Optimized clinical management of Parkinson's disease with opicapone. Recommendations from Spanish experts

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Summary. Motor fluctuations are frequently seen in Parkinson disease patients on chronic treatment with levodopa. Management of motor fluctuation includes the addition of catechol-O-methyl transferase (COMT) inhibitors. Opicapone is a recent and selective third-generation COMT inhibitor which achieves marked increase in the bioavailability of levodopa. We present a consensus of a group of Spanish neurologists with extensive experience in the clinical management of motor fluctuations. The clinical experience of this group of experts is in line with clinical trials and confirms that opicapone is an effective drug in the control of motor fluctuations, regardless of the daily levodopa dose, or the use of other antiparkinsonian drugs. However, in the opinion of these experts, the ideal patient with Parkinson's disease to initiate treatment with opicapone is the one with mild motor fluctuations, since the ratio between clinical efficacy and adverse effects is more favorable. In general, it is an easy-to-use drug both in those first treated with a COMT inhibitor or those already on entacapone. In any case, the secondary side effects are easily managed.

Key words. Catechol-O-methyl transferase inhibitors (COMT). Dyskinesias. Motor fluctuation. Opicapone. Parkinson's disease.

Introduction

Levodopa is a standard symptomatic treatment of Parkinson's disease [1]. However, long-term use of levodopa has limitations associated with the occurrence of motor complications, including motor fluctuations (initially the end-of-dose deterioration or 'wearing-off'), freezing of gait and dyskinesias [2]. After two years of levodopa therapy, up to 50% of patients with Parkinson's disease may experience motor fluctuations [3], being their occurrence associated with a significant impact on the patient's quality of life [4,5]. Control of motor fluctuations is an important clinical need in terms of prevention, early detection and management [2,5].

As regards detection, these motor fluctuations are under-diagnosed during routine neurological assessment [4]. Therefore, the use of scales or questionnaires in clinical practice and the incorporation of some simple questions during the history-taking could facilitate the identification of this important complication:

- Do you have tremor, foot stiffness or a feeling of clumsiness when you wake up in the morning?
- Do you feel better in the morning or in the afternoon?
- Do you feel the same way throughout the whole day?
- Do the symptoms get better after taking the medication?

There are several therapeutic options for managing fluctuations, including levodopa dosage optimisation, adjuvant dopamine agonist therapy, the use of monoamine oxidase type B (MAO-B) inhibitors and the use of catechol-O-methyltransferase (COMT) inhibitors [6].

Levodopa dosage optimisation (dosage/frequency increase) is a simple strategy, nevertheless the results are often variable or transient [7].

The addition of COMT inhibitors prevents the conversion of levodopa to 3-O-methyldopa and increases the bioavailability of levodopa [8]. In addition, because 3-O-methyldopa accumulates over time and can compete with levodopa in its passage across the blood-brain barrier, the inhibition of its formation also contributes to the increased bioavailability of levodopa [8].

During the nineties two COMT inhibitors were developed, entacapone and tolcapone, with which there is extensive clinical experience [8]. Both COMT inhibitors proved to be effective in the treatment of motor fluctuations in combination with levodopa [8,9], although with important differences in their clinical use. Entacapone acts peripherally and has a short half-life (approximately 1.3 hours) so it requires frequent administration. Tolcapone, on the other hand, acts on the peripheral and central nervous system and has a short half-life (4 hours) and greater bioavailability. Although no direct comparisons have been performed, several studies indicate

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Funding:
Laboratorios Bial S.A.

Conflict of interests:
G.L.C. is CEO of VIVEbiotech S.L.; he has been paid fees for being a member of advisory committees, giving lectures, participating in courses and seminars, and conducting research projects and clinical trials by Novartis, UCB, Lundbeck, Bial, →

Abbvie, Asta, Teva, Krka, Medtronic, Eisai, Cortexyme, Boehringer, Schering, Pharmacia, Lilly, Dupont, Italfármaco, Allergan, Ipsen, Merz, Zambón, Biogen, Roche, Genentech and Oryzon. L.J.L.V. has been paid consultancy fees by Bial, Zambón and Abbvie. P.G.R.R. has received research grants from Allergan and UCB; fees for consultancy or for being a member of the advisory committee from Italfarmaco, Britannia, Bial and Zambón, and has been paid fees for conference papers by Italfármaco, UCB, Zambón, Allergan and Abbvie. L.L.M. has been paid fees for advisory services, consultancy, research grants and for conference papers by Abbvie, Acorda, Bial, Intec Pharma, Italfármaco, Orion Pharma, Roche, Teva, UCB and Zambón. M.R.L.P. has been paid fees for presenting conference papers by Bial, Zambón, Teva, Lundbeck and Abbvie; research grants from the European Commission and the Instituto de Salud Carlos III; consultancy fees from Bial, Zambón and Teva, and travelling expenses by Bial, Zambón, Teva and Abbvie. J.C.M.C. is a member of the advisory committees of Allergan, Abbvie, Bial, Zambón and Orion Pharma; he has been paid fees for presenting conference papers by Allergan, Abbvie, Bial, Zambón, Teva, Italfármaco and Ipsen; received research grants from Allergan, Abbvie, Bial and Zambón, and travelling expenses by Allergan, Abbvie, Bial, Zambón, Teva and Italfármaco. P.M. has been paid fees for consultancy or conference papers by Bial, Zambón, UCB, Allergan, Abbvie and Merz. J.P.M. has been paid fees for consultancy or conference papers by Bial, Zambón, UCB, Allergan and Abbvie.

Note:
All the authors have made a similar contribution to the preparation of this manuscript. G.L.C. and L.J.L.V. were the coordinators of this work.

Accepted:
25.03.20.

How to cite this paper:
Linazasoro-Cristóbal G, López del Val LJ, García Ruiz-Espiga P, López-Manzanares L, Luquin-Piudo MR, Martínez-Castrillo JC, et al. Optimized clinical management of Parkinson's disease with opicapone. Recommendations from Spanish experts. Rev Neurol 2020; 70 (Supl 1): S1-11. doi: 10.33588/rn.70S01.2019340.

Versión española disponible en www.neurologia.com

that tolcapone is more effective than entacapone [10]. Tolcapone, however, is associated with sometimes very severe liver toxicity and requires frequent liver monitoring and, as a result, the guidelines do not consider it a drug of first choice [6]. Recently, a third generation COMT inhibitor has been developed, opicapone (authorised in Europe in June 2016 and marketed in Spain since May 2017), which is indicated as adjuvant therapy to levodopa with dopadescarboxylase inhibitors (levodopa/DDCI) in adult patients with Parkinson's disease and end-of-dose motor fluctuations that cannot be stabilised with these combinations [11].

Opicapone has a high selectivity and affinity, long duration of action *in vivo* and a long dissociation constant of the COMT-opicapone complex [12]; this allows for a single administration, once a day, despite having a short half-life [13]. Adjuvant opicapone administration increases the bioavailability of levodopa by 65% with respect to levodopa/carbidopa or levodopa/benserazide alone [14], and by 45% in comparison to levodopa/carbidopa + entacapone [15]. Opicapone 50 mg/day reduces fluctuations in peak-to-trough concentrations and achieves higher levodopa trough concentrations [16].

Two controlled clinical trials (BIPARK-I and BIPARK-II) on advanced Parkinson's disease with end-of-dose motor fluctuations showed that adjuvant treatment with opicapone 50 mg reduces the off time by nearly two hours overall and approximately one hour compared to the addition of placebo [17,18]. The percentage of patients who responded (i.e. those who reduced the off time > 1 h) was 66-70% [17,18]. One of the trials included entacapone as an active control and demonstrated that opicapone was not inferior to entacapone [17]. The results of the extension phases of these trials showed that the effect of opicapone is maintained for at least one year, with a reduction in off time and an increase in on time without any increment in the frequency of problematic or disabling dyskinesias [19]. The safety analysis of these trials suggests that opicapone is safe and well-tolerated, with no relevant alterations in the clinical signs, laboratory tests or electrocardiogram, and no serious adverse effects indicative of liver toxicity [20]. The results of a recent observational study [21] confirm the findings of the pivotal clinical trials.

The results of the randomised clinical trials allow the health authorities to establish the overall risk-benefit ratio and the recommendations for the use of drugs, which are noted in the Summary of Product Characteristics. However, when choosing the adjuvant treatment to levodopa in Parkinson's disease with motor fluctuations it is necessary to take into account each patient's circumstances (clinical signs and symptoms, comorbidities and risk from polypharmacy), lifestyle, preferences, needs and goals [1]. This implies a knowledge of the management of the drug that is derived from both research evidence and clinical experience.

This paper presents the consensus of a group of experts in Parkinson's disease with experience in the use of opicapone regarding key aspects of motor fluctuations (especially end-of-dose fluctuations). To this end, the two consensus coordinators drew up a list of points concerning opicapone management that might be of interest to neurologists involved in the treatment of Parkinson's disease. This list was distributed among those participating in the consensus for completion. The different responses were gathered in a single working document. In a face-to-face meeting with all the authors, and based on the content of that working paper, the wording of the recommendation that best suited the majority opinion of the group was discussed and agreed on. Furthermore, an agreement was also reached on the content that should appear in the manuscript and that would support the recommendation.

Ideal patient profile for introducing opicapone in the treatment

1. What is the ideal clinical profile of a patient who is eligible to start treatment with opicapone?

The ideal profile will be any patient who presents end-of-dose motor fluctuations, without any serious dyskinesias or hallucinations or severe neuropsychiatric disorders. The ideal patient is likely to be one who has mild motor fluctuations because this shows a better relationship between clinical efficacy and adverse effects.

The patient profile included in the pivotal studies BIPARK-I and BIPARK-II consisted of patients between 30 and 83 years old, with a disease history of at least three years, in stage 1-3 of the Hoehn and Yahr classification, who had been receiving 3-8 doses of levodopa for at least one year and who experienced end-of-dose motor deterioration. Patients with severe or completely disabling dyskinesias and psychiatric diseases were excluded [17,18]. These studies evidenced a significant improvement in the motor fluctuations. In the extension phase of BIPARK-I, a change of –3.8 points (95% confidence interval, 95% CI = –7.5 to –0.2) [22] was observed on the non-motor symptom assessment scale.

Some data suggest that opicapone 50 mg may be especially useful in patients with early fluctuations (motor fluctuations coursing for less than two years). An analysis performed in BIPARK-1 showed that the improvement in quality of life assessed by the Parkinson's Disease Questionnaire-39 was greater in patients with early fluctuations (–3.8 points) than in the overall study population (–2.8 points) [23]. In a retrospective observational study conducted in our setting, administration of opicapone to patients with early fluctuations appeared to be more favourable than in patients with advanced Parkinson's disease, and the frequency of hallucinations and disabling dyskinesias was lower in patients with early fluctuations [24]. A *post hoc* analysis of the double-blind phase of the BIPARK-I trial in the subpopulation with early fluctuations showed a –3.9 point change (95% CI = –7.7 to –0.11) on the assessment scale for non-motor symptoms with opicapone [25].

2. From which dose of levodopa is it optimal to add opicapone as an adjuvant treatment in a patient showing motor fluctuations in the clinical practice?

Any patient with Parkinson's disease and end-of-dose motor fluctuations may be treated with opicapone, regardless of the dosage of levodopa and whether they are taking any other dopaminergic drugs. Clinical experience shows that, from 300-400 mg/day upwards, a patient with Parkinson's disease can present motor fluctuations. It is not necessary to wait for a patient to take higher doses before starting treatment with opicapone.

In clinical practice, fluctuations increase over time and with the duration of treatment, although it should be reminded that the Earlier-vs-Later L-Dopa (ELLDOPA) study showed that some patients already had fluctuations 5-6 months after starting treatment with levodopa [26].

The occurrence of motor fluctuations with levodopa is partly related to the short half-life of the drug (and its potential to induce pulsatile stimulation of dopamine receptors) rather than to the specific properties of the molecule [26]. Taking levodopa three times a day is associated with very low trough levels of levodopa, and increasing the frequency of administration to five times a day does not improve those trough levels [26]. If levodopa can be delivered in a more physiological and less pulsatile manner, we avoid low trough levels and provide more consistent dopamine activation. This could enhance long-term symptomatic efficacy and prevent the development of motor complications (including wearing-off and dyskinesias) [27]. Adjuvant administration of COMT inhibitors increases the bioavailability of levodopa, improves its pharmacokinetics, decreases peak-to-trough fluctuations and provides higher levodopa trough concentrations [16]. In addition, opicapone (50 mg) provides persistent inhibition of COMT for at least 24 hours and facilitates the administration of different treatment schedules, dosages and formulations of levodopa/DDCI [15,28].

In a retrospective study conducted in our setting on 32 patients with moderate Parkinson's disease and motor fluctuations treated with levodopa (mean dosage: 395.5 mg/day), the addition of opicapone was associated with an improvement in motor symptoms and was well tolerated [29].

3. What range of dosages of levodopa offer the greatest clinical benefits with opicapone?

There is no defined range of dosages of levodopa to predict greater clinical benefit with the use of opicapone. It is effective in patients taking both high and low doses of levodopa. However, if we define clinical benefit as clinical improvement with minimal adverse effects, in practice it is observed that, if opicapone is added to the patient with dosages of levodopa of 300-600 mg/day, the clinical benefit is better and more predictable than when the patient takes higher doses of levodopa and the treatment is more complex.

The ELLDOPA study, conducted in patients with early Parkinson's disease, showed a motor improvement dependent on the dosage of levodopa (150, 300 and 600 mg/day) associated with a higher frequency of motor complications: wearing-off (16% vs. 18% and 30%, respectively) and dyskinesias (3.3% vs. 2.3% and 16.5%, respectively) [30]. In addition, the STRIDE-PD study noted that the risk of motor complications (wearing-off and dyskinesias) was associated with the dosage of levodopa. These data suggest that, to minimise the risk of developing wearing-off and dyskinesias, levodopa should be administered at the lowest possible dosage with which satisfactory clinical control is obtained [3].

A sub-analysis of the BIPARK-I trial showed that treatment with opicapone 50 mg is associated with dopaminergic adverse effects in 22% of the patients [31], but these levodopa-related adverse effects were mainly observed in patients receiving dosages of levodopa of 700 mg/day or higher [31,32]. Together, these data would support the idea that the best benefit-risk ratio of levodopa and opicapone

treatment would be obtained with dosages of levodopa below 700 mg/day. If the patient is receiving 700 mg/day or more of levodopa, they would benefit from a reduction in levodopa dosage and closer monitoring of treatment with opicapone during the first few weeks [32]. This BIPARK-I analysis also showed that patients receiving high dosages of levodopa who reduced their levodopa dosage during the dosage-adjustment period exhibited no new adverse effects, such as dyskinesias, during maintenance with opicapone 50 mg [32].

4. Is there an upper limit to the dosage of levodopa that could advise against the use of opicapone?

There is no limit to the dosage of levodopa that advises against the use of opicapone, but it is true that the higher the dosage of levodopa is, the greater the risk of developing adverse effects will be, especially if the patient is also taking dopamine agonists or other antiparkinsonian drugs. Nevertheless, opicapone has been found to be useful in patients with continuous intestinal infusion of levodopa-carbidopa (Duodopa ®), with very high dosages of levodopa.

The motor fluctuations and dyskinesias associated with levodopa use are primarily related to longer disease duration and high dosages of levodopa, but not with a longer duration of treatment [33]. This is consistent with the sub-analysis of the BIPARK-I study, which showed that patients with baseline levodopa dosages of 700 mg/day or higher are at increased risk of developing dyskinesias. This same sub-analysis also indicated that concomitant use of dopamine agonists is a risk factor for the development of dyskinesias [32]. In addition, in another observational study conducted on 90 patients in Germany, the authors noted that dyskinesias were more intense if the daily dosage of levodopa was not reduced [34].

However, in a study of 30 patients with advanced Parkinson's disease in which, in addition to levodopa, the patients were receiving dopamine agonists (47%), MAO inhibitors (37%), deep brain stimulation (13%) or continuous levodopa-carbidopa intestinal infusion (17%), opicapone 50 mg was effective in controlling motor fluctuations without significant worsening of the dyskinesias and maintaining the daily levodopa equivalent dosage (1,171 mg versus 1,134 mg before and after opicapone treatment: $p = 0.32$) [35]. In another observational study evaluating the administration of opicapone 50 mg in eight patients with Parkinson's disease treated with continuous intestinal infusion of levodopa-carbidopa, the levodopa dosage was reduced from 1,471 mg to 1,062.5 mg (approximately 28%) with no significant change in bradykinesia or dyskinesias [36].

Although clinical experience with opicapone and other COMT inhibitors suggests that tolerability will be better the lower the levodopa dosage is, opicapone 50 mg can be administered to patients with relatively high levodopa dosages.

5. Are there any differences in the clinical response to opicapone depending on the patient profile?

In our experience, in the profile of the patient with simple motor fluctuations (which is often synonymous with low-dosage levodopa and mild-moderate Parkinson's disease), the clinical response to opicapone is more predictable in terms of efficacy and tolerability. In contrast, in patients with more complex motor complications and have usually been treated with levodopa for more years or who have other complications (e.g. neuropsychiatric disorders), the outcome is more uncertain and there is a greater chance of developing adverse effects.

A *post hoc* analysis of the results of BIPARK-I and BIPARK-II showed that the change from the baseline off time per day when adding 50 mg opicapone did not vary according to the stage of the disease or its duration [37]. Thus, the change in off time with opicapone 50 mg versus placebo was −125 min versus −43 min ($p < 0.0001$) in patients with a Hoehn and Yahr stage < 2.5, and −111 min versus −70 min ($p = 0.0214$) in those with a Hoehn and Yahr stage ≥ 2.5. Similarly, the difference was −117 min versus −54 min ($p = 0.0001$) in patients with a disease duration of less than eight years, and −116 min versus −68 min ($p = 0.0283$) in those with a disease duration of at least eight years [37]. In any case, it is clear that patients with advanced Parkinson's disease are at greater risk of developing complications [38,39].

6. How should the effectiveness of opicapone be evaluated quantitatively or qualitatively?

The results of treatment with opicapone are best evaluated through a detailed case history and confirmed by one or more of the following measures: patient diaries, clinical global impression scale for improvement, improvement of motor symptoms in off and on, dyskinesia scales and evaluation of patient-reported outcomes, including quality of life.

Multiple instruments have been developed for the evaluation of motor symptoms and other symptomatic areas of Parkinson's disease [39]. However,

'no method of evaluation can replace clinical judgement' [39]. In addition, in general neurology services, there is not always time to administer these instruments and so the recommendation is to ask specific direct questions (e.g. Since opicapone was introduced, do you feel better, the same or worse? Do you feel you are blocked for less time? etc.).

Switching from other COMT inhibitors

7. What are the key symptoms for considering the need to switch from entacapone to opicapone?

The need to change from entacapone to opicapone arises in cases of insufficient therapeutic control or when the need for multiple dosages or increased fractioning of entacapone treatment puts therapy adherence at risk. It may also arise when specific adverse effects from entacapone occur (including diarrhoea and colouring of urine).

Switching from entacapone to opicapone can be considered in cases of insufficient therapeutic control and appearance of predictable or unpredictable fluctuations [40]. Opicapone induces a powerful and persistent inhibition of COMT that is greater than that of other COMT inhibitors. The efficacy of switching from entacapone to opicapone has been analysed in the BIPARK-I extension phase; after the double-blind period, all patients, including those in the entacapone group, were changed to opicapone [41]. After 52 weeks of treatment, patients who switched from entacapone to opicapone 50 mg had an additional benefit of a 68-min reduction in off time [41]. In addition, opicapone did not cause diarrhoea or any changes in urine colour [28], which are common adverse effects of entacapone and were one of the most frequent causes of discontinuation of treatment with entacapone in the clinical trials [42]. In these cases, switching to opicapone may also be helpful [40].

8. Based on your clinical practice, how do you recommend switching from entacapone to opicapone?

From one day to the next – suspending the last dose of entacapone one day and immediately starting the first administration of opicapone.

The switch from entacapone to opicapone 50 mg may lead to a further increase in the bioavailability of levodopa, and thus some variation from the BIPARK-I switching scheme is considered advisable. The recommended way to go about it is as follows: on the day before the switch, administer levodopa-carbidopa together with entacapone all day in the usual regimen. On the day of the switch, administer levodopa-carbidopa together with entacapone all day, but eliminate the last dose of entacapone of the day and add opicapone 50 mg at least one hour after the dose of levodopa. On the day after the switch, administer levodopa-carbidopa only (i.e. no entacapone), and opicapone at bedtime (Figure) [43].

When entacapone is given as part of a fixed-dosage levodopa-carbidopa-entacapone combination, a group of experts from the UK suggests replacing the last dose of the combination with opicapone 50 mg and the levodopa-DDCI component with levodopa-carbidopa or levodopa-benserazide on the day of the switch-over [40]. Whether starting with a fixed-dosage combination or with the individual components, these experts note that in the moment of switching it is usually not necessary to adjust the levodopa dosage, and recommend closer monitoring of the patient (e.g. by phone) to assess the occurrence of adverse effects, including levodopa peak effects (such as postural hypotension, dyskinesia, psychosis). If these adverse effects occur, the levodopa-DDCI dosage should be reduced (possibly by first increasing the time interval between doses) [40].

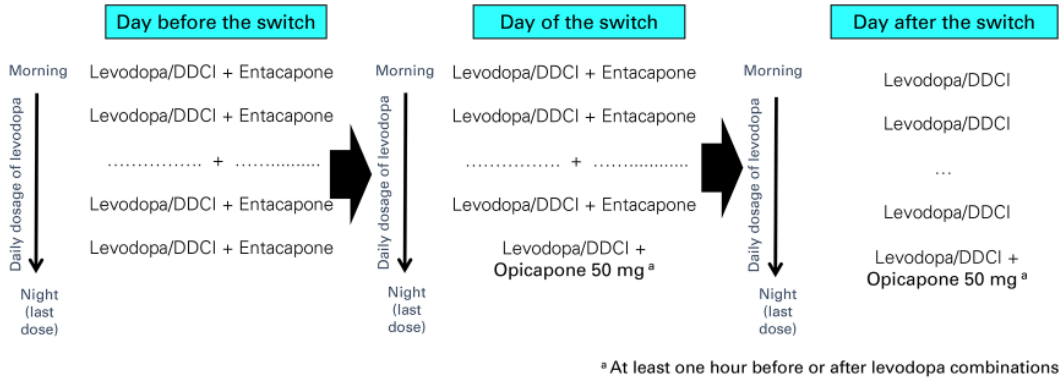
Opicapone and other concomitant drugs: dopamine agonists, MAO inhibitors, antidepressants, etc.

9. Based on your clinical practice, what is your experience with the management of other concomitant drugs with opicapone in terms of their overall efficacy?

Opicapone can be administered in conjunction with any other antiparkinsonian drug. There is usually no need to modify the dosages or change any of the drugs the patient is taking (see also sections 10 and 11 for situations that may require modification of the therapeutic regimen). Closer clinical supervision is advised for patients treated with any drug that may interfere with the capacity of opicapone to inhibit COMT (e.g. apomorphine).

In the BIPARK-I and BIPARK-II studies the administration of antiparkinsonian drugs was allowed, except tolcapone and apomorphine [17,18]. Most patients were already receiving another antiparkinsonian drug (including pramipexole > 30%, ropinirole > 25%, amantadine > 20% and rasagiline > 10%). Several *post hoc* analysis of these studies showed that the efficacy and tolerability of opicapone remained independent of the administration

Figure. Strategy for switching from entacapone to opicapone.



of dopamine agonists or MAO-B inhibitors [44,45] and, more specifically, pramipexole [46] or rasagiline [47].

No studies have been conducted to investigate the interactions of opicapone with safinamide, but results from observational studies suggest a potential therapeutic utility of the combination with good tolerability [48,49].

As noted on its Summary of Product Characteristics, opicapone may interfere with the metabolism of drugs containing a catechol group that are metabolised by COMT (including rimiterol, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine or dopexamine), thereby enhancing the effect of these drugs [28]. They also include apomorphine. Careful supervision of patients being treated with these products is advised when using opicapone [28].

The opicapone Summary of Product Characteristics also states that it is a weak inhibitor of CYP2C8. A study in healthy subjects using a dosage of 25 mg, a less optimal formulation, showed an average 30% increase in the rate of exposure to repaglinide – an oral antidiabetic – when administered in conjunction with opicapone, most likely caused by an inhibition of CYP2C8. According to the opicapone Summary of Product Characteristics, special caution is advised with drugs metabolised by CYP2C8 and co-administration should be avoided. However, the potential interaction of opicapone 50 mg with repaglinide was evaluated in a recent pharmacokinetics study [50]. The results showed that opicapone 50 mg does not affect the pharmacokinetics of repaglinide, and the authors concluded that the administration of opicapone is not expected to affect other drugs using CYP2C8 as a metabolic pathway [50].

10. Based on your clinical practice, what is your experience with managing other concomitant drugs with opicapone in terms of adverse effects?

Increased dopaminergic stimulus entails an increased risk of adverse effects, such as dyskinesias and psychiatric problems. Close clinical supervision and monitoring for hallucinations or impulse control disorders are advised in patients treated with dopamine agonists.

A *post hoc* analysis of the BIPARK-I trial showed that patients treated with dosages of levodopa above 700 mg/day were at increased risk of dyskinesias, especially those treated with dopamine agonists [32]. In these polymedicated patients, closer monitoring is recommended at the start of treatment with opicapone and the levodopa dosage should be reduced if dyskinesias appear [32].

Adverse effects of opicapone

11. What are the most frequent or predictable adverse effects of opicapone?

The most common and predictable adverse effects are those associated with dopamine stimulation, including dyskinesias. They can be controlled by reducing the daily dosage of levodopa. Other effects include nausea, vomiting, dizziness, drowsiness/in-

somnia, orthostatic hypotension, hallucinations and, in some cases, impulse control disorders, especially if the patient is concomitantly being given dopamine agonists.

The most common adverse effects in BIPARK-I and BIPARK-II trials are presented in Table I. Dyskinesias were reported in 20% of patients treated with opicapone versus 6% of those treated with placebo [20]. Other common adverse effects were constipation (6% with opicapone versus 2% with placebo) and increased creatine phosphokinase (5% with opicapone versus 2% with placebo) [20]. Overall, opicapone was well tolerated and safe, with only 9% of patients treated with opicapone 50 mg discontinuing treatment, compared to 7% with placebo, and the frequency of serious adverse effects was similar to that of placebo (5% with opicapone 50 mg versus 4% with placebo) [20].

During the two phase III trials with opicapone there were no serious adverse effects suggestive of hepatotoxicity, and the frequency of gastrointestinal adverse effects, such as nausea or diarrhoea, was low [20]. There were no relevant changes in the lab tests, including liver enzymes, vital signs, neurological assessments or electrocardiogram [20].

With respect to impulse control disorders, an analysis of the double-blind and extension phase of the BIPARK-I and BIPARK-II trials showed that only 14 (1.5%) out of a total of 951 patients analysed presented such disorders and, of these, 11 (79%) were receiving concomitant dopamine agonists [51].

Table I. Tolerability of opicapone 50 mg in the BIPARK-I and BIPARK-II studies (based on [20]).

	Placebo (*n* = 257)	Opicapone 50 mg (*n* = 265)	Placebo-adjusted frequency [a]
All the TEAE	147 (57%)	170 (64%)	7%
Severe TEAE	11 (4%)	13 (5%)	1%
Deaths	1 (0.4%)	0 (0%)	–0.4%
TEAE causing discontinuation of treatment	18 (7%)	23 (9%)	2%
Dyskinesia	16 (6%)	54 (20%)	14%
Constipation	5 (2%)	17 (6%)	4%
Insomnia	4 (2%)	9 (3%)	1%
Dry mouth	3 (1%)	8 (3%)	2%
Increased creatine phosphokinase	5 (2%)	14 (5%)	3%
Dizziness	3 (1%)	9 (3%)	2%
Drowsiness	5 (2%)	5 (2%)	0%
Urinary infection	2 (1%)	10 (4%)	3%
Weight loss	0	10 (4%)	4%
Hallucinations	1 (0.4%)	3 (1%)	1%

Percentages rounded off unless they were < 0.5%. TEAE: treatment emergent adverse event. [a] Frequency with opicapone 50 mg minus frequency with placebo.

12. How do you recommend managing these adverse effects?

If the adverse effects are a result of increasing the dopaminergic stimulus, it may be necessary to reduce the total daily dosage of levodopa, or to reduce or discontinue other dopaminergic drugs. If the side effects are non-specific (for example, nausea or vomiting), but interfere with the patient's daily life, they may require symptomatic treatment (for example, domperidone).

The most common strategy in the management of dyskinesias is to reduce the dosage of levodopa. Two-thirds of patients who developed dyskinesias in BIPARK-1 required a reduction in the dosage of levodopa (25%) [32]. In general, close monitoring of patients at the beginning of treatment with opicapone is recommended to assess the need for dosage adjustment, especially in patients who are receiving high dosages of levodopa (≥ 700 mg/day) [32] or dopamine agonists. Other options include increasing the time interval between doses of levodopa. One of the advantages of opicapone over other COMT inhibitors is that a single daily administration facilitates levodopa dosage management independent of that of opicapone [40].

Hallucinations may be treatment-derived or secondary to a concomitant psychiatric condition. If they are considered secondary to treatment, reduction or even discontinuation of treatment with dopamine agonists may be required.

Impulse control disorder occurs more often in patients who are concomitantly receiving a dopamine agonist. Dosage reduction or withdrawal of the dopamine agonist is usually effective in the management of this adverse effect, but requires adequate patient follow-up and often caregiver involvement [52].

Table II shows an outline of possible strategies in the management of the adverse effects that may arise during treatment with opicapone, according to the authors of these recommendations.

Table II. Possible clinical management of the adverse effects.

Mild or only slightly bothersome dyskinesias	Do not change treatment, after evaluation with the patient
Severe or troublesome dyskinesias	Reduce overall dosage of levodopa or increase time between administrations
Orthostatic hypotension	If the patient is receiving hypotensive drugs, administer them at night
Impulse control disorder	Decrease the dosage of the dopamine agonist or other dopaminergic drugs
Dizziness, nausea or vomiting	Administer domperidone
Insomnia	Consider the possible administration of opicapone in the morning
Hallucinations	Reduce the dosage of the dopamine agonist and, if necessary, withdraw other dopaminergic drugs

13. What follow-up do you recommend to your patients when they start treatment with opicapone?

In general, a follow-up visit is recommended at about three months. It is therefore important to inform the patient of what to expect from the treatment, the clinical effects and the possible side effects.

National [53] and international [1] Parkinson's disease clinical practice guidelines do not include specific recommendations on the frequency of follow-up for these patients. In some recommendations by the Andalusian Movement Disorders Group and the Andalusian Society of Neurology, it is noted that there is no established frequency of the follow-up visits, and that this should be based on the clinical severity [54]. In a very general sense, they recommend that, once treatment has begun, follow-up should be carried out every two or three months, and that in stabilised patients this frequency of visits can be spaced out to a maximum of six months [54].

More complex patients or those requiring a change of therapy may require closer follow-up, especially at the beginning of treatment.

How to use opicapone

14. Based on your clinical practice, how do you recommend administering opicapone with respect to dosages and doses of levodopa?

According to the Summary of Product Characteristics, opicapone should be taken once a day at bedtime, at least one hour before or after levodopa combinations [28].

Pharmacokinetics studies suggest some degree of interaction of opicapone with levodopa absorption, which was minimised with a one-hour interval between opicapone and levodopa administration [55]. This is also the reason for recommending administration at night, as it allows the physician to adjust the levodopa dosage, thus reducing the risk of that potential interaction. Clinical practice guidelines and experts recommend that drug treatment should be tailored to the lifestyle, preferences, needs and goals of each patient [1].

15. Based on your clinical practice, how do you recommend administering opicapone depending on other factors (food intake, etc.)?

There is no evidence that food intake or any other factors significantly modify the absorption/efficacy of opicapone.

Opicapone can be administered concomitantly with a moderate meal without affecting its inhibitory action on COMT [56]. The available data do not show any relevant age-, sex- or race-related effects on the pharmacokinetics or inhibitory activity of opicapone on COMT [56]. The bioavailability of opicapone was significantly higher in patients with moderate chronic liver failure and no safety issues were observed. However, because opicapone should be used as adjunctive therapy to levodopa preparations, dosage adjustments should be considered based on the potential increased dopaminergic response of levodopa and its associated tolerability issues [28]. Since there is no clinical experience in patients with severe liver failure, the use of opicapone is not recommended in these patients [28]. There are no data for patients with severe kidney failure, but it is unlikely that dosage adjustments will be required in these patients, as opicapone is not secreted by the kidneys [56].

Conclusions

In sum, this group of experts consider that:

- The experience with opicapone in clinical practice to date, in line with published clinical trials, confirms that opicapone is an effective drug in controlling end-of-dose motor fluctuations in patients with Parkinson's disease, regardless of the dosage of levodopa they are receiving or the use of other antiparkinsonian drugs.
- The ideal patient to start treatment with opicapone is one with mild motor fluctuations who is receiving doses of 300-600 mg/day of levodopa, because they exhibit a better relationship between clinical efficacy and adverse effects. Nevertheless, in patients with more complex fluctuations, treated with higher dosages of levodopa or other antiparkinsonian drugs, significant clinical improvement can also be achieved, but with an increased risk of developing adverse effects from dopamine hyperstimulation (dyskinesias, hallucinations and impulse control disorder). These patients will require a closer clinical follow-up.
- The appearance of dyskinesias is the main adverse effect of opicapone. This is consistent with its pharmacological profile, but their frequency and impact can be reduced by lowering the daily dosage of levodopa or other antiparkinsonian drugs, and by closer monitoring at the start of treatment, especially in patients who are receiving high dosages of levodopa or dopamine agonists.
- Switching from entacapone to opicapone may be considered in the event of insufficient therapeutic control. Switching may also be considered in the presence of specific adverse effects of entacapone. This benefit is accompanied by a greater ease of use of opicapone, as its prolonged inhibition of COMT allows for daily dosing which, in turn, can improve adherence and simplifies its use with different levodopa dosing schedules.
- The absence of relevant interactions with other antiparkinsonian drugs, with the exception of apomorphine, also contributes to this greater ease of use and, unlike tolcapone, it does not require laboratory monitoring for possible hepatotoxicity.

In conclusion, motor fluctuations (especially end-of-dose fluctuations) are common in patients with Parkinson's disease on sustained levodopa therapy. Opicapone, with its high affinity for COMT, achieves a marked increase in the bioavailability of levodopa and constitutes a new and effective therapeutic option as adjuvant treatment for these patients.

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Optimización del manejo clínico de opicapona en la enfermedad de Parkinson. Recomendaciones de expertos españoles

Resumen. Las fluctuaciones motoras constituyen una importante complicación en los pacientes con enfermedad de Parkinson tratados con levodopa. Entre las opciones terapéuticas para el manejo de las fluctuaciones motoras se cuenta con los inhibidores de la catecol-O-metil-transferasa (COMT), incluyendo la opicapona. La opicapona muestra una elevada afinidad por la COMT y consigue un aumento marcado de la biodisponibilidad de la levodopa. Se presenta el consenso de un grupo de expertos españoles en la enfermedad de Parkinson con experiencia en el tratamiento clínico de fluctuaciones motoras y el empleo de opicapona. La experiencia de este grupo de expertos, en consonancia con los ensayos clínicos, confirma que la opicapona es un fármaco eficaz en el control de las fluctuaciones motoras de la enfermedad de Parkinson, con independencia de la dosis de levodopa recibida o de la utilización de otros fármacos antiparkinsonianos. No obstante, a juicio de estos expertos, el paciente ideal para iniciar el tratamiento con opicapona es el que presenta fluctuaciones motoras leves, ya que muestra una mejor relación entre eficacia clínica y efectos adversos. En general, la opicapona es un fármaco de fácil manejo, tanto en pacientes que requieren opicapona como primer inhibidor de la COMT como en los previamente tratados con entacapona, o en los que están en tratamiento concomitante con otros fármacos antiparkinsonianos. En cualquier caso, los efectos secundarios son fácilmente corregibles.

Palabras clave. Discinesias. Enfermedad de Parkinson. Fluctuaciones motoras. Inhibidores de la catecol-O-metil-transferasa (COMT). Opicapona.