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Expert Panel Discussions

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Discussion 1:

The Current State of Management for Early Parkinson's Disease: Where Do We Stand?

Discussion 2:

Exploring the Role of Adjunctive Therapy in the Management of Advanced Parkinson's Disease

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Optimizing the Management of Parkinson's Disease: Considerations for Treating Early Disease and Minimizing Motor Complications in Advanced Disease

Activity Highlights

- Assessment of available and emerging therapies in the early treatment of Parkinson's disease (PD)
- Exploration of the role of levodopa in the early PD setting: Should it be reserved for patients with advanced disease?
- Adjunctive therapy in the management of advanced PD: Where do we stand?
- Additional considerations for the management of advanced PD

For a list of abbreviations and references, click on the right-hand tab.

Dr. Rodriguez:

Hello, this is Dr. Ramon Rodriguez from the University of Florida Center for Movement Disorders & Neurorestoration. Welcome to this activity. Joining me in a discussion on optimizing the management of Parkinson's disease are Dr. Hubert Fernandez from the Cleveland Clinic Center for Neurological Restoration and Dr. Michael Okun from the University of Florida Center for Movement Disorders & Neurorestoration.

This activity comprises two separate presentations. Once a presentation has completed, the next will begin automatically after a few seconds.

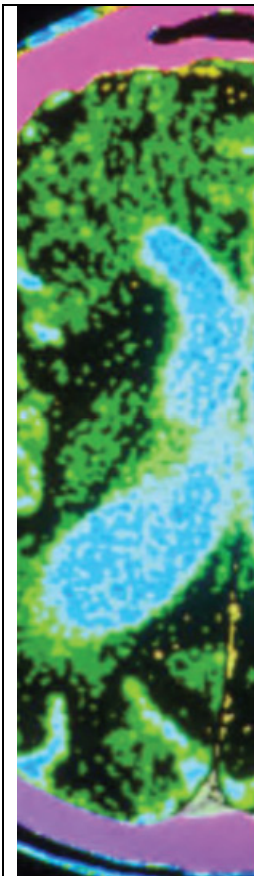
Throughout the activity, you will be asked to respond to several PeerView Challenge Questions. The answers to these questions can be found in the subsequent slides and narrative.



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Dr. Rodriguez:

The slides, transcript, audio, Practice Aids, and other activity features are available for download for easy access anytime, anywhere.



The Current State of Management for Early Parkinson's Disease: Where Do We Stand?

Discussion Highlights

- Overview of symptomatic therapies for the management of Parkinson's disease (PD)
- Analysis of key data sets on available therapies for the management of early PD
- Emerging therapies for the management of early PD
- Levodopa: Should it be reserved for patients with advanced disease or used in early PD?

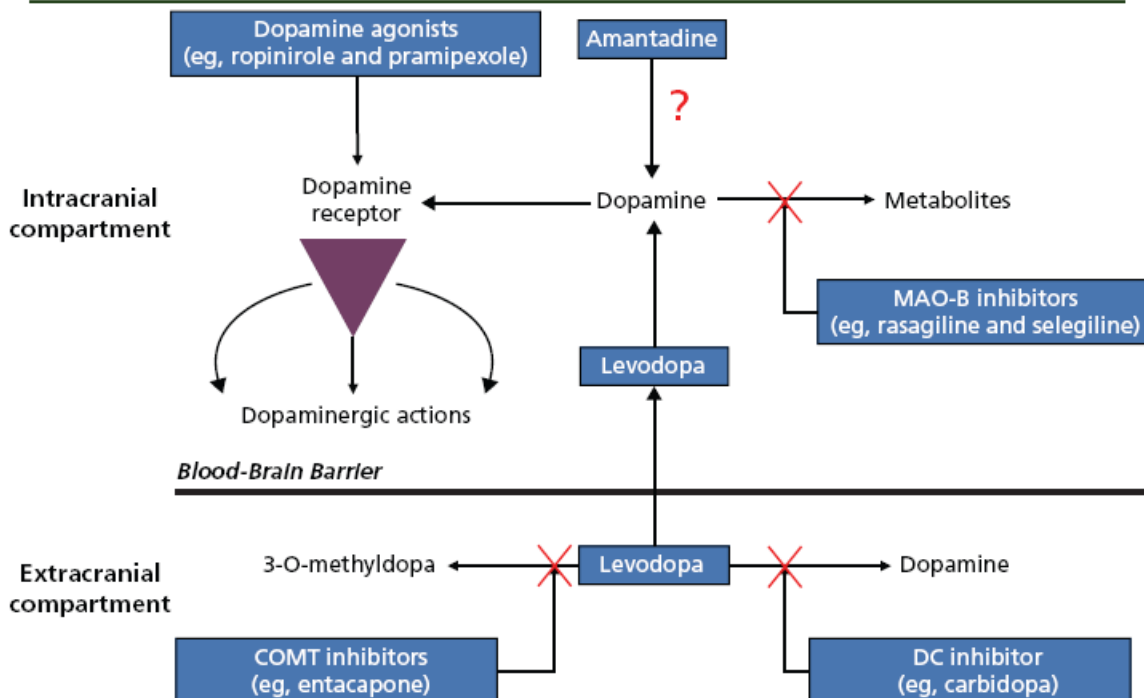
Narrator:

In general, the treatment of Parkinson's disease focuses on the replacement or augmentation of dopamine. However, the best approach to the medical management of early Parkinson's disease remains highly debated. In the first segment of this activity, Dr. Ramon Rodriguez leads a discussion with Dr. Hubert Fernandez and Dr. Michael Okun on key considerations for the management of early Parkinson's disease. They begin their discussion with an overview of available therapies and an assessment of the current practice parameter for treatment initiation in patients with this disease.

Dr. Rodriguez:

Dr. Fernandez and Dr. Okun, I would like to discuss the currently available therapies for the treatment of Parkinson's disease and to pay attention to the management of the symptomatic early Parkinson's disease patient. I would like to try to get an idea about how do you decide to manage the patient with Parkinson's disease immediately after the diagnosis. Dr. Fernandez, what's your choice? What's your algorithm when you decide to treat a patient with early Parkinson's disease?

Available Symptomatic Therapies for the Treatment of Parkinson's Disease¹



COMT: catechol-O-methyltransferase; DC: dopa-decarboxylase; MAO-B: monoamine oxidase B.

1. Olanow CW et al. *Neurology*. 2009;72(suppl 4):S1-S136.

Dr. Fernandez:

As you know, there is no one-size-fits-all in choosing the best therapy or the most appropriate therapy for early Parkinson's patients. There are a few things that I look into. One is how bothered they are with their symptoms, what their occupation is, how old they are, and even their finances and their ability to comply with treatments.

Dr. Rodriguez:

We know that we have the monoamine oxidase inhibitors. Then we have amantadine, we have levodopa and the dopamine agonists. Then we have the COMT [catechol-O-methyltransferase] inhibitors. Tell me how you choose between deciding a patient be started on a monoamine oxidase inhibitor versus a dopamine agonist, as an example.

Dr. Fernandez:

That's a very interesting question, mainly because there is really no head-to-head comparison that we know of between a dopamine agonist versus an MAO-B inhibitor. So

because of that, we don't really have solid evidence that one drug is superior to the other in the management of early Parkinson's disease.

Dopamine agonists and MAO-B inhibitors are good alternatives to levodopa in early management of Parkinson's disease, given certain conditions. For example, dopamine agonists and MAO-B inhibitors could be considered when the functional decline is not to a sufficient degree that the clinician is not so desperate to start with levodopa. But choosing between dopamine agonists and MAO-B inhibitors, it's a tougher call.

Current Practice Parameter for Initiation of Treatment in PD¹: Is It Time for a Guideline Update?

Dopaminergic Therapy

- In patients with PD who require initiation of dopaminergic treatment, either levodopa or a dopamine agonist may be used
- Choice depends on whether goals are to
 - Improve motor disability (levodopa better)
 - Lessen motor complications (dopamine agonists better)

MAO-B Inhibitors

- Initial symptomatic treatment of patients with PD with selegiline, in order to confer mild, symptomatic benefit prior to the institution of dopaminergic therapy, may be considered

Amantadine

- Has a modest effect on all features of the disease and has a low adverse effect profile

1. Miyasaki JM et al. *Neurology*. 2002;58:11-17.

Dr. Rodriguez:

I would like to bring some points about the practice parameters that were published in the *Neurology* journal in 2002. Dopaminergic therapy was the recommendation and the monoamine oxidase B inhibitor was the consideration at that point, very similar to the use of amantadine. Now it has been about 10 years from the time that this practice parameter was published. I think that at this point it is outdated. And I think that there is a bigger role for other medications.

I use monoamine oxidase inhibitors as an initial choice for those patients with Parkinson's disease that do not have very severe symptoms because I will be taking into consideration that the drug may not be as powerful as the dopamine agonists or levodopa. The reason why I do this is because these drugs are usually once a day, in the case of rasagiline, or twice a day, in the case of selegiline. Then eventually the disease continues to progress; I move on to dopamine agonists in those patients that I deem that are very good candidates, who are usually younger patients and eventually will go into levodopa.

Do you think that there is enough data available to make a decision just like this management that I have been doing so far? The question is for Dr. Okun here.

Dr. Okun:

Thank you, Dr. Rodriguez. I believe that you have summarized very nicely the guidelines that were presented in *Neurology* almost 10 years ago. The first point that I would like to make is that those guidelines are not evidence-based guidelines.

The guidelines did make some important assertions, including the use of some therapies such as MAO-B inhibitors potentially early in Parkinson's disease. And I think we all agree that the studies show there are some symptomatic benefits.

Then the question as to using dopamine agonists versus levodopa I think really gets at looking at your patient carefully and tailoring the therapy to the patient. It's important to note that with dopamine agonists, if people have a lot of comorbidities, they're going to have potentially more side effects on these medications. And so I think the sicker your patients are, the more there is a tendency to use plain levodopa with or without an MAO-B inhibitor in practice.

Trials Assessing Levodopa in Early PD

Study	Treatment Arms	Outcomes		
		Arm	Δ UPDRS (0-42 wk)	$[^{123}\text{I}]\beta\text{-CIT}$ Uptake (40 wk)
ELLDOPA¹ <ul style="list-style-type: none"> N = 361 Early PD 42-wk study (40 wk on tx; 2-wk washout) 	Carbidopa-levodopa (CL); split TID (1) 150 mg/d (2) 300 mg/d (3) 600 mg/d Placebo	Placebo	+7.8	-1.4%
		150 mg/d CL	+1.9	-6.0%
		300 mg/d CL	+1.9	-4.0%
		600 mg/d CL	-1.4	-7.2%
		<i>P</i> for trend	< .001	.036
		<ul style="list-style-type: none"> Patients on 600 mg/d CL had significantly more dyskinesia, hypertonia, infection, headache, and nausea than those on placebo 		
STRIDE-PD² <ul style="list-style-type: none"> N = 747 Early PD 134-wk study 	Carbidopa-levodopa Carbidopa-levodopa-entacapone (CLE) Both treatments administered 4x/d at 3.5 h intervals	CLE vs CL		
		<ul style="list-style-type: none"> Time to dyskinesia onset: HR = 1.29; <i>P</i> = .04 Dyskinesia frequency at 134 wk = 42% vs 32%; <i>P</i> = .02 Time to wearing-off and motor scores did not significantly differ between groups CLE group received greater levodopa dose equivalents than CL group (<i>P</i> < .001) 		

$[^{123}\text{I}]\beta\text{-CIT}$: iodine-123-labeled 2- β -carboxymethoxy-3- β -(4-iodophenyl) tropane; UPDRS: Unified Parkinson's Disease Rating Scale.

1. Fahn S et al. *N Engl J Med*. 2004;351:2498-2508. 2. Stocchi F et al. *Ann Neurol*. 2010;68:18-27.

Narrator:

Drs. Rodriguez, Okun, and Fernandez now discuss and review the relevant clinical trial data supporting the use of available symptomatic therapies in patients with early Parkinson's disease.

Dr. Rodriguez:

We all have the impression that levodopa seems to be a lot more powerful medication than the dopamine agonists and monoamine oxidase inhibitors in terms of the benefit that is provided from the motor standpoint.

What I would like to do now is to cover the early studies of levodopa in the management of early Parkinson's disease. The ELLDOPA study included 361 patients with early Parkinson's disease. In the study, it is actually very interesting that [in] the patients that were receiving the 600 mg a day, even though they seemed to have much more benefit from the motor standpoint, there was also a significant increase of dyskinesia, hypertonia,

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as well as some other side effects. The question is whether to begin levodopa in early Parkinson's disease.

Along with this, I want to bring to your attention the STRIDE-PD study. This study was very interesting because what it showed is that the time to wearing-off or motor scores did not significantly differ between the two groups. However, there was a higher dyskinesia frequency in the carbidopa-levodopa-entacapone group.

Based on this information I would like to hear what Dr. Okun has to say, whether we should actually use levodopa in the early stages of Parkinson's disease or whether we should delay the introduction of levodopa and try to use the other alternative medications available.

Dr. Okun:

The question as to whether we should introduce levodopa early in Parkinson's disease is one that has been asked by many experts and many practitioners from all over the world.

There was a margination toward not using levodopa because of fear of long-term complications and so we had patients that were worried and trying to underdose themselves or not take medications for fear that later on they were going to end up with dyskinesias or so-called "on-off" fluctuations.

The most important thing a practitioner needs to keep in mind is that it's a question of what's best for the patient, and when the patient has problems we have to change the dose and the interval to fit the circumstances.

I think it's much less important as to what you take as it is to improving the symptom score in an individual patient. You also have to consider when patients take levodopa that they're at high risk for things such as hallucinations, orthostasis. So all of these factors have to be taken into account. But when it comes to treating an individual patient I will choose the therapy that's best for the patient, and I am not opposed to using regular levodopa out the door.

Dopamine Agonists: What Is Their Role in the Treatment of Early PD?

Pramipexole¹⁻⁴

- Associated with significantly lower incidence of motor fluctuations compared with levodopa
- Reduced rate of decline of β -CIT uptake by 36% compared with levodopa in CALM-PD study
- In terms of improvements in UPDRS total scores, inferior to levodopa
- Extended-release formulation is noninferior to immediate-release formulation

Ropinirole⁴⁻⁶

- Associated with significantly lower incidence of motor fluctuations compared with levodopa
- Reduced rate of decline of striatal fluorodopa uptake on PET by 35% compared with levodopa in REAL-PET trial
- No significant difference in ADL scores when compared with levodopa in a 5-year study

The dopamine agonists bromocriptine, cabergoline, pergolide, and lisuride have also been studied in previously untreated patients with PD⁴

1. Parkinson Study Group. *JAMA*. 2000;284:1931-1938. 2. Holloway RG et al. *Arch Neurol*. 2004;61:1044-1053. 3. Poewe W et al. *Neurology*. 2011;77:759-766. 4. Hauser RA. *Parkinsonism Relat Disord*. 2009;15(suppl 3):S17-S21. 5. Rascol O et al. *N Engl J Med*. 2000;342:1484-1491. 6. Whone AL et al. *Ann Neurol*. 2003;54:93-101.

Dr. Rodriguez:

At this point what I would like to do is actually summarize some of the clinical data available in terms of the use of dopamine agonists in the treatment of early Parkinson's disease. The CALM-PD study revealed that the use of pramipexole was associated with a significantly lower incidence of motor fluctuations compared to levodopa, once again bringing to the attention what defines the end stage of Parkinson's disease. For many clinicians actually, it's that—it's the development of motor fluctuations and the dyskinesia.

Looking into ropinirole, once again the use of ropinirole was associated with a significantly lower incidence of motor fluctuations compared to levodopa, raising the question whether we should use these kinds of medications earlier in the course of Parkinson's disease. There was also a reduced rate of decline in the striatal fluorodopa uptake compared [with levodopa], by 35%.

Dr. Okun:

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What we now know is based on the clinical trials that are available and also from lots of expert commentary and trying to examine the features of these trials. In summary, dopamine agonists are less potent than levodopa. If you give somebody a dopamine agonist, their disability on a motor scale is not going to improve as much as when you give levodopa. Both drugs work well in terms of improving those scores. Of course, one is stronger than the other, and so if you give regular dopamine replacement you can end up with these features of dyskinesias and "on-off" fluctuations down the road, but you also have to consider you can end up with these features when you use a dopamine agonist as well.

One must consider when taking a dopamine agonist that one in five patients now will end up having some sort of impulse control disorder, so these are things like inappropriate shopping, gambling, and other behaviors. And patients need to be warned of this.

MAO-B Inhibitors in the Treatment of Early PD: Do They Have Efficacy Beyond Symptomatic Benefit?

Study	Key Findings
DATATOP¹ <ul style="list-style-type: none"> N = 800 Untreated PD Comparison of selegiline and/or tocopherol with placebo 	<ul style="list-style-type: none"> Selegiline provided benefit over tocopherol and placebo
SELEDO² <ul style="list-style-type: none"> N = 116 Early PD Selegiline vs placebo All patients received levodopa 	Selegiline vs Placebo <ul style="list-style-type: none"> Life-table analysis = 50.4% vs 74.1%; $P = .027$ Median time to levodopa dose increased $\geq 50\%$ from titrated dose = 4.9 y vs 2.6 y
TEMPO³ <ul style="list-style-type: none"> N = 404 Untreated PD Early vs delayed rasagiline 	<ul style="list-style-type: none"> At 12 mo, significant difference in UPDRS scores observed in early group vs delayed-start group suggestive of additional efficacy beyond symptomatic benefit At 6.5 y follow-up, patients in early tx arm had significantly less worsening of total UPDRS compared with delayed-start group⁴
ADAGIO⁵ <ul style="list-style-type: none"> N = 1,176 Untreated PD Early vs delayed rasagiline 	<ul style="list-style-type: none"> Patients treated early with 1 mg/d did significantly better at end of study than those who had the agent withheld These findings were not observed in patients who received early vs delayed tx at 2 mg/d

1. LeWitt PA; The Parkinson Study Group. *Acta Neurol Scand.* 1991;84(suppl 136):79-86.
 2. Pruzntek H et al. *Eur J Neurol.* 1999;6:141-150. 3. Parkinson Study Group. *Arch Neurol.* 2004;61:561-566. 4. Hauser RA et al. *Mov Disord.* 2009;24:564-573. 5. Olanow CW et al. *N Engl J Med.* 2009;361:1268-1278.

Dr. Rodriguez:

I would like to discuss the monoamine oxidase inhibitors and some of the data available in the early stages of Parkinson's disease.

The DATATOP study was a comparison of selegiline and tocopherol with placebo. Basically, what the study showed at the end was that selegiline provided benefit over tocopherol and placebo.

The SELEDO study, which is the study of selegiline versus placebo in early Parkinson's disease. There was a median time to levodopa dose increase of more than 50% in the selegiline group compared to the placebo arm.

The TEMPO study was an early versus a delayed start for rasagiline. At 12 months a significant difference in the UPDRS score [was] observed in the early treatment compared

to the delayed-start group, suggesting that there may have been some additional efficacy beyond symptomatic benefit.

Last but not least, the ADAGIO study included 1,176 medication-naïve Parkinson's disease patients. Again this was an early- versus a delayed-start rasagiline. In this particular study, there was a comparison of rasagiline 1 mg and rasagiline 2 mg versus placebo. It shows that patients treated early with the 1 mg a day did much better at the end of the study than those that were on the placebo arm. This benefit was not seen in the 2-mg dose, which is one of the biggest questions that we have at this point.

Dr. Fernandez, based on this information, are you using selegiline in some patients with early Parkinson's disease? And are you concerned about any potential side effects that have been associated with the use of the monoamine oxidase inhibitors?

Dr. Fernandez:

Thank you very much, Dr. Rodriguez for your wonderful summary of the MAO-B inhibitor clinical trials that we have done to date. I totally agree with you with several points. One is that the earlier studies on selegiline, they really just compared selegiline versus placebo.

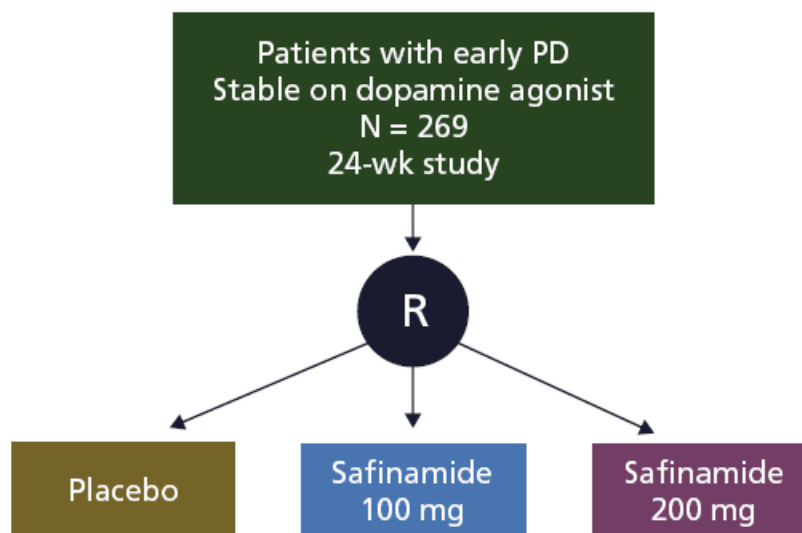
Now selegiline has some symptomatic benefit. The TEMPO study hinted on the possibility that earlier treatment of rasagiline might delay not only the use of levodopa but delay the onset of motor fluctuations, etc. And so the ADAGIO study was done. The problem with this study is that the 1-mg arm was able to meet all criteria with regard to their definition of a possible disease-modifying effect, whereas the 2-mg arm did not.

Because we have no definitive proof that it has a disease-modifying effect, I use rasagiline and selegiline for the definitive evidence we have, which is it is a reasonable agent, in fact a very good agent, for early Parkinson's disease and later on as adjunctive treatment for moderate to advanced Parkinson's disease [with] levodopa.

Now with regard to your second question: Are you concerned with the side effect profile of MAO-B inhibitors? Probably the strongest suit of MAO-B inhibitors is their safety and tolerability. In fact, in the placebo-controlled trials in rasagiline, the side effect profile in early treatment for Parkinson's disease is virtually identical to that of placebo, so it is a very well tolerated drug.

To answer your question, the side effect profile rarely comes into significant play in my choice for the use of MAO-B inhibitors. It is more of what I think is the symptomatic benefit that they can get from the use of these MAO-B inhibitors.

Safinamide, an MAO-B/Glutamate Release Inhibitor, as Adjunctive Therapy to Dopamine Agonists in Early PD¹



1. Stocchi F et al. *Mov Disord*. 2011 Sep 12. doi:10.1002/mds.23954. [Epub ahead of print].

Narrator:

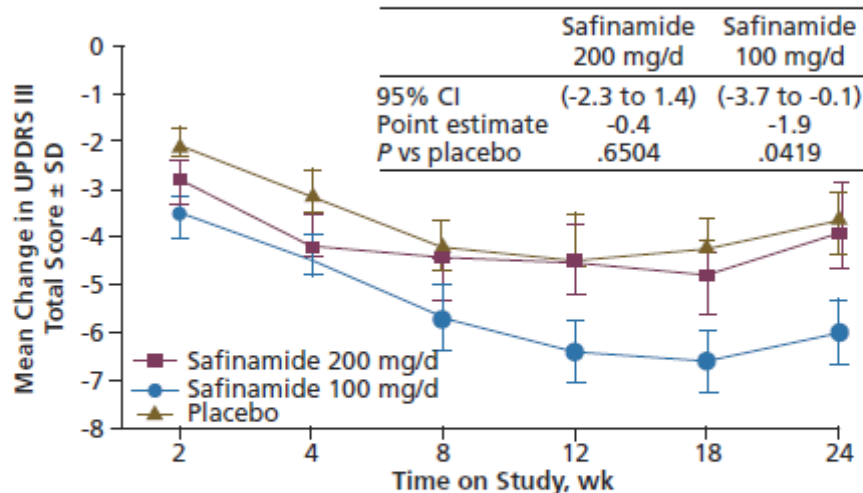
Before concluding their discussion on the management of early Parkinson's disease, Drs. Rodriguez, Okun, and Fernandez briefly assess recent clinical trial data on safinamide, a novel dual-action MAO-B/glutamate release inhibitor.

Dr. Rodriguez:

Safinamide is another monoamine oxidase inhibitor that is under evaluation right now for the treatment of Parkinson's disease.

It works as a monoamine oxidase inhibitor but also works as a glutamate release inhibitor. A study was published by Fabrizio Stocchi, looking into the use of safinamide as an adjunctive therapy to dopamine agonists in patients with early Parkinson's disease.

It was a 24-week study and the primary endpoint was the comparison of safinamide 200 mg versus placebo, and then as other exploratory outcomes they had safinamide 100 mg versus placebo.

Safinamide as Adjunctive Therapy to Dopamine Agonists in Early PD: Efficacy and Safety¹

- Most common AEs associated with safinamide (generally mild to moderate) were nausea, headache, abdominal pain, vomiting, pyrexia, cough, hypertension, blurred vision, gastritis, peripheral edema, nasopharyngitis, dizziness, back pain, and tremor
- Safinamide is currently being evaluated as an add-on to dopamine agonists in early PD in the phase 3 MOTION trial²

1. Stocchi F et al. *Mov Disord*. 2011 Sep 12. doi:10.1002/mds.23954. [Epub ahead of print]. 2. <http://clinicaltrials.gov/ct2/show/NCT01028586>. Accessed November 21, 2011.

Dr. Rodriguez:

There was actually no difference between the safinamide 200 mg versus placebo. However, there was a significant difference with safinamide 100 mg versus placebo in terms of providing increased "on" time in those patients on dopamine agonists in early Parkinson's disease. There is another study going on right now looking into this, which is the phase 3 MOTION trial.

I think that is a very interesting situation where twice the dose of the medication does not provide the benefit that we expect to see, trying to use some logic. But then the 100 mg is able to produce the benefit. Dr. Okun, why do you think this happens?

Dr. Okun:

Well safinamide is an interesting drug. The idea that doubling a dose of a medication is going to double efficacy is something that has been around for a long time, although the literature is replete with examples of where this doesn't necessarily happen. It is interesting with this drug that there is a question as to whether or not there [are] going to be benefits in terms of Parkinsonian symptom improvement being prolonged, especially when used

along with levodopa and improving "on" time. However, those types of conclusions can only be brought forward once we see the results of the phase 3 study.

Dr. Fernandez:

I cannot agree more with your statements, Dr. Okun. In safinamide, it's intriguing. Its early hints are that it can improve the "on" time or the Parkinson's motor score without worsening the dyskinesias. Its potential improvement in cognition is also intriguing. But these need to be tested in a definitive phase 3 trial.

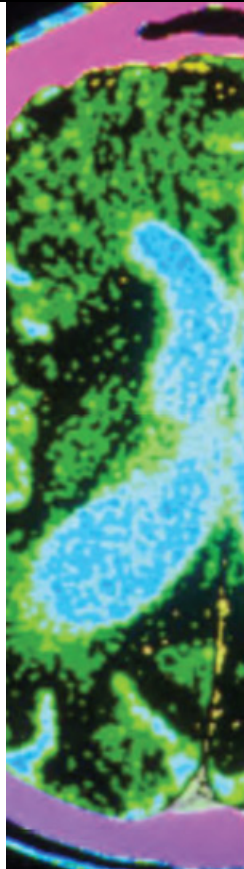
The last thing I would comment on in this is that it is perhaps one of the first drugs that actually tried to conduct in a clinical trial what we have been conducting in the clinical setting—to add a dopamine agonist to an MAO-B inhibitor, or vice versa, in our desire to delay the use of levodopa as much as possible, especially to higher risk patients in developing dyskinesias. We've done it in clinical practice but we don't really have evidence that this is good one way or the other.

Conclusions

- Early treatment of PD offers the opportunity to forestall clinical progression
- MAO-B inhibitors provide mild symptomatic benefit and are very well tolerated
- Dopamine agonists provide moderate symptomatic efficacy and delay the onset of motor complications, but are associated with somnolence and sudden-onset sleep, and impulse control disorders
- Levodopa provides the greatest symptomatic benefit but is associated with development of motor fluctuations and dyskinesias
- Optimal selection of medications for each patient depends on the anticipated individual risk for side effects and need for symptomatic improvement

Dr. Rodriguez:

There is a role for the use of monoamine oxidase B inhibitors in the early stages of Parkinson's disease. Dopamine agonists are also a very reasonable option. Then levodopa, definitely very powerful medication, very efficacious. It seems that most of the medical community chooses to use this medication a little bit more in the more advanced stages of the disease, or when the motor symptoms seem to be more pronounced, than the true early Parkinson's disease patients.



Exploring the Role of Adjunctive Therapy in the Management of Advanced Parkinson's Disease

Discussion Highlights

- Clinical characteristics of advanced Parkinson's disease (PD)
- Motor complications: An ongoing challenge in the management of advanced PD
- Considerations for the use of adjunctive therapy in the management of advanced PD
- Recent developments in the management of advanced PD

Motor State	Conventional median %	Infusion median %	P
+2 to +3 ("on" with dyskinesia)	15.4	0	< .01
	0	0	1

* Conventional oral and subcutaneous pharmacotherapy.
* Intravenous levodopa/carbidopa gel infusion.

Narrator:

In the second and final segment of this activity, Dr. Ramon Rodriguez, Dr. Hubert Fernandez, and Dr. Michael Okun continue their discussion on the management of Parkinson's disease, focusing on the treatment of patients with advanced disease. They begin with a brief overview of the clinical characteristics of patients with advanced disease.

Advanced Parkinson's Disease: Clinical Characteristics¹

Hoehn and Yahr Stages 4 or 5	✓
Limited mobility without assistance	✓
Severe motor deficits	✓
High risk for falls	✓
Cognitive and psychotic problems	✓
Enhanced sensitivity to small changes in plasma levodopa levels (ie, narrow therapeutic window and presence of motor complications)	✓

1. Varanese S et al. *Parkinsons Dis.* 2010;2010: doi:10.4061/2010/480260.

Dr. Rodriguez:

I would like to hear Dr. Fernandez's opinion about how he defines the patient with advanced Parkinson's disease.

Dr. Fernandez:

The definition of an advanced Parkinson's disease is really not clear-cut. The study here by Varanese et al. is a good guideline. When they looked at features that were consistent with advanced Parkinson's disease, having Hoehn and Yahr stage of 4 or 5, which means there was clear postural instability, limited mobility, severe motor deficits, high risk for falls, and cognitive problems, I think they're very reasonable criteria to employ in defining advanced Parkinson's disease.

But the bottom line is I think there is no clear-cut stage or point in time that you can apply to all Parkinson's patients in considering whether they're advanced or moderate or early stage Parkinson's disease.

We as clinicians think that we define advanced Parkinson's as someone who is falling, someone who has dyskinesias, someone who has motor fluctuations. But when you look at

advanced Parkinson's patients and ask them what they're most troubled about, the nonmotor problems really rise up the ladder. They're quite bothered by their cognitive and neurobehavioral issues. Of course there will be some patients that are very bothered by dyskinesias, but the wearing-off is bothersome, the nonmotor features are bothersome. Pain and fatigue now come into play, whereas they weren't really bigger issues in early Parkinson's disease.

Dr. Rodriguez:

Thank you for your answers. The way that I usually explain it to my patient is the early Parkinson's disease is the one that I usually treat with one pill twice a day, or one pill three times a day or four times a day but the dosages connect very well. For me, I actually say that the moderate stage Parkinson's disease patient is that one that you still can do some changes in the medication regimen so that you can provide a very continuous benefit from the medical standpoint. Then the advanced patient is the one that will be a lot more difficult trying to provide a continuous "on" time.

Motor Complications: An Ongoing Challenge in Managing Patients With Advanced PD¹

"Wearing-Off"

- Recurrence of motor and nonmotor symptoms preceding a scheduled dose of levodopa
- Direct consequence of nonphysiological, pulsate dopaminergic stimulation
- Occurrence generally predictable following levodopa administration

"On-Off" Fluctuations

- Sudden unpredictable shifts between a well- or overtreated state ("on") and undertreated state ("off")
- Overlap with wearing-off

Dyskinesia

- Results from overtreatment with dopaminergic therapy
- Diminished voluntary movement
- Presence of involuntary, jerky, dance-like movements of arms and/or head

1. Varanese S et al. *Parkinsons Dis.* 2010;2010: doi:10.4061/2010/480260.

Dr. Rodriguez:

At this point what I would like to do is define some of the stages of the advanced Parkinson's disease patients. And the first one would be "wearing-off." Wearing-off is probably the most common motor fluctuations that patients with Parkinson's disease experience. The definition of wearing-off is a recurrence of the motor and the nonmotor symptoms preceding a scheduled dose of levodopa.

"On-off" fluctuations are basically the sudden unpredictable shift between the "on" medication state, which is where the patient is doing well, and the "off" medication state, which is where the patient is having a major recurrence of the Parkinsonian symptoms.

Then the dyskinesia is basically the appearance of the involuntary, jerky, dance-like movements—that of course all over the body; however, they seem to be more common in the upper extremities but also may be seen in the head, in the face, as well as the trunk.

PD Practice Parameter: Adjunctive Therapies for Management of Motor Fluctuations¹

COMT Inhibitors

- Entacapone should be offered to reduce "off" time (Level A)
- Tolcapone should be considered to reduce "off" time (Level B)

MAO-B Inhibitors

- Rasagiline should be offered to reduce "off" time (Level A)
- Selegiline may be considered to reduce "off" time (Level C)

Dopamine Agonists

- Pergolide, pramipexole, ropinirole should be considered to reduce "off" time (Level B)
- Apomorphine and cabergoline may be considered to reduce "off" time (Level C)

Other

- Amantadine may be considered to reduce dyskinesia (Level C)
- Deep brain stimulation of the STN may be considered to:
 - Improve motor function (Level C)
 - Reduce "off" time (Level C)
 - Reduce dyskinesia (Level C)
 - Reduce medication usage (Level C)

STN: subthalamic nucleus.

1. Pahwa R et al. *Neurology*. 2006;66:983-995.

Dr. Rodriguez:

I want to mention the practice parameter for adjunctive therapy in the management of motor fluctuations in patients with Parkinson's disease. This was published in the year 2006. It's talking about COMT inhibitors, monoamine oxidase B inhibitors, dopamine agonists, as well as some other therapies.

From the medical standpoint I would like to begin the discussion with the COMT inhibitors. I would like to ask Dr. Okun, what his experience is, how frequently he recurs to the use of these medications, and how he feels about it.

Dr. Okun:

Thank you, Dr. Rodriguez. The idea of adding a COMT inhibitor, or catechol-O-methyltransferase inhibitor, to existing therapy or even starting a patient on levodopa with a COMT inhibitor is interesting and has provided some benefit for a subset of patients.

The original idea of using a COMT inhibitor was to extend the life of levodopa. So when you talk about wearing-off between dosages, the idea is adding this to each dose will effectively, at least theoretically, extend the life of dopamine. Once you employ this in practice, it actually raises the level of levodopa and one can then see dyskinesia and other motor fluctuations, and so sometimes you have to decrease the dose of levodopa when adding a COMT inhibitor. People need to be aware of that.

The main benefit is improving the amount of "on" time. There are two of these that are used commonly. One is entacapone and the other is tolcapone. Tolcapone is much stronger than entacapone but requires the monitoring of liver enzymes. In my experience, tolcapone has been better for patients with very severe dyskinesia and "on-off" fluctuations. It can help a lot of patients, particularly the ones that have these severe fluctuations and might even be considering a surgical option, such as a pallidotomy or deep brain stimulation.

Dr. Rodriguez:

Thank you, Dr. Okun. The parameters [also] recommended that rasagiline should be offered to reduce the "off" time and selegiline may be considered to reduce the "off" time. Again, dopamine agonists, pergolide, pramipexole, ropinirole, should be considered to reduce the "off" time, and the apomorphine and cabergoline may be considered to reduce "off" time.

Recent Studies of Adjunctive Therapies in Patients With Advanced PD

Study of Advanced PD	Key Findings
PREPARED¹ <ul style="list-style-type: none"> N = 350 Ropinirole IR vs ropinirole PR as adjunctive tx to levodopa 	Ropinirole PR vs Ropinirole IR <ul style="list-style-type: none"> ≥20% reduction in "off" time: HR = 1.82; P = .009 Mean dose wk 24 LOCF = 18.6 mg/d vs 10.6 mg/d Mean reduction in levodopa dosage from baseline = -162 mg vs -113 mg Nausea, dyskinesia, and dizziness were most common AEs in both tx groups
Schapira et al.² <ul style="list-style-type: none"> N = 518 Pramipexole IR and pramipexole ER vs placebo as adjunctive tx to levodopa 	Placebo vs Pramipexole IR and Pramipexole ER <ul style="list-style-type: none"> Decrease in UPDRS II+III scores = -6.1 vs -12.8 (P < .0001) and -11.0 (P < .0001) Decrease in daily "off" time = -1.4 h vs -2.5 h (P < .0001) and -2.1 h (P = .0122) Dyskinesia, somnolence, and nausea were most common AEs in pramipexole groups

ER: extended release; IR: immediate release; PR: prolonged release.

1. Stocchi F et al. *Mov Disord.* 2011;26:1259-1265. 2. Schapira AH et al. *Neurology.* 2011;77:767-774.

Narrator:

Drs. Rodriguez, Okun, and Fernandez now review recent clinical trial data on available and emerging therapies in patients with advanced Parkinson's disease.

Dr. Rodriguez

I would like to cover some of the recent studies of adjunctive therapies in patients with advanced Parkinson's disease.

The PREPARED study shows us that there was a more than 20% reduction in "off" time in those patients using the prolonged-release formulation compared to the immediate-release formulation of ropinirole. And the main side effects that were in that study were nausea, dyskinesia, and dizziness. The prolonged-release formulation group was able to decrease the amount of levodopa that they were using by 162 mg compared to 113 mg in the immediate-release group.

The following study [of] placebo versus pramipexole immediate-release versus pramipexole extended-release showed a decrease in the UPDRS II and III scores in the group that was using both pramipexole immediate-release and pramipexole extended-release versus the placebo. There was also a decrease in the amount of "off" time for the patients in the pramipexole group.

Recent Studies of Adjunctive Therapies in Patients With Advanced PD (Cont'd)

Study of Advanced PD	Key Findings
PREFER¹ <ul style="list-style-type: none"> N = 351 Rotigotine 8 mg/d and 12 mg/d vs placebo as adjunctive tx to levodopa 	Placebo vs Rotigotine 8 mg/d and 12 mg/d <ul style="list-style-type: none"> Mean reduction in daily "off" time = -0.9 h vs -2.7 h ($P < .001$) and -2.1 h ($P < .001$) $\geq 30\%$ reduction in "off" time = 34.5% vs 56.6% ($P < .001$) and 55.1% ($P < .001$) Somnolence, nausea/vomiting, dizziness, and dyskinesia were most common AEs associated with rotigotine
Borghain R et al.² <ul style="list-style-type: none"> N = 669 Safinamide 50 mg/d and 100 mg/d vs placebo as adjunctive tx to levodopa 	Placebo vs Safinamide 50 mg/d and 100 mg/d <ul style="list-style-type: none"> Increase in total daily "on" time = 1.0 h vs 1.5 h ($P = .0082$) and 1.6 h ($P = .0048$) Safinamide also improved UPDRS score vs placebo No significant differences between groups for "on" time with minor dyskinesias, "on" time with troublesome dyskinesias, or time asleep

1. LeWitt PA et al. *Neurology*. 2007;68:1262-1267. 2. Borghain R et al. 13th International Congress of Parkinson's Disease and Movement Disorders. 2009. Abstract LB-14.

Dr. Rodriguez:

The PREFER study showed that there was a mean reduction in the "off" time for the rotigotine 8 mg and the rotigotine 12 mg compared to the placebo arm. There was a more than 30% reduction in the "off" time for the rotigotine arms.

The main side effects observed in this particular study were somnolence, nausea and vomiting, dizziness, and dyskinesias.

One of the most recent studies is the safinamide 50 mg a day and safinamide 100 mg a day versus placebo. The result of this study is that the safinamide 50 mg and the safinamide 100 mg showed an increase in total daily "on" time. There was also an improvement in the UPDRS score versus placebo for the safinamide arm.

Assessing the Role of Intraduodenal Levodopa in Patients With Advanced PD

DIREQT Trial¹

N = 24

- Advanced PD
- Motor fluctuations and dyskinesia

R

Conventional^a → Infusion^b

Infusion → Conventional

Outcomes: Percentage of Patient Ratings in Different Motor States on the Treatment Response Scale

Motor State	Conventional, median %	Infusion, median %	P
-1 to +1 ("on")	81.3	100	< .01
-3 to +2 ("off")	15.4	0	< .01
+2 to +3 ("on" with dyskinesia)	0	0	1

- Overall incidence of adverse effects was lower in infusion arm vs conventional arm
- Intraduodenal levodopa is currently undergoing phase 3 evaluation in patients with advanced PD

^aConventional oral and subcutaneous pharmacotherapy.

^bIntraduodenal levodopa/carbidopa gel infusion.

1. Nyholm D et al. *Neurology*. 2005;64:216-223.

Dr. Rodriguez:

At this point, I would like to call both Dr. Fernandez and Dr. Okun. What I would like to do is address some questions. So Dr. Fernandez, what do you think is the role or the utility of the intraduodenal levodopa that we know is approved in some European countries and has been under study here in the United States?

Dr. Fernandez:

To answer your question, I think there is a significant role of intraduodenal levodopa in the management of advanced Parkinson's patients. This is being investigated because it uses the same drug that we already know is the most efficacious in Parkinson's disease, which is levodopa, and delivering it in a novel way by continuous delivery through the duodenum, and therefore, hopefully, bypassing the need for frequent dosing and also satisfying the continuous dopaminergic stimulation hypothesis in advanced Parkinson's patients.

Advantages and Disadvantages of Apomorphine Injection in Advanced PD¹

Advantages

- Exerts antiparkinsonian effect via direct stimulation of striatal postsynaptic dopamine D1 and D2 receptors
- C_{max} = 20 min
- Effects apparent 5 to 15 min following injection
- Produces 50%-80% improvement in "off" time

Disadvantages

- Use limited by compliance and skin reactions at injection site
- $t_{1/2}$ = 43 min
- High doses poorly tolerated by many patients
- Dyskinesia improvements debatable

1. Antonini A, Odin P. *Parkinsonism Relat Disord*. 2009;15(suppl 4):S97-S100.

Dr. Rodriguez:

I would like to ask Dr. Fernandez just for a quick summary of his experience in the use of apomorphine.

Dr. Fernandez:

Apomorphine is a dopamine agonist. It is unique in the sense that it is in an injectable formulation. It works within 5 to 10 minutes, but its one disadvantage is that it does not last long. It is FDA approved for wearing-off as a rescue therapy.

With my clinical practice, I use apomorphine in those with severe wearing-off or painful wearing-off that needs to be relieved immediately or those with sudden-off. They get relief within 5 [to] 7 minutes of their significant, painful, or severe "off" spells. The drug only lasts for an hour so they have to continue taking their levodopa, or other dopamine agonists, or COMT inhibitor, or MAO-B inhibitor, or amantadine.

Exploring the Potential Role of Gene Therapy in Advanced PD

Study	Treatment Arms	Outcomes
Marks et al.¹ <ul style="list-style-type: none"> N = 58 Advanced PD Off-medication motor subscore UPDRS ≥ 30 12-mo study 	(1) CERE-120 (delivered bilaterally to putamen) (2) Sham surgery	<ul style="list-style-type: none"> Change in UPDRS motor subscore from baseline to 12 mo did not significantly differ between CERE-120 and sham surgery ($P = .91$) Headache and nausea were most common AEs associated with CERE-120 3 pts in CERE-120 group and 2 pts in sham surgery group developed tumors
LeWitt et al.² <ul style="list-style-type: none"> N = 45 Advanced PD Overnight off-medication motor subscore UPDRS ≥ 25 6-mo study 	(1) AAV2-GAD (2) Sham surgery	<ul style="list-style-type: none"> Change in off-medication UPDRS at 6 mo vs baseline: <ul style="list-style-type: none"> AAV2-GAD = -8.1 ($P < .001$) Sham surgery -4.7 ($P = .003$) AAV2-GAD showed significant improvements in UPDRS scores from baseline vs sham surgery ($P = .04$) Headache and nausea were most common AEs associated with AAV2-GAD

CERE-120: adeno-associated type-2 vector neurturin gene therapy; AAV2-GAD: adeno-associated type-2 vector glutamic acid decarboxylase gene transfer therapy.

1. Marks WJ Jr. et al. *Lancet Neurol.* 2010;9:1164-1172. 2. LeWitt Pa et al. *Lancet Neurol.* 2011;10:309-319.

Dr. Rodriguez:

Dr. Okun, gene therapy has been gaining more and more attention in the management of advanced Parkinson's disease. Can you give us a summary of what is the state now in terms of gene therapy, and if you think that this is something that is going to have a big impact on Parkinson's?

Dr. Okun:

Gene therapy is really interesting and really exciting for a lot of the patients and scientists who follow the Parkinson's field. First is CERE-120, and that's a neurotrophic factor. It will promote development, survival, and also better functioning of neurons or brain cells. Neurturin is one of these factors, and it's a member of a family of ligands that we call the glial-derived neurotrophic factor.

But what's important to remember now is that GDNF and CERE-120 don't actually cross the blood-brain barrier. So what they do is they attach these things to adeno-associated viruses.

In a randomized, double-blind, placebo trial of patients receiving CERE-120, it did not meet its endpoint. Because of that, the trial is now being redone, but this time with injections directly into the substantia nigra as well as into the putamen. Hopefully we'll see some results in the next 24 to 36 months.

The other trial that's important to be aware of is what's called glutamic acid decarboxylase gene transfer therapy, that can actually catalyze the synthesis of gamma-aminobutyric acid, or GABA, and suddenly change that structure from pumping out glutamate to pumping out GABA, therefore making it inhibitory and potentially changing the downstream circuit for Parkinson's disease.

It's a really quite novel idea. Investigators that have been involved with this have shown in early studies that it looks safe. There were some promising changes in motor, more than activities of daily living, and they moved on to a phase 2, double-blind, randomized trial where they did 45 patients and included 37 in the statistical analysis. What they found were important improvements. They reported motor score improving by 8 points in the gene transfer group and 4.7 points in the sham surgery group.

Although, at this time, it doesn't look like the benefits of this type of therapy are at the same level as some of the other things such as surgical therapies like deep brain stimulation or pallidotomies, it is promising.

Conclusions

- The management of advanced PD remains a challenge for clinicians, patients, and their families alike
- Medication management can become arduous due to "on-off" fluctuations and dyskinesias, as well as the development of nonmotor symptoms
- In this respect, adjunctive therapy plays a prominent role in the management of motor symptoms
- Emerging therapies have the potential to further aid clinicians in achieving an optimal balance between minimizing wearing-off and preventing dyskinesia

Dr. Rodriguez:

Every patient with Parkinson's disease is different, and they are very complex. Instead of following an algorithm for the management of Parkinson's disease, you have to take each patient in a case-by-case scenario and try to find out what are the symptoms that bother the patient the most and how can we treat them the best. The management of "on" and "off" fluctuations and dyskinesias can be very complex as well. Then if things don't get better in those patients that develop nonmotor symptoms—that seems to be quite resistant to the current pharmacological therapy available for Parkinson's disease—some of these patients will require invasive treatments to try to improve their symptoms, which brings another complexity to the management.

Then there are some other therapies that are coming into the picture that seem to be quite promising, and we'll be looking forward to see how they will develop and what will be their place in the management of Parkinson's disease.

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Narrator:

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CME/CPE Post-Test: Please write your answers in the answer key on the next page.

A score of 80% or higher is needed to obtain CME credit, a score of 70% or higher is needed to obtain CPE credit.

1. R.B. is a 45-year-old female patient with symptomatic early Parkinson's disease (PD). According to the current published practice parameter for treatment initiation in patients with PD, which of the following therapies should be used to manage R.B.?
 - a. Amantadine
 - b. Catechol-o-methyltransferase (COMT) inhibitors
 - c. Dopamine agonists
 - d. Monoamine oxidase B (MAO-B) inhibitors
2. Which of the following statements is true with respect to the outcomes of the double-blind, delayed-start ADAGIO trial?
 - a. Early treatment with either 1 mg or 2 mg/day rasagiline provided a symptomatic benefit in patients with PD.
 - b. Early treatment with 1 mg/day rasagiline provided a symptomatic benefit in patients with PD, but 2 mg/day rasagiline did not.
 - c. Early treatment with 2 mg/day rasagiline provided a symptomatic benefit in patients with PD, but 1 mg/day rasagiline did not.
 - d. Early treatment with neither 1 mg nor 2 mg/day rasagiline provided a symptomatic benefit in patients with PD.
3. Which of the following statements best summarizes the results of a recent phase 2 trial evaluating the dual action MAO-B/glutamate release inhibitor, safinamide, as an adjunctive therapy to dopamine agonists in patients with early PD?
 - a. When compared with placebo, the addition of 100 mg or 200 mg safinamide improved motor symptoms.
 - b. When compared with placebo, the addition of 100 mg—but not 200 mg—safinamide improved motor symptoms.
 - c. When compared with placebo, the addition of 200 mg—but not 100 mg—safinamide improved motor symptoms.
 - d. When compared with placebo, neither the addition of 100 mg nor 200 mg safinamide improved motor symptoms.
4. T.S. is a 53-year-old female patient with advanced PD who is experiencing "wearing-off" despite optimization of her carbidopa-levodopa regimen. According to the current practice parameter for the use of adjunctive medications in patients with PD, which of the following therapies should be offered to this patient to reduce her "off" time?
 - a. Either entacapone or rasagiline
 - b. Entacapone only
 - c. Rasagiline only
 - d. Ropinirole only
 - e. Tolcapone only
5. According to the results of a recent phase 2 study, by how many points was glutamic acid decarboxylase gene transfer therapy shown to improve overnight off-medication UPDRS motor subscores at 6 months compared with baseline in patients with advanced PD?
 - a. 10.1
 - b. 8.1
 - c. 6.1
 - d. 4.1
 - e. 2.1

Optimizing the Management of Parkinson's Disease: Considerations for Treating Early Disease and Minimizing Motor Complications in Advanced Disease

Post-Test Answer Key: Please write your answers to the 5 CME/CPE questions in this key.

1. _____	2. _____	3. _____	4. _____	5. _____
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1. As a result of your participation in this activity, please indicate **how much your ability to meet each of the stated educational objectives increased.**

	No more able to meet this objective after participating		Somewhat more able to meet this objective after participating			Much more able to meet this objective after participating	
Apply recent efficacy and safety data related to the symptomatic treatment of early Parkinson's disease	1	2	3	4	5	6	7
Employ adjunctive treatment strategies for the management of motor complications in patients with advanced Parkinson's disease	1	2	3	4	5	6	7

2. In your opinion, **how effective were the preceding post-test questions** at measuring the educational objectives of this activity?

Not at all effective		Somewhat effective				Very effective	
1	2	3	4	5	6	7	

3. Please rate the **overall quality of the faculty** with respect to the content and clarity of their presentation.

	Overall quality was very poor			Overall quality was average		Overall quality was excellent	
Ramon L. Rodriguez, MD	1	2	3	4	5	6	7
Michael S. Okun, MD	1	2	3	4	5	6	7
Hubert H. Fernandez, MD	1	2	3	4	5	6	7

4. Please rate your level of agreement with the following statement: The content of this activity was **fair, balanced, and free of commercial bias.**

I strongly disagree		I neither agree nor disagree				I strongly agree	
1	2	3	4	5	6	7	

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1	2	3	4	5	6	7	

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I strongly disagree		I neither agree nor disagree				I strongly agree	
1	2	3	4	5	6	7	

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Not at all likely		Somewhat likely				Very likely	
1	2	3	4	5	6	7	

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Yes No

11. Do you foresee any **potential barriers to implementing** what you learned in this activity into your own practice of medicine? You may write in specific details in the space provided below.

Yes No

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