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Review

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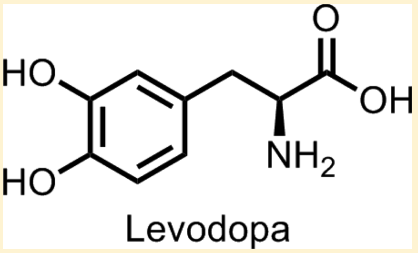
Classics in Chemical Neuroscience: Levodopa

A. Connor Whitfield,[†] Ben T. Moore,[†] and R. Nathan Daniels*[,†,‡]

[†]Department of Pharmaceutical Sciences, Lipscomb University College of Pharmacy and Health Sciences, Nashville, Tennessee 37204, United States

[‡]Department of Pharmacology, Vanderbilt University Medical Center, Nashville, Tennessee 37232-6600, United States

ABSTRACT: Levodopa was the first and most successful breakthrough in the treatment of Parkinson's disease (PD). It is estimated that PD affects approximately 1 million people in the United States alone. Although PD was discovered in 1817, prior to levodopa's discovery there was not an effective treatment for managing its symptoms. In 1961, Hornykiewicz pioneered the use of levodopa to enhance dopamine levels in the striatum, significantly improving symptoms in many patients. With the addition of carbidopa in 1974, the frequency of gastrointestinal adverse drug reactions (ADRs) was significantly reduced, leading to the modern treatment of PD. Although levodopa treatment is more than 50 years old, it remains the "gold standard" for PD treatment. This Review describes in detail the synthesis, metabolism, pharmacology, ADRs, and importance of levodopa therapy to neuroscience in the past and present.



KEYWORDS: *Levodopa, Parkinson's disease, carbidopa, L-dopa, dopamine, dopamine replacement*

Parkinson's disease (PD) is an age-related condition of the substantia nigra in the mesencephalon, in which low concentrations of dopamine (**1**) (Figure 1) result in tremor, muscle rigidity, bradykinesia, and postural instability.[1−3] Additionally, the loss of dopaminergic neurons in the substantia nigra and the development of Lewy bodies contribute to the onset of PD, although the exact mechanisms causing neurodegeneration are not yet known. Different paths to neurodegeneration such as genetic factors and environmental toxins are currently being investigated.[4] It is estimated that PD affects approximately 1 million people in the United States, with an average age for onset of symptoms being 60 years of age.[5] In the 19th Century, following the discovery and characterization of the disease, early medicinal treatment involved the use of belladonna alkaloids, specifically hyoscyamine. In addition, physical treatments such as blood letting, muscular stimulation (stretching, electrical, or vibratory), and rest were used with limited effects.[6]

In 1958, Carlsson discovered that high concentrations of dopamine were present in the striatum. He further noted that reserpine, an alkaloid typically used in the treatment of hypertension, mimics PD by depleting dopamine concentrations in the brain and that concentrations could be restored upon administration of levodopa [L-dopa (**2**)], a dopamine precursor. This model led Carlsson to conclude that decreased levels of dopamine were responsible for PD.[6−10] His theory was tested one year later by Hornykiewicz, who linked low dopamine concentrations with PD. Hornykiewicz first proposed treatment of PD with levodopa, which had been shown to replace dopamine levels in the striatum.[6,7,9,11] Early trials found that nearly 75% of PD patients had symptoms alleviated upon treatment with L-dopa.[6,7,12,13] Because L-dopa, given alone, can be metabolized in the periphery [leading to significant gastrointestinal (GI) adverse drug reactions (ADRs)], carbidopa (**3**), a decarboxylase inhibitor (DCI), was added to the drug regimen. Carbidopa allows for L-dopa to cross the blood−brain barrier (BBB) intact, where it is then metabolized to release dopamine. Levodopa/carbidopa treatment is currently the most effective Parkinson's treatment, though other methods, such as monoamine oxidase-B (MAO-B) and catechol *O*-methyltransferase inhibitors, are frequently used.[7,14,15]

Although considered the "gold standard", L-dopa is not without its drawbacks. GI ADRs are very common, even with the blocked peripheral metabolism effect of carbidopa.[7,14−16] Prolonged treatment with L-dopa is necessary in PD patients because L-dopa treats only the symptoms without halting neurodegeneration. Additional ADRs, such as dyskinesias, occur in ∼80% of patients after treatment for only 10 years. As the disease progresses, Parkinsonian symptoms worsen, and L-dopa's therapeutic window becomes limited. A phenomenon termed "on−off" is common. In the "on" phase, treatments are effective and symptoms are reduced. In the "off" phase, symptoms are more severe. This phenomenon occurs somewhat unpredictably, with frequent switches between the two phases. To alleviate this, patients will often receive larger doses of L-dopa, though this causes a greater likelihood of further side effects.[7,12,13,16,17]

This paper will describe in detail the synthesis, metabolism, pharmacology, ADRs, and importance of L-dopa therapy to neuroscience in the past and present.

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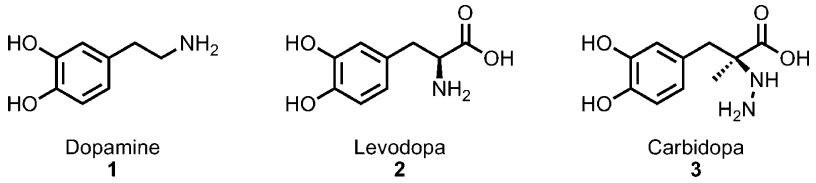
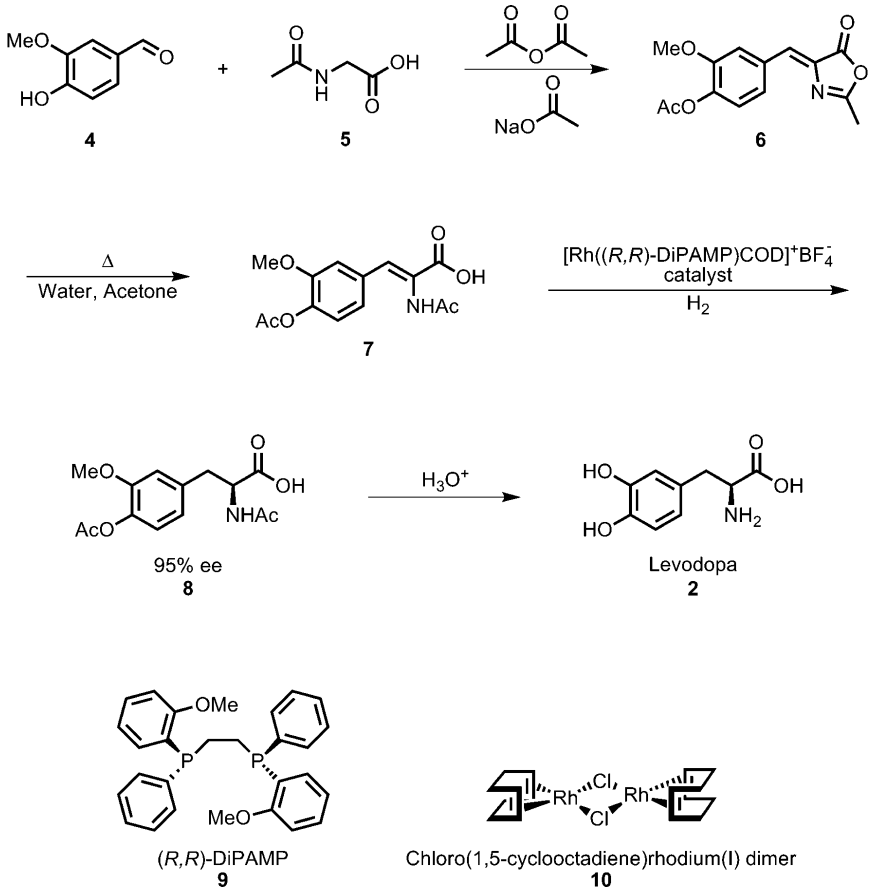


Figure 1. Dopamine and breakthrough medications for Parkinson's disease. Structures of dopamine (**1**), levodopa (**2**), and carbidopa (**3**).

Scheme I. Monsanto Process That Streamlined the Synthesis of the Naturally Occurring L isoform, L-dopa



CHEMICAL SYNTHESIS

L-dopa (**2**) [CAS Registry No. 59-92-7; (2*S*)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid, $C_9H_{11}NO_4$] is a catecholamine (MW = 194.19) with four hydrogen bond donors, five hydrogen bond acceptors, and a Log P of −2.7. Therefore, L-dopa not only conforms to Lipinski's rules but also easily crosses the BBB, unlike dopamine, its metabolic successor. L-dopa is white, crystalline, odorless, tasteless in nature, and slightly soluble in water.[18−20] L-dopa was first synthesized in 1911 by Torquato Torquati from the *Vicia faba* bean and, in a separate experiment, by Casimir Funk, who synthesized a racemic mixture of D,L-dopa in the same year. In 1913, Marcus Guggenheim isolated L-dopa from the *V. faba* bean and discovered its chemical structure. He ingested 2.5 g of L-dopa, concluding that the drug had no pharmacological effect outside of nausea and vomiting.[9,21,22] In 1974, William Knowles, working for Monsanto, discovered a method of catalytic asymmetric hydrogenation, a method for which he won the Nobel Prize in 2001.[23−26] This method, which came to be known as the Monsanto Process, helped to streamline the synthesis of the naturally occurring L isoform known as L-dopa (Scheme I).[23]

Beginning with 4-hydroxy-3-methoxybenzaldehyde (**4**) and acetylglycine (**5**), Knowles used Erlenmeyer-Plochl azlactone synthesis to produce 2-methyl-4-(3′-methoxy-4′-acetoxybenzal)-5-oxazolone (**6**). **6** then underwent mild hydrolysis to form the key intermediate α-acetamido-4-hydroxy-3-methoxy-cinnamic acid acetate (**7**). The key step in this synthesis is the asymmetric catalytic hydrogenation using the air stable $[Rh((R,R)\text{-DiPAMP})COD]^+BF_4^-$ as the catalyst precursor to convert **7** to *N*-acetyl-3-(4-hydroxy-3-methoxyphenyl)-alanine acetate (**8**) in quantitative yield and 95% enantiomeric excess (ee). This catalyst is prepared by reacting 2 equiv of the phosphine, ethane-1,2-diylbis[(2-methoxyphenyl)phenyl]-phosphane [(*R*,*R*)-DiPAMP (**9**)], with 1 equiv of chloro(1,5-cyclooctadiene)rhodium(I) dimer (**10**) in alcohol. To complete the synthesis, **8** undergoes a simple acid-catalyzed hydrolysis to yield L-dopa (**2**).[23,25]

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DRUG METABOLISM

L-dopa must be converted to dopamine in the brain for any therapeutic effects to be observed. There are three main enzymes that contribute to the metabolism of L-dopa/dopamine: aromatic L-amino acid decarboxylase (AADC), catechol *O*-methyltransferase (COMT), and monoamine oxidase (MAO). L-dopa, upon passing through the stomach, is primarily absorbed by active long chain neutral amino acid transporters in the upper small intestine. In the small intestine mucosa, the enzyme AADC converts the absorbed L-dopa to dopamine (**1**). AADC is the main pathway for the metabolism of L-dopa (Figure 2).[7,21]

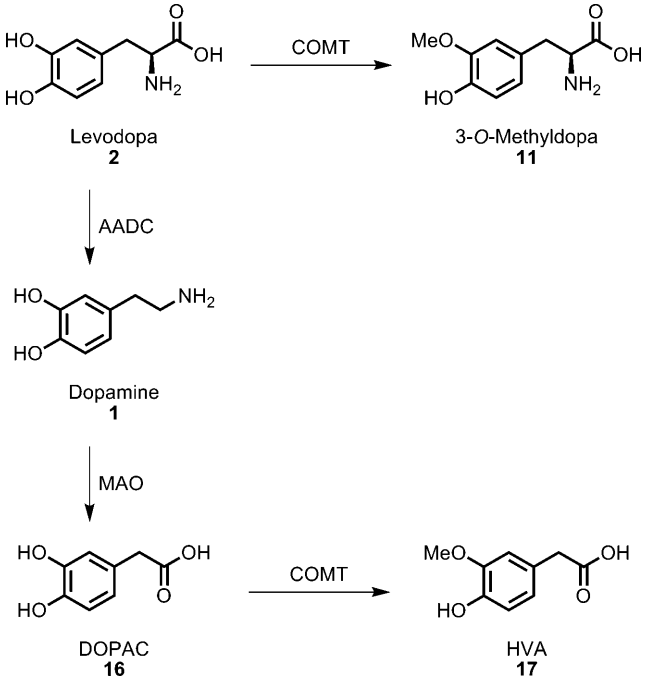

Figure 2. Levodopa's major pathways of metabolism by enzymes AADC, COMT, and MAO.[27]

Dopamine cannot cross the BBB, so any L-dopa converted before reaching the BBB will be of no therapeutic benefit.[21] Carbidopa, a decarboxylase inhibitor, is formulated with L-dopa to prevent premature metabolism by AADC. While AADC acts primarily in the intestine, it is also found in the liver, kidneys, catecholaminergic neurons in the central nervous system (CNS) (where L-dopa is converted to active dopamine), and, sparsely, other organs throughout the body.[28]

Decarboxylase inhibitors (DCIs) greatly increase L-dopa concentrations that reach the brain by increasing the availability of L-dopa available to cross the BBB up to 4-fold.[7] This effect allows for administration of lower L-dopa concentrations in a particular dose to obtain equal therapeutic effects for patients, and it decreases the side effects attributed to peripheral L-dopa metabolism, specifically, nausea and vomiting.[7,21]

COMT enzymes are located throughout the body's organs, with the greatest activity in the kidneys, liver, and neurons of the CNS.[29] COMT is responsible for inactivating catecholamines (dopamine, norepinephrine, and epinephrine) by adding a methyl group to the phenol at position 3 on the aromatic ring of **2**. In L-dopa metabolism, COMT metabolizes L-dopa to 3-*O*-methyldopa [3-OMD (**11**)]. Unlike dopamine, however, **11** has no peripheral side effects.[21] Although **11** shares some affinity for the same BBB transporter as L-dopa, it has little effect on displacing the L-dopa from the transporter.[30]

When AADC is inhibited by DCIs, COMT becomes the main pathway for levodopa metabolism. Adding a COMT inhibitor, such as tolcapone (**12**) (Tasmar, Roche) or entacapone (**13**) (Comtess, Orion, and Comtan, Novartis), in addition to a DCI, greatly enhances the therapeutic benefit of L-dopa therapy because of the decreased rate of metabolism (Figure 3).[21,31]

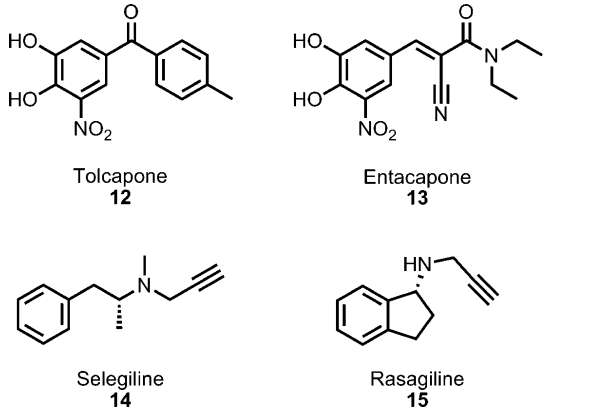

Figure 3. Commercially used inhibitors of COMT, tolcapone (**12**) and entacapone (**13**), and MAO-B, selegiline (**14**) and rasagiline (**15**), used in combination with L-dopa.

Tolcapone, given with L-dopa and a DCI, increases the plasma half-life of L-dopa and its bioavailability by approximately 2-fold.[31] Entacapone, from a study that utilized home diaries written by PD patients, was attributed to increasing their "on" time by an average of 1−2 h.[32] Entacapone cannot cross the BBB and acts peripherally by inhibiting COMT and increasing levels of L-dopa available for transport across the BBB. Tolcapone can cross the BBB, making it capable of decreasing the rate of dopamine metabolism by COMT in the CNS as well as in the periphery.[33] Entacapone is favored over Tolcapone because of a lowered risk of liver toxicity.[5,33]

MAO enzymes found in the outer mitochondrial wall are the third metabolism enzyme for dopamine. There are two different isoforms of MAO, isoforms A and B. Both isoforms have selectivity for the neurotransmitters that they oxidize. Dopamine is a substrate for both MAO-A and MAO-B, but a therapeutic effect is seen in Parkinson's when the B isoform is selectively inhibited. This effect is seen partially because MAO-A also deaminates tyramine and serotonin.[7,34,35] Inhibiting MAO-A can lead to the "cheese effect", a condition that causes rapid hypertension followed by other symptoms. This effect occurs if certain foods containing high levels of tyramine, such as certain fermenting cheeses and some red wines, are ingested; without MAO-A activity, tyramine can act as a neurotransmitter and displace norepinephrine at synaptic vesicles. Selective irreversible MAO-B inhibitors selegiline (**14**) and rasagiline (**15**) prevent the cheese effect from occurring and are therefore both used currently in PD therapy.[7] They can be used as adjunctive therapy with L-dopa or as monotherapy. Data from selegiline trials suggest that 30−40% of a daily dose of L-dopa may be preserved when a MAO-B inhibitor is used as adjuvant therapy. Rasagiline is favored over selegiline for treatment of PD because of a better ADR profile in addition to higher potency.[34]

After AADC metabolizes L-dopa to dopamine, dopamine can undergo further metabolism by MAO to 3,4-dihydroxyphenylacetic acid [DOPAC (**16**)] (Figure 2). **16** can then be metabolized by COMT to homovanillic acid [HVA (**17**)]. While **16** and **17** are the main metabolites found in the urine, other dopamine conjugates can be found, as well.[2,36]

AADC and the activity of COMT and MAO combine to contribute to both a low bioavailability of approximately 30% and a short half-life for oral L-dopa alone of approximately 50 min. The amount of L-dopa that survives first-pass metabolism still has to reach and cross the BBB; very small amounts (1−3% of the initial dose) do this successfully.[16,21] However, L-dopa orally administered with the decarboxylase inhibitor carbidopa has a bioavailability increased by 2−3-fold, and an increased half-life of approximately 90 min. The addition of carbidopa also increases the amount of L-dopa that reaches and crosses the BBB.[19,37] Peak plasma levels of L-dopa/carbidopa are seen approximately 1−2 h after ingestion.[16,21]

MANUFACTURING INFORMATION

Roche, in 1970, was the first pharmaceutical company to bring levodopa to market under the name Larodopa.[21] Levodopa, in combination with carbidopa, is currently manufactured under the brand name Sinemet by Merck. Several other brand names and combination products exist, including Bidopal, Atamat, Duodopa, Madopar, and Stalevo. There are several generic manufacturers of L-dopa (Actavis US, Sandoz, and Teva Pharmaceuticals). Sinemet also comes in a controlled release formulation (Sinemet CR or Madopar HBS) that keeps plasma levels of L-dopa steady but also reduces bioavailability. Controlled release formulations have not been shown to be as effective in controlling motor fluctuations as immediate release formulations taken more frequently.[21] Sinemet is available in three dosage strengths (carbidopa/levodopa): 25 mg/100 mg, 10 mg/100 mg, and 25 mg/250 mg.[7,19]

As previously stated, combinations of L-dopa and carbidopa can be given with COMT inhibitors, such as tolcapone and entacapone. Roche first manufactured tolcapone in 1997 under the brand name Tasmar. There is not a combination formulation of levodopa, carbidopa, and tolcapone currently available. Entacapone was manufactured in 1998 under the names Comtess (Orion) and Comtan (Novartis). Stalevo is the brand name of the combination formulation of levodopa, carbidopa, and entacapone.[21] There are currently six different dosage strengths of Stalevo (carbidopa/levodopa/entacapone): 12.5 mg/50 mg/200 mg, 18.75 mg/75 mg/200 mg, 25 mg/100 mg/200 mg, 31.25 mg/125 mg/200 mg, 37.5 mg/150 mg/200 mg, and 50 mg/200 mg/200 mg.[29]

PHARMACOLOGY, ADVERSE REACTIONS, AND DOSAGE

While L-dopa's mechanism of action is unconfirmed, current theory suggests that L-dopa is absorbed in the small intestine and transported to the brain. L-dopa is transported across the BBB by LAT1, a system L neutral amino acid transporter.[19,38−40] Because it is a prodrug, L-dopa is inactive until it crosses the BBB and is decarboxylated to dopamine in the striatum.[19,38] It is believed that the therapeutic benefits from L-dopa therapy emerge from stimulation of D_2 receptors, though D_1 stimulation may play a role.[16] Dopamine levels in the striatum are increased, providing relief of motor symptoms. It has been estimated that by the time a patient is diagnosed with PD, approximately 70−80% of their dopaminergic neurons have degenerated.[32] Over time, the neurodegeneration continues, thereby limiting L-dopa's therapeutic effects. The addition of carbidopa allows for treatment with smaller doses of levodopa, as carbidopa blocks peripheral metabolism of levodopa to dopamine, and, because it cannot cross the BBB, does not interfere with the metabolism of levodopa to dopamine in the brain.[14,15,19]

Perhaps the greatest obstacles to effective L-dopa treatment are the severe ADRs associated with its use. Drug-induced dyskinesia, or involuntary movement, is the most prevalent and dose-limiting ADR. As levodopa doses increase over time, dyskinesias become more common, seen in up to one-third of patients after treatment for 2 years and approximately 80% after treatment for 10 years.[12,13,16,17,19,41,42] Furthermore, no treatment for preventing or eliminating these dyskinesias exists, and their etiology remains unknown. These dyskinesias can become so severe as to negate any positive effects from L-dopa treatment.[38,42] The "on−off" phenomenon, denoting when a patient's treatment is working and when it is not, is another common adverse reaction after long-term treatment.[16,17] Increased L-dopa doses and more frequent dosing intervals are needed to compensate for the patient's increasing off time, although this leads to a higher risk of ADRs.[31]

Neurological adverse effects are also widespread in levodopa treatment. These effects include depression, hallucinations, anxiety, and nightmares, all of which are exacerbated with the addition of carbidopa to the drug regimen (most probably because of increased amounts of levodopa reaching the brain).[12,16,19,42] Furthermore, impulse control disorders have been linked to levodopa treatment, although the biological mechanism is not fully understood.[43] While treatment for these neurological effects does exist, a need for discontinuation of levodopa therapy may occur.[12,16,19,42,43]

Gastrointestinal and cardiovascular ADRs are prevalent with L-dopa used alone. The amount of peripheral dopamine produced by decarboxylases causes in addition to other ADRs, nausea, vomiting, cardiac arrhythmias, and hypotension.[7,12,14,15,19,21,42] These ADRs can be reduced by slowly increasing the dose of levodopa and by adding carbidopa to the drug regimen.[7,13−15]

The short half-life of L-dopa (~90 min) with a DCI[21] makes establishing steady plasma levels of L-dopa extremely difficult.[42,44] Inconsistent plasma levels of L-dopa correlate to inconsistent dopamine levels at the target neurons in the brain. Therefore, L-dopa must be administered multiple times per day. However, even three doses of L-dopa a day has not achieved steady plasma levels consistently.[42]

HISTORY AND IMPORTANCE IN NEUROSCIENCE

Although PD was discovered in 1817, prior to L-dopa's discovery there was not an effective treatment for managing the symptoms of PD.[38] It is important to note, however, that Jean-Martin Charcot and William Gowers made significant headway in prescribing hyoscyamine, an anticholinergic drug that has some effect on dopamine levels in the striatum.[6] In 1961, Hornykiewicz pioneered the use of levodopa to enhance dopamine levels in the striatum, significantly improving symptoms in many patients.[6,7] With the addition of carbidopa in 1974, the frequency of GI ADRs was significantly reduced, leading to the modern treatment of PD.[21]

Although levodopa treatment is more than 50 years old, it remains the gold standard for Parkinson's treatment.

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Unfortunately, levodopa treats symptoms without stalling disease progression, allowing for worsening symptoms over time.[21,41,44] This is further complicated because as a patient's PD progresses, their response to L-dopa decreases, causing the therapeutic window to be reduced and increasing the frequency of ADRs. Not surprisingly, the gradual lengthening of the "off" time is the most problematic issue of long-term levodopa treatment.[21,41]

There are currently several drugs used to supplement L-dopa therapy in an effort to manage the motor symptoms of worsening "off" times. Apomorphine is commonly prescribed to help rescue patients from the symptoms of "off" episodes. The major downside to this therapy is the subcutaneous dosage form that must be injected in the lower abdominal wall or upper thighs. In the future, apomorphine may be available in other dosage forms, such as a sublingual film that is currently in clinical trials.[45] Another rescue medication that is showing promising results is an inhaled L-dopa delivery system. Inhaled L-dopa would have the benefits of faster access to the CNS in addition to less degradation by intestinal enzymes. Civitas Therapeutics has an inhaled levodopa formulation (CVT-301) currently in phase 2 clinical trials. The drug is administered when interdose motor symptoms occur. The inhaled L-dopa, in theory, would rapidly increase levels in the bloodstream to achieve therapeutic effects between baseline oral doses.[46,47]

Future treatments of PD will likely focus on stem cell treatment, neuroprotective effects, or small molecule therapies. One exciting avenue of research is T-type Ca^{2+} channel inhibitors, which could be used to prevent tremors.[48] In addition, positive allosteric modulators of mGluR4 are showing promising neuroprotective and motor effects.[49−51] These future therapies could be used in combination with L-dopa or as stand-alone therapy.[48−51] At present, however, L-dopa remains the best and most widely used treatment for Parkinson's disease.[21,26] L-dopa is truly a classic in chemical neuroscience.

AUTHOR INFORMATION

Corresponding Author

*E-mail: nate.daniels@lipscomb.edu.

Notes

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