing-off. A combination of disease progression (loss of nigrostriatal dopamine terminals) and fluctuating levodopa levels (due to both central and peripheral mechanisms) likely give rise to the motor complications of PD. In the first years of dopaminergic therapy, there is usually a perception of excellent response to treatment. Patients often do not notice any fluctuation in response to individual doses of levodopa, and if they miss or are late taking a dose, they may not report any issues. In clinical practice, patients rarely spontaneously report wearing-off. However, questionnaire-based evaluations of wearing-off have consistently demonstrated that the phenomenon is under-recognised by treating clinicians in up to 25% of patients. For instance, in a cross-sectional cohort, nearly two-thirds of patients with <5 years disease duration had wearing-off when a systematic questionnaire was applied.<sup>10</sup> Moreover, routine clinical assessment identified only a half of those patients found to have wearing-off on a wearing-off questionnaire. Another large study found that wearing-off is particularly under-recognised in early disease.<sup>11</sup> It is proposed that this under-recognition of



**Figure 4** Dose of levodopa at first and subsequent add-on therapy. Proportion of patients per levodopa dose for each first, second, third and fourth add-on therapies.

wearing-off may be impacted by factors such as time that a clinician allows for the consultation, communication problems, the magnitude of the change in Parkinson's signs from OFF to ON and clinician's experience.

Identification of wearing-off is important. Patients identified as having wearing-off symptoms experience worse QoL compared with patients without wearing-off.<sup>12</sup> Not surprisingly, treating wearing-off improves QoL. An open-label, 6-week study, evaluated the effects of entacapone add-on therapy to conventional levodopa formulations in patients with PD on either three or four intakes of levodopa per day and had at least one symptom of wearing-off, identified on the 9-item Wearing-off Questionnaire (WOQ-9).<sup>13</sup> Study recruitment was particularly fast and improvements were found in all primary and secondary efficacy parameters. The authors suggested that



**Figure 3** Type of add-on therapy by dose. COMT, catechol-O-methyltransferase inhibitors; DA, dopamine agonists; DAT, device-assisted therapies; MAO-B, monoamine oxidase type B inhibitors. Percentage of patients per levodopa add-on dose by type of add-on therapy.

early management of wearing-off might benefit patients who could otherwise be considered to be 'doing fine' and may be unaware of wearing-off. In another study using objective measures of wearing-off, 200 patients with PD not thought to have wearing-off clinically were studied for evidence of wearing-off using a continuously worn wearable system.<sup>14</sup> Eighty-five patients (43%) were found to have wearing-off and treatment was changed to mitigate the effects of wearing-off. QoL significantly improved in patients with PD when wearing-off was treated.

In our study, neurologists were found to provide a disproportionate percentage of prescriptions for add-on therapy (67%), compared with the total percentage of patients for whom they wrote levodopa prescriptions (39%). When wearing-off effects signal the onset of symptomatic motor fluctuations, one proposed strategy is to reduce the levodopa dosing interval thereby increasing the number of doses and resulting in an increase in total levodopa intake. This tactic may be effective for a while but on the basis of these data, it is a strategy less commonly adopted by neurologists (figure 1D). This suggests that neurologists are more prone to the earlier recognition of wearing-off and may be more comfortable prescribing add-on therapies. It has previously been found in an incident PD cohort, that early neurologist involvement in care was associated with a lower morbidity (eg, risk of hip fracture or nursing home care) and lower adjusted mortality rates.<sup>15</sup> Moreover, it has been suggested that consistent neurologist care for PD may lead to reduced risk of hospitalisation for conditions specifically to PD-related complications.<sup>16</sup> It has been proposed that this may also be due to neurologists being more successful in the early recognition and management of common PD-associated comorbidities such as anxiety, depression, psychosis and dysautonomia.

In relation to timing of add-on therapy to levodopa, the data suggest that patients will undergo treatment with levodopa for approximately 5 years before add-on therapy is prescribed, and the choice of first add-on therapy varies with the dose of levodopa. It seems, from the data, that at lower doses of levodopa, dopamine agonists may be prescribed in an effort to increase dopaminergic stimulation, whereas at higher doses of levodopa, there is a smaller tendency to add-on dopamine agonists. There could be a number of reasons for this including that the addition of further dopaminergic stimulation may be too much once the dose of levodopa is already high and comes with the enhanced risk of dyskinesias.<sup>6</sup> Also, there is potential for higher doses of levodopa to augment the risk of dopamine agonist-induced compulsive behaviours.<sup>17</sup>

As in clinical practice, the dose of levodopa increased with each additional add-on therapy, suggesting that control of wearing-off symptoms becomes increasingly difficult with higher daily doses of levodopa. In registrational studies of rasagiline, pramipexole, safinamide and entacapone all were prescribed as add-on therapy to levodopa, thus supporting their indications in this setting.<sup>18</sup> The median doses of levodopa at add-on were

>700 mg/day in PRESTO (rasagiline) and LARGO (rasagiline and entacapone)<sup>18 19</sup>; approximately 650 mg/day in the European multicentre study and >800 mg/day in the pramipexole registration study; and between 570 mg/day and 622 mg/day in study 018 (safinamide).<sup>19</sup> In contrast, a recent Japanese registrational study of safinamide reported mean doses of <450 mg where the addition of safinamide improved mean daily on-time without troublesome dyskinesias, thus demonstrating that safinamide can be efficacious when added on to lower daily doses of levodopa.<sup>20</sup> Studies where there has been open-label extended evaluation effects of add-on therapies such as safinamide typically demonstrate prolonged periods of sustained improvements in ON time.<sup>21 22</sup>

In general, it has been reported that lower daily doses of levodopa in the initial treatment of PD may delay the emergence of motor fluctuations. The STRIDE-PD (Stalevo Reduction in Dyskinesia Evaluation) study,<sup>23</sup> compared the combination of levodopa, carbidopa and entacapone with a conventional levodopa/carbidopa formulation in treatment of patients with drug-naïve PD. The authors found that the emergence of wearing-off was strongly predicted by a higher daily levodopa dose at baseline. Further evidence for this effect was provided in the Earlier versus Later Levodopa (ELLDOPA) study, where patients with untreated PD were randomised to fixed levodopa doses, and there were statistical subanalyses suggesting that higher levodopa doses increased the risk of developing wearing 'off' independently of the UPDRS (Unified Parkinson's Disease Rating Scale) motor score and disease severity (especially the 600 mg/day group).<sup>24</sup>

While highly speculative, some concerns have also been raised that the disabling phenomenon of freezing of gait (FOG) may be exacerbated by 'levodopa-induced maladaptive mechanisms'.<sup>25</sup> FOG is associated with increased disease severity and with prolonged levodopa treatment (although the latter could also be explained by greater disease severity). FOG is generally partially responsive to dopaminergic medication, and episodes are therefore more frequent and of longer duration when dopaminergic medication has worn off. Paradoxically, it has been found that higher daily doses of levodopa at baseline in a cohort study has been shown to predict worse FOG over time.<sup>26</sup>

Our study has several limitations. First, our initial identification of patients who were prescribed levodopa as being the 'pool' of patients with PD may have excluded those who were prescribed an adjunctive PD drug first. Of note, between 2007 and 2021, 106 120 patients were prescribed a dopamine agonist as their first-line therapy. There were only a relatively small number of patients aged 55 years or younger who received add-on therapies for their PD, therefore comparisons with this cohort should be interpreted with caution. No information on the patient's weight is available in the 10% PBS sample, which is a significant limitation given weight and gender are significant predictors for dyskinesias. A small percentage of

included patients might have had a diagnosis other than PD (eg, restless legs syndrome (RLS) (although not a recommended medication for RLS, levodopa is sometimes given for it nonetheless) or an atypical parkinsonian disorder), but the number of such patients is likely to have been negligible and not to have affected the results. It may be, for example, that patients with atypical parkinsonian disorders might not have had adjunctive therapy added to levodopa for the reason that such adjunctive therapies have no defined place in the treatment of those disorders. Also, the lack of clinical context to prescribing patterns leads to difficulties in interpretation of the findings. Other limitations include our definition of regular levodopa use being three prescriptions over a 12-month period, and our exclusion of people with <12 months of levodopa therapy. We did not include modified release formulations of levodopa/carbidopa which are available on the PBS only as a restricted benefit, and limited to those with fluctuations in motor function that are not adequately controlled by frequent dosing. Finally, prescribing could not be split between general neurologists and movement disorder specialists, who may differ in their prescribing practice.

## CONCLUSION

Our analysis of the PBS sample of patients prescribed add-on therapy to levodopa for the management of fluctuating PD suggests that a large proportion of patients in Australia are managed with levodopa monotherapy doses at high doses for a sufficient duration that they would likely be experiencing disability due to motor fluctuations and that these patients could potentially benefit from the earlier addition of add-on therapy to their medication regimen. Add-on therapy could potentially reduce the need to use even higher doses of levodopa to 'treat' wearing off symptoms and avoid the associated risks of high daily doses of levodopa monotherapy (including levodopa-induced maladaptive phenomena such as dyskinesia or impulsive compulsive behaviours). Thereby, earlier use of add-on therapies may leverage different mechanisms to benefit QoL of patients with PD.

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**Contributors** AE and BJW designed the study. BJW performed the analysis. Both the authors were involved in writing and editing the manuscript, and approved the final version of the manuscript that was submitted. AE accepts responsibility for the overall content.

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**Competing interests** AE reports honoraria for presentations from Merck, Allergan, Ipsen, Teva, UCB, Abbott, AbbVie, STADA. Participation in scientific advisory board meetings with Allergan, AbbVie, Ipsen and STADA. He holds shares in GKC and CSL. BJW from Model Solutions reports providing consulting services to a wide range of pharmaceutical and health technology companies, including Seqirus in the preceding 12 months.

**Patient consent for publication** Not applicable.

**Ethics approval** This study and the publication of results was approved by the Services Australia's External Request Evaluation Committee (approval number RMS2470). The authors confirm that patient consent was not required for this work, as the study involved anonymised structured data, which according to applicable legal requirements does not contain data subject to privacy laws. 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.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data may be obtained from a third party and are not publicly available. The data that support the findings of this study are available from Services Australia. Restrictions apply to the availability of these data, which were used under license for this study. Data are available at <https://www.servicesaustralia.gov.au/organisations/about-us/reports-and-statistics/statistical-information-and-data#request> with the permission of Services Australia's External Request Evaluation Committee.

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