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Is Extended-Release Amantadine Effective at Treating Levodopa-Induced Dyskinesia in Parkinson's Disease Patients?

Maegan M. Mendoza
Philadelphia College of Osteopathic Medicine

Is Extended-Release Amantadine Effective at Treating Levodopa-Induced Dyskinesia in Parkinson's Disease Patients?

Maegan M. Mendoza, PA-S

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ABSTRACT

Objective: "The objective of this selective EBM review is to determine "Is extended-release amantadine efficacious in treating levodopa-induced dyskinesia in Parkinson's disease patients?"

Study Design: A systematic review of three randomized controlled trials (RCT's) that were peer-reviewed and published in English after 2010.

Data Sources: All data sources were discovered in PubMed, NLM Catalog, EMBASE, and CINAHL. All articles were published in English in peer-reviewed journals and selected based on applicability to the clinical question and whether the outcomes were patient-oriented.

Outcome Measured: The primary outcome measure was a change from baseline in the Unified Dyskinesia Rating Scale total scores in Parkinson's disease patients randomized to Amantadine ER or placebo.

Results: All three studies found that Amantadine ER had a significant treatment effect on levodopa-induced dyskinesia in Parkinson's disease patients. (Pahwa et al., 2015) study found an NNT of four with a least-square [LS] mean treatment difference of -11.3, 95% confidence interval -19.1 to -3.5], P =0.005. This represents a 27% reduction in UDysRS from baseline compared to placebo. (Pahwa et al., 2017) found an NNT of three with a least-square [LS] mean treatment difference of -7.9, 95% confidence interval, -12.5 to -3.3; P<.001. The study revealed that 51(81%) patients in the Amantadine ER treated group vs. 21(36.2%) patients in the placebo group were assessed as improved in levodopa-induced dyskinesia. Lastly, Oertel et al. found an NNT of three with a least-squares mean treatment difference of -14.4 [95% CI -20.4 to -8.3], P<.0001. The study revealed that 19(51%) in the Amantadine ER treated group and 4(11%) placebo-treated group was assessed as moderately improved in dyskinesia.

Conclusion: All three studies revealed Amantadine ER as an effective treatment option for levodopa-induced dyskinesia in PD patients. Further studies should explore its long-term efficacy as levodopa, and dopaminergic therapy doses increase to compensate for disease progression.

Keywords: Parkinson's disease, extended-release amantadine, dyskinesia.

INTRODUCTION

Parkinson's disease (PD) is a progressive and irreversible neurodegenerative disease characterized by motor and nonmotor features.[1] These features are due to a loss of dopaminergic neurons in the substantia nigra.[1] This loss is responsible for the four most common cardinal signs of PD; bradykinesia, rigidity, rest tremor, and postural instability.[1] As degeneration continues, dopamine replacement therapy with levodopa becomes necessary to alleviate motor dysfunction. Carbidopa-levodopa (Sinemet) became FDA approved in 1975, and it quickly became the gold standard treatment for motor dysfunction in PD, but its long-term use is associated with dyskinesias.[2] Chronic use of this short-lived agent results in pulsatile stimulation of the neurons in the substantia nigra, which disrupts dopamine homeostasis leading to dyskinesia.[2]

Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease.[3] On average, 40%-60% of PD patients experience dyskinesia after five years of levodopa therapy and 90% after ten years.[4] According to the NCCPA Statistical Profile of Certified Physician Assistants, in 2016, there was approximately 755 Physician Assistant's (PA's) working in neurology, and statistics from 2020 reveal that 1,007 PA's practiced in Neurology.[5] This represents a 33.4% increase in the number of PAs working in Neurology in 2020.[5] Amantadine ER was FDA approved in 2017, and its exact cost is unknown but is estimated to be around $10,000 - $30,000 a year.[6] Comparatively, Amantadine IR has been used off-label for dyskinesia since the 1970s and is about 64 cents per pill.[6] The number of visits each patient attends varies considerably based on dyskinesia severity and treatment response. The most invasive and often the last option to treat dyskinesia is deep brain stimulation (DBS) which costs between $30,000 and $50,000 without insurance.[6]

It is well established that dyskinesia results from long-term levodopa therapy. Peak-dose dyskinesia is the most common form and presents when the patient receives a beneficial response to levodopa.[8] Research has shown that dyskinesia worsens with increased dopaminergic therapy and lessens with reductions in dopaminergic therapy.[8] It is well known that the early introduction of levodopa is associated with an earlier emergence of dyskinesia, especially in younger patients. It is unknown what other risk factors play a role in the development of dyskinesia, as not all patients on levodopa therapy experience peak dose dyskinesia.

Medication adjustments can be made to a patient's drug regimen to help reduce levodopa-induced dyskinesia (LID). Options include increasing the levodopa dosing interval, transitioning to extended-release levodopa, adding a COMT inhibitor such as entacapone, and adding an NMDA antagonist such as Amantadine IR. However, altering levodopa therapy without worsening motor dysfunction is difficult. More invasive options for severe and refractory dyskinesias include enteral levodopa administration (to smooth out the peaks and troughs) and DBS. DBS is the only other approved treatment option for refractory LID; despite its success in treating refractory LID, its cost, rigid qualifications, and time to recovery make DBS an unfeasible option for many patients.

Amantadine IR is an NMDA receptor antagonist initially indicated to treat influenza. However, it received an additional indication for LID in PD patients in 1970.[4] Amantadine IR is typically well-tolerated and is taken three times a day.[4] However, this daily dosage is insufficient at controlling dyskinesia for some patients, and at higher doses, side effects are often experienced. The most common side effects experienced by patients resulting in discontinuation are urinary retention, dry mouth, lower extremity edema, hallucinations, and insomnia.[4] These side effects limit its use, making there a clinical need for another treatment option. Additionally,

Amantadine ER was FDA approved in 2017 and is the first medication approved to treat LID as its primary indication. Compared to the three times a day usual Amantadine IR dosing, Amantadine ER is only dosed once nightly. Amantadine ER provides a higher and steadier peak plasma concentration than Amantadine IR, thus significantly improving motor fluctuations and compliance without the increased side effect potential.[4]

OBJECTIVE

The objective of this selective EBM review is to answer the following clinical question, "Is extended-release amantadine efficacious in treating levodopa-induced dyskinesia in Parkinson's disease patients?"

METHODS

Studies were selected by the author of this paper and were based on their relevance to the clinical question, credibility, and incorporation of patient-oriented outcomes (POEM). It was required that all studies were in the English language, were randomized controlled trials, and were published after 2010 in peer-reviewed journals. Excluded studies were published before 2010, observational studies, and studies on atypical Parkinsonian syndromes. It was required that all studies be directed at PD patients who experience LID, with the intervention being Amantadine ER vs. placebo. The studies pertaining to this review were found on PubMed using keywords "Parkinson's disease," "extended-release amantadine," and "dyskinesia." All three studies were funded and supported by Adamas Pharmaceutics, Inc., and thus have identical inclusion and exclusion criteria and study design. Except for Pahwa et al., 2017, and Oertel et al., which excluded patients who are on medications that have the potential for QT prolongation and torsades de pointes; and Pahwa et al., 2015, whose protocol was amended to expand the LID inclusion criteria time window (Table 1). Pahwa et al., 2017, and Oertel et al., studies are phase 3

randomized, double-blind, placebo-control trials, while Pawha et al., 2015, is a randomized, double-blinded, placebo-controlled trial four-arm parallel-group study. The outcome measured for each study was the change from baseline in LID using the Unified Dyskinesia Rating Scale (UDysRS) in patients randomized to Amantadine ER or placebo. Each study evaluated Amantadine ER vs. placebo at different weeks using different Amantadine ER dosages (Table 1). In this paper, the treatment effect will be noted by the NNT as all three studies provided their data in a dichotomous form.

OUTCOME MEASURED

The primary outcome measured for all three studies was measured using the Unified Dyskinesia Rating Scale (UDysRS) total score. Parts I and II are questionnaires evaluating patients' perceptions of dyskinesia impact during 'ON' time (maximum of 44 points) and severity of 'OFF' time dystonia (maximum of 16 points).[9] Part III evaluates dyskinesia impairment where raters assess the severity of dyskinesia and type (dystonic or choreic) and the anatomical distribution over seven body regions based on four activities observed in clinic or video recorded (maximum of 28 points).[9] In part IV, the rater rates the degree of disability based on the activities in part III (maximum of 16 points).[9] The total score is calculated by totaling the scores from each section.

RESULTS

Pahwa et al., 2015, was a randomized, double-blind, placebo-controlled, four-arm parallel study that was conducted at 31 sites across the US. Eighty-three patients were randomized in a 1:1 ratio to receive amantadine 340 mg ER (n = 21) or placebo (n = 22); which was administered nightly for 8 weeks.[10]

Table 1. Demographics & Characteristics of Included Studies.

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Pahwa[10] (2015)	RCT	43	30-85	• Patients must have a diagnosis of PD • At least a 2 on part IV (functional impact of dyskinesia) on the MDS-UPDRS at screening and at baseline. • Have 2 half-hour periods of ON time with troublesome dyskinesia between 10 am- 4 pm on a PD patient diary on 2 consecutive days just before day 1. • All antiparkinsonian medications must be unchanged for at least 30 days prior to screening and during study participation. • Levodopa must be administrated at least three times daily.	• All dyskinesia that is not peak dose dyskinesia. • Patients that have a neurosurgical intervention related to PD. • Atypical parkinsonism. • Levodopa or dopamine agonist-induced psychosis. • MMSE score less than 24 during screening. • GFR < 50 mL/min. • Amantadine IR use within 30 days before screening, documented inability to tolerate or lack of dyskinesia response to prior amantadine treatment. • Current treatment with apomorphine, or dopamine receptor blocking agents, clinically significant EKG abnormalities, history of hypersensitivity to amantadine, rimantadine, or memantine.	3	340 mg Amantadine ER vs. placebo nightly for 8 weeks.
Pahwa[11] (2017)	RCT	126	30-85	• Patients must have a diagnosis of PD. • Least a 2 on part IV (functional impact of dyskinesia) on the MDS-UPDRS at screening and at baseline. • Have 2 half-hour periods of ON time with troublesome dyskinesia between 9 am- 4 pm on a PD patient diary on 2 consecutive days just before day 1. • All antiparkinsonian medications must be unchanged for at least 30 days prior to screening and during study participation. • Levodopa must be administrated at least three times daily.	• All dyskinesia that is not peak dose dyskinesia. • Patients that have a neurosurgical intervention related to PD • Atypical parkinsonism. • Levodopa or dopamine agonist-induced psychosis. • An MMSE score less than 24 during screening. • A GFR < 50 mL/min, amantadine use within 30 days before screening, documented inability to tolerate or lack of dyskinesia response to prior amantadine treatment. • Current treatment with apomorphine, or dopamine receptor blocking agents, clinically significant EKG abnormalities, current use of medications that have the potential for QT prolongation, a known risk of torsades de pointes, • Use of rimantadine or a history of hypersensitivity to amantadine, rimantadine, or memantine.	13	274 mg Amantadine ER vs. placebo nightly for 12 weeks.
Oertel[12] (2017)	RCT	75	30-85	• Inclusion Criteria is the same as Pahwa et al., 2017.	Exclusion Criteria is the same as Pahwa et al., 2017.	2	274 mg Amantadine ER vs. placebo nightly for 13 weeks.

Patients randomized to receive 340 mg Amantadine ER received one capsule of 260 mg once nightly during week 1 and 340 mg Amantadine ER for 8 weeks.[10] Amongst patients who received 340 mg Amantadine ER, a statistically significant decrease in LID from baseline was observed when compared to placebo (least-square [LS] mean treatment difference = -11.3 [95% CI: -19.1,-3.5], *P*=0.005).[10] This represented a 27% reduction in LID from baseline compared to placebo (43% and 16% reduction for 340 mg Amantadine ER and placebo, respectively).[10] Because the data was given dichotomously in the study, an NNT of 4 was calculated, using the data above, indicating a large treatment effect. Clinically, this means for every 4 patients treated with 340 mg Amantadine ER nightly, one patient will experience a significant reduction in dyskinesia. Adverse events (AEs) were experienced by 82% of placebo patients and 95% of patients in the Amantadine ER-treated group.[10] 3 of the 5 patients in the interventional group discontinued treatment due to visual hallucinations, an AE that was not experienced by those randomized to placebo.[10] The most common AEs experienced by at least >10% or >2 patients in the active arm include dizziness, constipation, hallucinations, dry mouth, and falls (Table 5).[10]

Table 4. Calculations for NNT in Pahwa et al., 2015

Study	CER	EER	RBI	ABI	NNT
Pahwa et al.(2015)	0.16	0.43	1.68	0.27	4

Table 5. Most Common AEs *n* (%) Experienced in Pahwa et al., 2015 Study[10]

Group	Dizziness	Constipation	Hallucinations	Dry Mouth	Fall
340 mg Amantadine ER (*n* = 21)	6 (28.6)	5 (23.8)	5 (23.8)	4 (19.0)	3 (14.3)
Placebo (*n* = 22)	1 (4.5)	2 (9.1)	0	0	3 (13.6)

Pahwa et al., 2017, was a phase 3, randomized, double-blind, placebo-controlled study that was conducted at 44 North American Sites. 126 patients were randomized in a 1:1 ratio to receive either 274 mg Amantadine ER (n = 63) or placebo (60). Patients randomized to the

interventional group received one capsule containing 137 mg Amantadine ER nightly on weeks 1 and 13.[11] On weeks 2 through 12, patients received two capsules containing 137 mg Amantadine ER nightly.[11] Patients randomized to the control group received two placebo capsules nightly for 12 weeks.[11] A significant decrease in LID was observed in patients who received Amantadine ER when compared to placebo (least-square [LS] mean treatment difference = -7.9 [95% CI, -12.5 to -3.3; P<.001).[11] 81% or 51 of 63 patients in the Amantadine ER group and 36.2% or 21 of the 58 patients in the placebo group were assessed as having improvement in LID at week 12.[11] The data was given dichotomously, and the NNT of 3 was calculated using the above data (Table 6). This indicates a significant treatment effect. For every 3 patients treated with 274 mg ER Amantadine nightly, one patient will experience a clinically significant reduction in dyskinesia. In addition, 88.9% or 56 of 63 patients in the Amantadine ER group and 60% or 36 of 60 patients in the placebo group experienced AEs.[11] The most common AEs experienced by ≥5% of patients in the active arm included visual hallucinations, peripheral edema, dizziness, dry mouth, constipation, and falls (Table 7).[11]

Table 6. Calculations for NNT in Pahwa et al., 2017

Study	CER	EER	RBI	ABI	NNT
Pahwa et al., 2017	0.36	0.81	1.24	0.45	3

Table 7. Most Common AEs *n* (%) Experienced in Pahwa et al., 2017 Study[11]

Group	Visual hallucinations	Peripheral edema	Dizziness	Dry mouth	Constipation	Fall
274 Amantadine ER (*n* = 56)	15 (23.8)	15 (23.8)	14 (22.2)	11 (17.5)	10 (15.9)	10 (15.9)
Placebo (*n* = 36)	1 (1.7)	0	0	0	3 (5.0)	5 (8.3)

Oertel et al. study was a randomized, double-blind, placebo-controlled study that was conducted at 39 sites across the US. 77 PD patients were randomized in a 1:1 ratio to receive either 274 mg Amantadine ER (n = 37) or placebo (n = 38) for 13 weeks. For week 1 of dosing,

patients randomized to Amantadine ER received a nightly dose of 137 mg (one capsule contained Amantadine ER, and the other capsule was placebo).[12] For weeks 2 through 12, a total daily dose of 274 mg Amantadine ER, administered as two 137 mg capsules, was given nightly.[12] On week 13, the daily dose was reduced to 1 capsule of 137 mg Amantadine ER.[12] Those randomized to placebo received two placebo capsules nightly for 13 weeks.[12] The study's primary efficacy analysis was completed at week 12. The results demonstrated a significant reduction in UDysRS total score in the interventional group when compared to placebo (least-squares mean treatment difference = -14.4 [95% CI -20.4 to -8.3], P <.0001).[12] The study stated that 51% or 19 of 37 patients in the Amantadine ER group and 11% or 4 of 38 patients in the placebo group were assessed as having a moderately to markedly improvement in dyskinesia at 12 weeks.[12] Since the data in the study was given in a dichotomous form, an NNT of 3 was calculated using the above data (Table 8). Clinically, this means for every 3 patients treated with 274 mg Amantadine ER nightly, one patient will experience a reduction in dyskinesia. Additionally, 84% of patients in the Amantadine ER group and 50% of patients in the placebo group experienced AEs.[12] The most common AEs experienced by $\geq$ 5% of patients in the active arm included dry mouth, nausea, decreased appetite, insomnia, orthostatic hypotension, constipation, falls, and visual hallucinations (Table 9).[12] 7 patients in the Amantadine ER group and 3 patients in the placebo group discontinued treatment.[12] Two patients who were randomized to Amantadine ER reported serious adverse events.[12] One patient experienced suicidal ideation, and another attempted suicide.[12]

Table 8. Calculations for NNT in Oertel et al.

Study	CER	EER	RBI	ABI	NNT
Oertel et al.	0.11	0.51	3.6	0.4	3

Table 9. Most Common AEs *n* (%) Experienced in Oertel et al.[12]

Group	Hallucinations	Dry mouth	Decreased appetite	Orthostatic hypotension	Constipation	Nausea	Fall
274 mg Amantadine ER	3 (8.1)	5 (13.5)	4 (10.8)	4 (10.8)	3 (8.1)	5 (13.5)	3 (8.1)
Placebo	2 (5.3)	1 (2.6)	0	0	0	1 (2.6)	2 (5.3)

DISCUSSION

Amantadine ER is administered once nightly, has a slow rise in concentration with a prolonged T_{max}, and does not exacerbate AEs.[12] It provides a peak concentration in the morning and provides continual coverage for LID throughout the day. This review evaluated the efficacy of Amantadine ER for the treatment of LID in PD patients. All three studies found a statistically significant reduction in the total UDysPD scores after treatment with Amantadine ER, with a substantial change from baseline in the intervention group, statistically significant NNT values, and a large treatment effect. No unblinding was necessary for any of the trials, and an attempt to keep the same UPDyRS rater was made for all subsequent study visits. Blinding was maintained in all three trials. For each study, all patients were accounted for, and losses to follow-up were < 20%. Each study had patients who discontinued the study drug (Table 1); however, each study's mITT population included randomized patients who received treatment and provided 1 or more baseline assessments of the UDysRS. No study completed a “worst-case” analysis. Pahwa et al., 2015, study utilized the Last Observation Carried Forward approach, which can underestimate the study results and provide biased estimates of the treatment effect.

In the Oertel et al. study, the rate of hallucinations in the Amantadine ER-treated group was lower than that reported in the previous phase 3 trial by Pahwa et al., 2017 (24% vs. 8%). It is important to note that patients reported lower mean baseline total daily levodopa doses in the Oertel et al. study compared to the Pahwa et al., 2017 study. This explains the increase in AEs

experienced in the Pahwa et al., 2017 trial. The average total levodopa dose was 671.9 mg and 905.6 mg in the Oertel et al. and Pahwa et al., 2017 studies, respectively. It is also important to note that patients in each study were concomitantly on either a dopamine agonist, an MAO-B inhibitor, a COMT inhibitor, and an anticholinergic medication which increases the potential for hallucinations.

Additionally, in the three studies discussed in this EBM review, Amantadine ER was shown to significantly improve 'OFF' time in PD patients, which led to it receiving a second indication for the treatment of 'OFF'. Additionally, Amantadine IR has been used off-label for restless leg syndrome, traumatic brain injury, fatigue associated with multiple sclerosis, and weight gain associated with antipsychotic use. Current trials reveal that it is probable for Amantadine ER to be used in the future for the indications above. For example, Adamas Pharmaceuticals, Inc., is supporting active phase 3 trial investigating the efficacy of Amantadine ER on walking in multiple sclerosis patients.

The only current contraindication for the use of Amantadine ER is in patients with end-stage renal disease. A lower initial dose is recommended for patients with moderate to severe renal failure, kidney disease stages 3 and 4, respectively. Additionally, live attenuated influenza vaccines are not recommended as Amantadine ER interferes with its efficacy due to its antiviral properties.[12] Furthermore, the prevalence of falls in each study is concerning as PD patients' motor difficulties already pose an increased risk for falls and injury. No study reported any injuries resulting from the falls that occurred during the duration of the studies.

The generalizability limitations of all three studies include a small sample size, excluding patients who did not experience at least two half-hour periods of LID. Limiting the time window

of experienced LID, excluding those on Amantadine IR within the last 30 days. However, these studies and their findings are clinically significant as Amantadine ER is a non-invasive and overall well-tolerated treatment option for LID in PD patients.

CONCLUSION

This systematic review showed that Amantadine ER effectively reduces levodopa-induced dyskinesia in PD patients. Statistical significance and large treatment effects were found in all three studies with small NNT values of 4, 3, and 3 for Pawha et al., 2015; Pawha et al., 2017; and Oertel et al., respectively. To further demonstrate the potential that Amantadine ER has, a head-to-head trial comparing the efficacy of Amantadine ER vs. Amantadine IR should be done. Since there is a lack of treatment options for LID, it would be interesting to see if patients who experienced AEs from Amantadine IR could benefit from Amantadine ER, as patients who did not tolerate Amantadine IR were excluded from all three studies. Additionally, a longitudinal study should be done to evaluate the long-term efficacy of Amantadine ER, as patients' disease severity worsens and with increases in levodopa and dopaminergic therapy. The Hoehn and Yahr scale can measure PD severity in the study, and UDysRS can measure LID improvement over time. It would also be interesting to evaluate its role as a prophylactic treatment for dyskinesia in patients at an increased risk of developing LID in the future, for example, in young-onset PD patients. Lastly, due to the increase in falls in all three the studies, there is an active phase 4 trial investigating the effect of Amantadine ER on gait and balance. Hopefully, future studies will further identify more effective treatments for LID in PD patients to help increase quality of life.

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