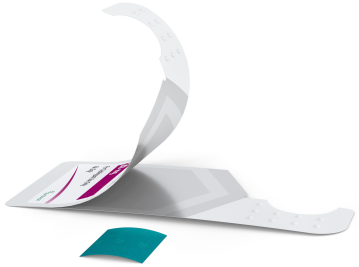
Advanced Therapies Panel Series: Apomorphine



Parkinson Society British Columbia

fraserhealth Better health. Best in health care.

Dr. Anish Kanungo

Movement Disorder Neurologist
Fraser Health Movement Disorder Clinic

Disclosures and acknowledgements

- I have also served as a consultant on Advisory Boards for Sunovion Pharmaceuticals and Paladin Labs, for which I have received compensation for my involvement
- I am not a patent holder, shareholder or financially invested in any of the pharmaceutical products discussed in this presentation, and I am not receiving financial support in the form of research grants from any industry or commercial supporters

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une compagnie de endo international
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Outline

- General discussion of how Parkinson's medications work, and why they stop working adequately (aka "motor fluctuations")

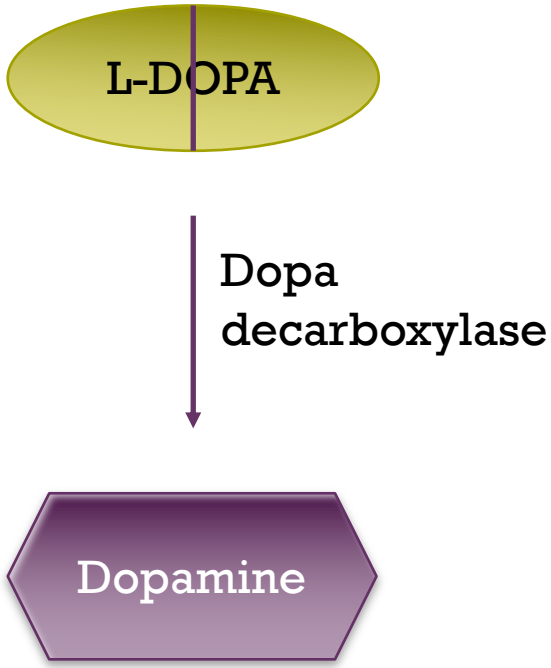
- Introduction to Apomorphine
  - How dose it work
  - Advantages and disadvantages

- Discuss how Kynombi™ (sublingual apomorphine) and Movapo™ (subcutaneous apomorphine) are used

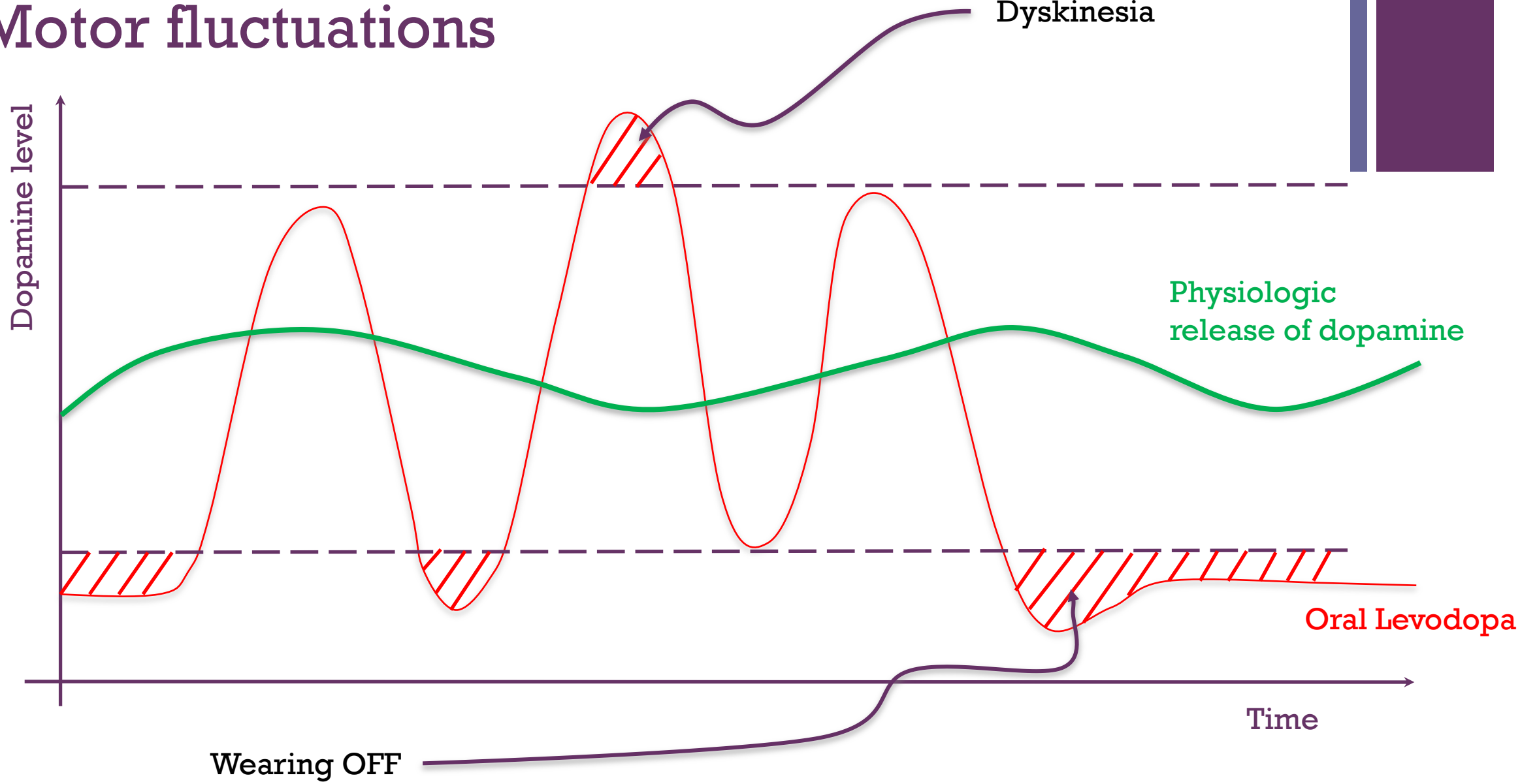
Levodopa/carbidopa

- **L(eva)-dopa** = chemical building block of dopamine
  - Requires absorption in small intestine - works within 30-90 minutes
    - Protein - reduces absorption
    - Diarrhea/constipation – reduces absorption
    - Carbonated beverages - increases absorption speed

- Carbidopa = Dopa decarboxylase inhibitor
  - Prevents peripheral conversion of levodopa → dopamine
    - Reduces systemic side effects
  - Increases the amount of levodopa transported to the brain
    - Improves duration of levodopa action by 1.5 hours



Motor fluctuations



Wearing OFF

- **In the early stages** …. a low dose of Levodopa effectively tops up the dopamine levels in the brain, such that most people get consistent symptom control with 3 doses per day

- **As the disease progresses** …. the loss of more dopamine-producing brain cells, makes it harder for each dose of Levodopa to prevent symptoms from re-emerging and people experience the phenomenon of **"wearing OFF"**
  - **The effects of Levodopa diminish before it is time for the next dose** … experience a return of slowness/stiffness/tremor (motor symptoms) and other non-motor symptoms between doses of Levodopa

Types of OFF episodes

- **Wearing OFF between doses of Levodopa**
  - May occur between every dose or only following certain doses
- **Morning OFF** – when a person awakens in the morning in an OFF state prior to taking their first dose of Levodopa
- **Late afternoon wearing OFF**
- **Delayed ON** - a delay in symptom improvement after dose of Levodopa is taken
- **Partial or Failed ON** – less than optimal symptom improvement after taking a dose of Levodopa, by comparison to a person's normal response to Levodopa
- **Unpredictable OFF** – abrupt and random changes from an ON state to a OFF state over seconds to minutes

Impact of OFF episodes

- Reduced quality of life from:
  - Impaired mobility (e.g. using the bathroom, unable to be active in the morning, unable to maintain active lifestyle)
  - Re-emergence of tremor → affects dexterity (e.g. difficulty with meals, performing house chores or work tasks)
  - Pain from rigidity (e.g. difficulty rolling in bed, frozen shoulder) and/or dystonia (e.g. twisting of feet, curling of toes)
  - Anxiety and depression

- Increased number of ER visits, hospitalizations, and ICU admissions [Thach et al., J Med Econ, 2021]
  - Translates into higher rates of nursing home placement and a higher economic burden on health care systems

- In an online survey of 3000 people with PD conducted by the Michael J Fox Foundation, 64% reported between 2-4 hours of OFF time per day

Strategies to reduce/alleviate OFF time

- Increase dose of Levodopa …. but can lead to toxicity (e.g. peak-dose dyskinesia) and side effects
- Decrease time between doses of Levodopa … but can lead to more side effects, and greater inconvenience (e.g. timing of protein-containing meals becomes more difficult to schedule)
- Increase time that Levodopa is active in brain … but can lead to more side effects and increased pill burden
  - COMT inhibitors (entacapone)
  - MAO B inhibitors (selegiline, rasagiline, safinamide)
- More consistent/continuous delivery of dopamine-stimulating medication
  - Transdermal Neupro™ (rotigotine) patch
  - Extended-release Levodopa (Rytari™ – not covered by Pharmacare)
  - Intestinal Levodopa gel via Duopoda™ pump

- Adjunctive therapies are used to reduce the overall OFF time …. BUT some people with Parkinson's will continue to experience OFF episodes no matter how aggressive we are with these therapies

Strategies to reduce/alleviate OFF time

- **On-demand therapies with rapid onset**
  - Movapo™ - subcutaneous apomorphine injection
  - Kynmobi™ - sublingual apomorphine film
  - Inbrija™ - levodopa inhalation powder

- Now there is something that can be done when a person with Parkinson's suffers a sudden unpredictable OFF episode, a failed ON, or to pre-emptively abort an OFF episode that is about to occur

Apomorphine

Not an Apotex generic Morphine!

Apo means “comes from” ..... a morphine derivative without opioid properties

Apomorphine

- **Non-ergot dopamine agonist** → acts on D2 dopamine receptors

Eur Neurol. 2013;69(6):321-4. doi: 10.1159/000346762. Epub 2013 Mar 14.

Erich Harnack (1852-1915) and a short history of apomorphine.

Taba P[1], Lees A, Stern G.

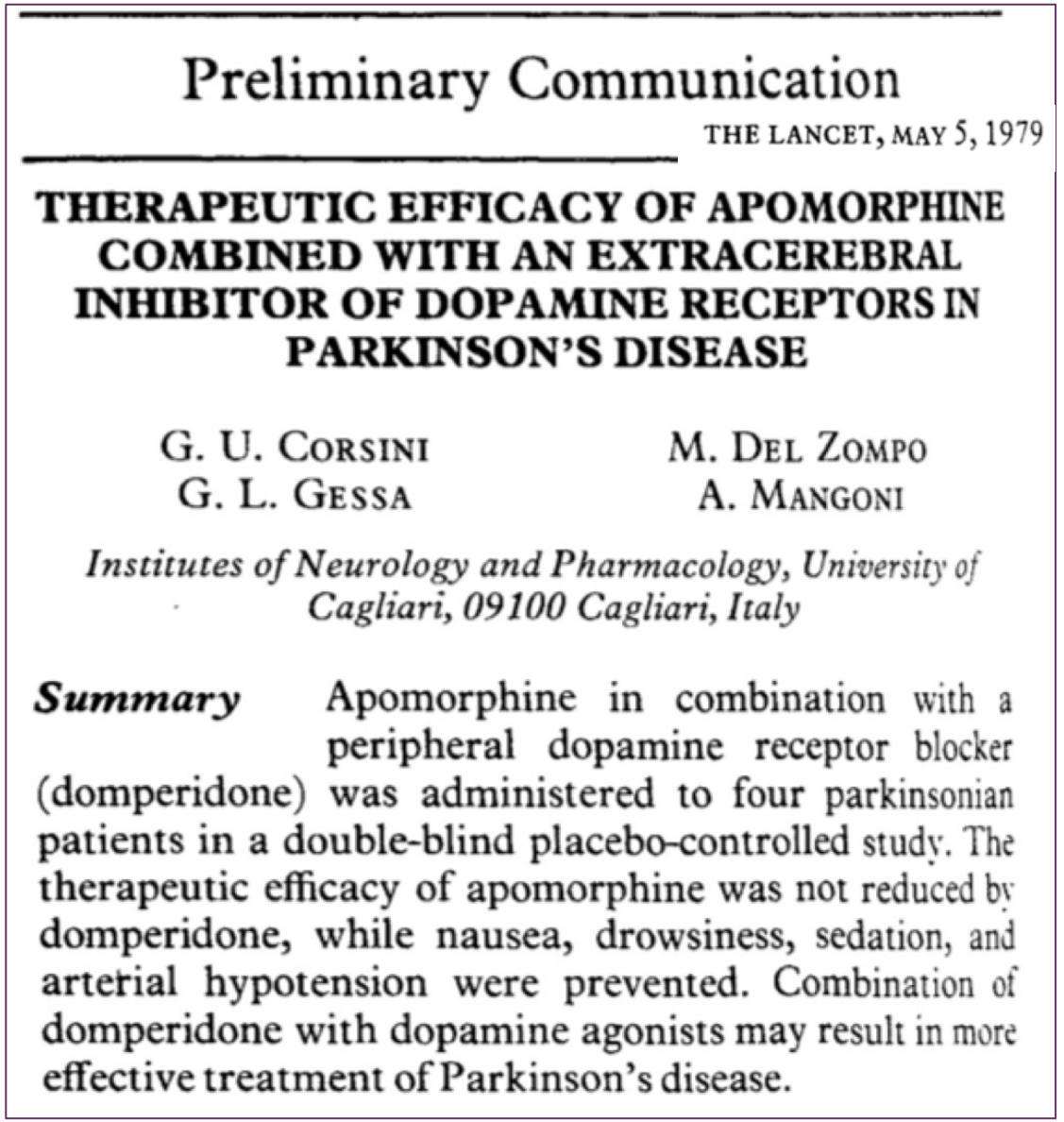
⊕ Author information

Abstract

Apomorphine, now established as an efficacious therapy for refractory motor fluctuations in levodopa-treated Parkinson's disease, has a long and chequered history in medical and veterinary therapeutics. The preclinical in vivo pharmacological effects of apomorphine were first studied about 150 years ago following which the drug was introduced for the treatment of behavioural vices in domesticated animals. Erich Harnack's early pharmacological studies in Dorpat (now Tartu, Estonia), where he belonged to the pharmacological dynasty of Buchheim and Schmiedeberg, are of particular historical significance as he emphasised that while apomorphine had potent emetic effects, the drug also had complex effects on the central nervous system.

Apomorphine

- Fell out a of favor for the treatment of Parkinson's motor symptoms due to severe systemic side effects and short duration of effect (by comparison to Levodopa)



Preliminary Communication

THE LANCET, MAY 5, 1979

THERAPEUTIC EFFICACY OF APOMORPHINE COMBINED WITH AN EXTRACEREBRAL INHIBITOR OF DOPAMINE RECEPTORS IN PARKINSON'S DISEASE

G. U. CORSINI, M. DEL ZOMPO, G. L. GESSA, A. MANGONI

Institutes of Neurology and Pharmacology, University of Cagliari, 09100 Cagliari, Italy

Summary Apomorphine in combination with a peripheral dopamine receptor blocker (domperidone) was administered to four parkinsonian patients in a double-blind placebo-controlled study. The therapeutic efficacy of apomorphine was not reduced by domperidone, while nausea, drowsiness, sedation, and arterial hypotension were prevented. Combination of domperidone with dopamine agonists may result in more effective treatment of Parkinson's disease.

Apomorphine – potential side effects

- Nausea 15-40 minutes post-dose
- Yawning and/or runny nose – when it "kicks in"
- Hypotension – 1st dose must be administered in clinic
- Dyskinesia possible with higher doses BUT low risk overall
- Hypomania (elevated mood) → **can be useful if patient is depressed/apathetic**
- May cause hypersexuality – but potential for other ICDs is predicted to be low → **may improve libido**
- Potential for Dopa dysregulation syndrome? → **uncertain how much of a problem this might be in the 'real world'**
- **Hypersensitivity reactions of the mouth and throat (Kynmobi™) or skin (Movapo™)**
- **Sleep attacks**

Apomorphine – pros and cons

Advantages

- Rapid onset of action with 10-15 minutes
- Tolerance does not develop over time → personal dose remains the same regardless of progression of disease
- Robust and reliable effect

- Disadvantages
  - Short duration of effect 60-90 minutes → not meant to replace Levodopa (but could potentially allow for lower daily amounts of Levodopa to be used)
  - Contraindicated if patient is on SSRIs and in patients with sulfite sensitivity

Subcutaneous apomorphine

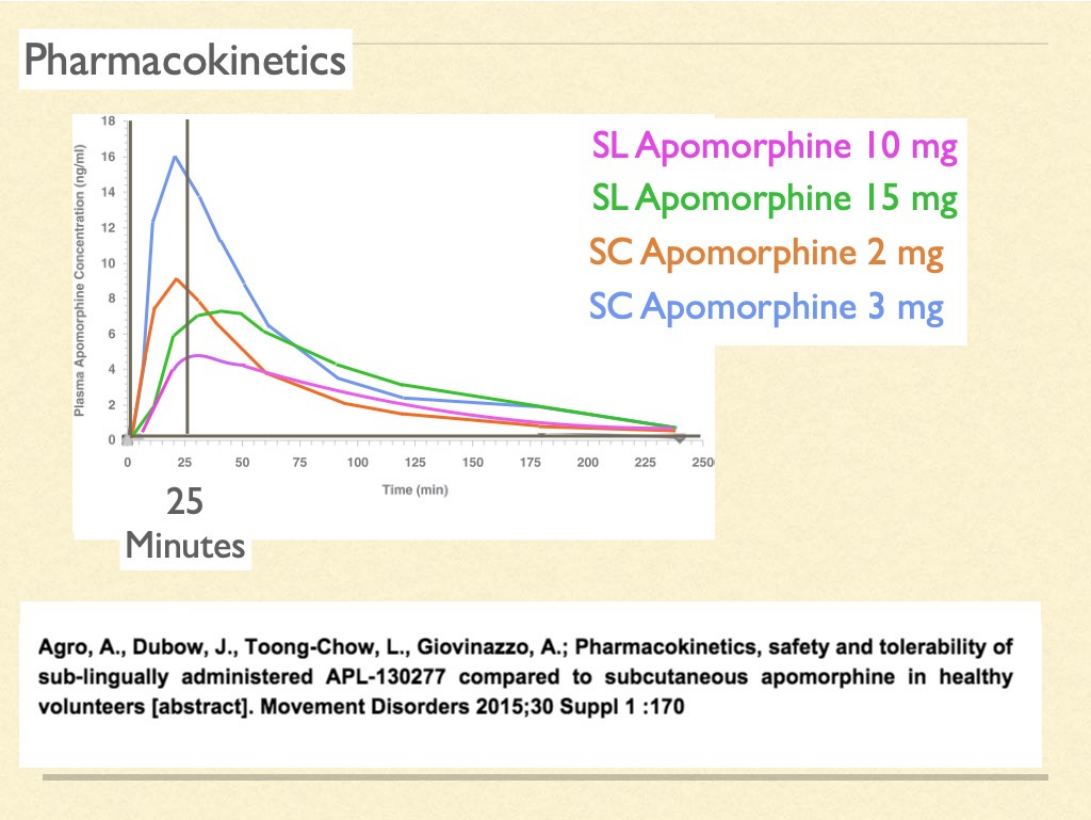
Movapo™ (Canada), Apokyn™ (USA)

Approved in Canada – November 2016
Launched in Canada 2018

paladin

Movapo™

- Indication: for the acute management of OFF episodes
  - Could also be used as a rescue medication in hospital (e.g. NPO patients for surgery)
- D1 and D2 agonist with weak D3 affinity
  - Onset 4-6 mins
  - Yawn/runny nose at 7 mins
  - Full effect in 10 mins
  - Duration of action = 50-60 mins
- Comes in 5 syringe packs (30 mg/syringe)
  - Must use syringe within 48 hours
- Liquid turns everything green

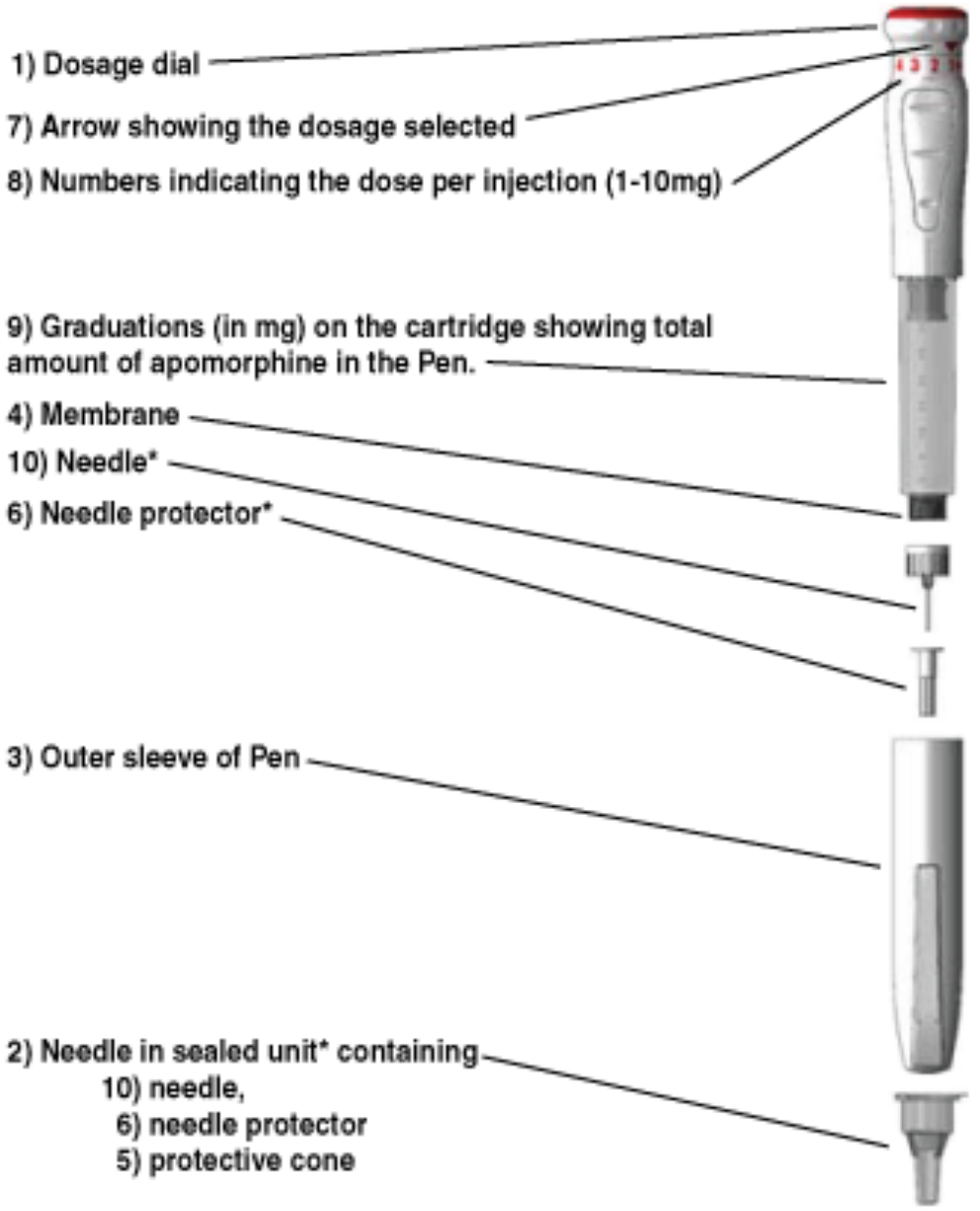


Movapo™ – in clinic titration

- Pre-educate
  - Caution if on anti-hypertensives
  - Contraindicated with ondasetron and serotonergic medications (e.g. SSRIs)
  - Injection technique
- Pretreat with domperidone 10 mg tid x 3 days (can be stopped within 2 months)
- **Titration Protocol Day**: patient comes to clinic in an OFF state
  - Give 2 mg while sitting → if pre-syncopal → position supine
    - Monitor for side effects: orthosatic hypotension, nausea, dyskinesia, rhinorrhea, drowsiness
    - BP monitored sitting and standing @ baseline, 20 minutes (peak) and if symptomatic
    - If no side effects → go up to 4 mg after another 1.5 hours or on another day

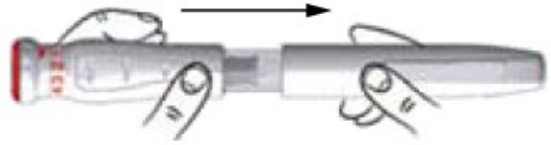
How to use Movapo ™

- MOVAPO comes as disposable multiple dose pen injector incorporating a cartridge containing apomorphine



How to use Movapo ™

1. Take off outer sleeve

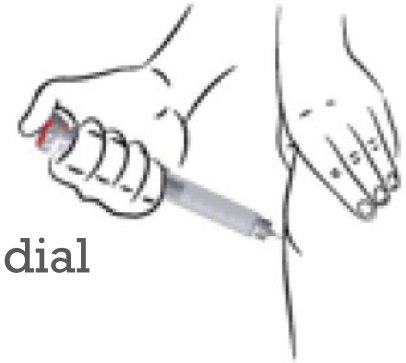


2. Wipe membrane with alcohol swab

3. Screw on needle and take off protective cone

4. Press and turn dosage dial until appropriate dose is selected

5. Sterilize area of skin with alcohol swab, insert needle, then press down on dosage dial



6. Safely dispose needle

Kynmobo™ - subcutaneous apomorphine

+

sunovion

Kynmobi ™

- Reformulated → sublingual wafer/film
  - Absorbed through the oral mucosa direct to bloodstream (bypasses the gut)
  - Bilayer – doesn't matter which side is applied
- Modifications
  - Pyridoxine – pH buffer to reduce acidity
  - Menthol flavor

  - Mean time to dissolve = 2-3 minutes
  - Onset: 12-15 mins in most patients
  - Duration: 90 minutes on average
  - Mean dose needed: 18 mg

RESEARCH ARTICLE

Sublingual Apomorphine (APL-130277) for the Acute Conversion of OFF to ON in Parkinson's Disease

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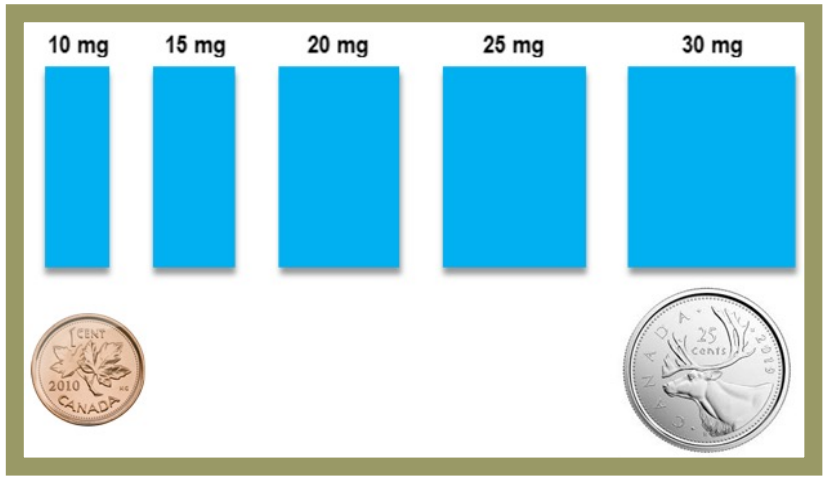
July 2016

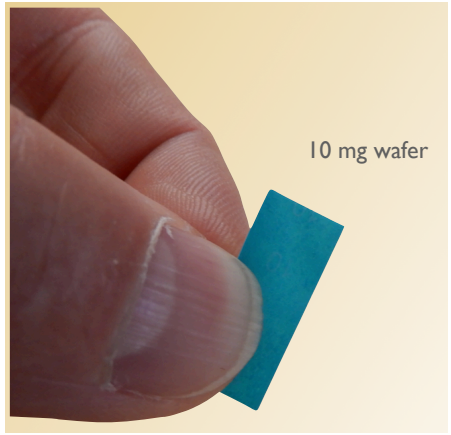
ABSTRACT **Introduction:** OFF episodes negatively impact quality of life in patients with Parkinson's disease (PD). There remains a need for an acute, effective, noninvasive treatment.
Background: APL-130277 is a sublingually administered apomorphine oral strip.
Methods: The authors conducted a phase 2, open-label, proof-of-concept study. Patients presented to clinic in the morning in the practically defined OFF state and were dosed with APL-130277 10 mg. Assessments of OFF or ON state and MDS-UPDRS part III were conducted predose and at 15, 30, 45, 60, and 90 minutes. If a full ON was not achieved within 3 hours, the dose was increased in 5 mg increments until a full ON was achieved or to a maximum dose of 30 mg. Patients could be dosed up to two times a day over 3 days. Patients were pretreated with trimethobenzamide for 3 days, which was continued during the study.
Results: Of 19 patients, 15 (78.9%) achieved a full ON response. All 15 achieved a full ON response within 30 minutes and 6 of the 15 patients (40.0%) achieved a full ON response within 15 minutes. The mean (SD) duration of ON was 50 (19.4) minutes. Of the 15 patients, 9 (60.0%) remained fully ON for ≥90 minutes. There were no discontinuations as a result of an adverse event. The most common adverse events were dizziness (36.8%), somnolence (31.6%), and nausea (21.1%).
Conclusion: This was the first study of a new sublingual apomorphine formulation in PD patients. In this open-label study, APL-130277 appeared to provide a convenient, rapid,

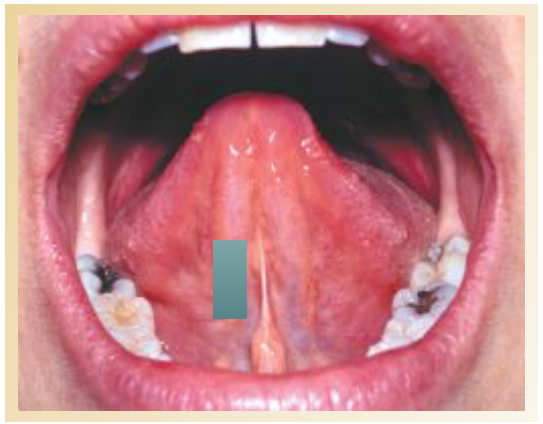
Kynmobi™

KYNMOBI comes in dosage strengths of **10 mg, 15 mg, 20 mg, 25 mg, and 30 mg**

- The maximum single dose of KYNMOBI is 30 mg (maximum daily dose is 90 mg)
- The average frequency of dosing in the clinical studies was approximately 2 times per day (maximum films per day is 5)
- Doses should be separated by at least 2 hours
- Administer one film for one “OFF” episode



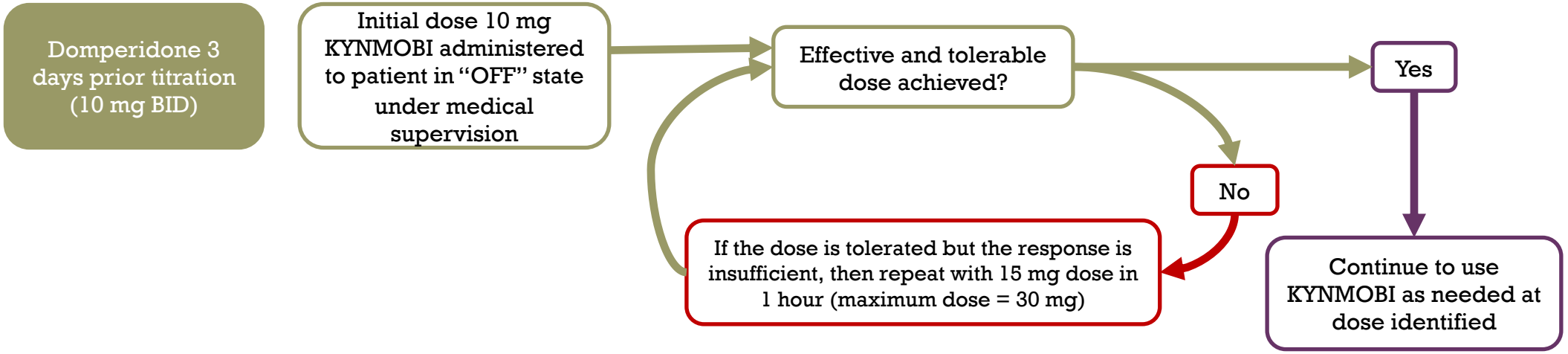




- KYNMOBI™ (apomorphine hydrochloride) sublingual film [Product Monograph]. Mississauga, ON: Sunovion Pharmaceuticals Canada Inc; June 2020.

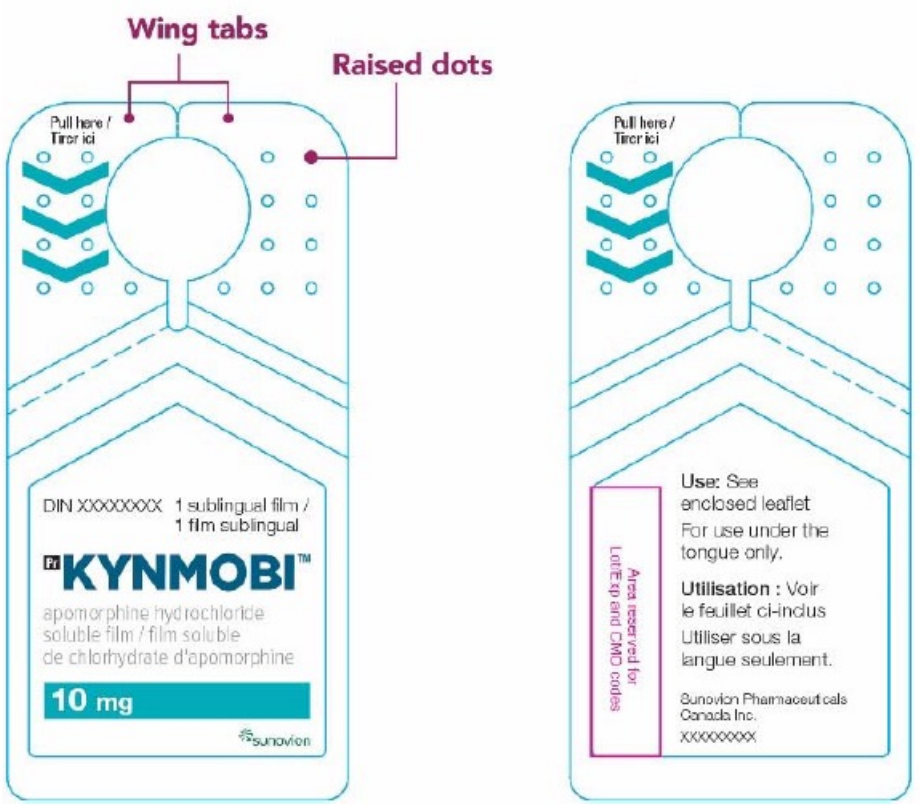
Kynmobi™

Dose initiation of KYNMOBI should occur when the patient is in an "OFF" state and in a setting where a healthcare provider can monitor blood pressure and pulse



- KYNMOBI™ (apomorphine hydrochloride) sublingual film [Product Monograph]. Mississauga, ON: Sunovion Pharmaceuticals Canada Inc; June 2020.

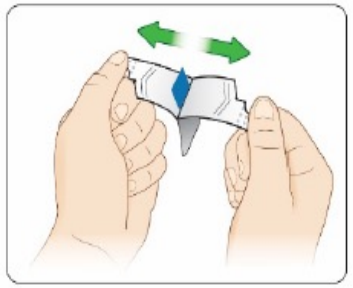
How to use Kynmobi™

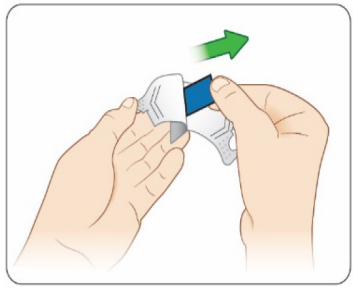


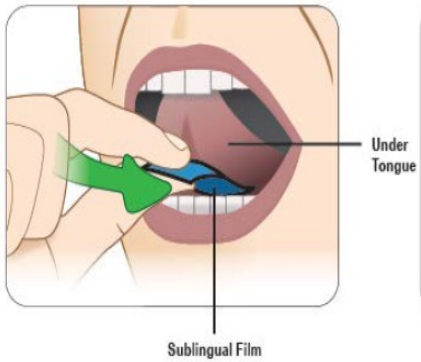
Each KYNMOBI sublingual film comes in a sealed foil pouch

- KYNMOBI™ (apomorphine hydrochloride) sublingual film [Product Monograph]. Mississauga, ON: Sunovion Pharmaceuticals Canada Inc; June 2020.

How to use Kynmobi™







STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
• Before taking each KYNMOBI, drink water to moisten your mouth. This helps the film dissolve more easily	• Hold the wing tabs using the raised dots on each wing tab to open the pouch	• Remove the film from the pouch	• Place entire KYNMOBI under your tongue, as far back under your tongue as possible	• Keep KYNMOBI in place until it has completely dissolved

- It can take about **3 minutes** for KYNMOBI to dissolve
- May see some leftover dye under tongue

- Do not chew or swallow KYNMOBI
- Do not talk while the film is dissolving

- KYNMOBI™ (apomorphine hydrochloride) sublingual film [Product Monograph]. Mississauga, ON: Sunovion Pharmaceuticals Canada Inc; June 2020.

Apomorphine – is it worth the hype?

Current experience with apomorphine

- Presently at Fraser Health Movement Disorder Clinic we have:
  - 11 people with PD on Movapo™
  - 3 people with PD on Kynmobi™
  - ➢ Too early to draw conclusions from such a small sample size

- Not a one-size fits all treatment
  - Not ideal if individual OFF periods are longer than 90 minutes
  - Does not 'prevent' wearing OFF episodes from occurring or worsening
  - For people with advanced Parkinson's disease who need assistance for medication administration – need to have highly engaged caregiver present to administer apomorphine in a timely manner
  - Cost may be prohibitive

How much does apomorphine cost?

Cost

- Movapo™
  - Covered under BC Pharmacare (must pay up to deductible first); requires Special Authority
  - Some private insurance plans may offer additional coverage

- Kynmobi™
  - Not yet covered under BC Pharmacare
  - Some private insurance plans may offer coverage
  - May get coverage under 'Physician Experience Program' - a limited time co-payment plan, until coverage under BC Pharmacare is approved

Future perspectives

+ Continuous subcutaneous apomorphine infusion pump (Apo-Go™)

BRITANNIA
PHARMACEUTICALS LTD

Thank you

- Movement Disorder Clinic (Fraser Health) in Surrey, BC

Coastal Clinics

fraserhealth

UBC
FACULTY OF MEDICINE