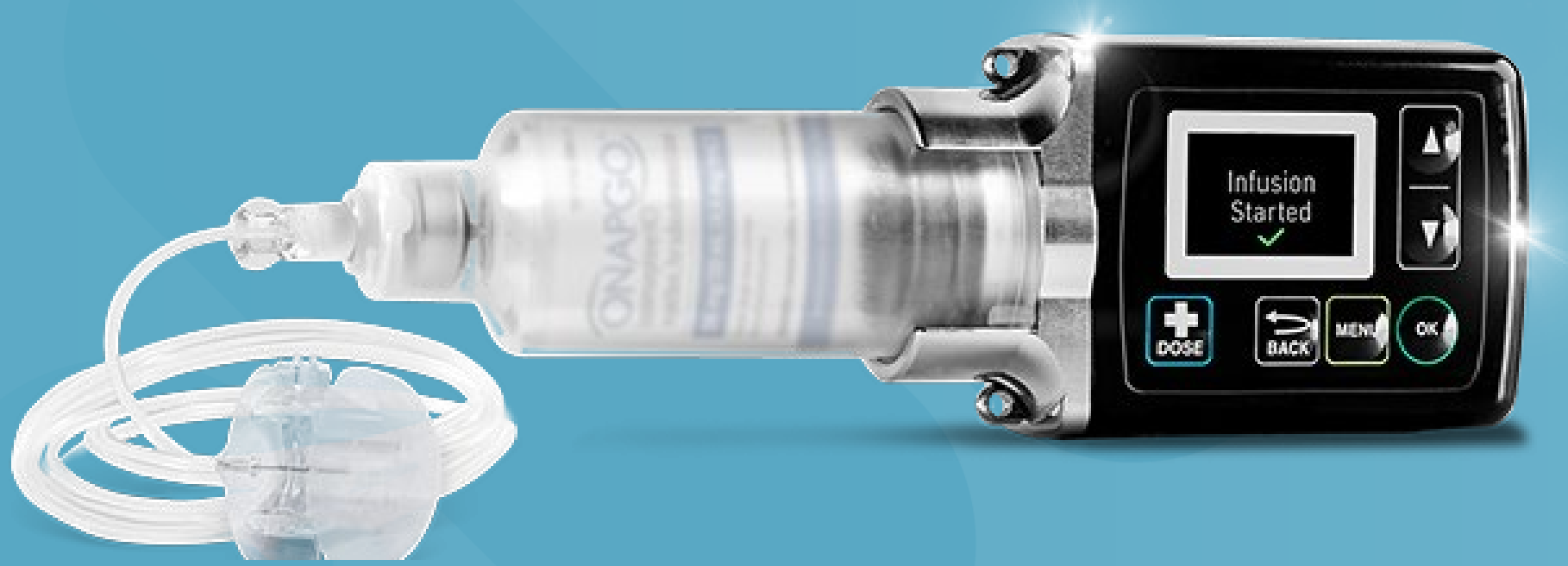

Apomorphine Subcutaneous Infusion Therapy

Alexis Gumble, PA-C

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Alexis C Gumble – Relevant Financial Relationships

- Speakers' Bureau, consultant, and/or advisory board member for Amneal.

All relevant financial relationships have been mitigated

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MOTOR FLUCTUATIONS IN PD

- Progressive loss of dopaminergic neurons
- Early in disease patients may start to experience “wearing off” or “end of dose deterioration”
- As the disease progresses, this gradual wearing off can become very rapid
  - Patients can have sudden and unexpected transitions between ON and OFF
- In addition, therapy can become complicated by dyskinesias
- Evidence suggests motor fluctuations are partly due to the pulsative nature of oral dopaminergic medications

Aradi SD, Hauser RA. Medical Management and Prevention of Motor Complications in Parkinson's Disease. Neurotherapeutics. 2020 Oct;17(4):1339-1365. doi: 10.1007/s13311-020-00889-4. PMID: 32761324; PMCID: PMC7851275.

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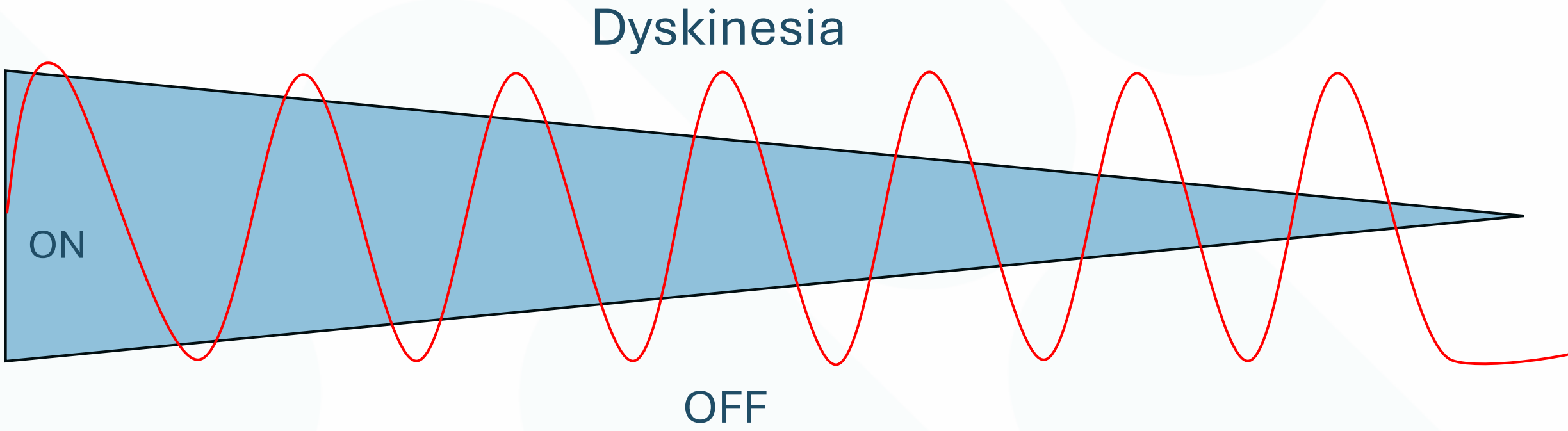
Disease Progression = Narrow Therapeutic Window



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LEVODOPA LIMITATIONS

GI Tract Limitations

- Dysphagia and Esophageal Dysfunction
  - Can lead to delayed ON or failed delivery to intestine (no ON)
- Delayed gastric emptying
  - Levodopa gets stuck in the stomach
    - Can induce pre-systemic metabolism
  - Can lead to dose failure or delayed ON
- Constipation
  - Prolongs levodopa transit
- Variable absorption in the small intestine
  - Only absorbed in a short segment of the proximal small intestine
- Competition with dietary proteins and amino acids
  - Levodopa uses large neutral amino acid transporters (LNAAs)
    - Proteins compete with levodopa for absorption

Leta V, Klingelhoefer L, Longardner K, et al. Gastrointestinal barriers to levodopa transport and absorption in Parkinson's disease. *Eur J Neurol*. 2023;30(5):1465-1480. doi:10.1111/ene.15734

Plasma Limitations

- Levodopa has a short half life
  - 90 minutes
- Metabolism by COMPT
  - Converts levodopa to 3-O-methyldopa (3-OMD)
- Formation of 3-OMD
  - Reduces available levodopa
  - Competes with levodopa for transport across BBB

Ray Chaudhuri K, Poewe W, Brooks D. Motor and Nonmotor Complications of Levodopa: Phenomenology, Risk Factors, and Imaging Features. *Mov Disord*. 2018;33(6):909-919. doi:10.1002/mds.27386

Männistö PT, Kaakkola S. Catechol-O-methyltransferase (COMT): biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. *Pharmacol Rev*. 1999;51(4):593-628.

Brain Limitations

- Needs transport across the blood brain barrier
  - LNAA transporters
- Competes with
  - amino acids
  - 3-OMD
- Less dopaminergic neurons = less dopamine conversion and storage

Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. *Lancet Neurol*. 2006;5(8):677-687. doi:10.1016/S1474-4422(06)70521-X

Schapira AH, Emre M, Jenner P, Poewe W. Levodopa in the treatment of Parkinson's disease. *Eur J Neurol*. 2009;16(9):982-989. doi:10.1111/j.1468-1331.2009.02697.x

APOMORPHINE

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Apomorphine OV

- Among the first few dopamine agonists to be found effective in Parkinson's Disease
- 100% bioavailability with subcutaneous infusion
  - Does not require absorption through GI tract
  - Freely crosses the blood brain barrier
    - Highly lipophilic
  - No metabolic conversion required
- Potent D1 and D2 receptor agonist
  - Motor efficacy is comparable to levodopa

Carbone F, Djamshidian A, Seppi K, Poewe W. Apomorphine for Parkinson's Disease: Efficacy and Safety of Current and New Formulations. CNS Drugs. 2019 Sep;33(9):905-918. doi: 10.1007/s40263-019-00661-z. PMID: 31473980; PMCID: PMC6776563

Apomorphine Differences from other DAs

- broad spectrum on all D1 and D2 – like receptors
  - Ropinerole and Pramipexole mainly have affinity for D2 and D3 receptors without significant affinity for D1 receptors
- Antagonist properties on:
  - Serotonergic 5HT2A, 5HT2B, 5HT2C
  - Adrenergic alpha 2A, 2B, and 2C receptors
- Agonist properties on:
  - Serotonergic 5HT1A receptors

Current and Notable Clinical-Stage Nonergoline DAs in PD and Their Dopamine Receptor Subtype Selectivity.

Name of DA[a]	Clinical status[b]	Dopamine receptor selectivity[c]
Pramipexole	Approved in the EU and United States [101,102]	D3 > D4 > D2≫D1,D5 [24]
Ropinirole	Approved in the EU and United States [103,104]	D3 > D2 ~ D4 > D1,D5 [24]
Rotigotine	Approved in the EU and United States [105,106]	D3≫D4 ~ D5 ~ D2 > D1 [40]
Apomorphine	Approved in the United States [21]	D4 > D5 > D3 > D2 > D1 [24]
Piribedil	Approved in the EU [107]	D2 ~ D3 ~ D4≫D1,D5 [24]
Tavapadon	Investigational, phase 3 [108–110]	D1, D5 selective [50]
KDT3594	Investigational, phase 2 [111]	D2 selective [112]
Lu AF28996	Investigational, phase 1 [113]	D1, D2 selective [114]

Stuart H. Isaacson, Robert A. Hauser, Rajesh Pahwa, David Gray, Sridhar Duvvuri, Dopamine agonists in Parkinson's disease: Impact of D1-like or D2-like dopamine receptor subtype selectivity and avenues for future treatment, Clinical Parkinsonism & Related Disorders, Volume 9, 2023, 100212, ISSN 2590-1125, https://doi.org/10.1016/j.prdoa.2023.100212.

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Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial

Katzenschlager R, Poewe W, Rascol O, et al. Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO):
a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Neurol*. 2018;17(9):749-759. doi:10.1016/S1474-4422(18)30239-4

TOLEDO - INTRODUCTION

Study Purpose

- Looked at continuous subcutaneous apomorphine infusion as an adjust to optimized PD therapy
- Assessed efficacy, safety, and tolerability

Study Design

- 12-week Phase 3, double blind, randomized, placebo-controlled trial
- Apomorphine infusion vs saline infusion

Katzenschlager R, Poewe W, Rascol O, et al. Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Neurol*. 2018;17(9):749-759. doi:10.1016/S1474-4422(18)30239-4

TOLEDO: Criteria

INCLUSION CRITERIA:

- Dx with PD > 3 years
- Levodopa-related motor fluctuations
- Hoehn and Yahr stage 3 or less in the ON and 2-5 in the OFF
- OFF time of 3 hr per day for 2 days

EXCLUSION CRITERIA:

- Secondary or atypical parkinsonism
- Recent apomorphine injection use
- Severe freezing of gait leading to falls during ON time
- Uncontrolled OH
- Prolonged QT
- MMSE < or equal to 24

Patients with very mild visual hallucinations with full insight were permitted

Katzenschlager R, Poewe W, Rascol O, et al. Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Neurol*. 2018;17(9):749-759. doi:10.1016/S1474-4422(18)30239-4

TOLEDO – Initiation & Titration

- Initial dose: 1mg/hour
  - To minimize early adverse effects: Nausea, OH, somnolence
- Gradual dose increases over 4 weeks
  - Increments typically 0.5-1mg/hr
  - Often adjusted every few days
- After week 4 → 8 week maintenance phase
- Use of extra dose was not permitted during the double-blind phase

Target dose = patients' individual optimized dose (3-8mg/hr)

Administered for 16 hours (14-18hr were permittable)

Titration tools

- Clinical indicators
  - Reduction in OFF time
  - Faster and more reliable ON periods
- Measurement tools
  - Patient-completed home diaries
  - Clinical assessments
  - Patient feedback
- Adverse effects

If adverse effects were met:

- Slowing or pausing dose escalation
- Temporary dose reduction
- Short term use of domperidone

Katzenschlager R, Poewe W, Rascol O, et al. Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Neurol*. 2018;17(9):749-759. doi:10.1016/S1474-4422(18)30239-4

TOLEDO – Initiation & Titration- Oral Meds

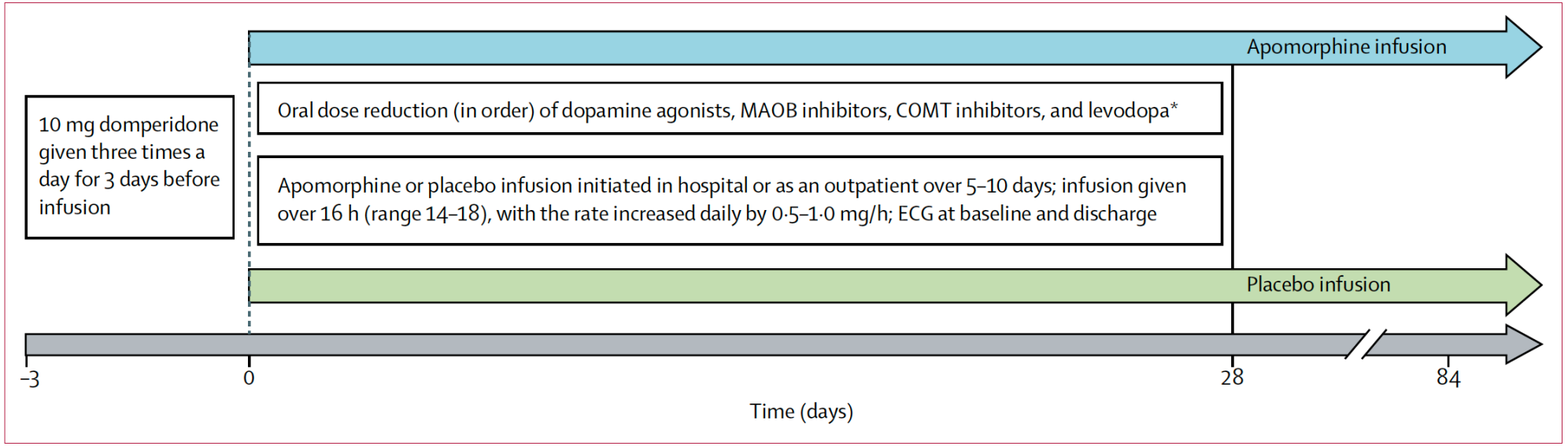
Adjustments allowed if side effects emerged

- Dyskinesia
- Nausea
- Hypotension
- Excessive Sleepiness

REDUCTIONS IN CONCOMTANT MEDICATIONS:

1. Discontinue dopamine agonists
2. MAOB inhibitors
3. Decrease levodopa dose
4. Increase time between levodopa doses

Anticholinergics and Amantadine not touched



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TOLEDO: Results

PRIMARY ENDPOINT

Absolute change in OFF time from baseline → week12

	Apomorphine (n=53)	Placebo (n=53)	Treatment difference (95% CI)	p value
Primary outcome				
Off time (h per day)	−2·47 (3·70)	−0·58 (2·80)	−1·89 (−3·16 to −0·62)	0·0025
Secondary outcomes				
Number of patients with ≥2 h reduction in off time	33 (62%)	15 (29%)	33·4% (15·5 to 51·4)	0·0008
PGIC score	3·23 (1·42)	4·43 (1·10)	−1·20 (−1·71 to −0·69)	<0·0001
On time without troublesome dyskinesia (h per day)	2·77 (3·26)	0·80 (2·93)	1·97 (0·69 to 3·24)	0·0008
Oral levodopa dose (mg)	−207·8 (439·5)	−94·3 (273·4)	−113·5 (−262·3 to 35·2)	0·0615
Levodopa-equivalent dose (mg)	−492·1 (618·3)	−163·7 (367·5)	−328·5 (−535·2 to −121·7)	0·0014
MDS-UPDRS Part III motor scores during on periods	−3·42 (11·69)	−0·89 (9·73)	−2·52 (−7·53 to 2·48)	0·4642
PDQ-8 score	−0·06 (14·37)	2·40 (11·83)	−2·47 (−7·62 to 2·69)	0·3971

Data are n (%) or mean (SD) unless otherwise specified. PGIC=Patient Global Impression of Change. MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale. PDQ-8=8-item Parkinson's Disease Questionnaire.

Table 2: **Change between baseline and week 12 in efficacy outcomes (full analysis set)**

- Mean final dose of study drug: 4.68mg/hr
- Significantly significant reduction in OFF (-2.47hr per day)
- Significant increase in ON time without troublesome dyskinesias (2.77hr per day)
- Patients were able to significantly reduce their concomitant medications

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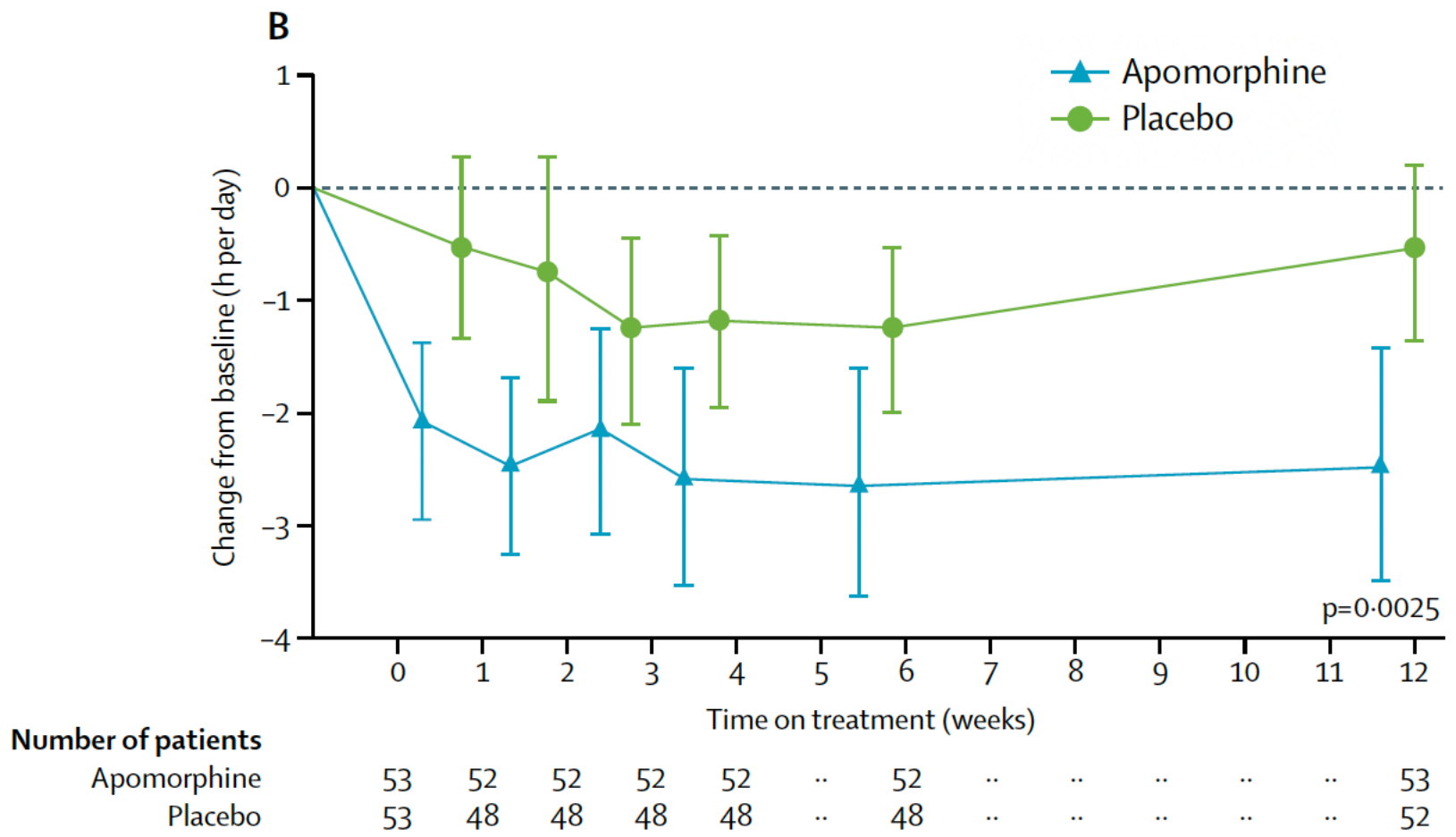
Change from baseline to week 12 in OFF time



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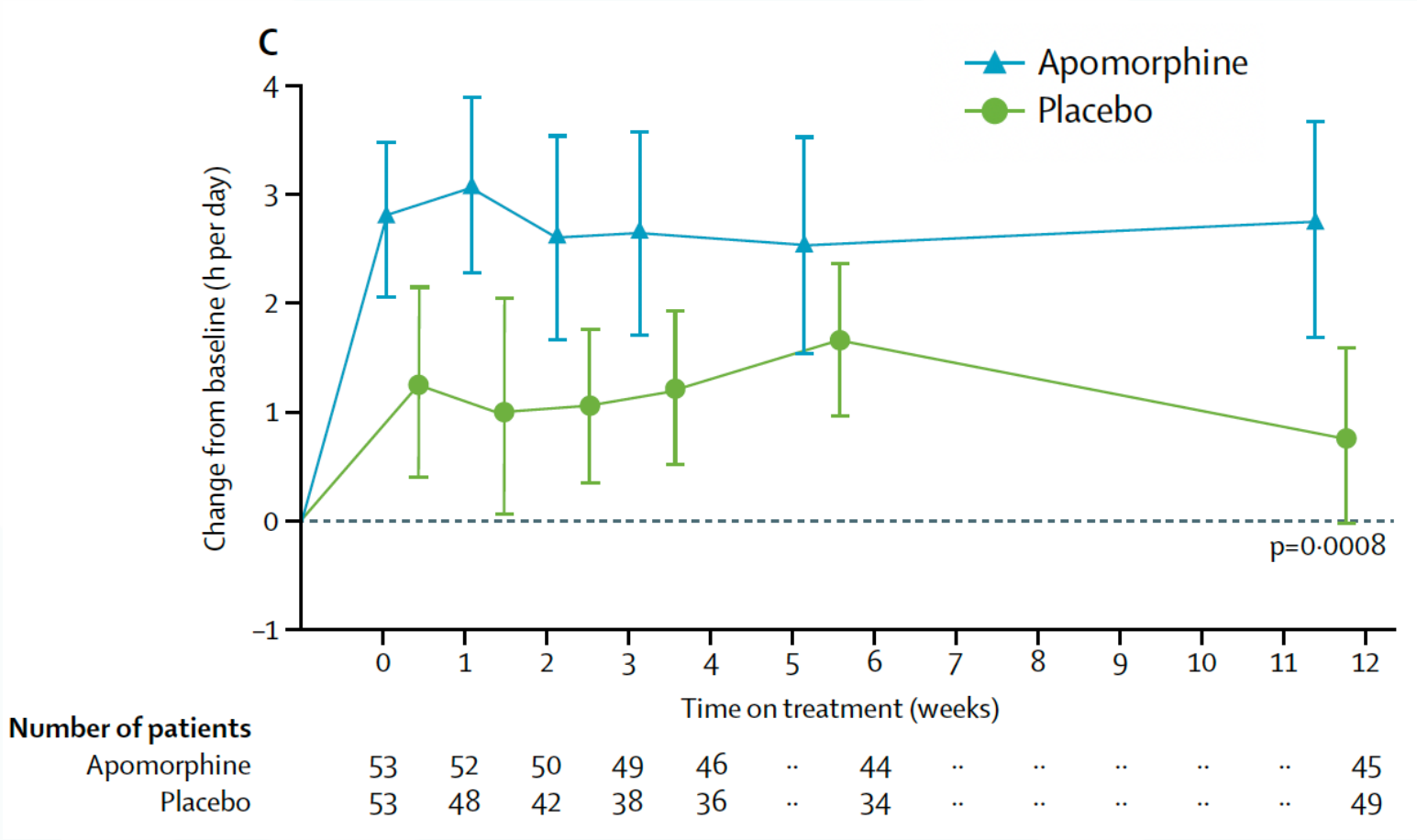
Change from baseline to week 12 in ON time without troublesome dyskinesias



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TOLEDO – Adverse Reactions

Skin Reactions:
- Nodules (44%)
- Erythema (17%)
- Bruising
- Pain at infusion site

→ **Occur due to:**
- Repeated skin use
- Pooling of apomorphine
- Continuous infusion

→ **Management:**
- Rotate the site
- Making sure canula is at correct depth
- Skin care
- Massage/warm compress

Nausea (22%)
**Early titration

→ **Occurs due to:**
- Peripheral dopamine receptor stimulation

→ **Management:**
- Domperidone
- Slow dose titration
- Dose reduction

Somnolence (22%)

→ **Occurs due to:**
- Central dopaminergic stimulation
- Multiple dopaminergic meds

→ **Management:**
- Dose reduction
- Reduction in concomitant DAs

Orthostatic Hypotension and Dizziness

→ **Occurs due to:**
- Dopamine mediated vasodilation
- Autonomic dysfunction

→ **Management:**
- slow titration
- Monitor BP

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TOLEDO – Adverse Reactions

Overall:

- Well tolerated
- Adverse reactions were
  - Mild- moderate
  - Occurred early
  - Manageable with dose adjustment or supportive care

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TOLEDO takeaways

- Continuous subcutaneous apomorphine infusion is effective
  - Significantly reduces OFF time and increases ON time without troublesome dyskinesias in patients with advanced PD
  - Improvements were seen as early as week 1 in the titration phase
  - Benefits maintained throughout the 12 weeks
- The safety profile was predictable, mild- moderate, and manageable

Katzenschlager R, Poewe W, Rascol O, et al. Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Neurol*. 2018;17(9):749-759. doi:10.1016/S1474-4422(18)30239-4

Continuous, subcutaneous apomorphine infusion for Parkinson disease motor fluctuations: Results from the phase 3, long-term, open-label United States InfusON study

Isaacson SH, Espay AJ, Pahwa R, et al. Continuous, subcutaneous apomorphine infusion for Parkinson disease motor fluctuations: Results from the phase 3, long-term, open-label United States InfusON study. *J Parkinsons Dis*. 2025;15(2):361-373. doi:10.1177/1877718X241310727

InfusON

Study Design

- Prospective 52-week open label phase 3 outpatient study
- Conducted at 19 US centers

Purpose:

- in order to show sustained benefit over time
- Use in U.S. Clinical practice

Isaacson SH, Espay AJ, Pahwa R, et al. Continuous, subcutaneous apomorphine infusion for Parkinson disease motor fluctuations: Results from the phase 3, long-term, open-label United States InfusON study. *J Parkinsons Dis*. 2025;15(2):361-373. doi:10.1177/1877718X241310727

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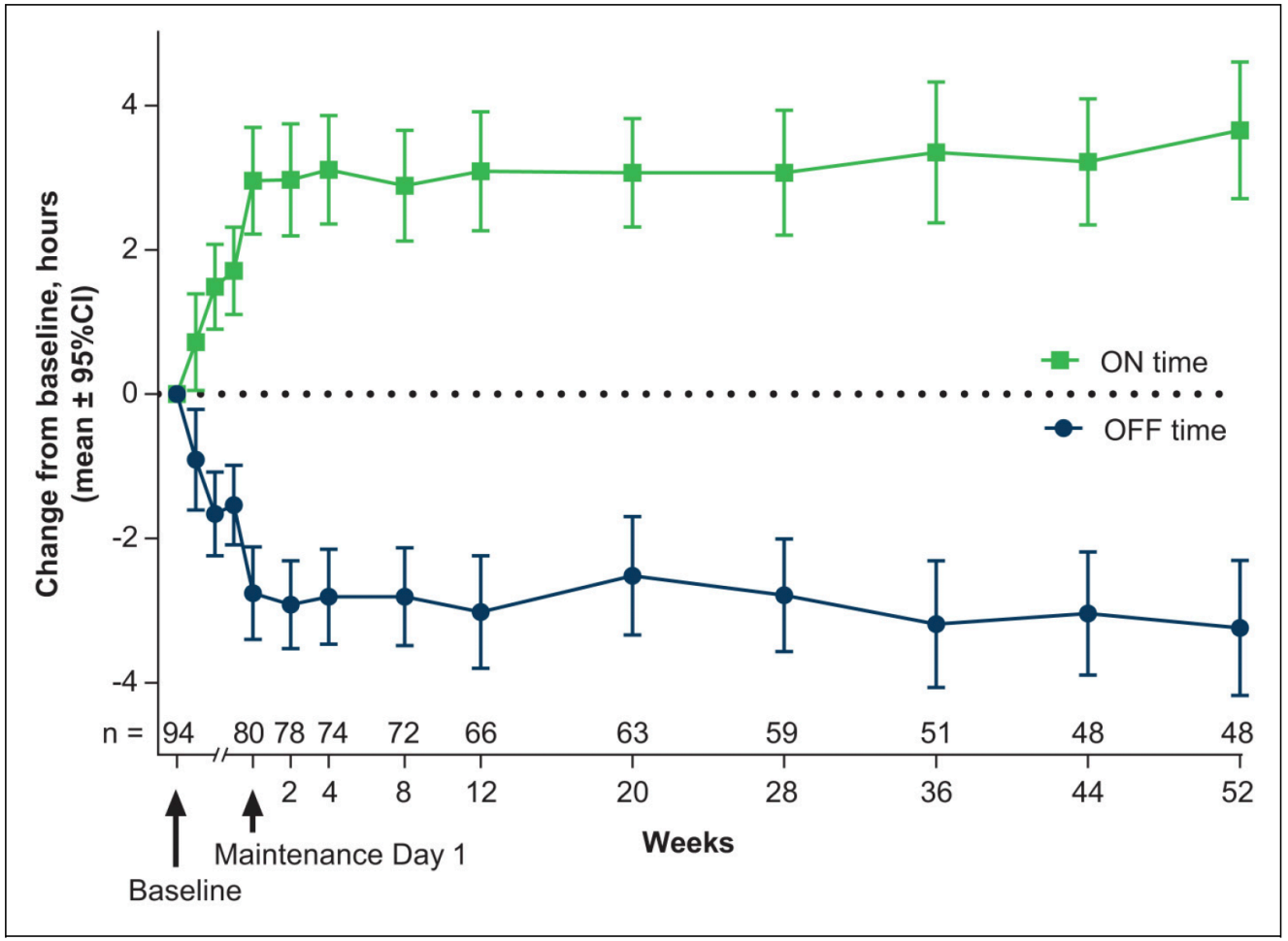
InfusON Results



Reduction in **OFF** time:

- Week 12: reduction of 3hr/day
- Week 52: reduction of 3.2hr/day

Increase in in **ON** time:

- Week12: increase by 3.1hr/day
- Week 52: increase by 3.7hrs/day

Isaacson SH, Espay AJ, Pahwa R, et al. Continuous, subcutaneous apomorphine infusion for Parkinson disease motor fluctuations: Results from the phase 3, long-term, open-label United States InfusON study. *J Parkinsons Dis*. 2025;15(2):361-373. doi:10.1177/1877718X241310727

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InfusON Takeaways

- Continuous subcutaneous apomorphine infusion provides sustained benefit

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Apomorphine Subcutaneous Infusion Therapy

DOSAGE:
-Maximum recommended daily dose including extra doses: 98mg
-Max continuous dose: 6mg/hr for 16 hours = 96mg
-Max extra dose = 2mg with 3 hours lockout with max 3 a day

CONTRAINDICATIONS:
-Concomitant use with 5HT3 antagonists

CANULA SITES:
-Abdomen at least 2 inches from the navel
-Top of the thigh
-Lower back
-Upper back

Figure AB

ONAPGO. Package insert. Supernus Pharmaceuticals

Questions?

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- Aradi SD, Hauser RA. Medical Management and Prevention of Motor Complications in Parkinson's Disease. Neurotherapeutics. 2020 Oct;17(4):1339-1365. doi: 10.1007/s13311-020-00889-4. PMID: 32761324; PMCID: PMC7851275.
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