26 April 2013

Apomorphine for Off Periods in Parkinson's Disease: Clinical Use and Potential of a Developmental Sublingual Formulation, APL130277

Anthony Giovinazzo, M.B.A., C.Dir., A.C.C.
President and C.E.O., Cynapsus Therapeutics, Inc.

Albert Agro, Ph.D.
Chief Medical Officer, Cynapsus Therapeutics, Inc.

Nathan Bryson, Ph.D.
Chief Scientific Officer, Cynapsus Therapeutics, Inc.

Timothy Tankosic, M.D.
Managing Director, Aqua Partners, LLC

Correspondence:
Anthony Giovinazzo, Cynapsus Therapeutics, Inc., Canada
Tel: +1 416 703-2449 x225
Email: ajg@cynapsus.ca

Summary

Nearly all patients with Parkinson's disease (PD) will experience motor fluctuations, known as freezing or *off* periods. Motor function and mobility may be severely reduced for substantial periods of time during *off* periods, causing deterioration in ability to perform activities of daily living, productivity, quality of life and psychological state. Apomorphine is the only available and effective drug for acute rescue treatment to rapidly reverse the *off* phases of PD. Unfortunately, apomorphine is currently available only as an injection (subcutaneous or SC), which has hindered its clinical acceptance and restricted the role of apomorphine in the care of the patient with PD. Disadvantages of the injection include inconvenience and pain, difficulty with self-injection during *off* episodes, increased caregiver burden and irritation and nodule formation at injection sites.

APL-130277 is a new sublingual (SL) thin filmstrip apomorphine formulation in clinical stage development to overcome the limitations of the injectable form. In pilot Phase 1 human clinical trials, APL-30277 reproduced the pharmacokinetic profile typically obtained by SC apomorphine injection. Larger trials will be initiated this year to determine whether it demonstrates bioequivalence with the approved SC apomorphine, with the goal of submitting a New Drug Application (NDA) in the US in 2015. The introduction of rapid-acting, non-injectable apomorphine, such as the SL formulation APL-130277, would benefit a large number of patients with PD. A SL film option would eliminate the injection for patients currently treated with SC apomorphine and improve management of patients with *off* periods that are currently untreated or ineffectively treated with levodopa dose adjustment.

Impact of off periods

Although the initial treatment of PD may restore motor function to normal or near normal, most patients will eventually develop motor fluctuations as the disease progresses. Motor fluctuations are *off* state motor symptoms, such as end of dose wearing off, sudden *on*/*off* and early morning akinesia. They occur even with optimized oral treatment with levodopa and dopamine agonists.

Early-morning akinesia is often the first motor complication of PD, noticed by the patient, after he/she begins to awaken with symptoms of Parkinsonism after the nightlong treatment-free period. Patients with early-morning akinesia often also experience a delay in restoration of their motor function after taking their initial morning dose of levodopa, which is known as slow or delayed *on* or latency to *on*. Patients may misguidedly take a higher than prescribed initial morning dose of levodopa, hoping to obtain a quicker *on*, but this can lead to dyskinesia (uncontrolled movements) and a hastening of tachyphylaxis to levodopa therapy.

End of dose wearing *off* is characterized by declining mobility as the dose period progresses to its end. End of dose wearing *off* is the most common motor fluctuation in PD and thought to be caused by a reduced duration of action of levodopa (more so than that observed with dopamine agonists). Sudden *on/off* fluctuations can occur at any time during the day or dose cycle. The unpredictability of sudden *off* is particularly disturbing to patients, causing anxiety, depression and feelings of loss of control. Dose failure or never *on* refers to the absence of any clinical response to a dose of levodopa and most often occurs in patients who require frequent dosing. [ref. 1-5]

Physicians often think of motor complications caused by chronic levodopa therapy as mid- or later-stage manifestations of chronic drug therapy. About 40% of patients develop motor complications 4-6 years after initiation of levodopa therapy; and 70% are affected at 9 years. [ref. 6] However, end of dose wearing *off* occurs in as many as 25% of patients within 6 months of the initiation of levodopa therapy and in as many as 50% within 18 months. [ref. 7]

The findings above and from other studies suggest that motor fluctuations (i.e., *off* periods) affect a larger population of patients with PD than may be fully appreciated. An observational registry known as, Implications of Motor Fluctuations in Parkinson's Disease Patients on Chronic Therapy (IMPACT), was established to catalog characteristics of *on-off* fluctuations in patients with PD who experience *off* periods and educate physicians to assist them in making more informed treatment decisions.

Inclusion of cases in IMPACT required completion of interviews by both patients and their physicians. Both interviews were completed in 1,196 of 1,256 enrolled patients. The three most common types of fluctuation were:
- Wearing *off* (reported by 81.2%; n=1,020)
- Sudden *on/off* fluctuations (reported by 42.3%; n=531)
- Latency to *on* (reported by 39.7%; n=499).

The most significant quality of life problems reported by patients were loss of mobility and decreased performance in activities of daily living. [ref. 8]

Intermittent rescue treatment of off periods with apomorphine

Apomorphine, a non-ergot, potent dopamine agonist that binds principally to D1-like and D2-like receptors, is the only available and effective drug for acute rescue treatment that reverses the *off* episodes of PD. Apomorphine was first used as a PD treatment as early as 1951. Clinical use was first reported in 1970, although the drug's emetic properties and short half-life rendered oral use impractical. A later study found that combining apomorphine with the peripheral dopamine receptor blocker, domperidone (10mg), improved results significantly.

Apomorphine must be administered by parenteral routes because absorption in the gut is very poor, resulting in low bioavailability (approximately 1%). The SC formulation was developed to bypass first-pass hepatic

metabolism and solve the problem of low oral bioavailability. The SC form also enabled the use of apomorphine for rescue treatment of *off* episodes because it exhibits the critical properties of rapid uptake and quick onset of action, usually within 5 to 15 minutes. The duration of action of SC apomorphine is relatively short (typically 60-90 minutes); the half-life is about 45 minutes.

Like other dopamine agonists, apomorphine is generally well tolerated but demonstrates emetic properties at high doses because of peripheral dopaminergic actions. Treatment with apomorphine requires premedication and continuing co-medication with an antiemetic in many patients. Domperidone may be administered to prevent emesis, bradycardia and hypotension. The antiemetic, trimethobenzamide, is used in the US because domperidone is not available. Patients may be able to discontinue co-administration of the antiemetic after about 2 months, without experiencing recurrence of the adverse effects of apomorphine. Antiemetic treatment is discontinued in nearly all patients (95%) within 3 to 6 months. Postural hypotension may affect approximately 15% of patients treated with apomorphine. Affected patients are identified and managed in higher risk groups. The total daily dose of apomorphine can range up to 20-25mg/daily. [ref. 9-13]

SC apomorphine has been available in Europe for the intermittent treatment of *off* periods of PD since 1993, was approved in the US in April 2004 and is not approved in Canada. The US FDA approval is for APOKYN (apomorphine hydrochloride injection; Britannia Pharmaceuticals Ltd.), which is indicated for *the acute, intermittent treatment of hypomobility, off episodes (end-of-dose wearing off and unpredictable on/off episodes) associated with advanced Parkinson's disease. APOKYN has been studied as an adjunct to other medications*. [ref. 14]

The clinical trial results that led to the US approval were reviewed. [ref.1] A currently ongoing clinical trial is studying SC apomorphine injection specifically for delayed onset of action of levodopa taken upon awakening. A sub-study of this trial is examining the effect of apomorphine on gastroparesis. Reduced motility of the stomach muscles is hypothesized to be an *off* period effect that contributes to the slow *on* of the initial morning dose of levodopa. See Box 1.

BOX 1: Ongoing trial: SC apomorphine for delayed onset of action of levodopa taken upon awakening

Apokyn for Motor IMProvement of Morning AKinesia Trial (AM IMPAKT) is an ongoing clinical trial testing the effectiveness of SC apomorphine for rapid improvement of motor symptoms in patients with PD who experience delayed onset of oral levodopa action after taking levodopa upon awakening. AM IMPAKT is a US, Phase IV, multi-center, open-label study with expected enrollment of 100 patients and anticipated completion in August 2013 [NCT01770145].

A gastroparesis sub-study of AM IMPAKT is examining the effect of apomorphine treatment on gastric emptying time. Patients with PD commonly experience gastroparesis, which may contribute to slowed levodopa absorption and onset of action after the first dose upon awakening. Patients enrolled in the gastroparesis sub-study undergo two gastric emptying imaging studies, once at baseline and once at the end of the apomorphine treatment period. Changes in gastric emptying times will be compared to assess the effect of apomorphine on gastroparesis.

It may be that, in addition to reversing *off* period hypomobility through direct dopaminergic action, apomorphine increases gastric motility and promotes absorption of the initial morning dose of levodopa.

Source: A Phase 4, Open-Label, Efficacy and Safety Study of Apokyn® for Rapid and Reliable Improvement of Motor Symptoms in Parkinson Disease Subjects With Delayed Onset of L-Dopa Action. US NIH Clinicaltrials.gov record NCT01770145. Accessed 18 April 2013 - http://clinicaltrials.gov/ct2/show/NCT01770145?term=apomorphine&rank=2

Limitations of the SC injection formulation

Despite its well-established efficacy for the intermittent rescue treatment of *off* episodes, the need for an SC injection has restricted the clinical use of apomorphine. The drawbacks of self-injection, generally, and SC apomorphine, specifically, have been described in many anecdotal reports. A recent study based on a survey of neurologists and movement disorder specialists provides insight into how treating physicians view apomorphine rescue treatment. [ref. 15]

Drawbacks of SC apomorphine injection include:

• Needle or injection phobia

• Pain of injection

• Lack of manual dexterity/ inability to self-inject, which is exacerbated in *off* phases and particularly difficult for elderly patients with PD. In addition to proper placement of the injector, some patients have had problems applying enough pressure to push down the plunger.

• Absence of caregiver to administer injection. Unskilled caregivers may be reluctant/ unable to inject patients.

• If a competent caregiver is present, the patient may be reluctant to give someone else control over their daily routine (loss of locus of control).

• Inflammation of subcutaneous adipose tissue (panniculitis) and subcutaneous nodule formation. Myalgia.

Because of these drawbacks, patients with PD may resist or be unable to comply with SC apomorphine treatment. [ref. 16-17]

A recent survey study of neurologists and movement disorder specialists (MDS) was conducted to assess their current clinical use of intermittent SC apomorphine treatment and perceptions of unmet clinical needs. *Trends in the treatment of Parkinson's disease* is based on a survey of 500 neurologists and MDS, of whom 374 were neurologists and 126 were MDS. By region: 150 were from the United States, 193 were from Europe and 157 were from Japan, China and other countries (India, Brazil, and Mexico). Collectively, the participating physicians treat approximately 62,000 Parkinson’s patients per year. [ref. 15]

EXHIBIT 1A shows the breakdowns by severity of all patients with PD treated by surveyed neurologists (includes general neurologists and MDS) and MDS, the percentages of patients they treat with apomorphine and the breakdown by severity of the patients treated with apomorphine. Notably, the MDS group treats a somewhat larger percentage of their patients with apomorphine than the aggregate group including general neurologists.

EXHIBIT 1A: Current Use of Apomorphine in Patients with PD-1: Selected Neurologist Survey Results[1]

SURVEY PARAMETER	ALL NEUROLOGISTS[2]	MDS[3]
PD severity[4] of patients in your practice		
Mild-moderate (Stages 1 and 2)	41.4%	42.9%
Moderate-severe (Stages 3 and 4)	42.2%	41.8%
Severe (Stage 5)	16.4%	15.4%
PD patients under your personal management currently receiving apomorphine	4.7%	6.6%
Among patients currently receiving apomorphine, what percentage fall under each of the following PD severity classifications?		
Mild-moderate (Stages 1 and 2)	6.4%	8.6%
Moderate-severe (Stages 3 and 4)	40.2%	40.9%
Severe (Stage 5)	53.4%	50.5%

1. Ref. 15.
2. Aggregate response, includes all study participants.
3. Movement disorders specialists' responses.
4. PD severity rankings are based on Hoehn and Yahr classification.

EXH 1B provides survey details about treatment practices with apomorphine and found that:

• MDS are more likely than the aggregate neurologist group to include apomorphine in their baseline treatment at all levels of disease severity.

Both groups reported that:

• The percentages of patients who experience motor fluctuations on levodopa treatment increase as disease severity increases.

• They increase their use of apomorphine after levodopa dose/ timing adjustment fails and after dyskinesia occurs.

• Approximately 25% of their patients who should be treated with injectable apomorphine will not accept this treatment because it requires a needle injection.

• Approximately 25% of their patients complain about injection-site reactions.

• Approximately 50% of their patients require at least some period of anti-emetic therapy.

EXHIBIT 1B: Current Use of Apomorphine in Patients with PD-1: Selected Neurologist Survey Results[1]

PD SEVERITY[2]	BASELINE TREATMENT INCLUDES APOMORPHINE		PATIENTS ON L-DOPA + INHIBITOR THERAPY WHO EXPERIENCE MOTOR FLUCTUATIONS		AFTER DOSE AND TIMING ADJUSTMENT FOR MOTOR FLUCTUATIONS, NEXT STEP IS TO **ADD APOMORPHINE**		AFTER DOSE AND TIMING ADJUSTMENT FOR MOTOR FLUCTUATIONS + DYSKINESIA, NEXT STEP IS TO **ADD APOMORPHINE**	
	All[3]	MDS[4]	All	MDS	All	MDS	All	MDS
Mild-moderate (Stages 1 and 2)	1.9%	2.6%	13.3%	14.0	1.4%	0.8%	3.0%	1.6%
Moderate-severe (Stages 3 and 4)	4.8%	6.3%	40.5%	44.4	5.8%	10.3%	8.2%	9.5%
Severe (Stage 5)	6.9%	8.5%	59.8%	62.3	24.6%	31.7%	20.4%	20.6%
Percentage of patients who should be on injectable apomorphine but won't because it is a needle							28.9%	24.6%
Percent of patients who complain about injection-site reactions							24.3%	25.3%
Percentage of patients who require anti-emetic therapy							51.3%	45.9%

1. Ref. 15.
2. PD severity rankings are based on Hoehn and Yahr classification.
3. Aggregate response, includes all study participants.
4. Movement disorders specialists' responses.

Non-injectable apomorphine: developmental challenges

Many studies suggest that a large number of patients with *off* periods would benefit from a non-injectable apomorphine formulation. This unmet clinical need was identified two decades ago and led to the early efforts to develop a non-injectable alternative. Most failed in preclinical or early stages of clinical development.

One of greatest challenges of developing a non-injectable apomorphine is achieving the rapid absorption and onset of action of the SC form, which is required of a rescue medication. Oral administration is not feasible because of slow absorption and onset of action (and also extensive first-pass metabolism and poor bioavailability). Transdermal delivery also demonstrates onset of action that is too slow for rescue from *off* episodes. The long duration of action of transdermal delivery is also problematic for this indication.

Systemic inhaled-pulmonary delivery could achieve rapid onset of action, but poses many other challenges related to drug stability, safety, cost of goods, self-administration in the *off* state and others. It is notable that only one NDA, for pulmonary insulin, has ever been approved in the US for *systemic* pulmonary delivery (i.e., not local delivery to treat lung tissue). The manufacturer later withdrew the product from the market. An inhaled-pulmonary apomorphine formulation completed a Phase II trial in 2010, but the company will not continue to develop the product.

Nasal and sublingual apomorphine formulations were somewhat successful in delivering apomorphine with sufficiently rapid onset of action. However, development of nasal formulations has been plagued by instability of solution phase apomorphine and irritation of the nasal mucosa. Powdered formulations can overcome the stability but not the nasal irritation issues. The most recent effort to develop nasal apomorphine was discontinued because of irritation. Developmental SL formulations were discontinued because clinically acceptable products could not be developed. In one case, SL tablets dissolved too slowly. Another was a cumbersome kit product that required the patient to mix liquid apomorphine with buffer solution immediately before each administration. [ref. 18]

APL130277 - a new sublingual (SL) apomorphine formulation

APL130277 (Cynapsus Therapeutics, Inc.; Toronto, Ontario, Canada) is a new SL apomorphine formulation currently in Phase 1 development. APL-130277 is a solid dosage form of apomorphine in a SL thin filmstrip formulation designed for rapid dissolution (typically in 1-2 minutes) and absorption directly into the blood.

A thin film vehicle was utilized because apomorphine is unstable in solution and a thin film allows incorporation of solid active ingredient and stabilizing excipients (buffer). The thin film dissolves rapidly in a minimal volume of saliva, much like Listerine® Breath Strips. Disintegration and dissolution occur with a high degree of intimacy between the drug and SL tissue where absorption occurs, which improves absorption compared to SL tablet formulations. The buffer reduces acidity and the potential for irritation at the site and maintains optimal absorption kinetics. Thin film is a relatively new vehicle for prescription drug delivery. Only a few prescription thin film formulations are FDA approved: Onsolis® (fentanyl, 2009), Suboxone® (buprenophine + naloxone; Reckitt Benckiser Pharmaceuticals, Inc.; 2010) and Zuplenz® (ondansetron, Vestiq Pharma, 2010).

APL130277 - Phase 1 trial positive; second, larger trial imminent

A 2012 human Phase 1 pilot trial demonstrated proof of concept of the use of APL-130277 (3mg) for the treatment of *off* episodes in PD. This trial assessed pharmacokinetics and safety /tolerability in 15 healthy volunteers; 12 received drug product and 3 received placebo. After washout, subjects were dosed a second time with APL-130277 placed in a different orientation under the tongue. Key findings included:

• Sublingual administration of APL 130277 reproduced the pharmacokinetic profile typically obtained with SC apomorphine injection.

• The observed mean T-max of <25 minutes for APL-130277 compares favorably with SC apomorphine. Maximum blood levels were reached within 20 minutes of administration in most subjects. The comparable mean T-max suggests that SL APL-130277 might reproduce the pharmacokinetic profile of the reference drug, which would allow a bioequivalence (BEQ) route for NDA submission.

• APL-130277 was safe and well tolerated. Adverse events (AE) were mild. Two (17%) drug-treated subjects had at least one AE: one experienced moderate nausea and dizziness. Systemic AE were similar to those commonly observed with SC apomorphine. One (33%) placebo-treated subject experience AE.

• SL orientation of APL-130277 affected the T-max and PK.

• Other pharmacokinetic parameters mirrored those observed with SC apomorphine injection after an expected dose adjustment.

After obtaining promising results from the pilot Phase 1 trial, funding was obtained from The Michael J. Fox Foundation for Parkinson's Research (MJFF; New York, NY) to conduct a Phase 1 trial comparing 3 doses of APL-130277 to 3 doses of Apokyn SC injection. BOX 2 provides details of the design of the imminent Phase 1 trial, funded by MJFF. Results of this trial will inform the design of 2 subsequent, larger trials, the first intended to demonstrate PK bioequivalence of APL-130277 and Apokyn SC injection and the second intended to demonstrate tolerability. The regulatory goal is the submission of a 505(b)2-type NDA by late 2015.

BOX 2: APL-130277: Phase 1 Trial Design

A Three-dose Active Comparator, Placebo-controlled Randomized Cross-over Pre-Bioequivalence (BEQ) Phase I Trial to Examine the Single Dose Pharmacokinetic Profile of Sub-Lingual Administered APL-130277 as Compared to Sub-Cutaneous Apomorphine in Healthy Volunteers

PRINCIPAL INVESTIGATORS:
– Albert Agro, PhD and Nathan Bryson, PhD

DRUGS:
– Investigational: APL-130277 (10mg, 15mg and 25mg sublingual strips)
– Reference product: apomorphine (2mg, 3mg and 4mg administered s.c.)

OBJECTIVES:
– The primary objective of this study is to evaluate the pharmacokinetics, safety and tolerability of a single 10mg, 15mg and 25mg dose of APL-130277 as compared to 2mg, 3mg and 4mg of s.c. apomorphine in a crossover design of three Cohorts of 16 subjects.
– Three Cohorts of 16 subjects each (2 subjects receive placebo) will receive either:
  • Cohort 1: 10mg APL-130277 or 2mg of s.c. apomorphine
  • Cohort 2: 15mg of APL- 130277 or 3mg of s.c. apomorphine
  • Cohort 3: 25mg APL-130277 or 4mg s.c. apomorphine
– The initial treatment will be followed by a 24-hour washout period. The same subjects will be crossed over to the treatment they didn't receive on Day 1. Placebo subjects will remain on placebo during the crossover.

SUBJECTS:
– 48 healthy male volunteers
– 16 subjects randomized (14 to comparator or study drug; 2 to placebo) and crossed over in each Cohort

DESCRIPTION:
– This single center Phase I pre-BEQ trial in healthy subjects will assess the single dose pharmacokinetics, safety and tolerability of a single dose of APL-130277 administered to three Cohorts (10mg, 15mg and 25mg) in a cross over design as compared to the pharmacokinetics of 2mg, 3mg and 4mg of s.c. apomorphine.

STUDY ENDPOINTS:
– 1. PK: Pharmacokinetic profile, including: C_{max}, T_{max}, λ_z, $t_{1/2}$, AUC, MRT, CL/F and V/F with historical comparisons between APL-130277 and s.c. apomorphine.
– 2. Safety and Tolerability: Evaluation of clinical laboratory tests, 12-lead ECGs, physical examinations, vital signs (including body temperature and weight), and adverse events.

RELEVANCE TO DIAGNOSIS/TREATMENT OF PARKINSON'S DISEASE:
– Apomorphine is an under-utilized medication in PD. Despite its strong efficacy and rapid onset of action, patients find injections painful and resist use until the latest stages of PD. Physicians find the dose initiation cumbersome. Eliminating some of these barriers are key objectives of Cynapsus' APL-130277. APL-130277 is an innovative, fast-dissolving, sublingually administered thin-film product for use as rescue medication for OFF episodes in Parkinson's disease. APL-130277 is easy to self-administer under the tongue.

ANTICIPATED OUTCOME:
– This three-dose active comparator, pre-BEQ study will lead directly into the registration study examining the BEQ of the thin strip formulation of APL-130277 with sc apomorphine. Completion of this study will enable Cynapsus to make an accurate assessment of sample size for the BEQ study, further examine the PK profile of the final (clinical/commercial grade) formulation of APL-130277 and further confirm, in a controlled study, the appropriate Tmax of APL-130277 as directly compared to sc apomorphine.

Source: Cynapsus Therapeutics, Inc. and The Michael J. Fox Foundation for Parkinson's Research (Parkinson's funded grant).

The successful development, regulatory submission and market introduction of a sublingual apomorphine formulation with a rapid onset of action could expand the use and transform the clinical role of apomorphine. When assuming FDA approval and availability of a SL formulation, surveyed neurologists predicted that their use of apomorphine would increase substantially across all 3 classes of PD severity. See EXHIBIT 2.

Key findings:

• Column 1.a shows the current use levels of SC apomorphine. Column 1.b: assuming the availability of SL apomorphine, surveyed neurologists would consider using it in 15.1% of mild-moderate cases, 38.1% of moderate-severe cases and 49.5% of severe cases of PD. These projected uses would represent approximately 30% of all patients with PD.

• Surveyed neurologists also believe that the availability of SL apomorphine could change patterns of levodopa use and that levodopa sparing, if achieved, would be beneficial:

– 75.6% of surveyed neurologists believe that SL apomorphine would/could be utilized to achieve fast *on* in the morning and one or two more times per day instead of levodopa.

– 73.2% surveyed neurologists believe that levodopa sparing, if provided by apomorphine, would have clinical benefits to patients.

EXHIBIT 2: Predicted Use of SL Apomorphine in Patients with PD: Selected Neurologist Survey Results[1, 2]

PD SEVERITY[2]	CURRENT USE OF INJECTION	PREDICTED USE OF NEW SL FORMULATION
	1.a What percent of the following patients groups receive apomorphine as an injection or infusion pump method of delivery?	1.b If a sublingual solid fast dissolving dosage form (an oral tablet or similar) of apomorphine were made available, in what percent of your patients in the following categories would you consider using this drug?
Mild-moderate - stages 1-2	3.2%[4]	15.1%
Moderate-severe - stages 3-4	14.6%[4]	38.1%
Severe - stage 5	18.3%[4]	49.5%

SURVEY QUESTION	YES	NO
2. Do you think that a sublingual solid fast dissolving dosage form would/could be utilized as an adjunct therapy by a patient to achieve fast on in the morning, and one or two more times per day instead of their levodopa?	75.6%	24.4%
3. As an adjunct therapy, do you believe the levodopa sparing that could be provided by apomorphine has clinical benefits to the patients over time?	73.2%	26.8%

1. Ref. 15.
2. Aggregate response, includes all study participants.
3. PD severity rankings are based on Hoehn and Yahr classification.
4. Includes both intermittent injection and constant infusion of apomorphine.

References

1. Stacy M, Silver D. Apomorphine for the acute treatment of "off" episodes in Parkinson's disease. Parkinsonism Relat Disord. 2008;14(2):85-92.

2. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease. Neurology. 2009 May 26;72(21 Suppl 4):S1-136.

3. Schapira AHV, Emrebe M, Jenner P, Poewe W. Levodopa in the treatment of Parkinson's disease. Eur J Neurology. 2009;16:982–989.

4. Khora S-P, Hsub A. The Pharmacokinetics and Pharmacodynamics of Levodopa in the Treatment of Parkinson's Disease. Curr Clin Pharmacol. 2007;2:234-243.

5. Chen JJ, Swope DM. Pharmacotherapy for Parkinson's Disease. Pharmacotherapy 2007;27(12 Pt 2):161S–173S.

6. Gunzler SA. Apomorphine in the treatment of Parkinson disease and other movement disorders. Expert Opin Pharmacother. 2009 Apr;10(6):1027-38.

7. Espay AJ. Management of motor complications in Parkinson disease: current and emerging therapies. Neurol Clin. 2010 Nov;28(4):913-25.

8. Anthony J, Spears J, Van Lunen B. Implications of motor fluctuations in Parkinson s disease patients on chronic therapy (IMPACT): Results from an observational registry. Movement Disorders. 2005;20(Suppl 10; Abs P494):S146.

9. Dent JY. Apomorphine Treatment of Addiction. British Journal of Addiction to Alcohol & Other Drugs. 1949;46(1):15-210.

10. Cotzias G, Papavasiliou P, Fehling C, Kaufman B, Mena I. Similarities between neurologic effects of L-dopa and of apomorphine. N Engl J Med. 1970;2102(1):31-33.

11. Corsini G, Del Zompo M, Gessa G, Mangoni A. Therapeutic efficacy of apomorphine combined with an extracerebral inhibitor of dopamine receptors in Parkinson's disease. Lancet. 1979;1(10123):954-56.

12. Millan MJ, Maiofiss L, Cussac D, Audinot V, Boutin JA, Newman-Tancredi A. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. I. A multivariate analysis of the binding profiles of 14 drugs at 21 native and cloned human receptor subtypes. J Pharmacol Exp Ther. 2002;303(2):791-804

13. Schwab R, Amador L, Lettvin J. Apomorphine in Parkinson's disease. Trans Am Neurol Assoc. 1951;56:251-253.

14. APOKYN® (apomorphine hydrochloride injection) FDA label Revised 01/2011; NDC code: 15054-0211-5; http://labels.fda.gov/packagecode.cfm.

15. Medacorp report. Trends in the treatment of Parkinson's disease (independent research survey conducted for Cynapsus Therapeutics). 2011 (Dec).

16. McGee P. Apomorphine treatment: A nurse's perspective. ACNR. 2002;2(5):23-24.

17. Gosney M, Harper A, Conroy S (Editors). Oxford Desk Reference: Geriatric Medicine (Oxford Desk Reference Series). 2012:297. [978-0-19-959234-0]

18. Giovinazzo A, Bryson N, Tankosic T. Creating systemic oral transmucosal drug delivery strategies: Case study of APL-130277. J Commercial Biotech. 2012;18:33–42.