What’s new in PD therapeutics?

Jane Wright Symposium
2017
Overview

• Recently approved medications
  • Motor symptoms
  • Non-motor symptoms

• New Surgical Procedures

• Treatments in the pipeline
Safinam ide (xadago)

• Approved 2017 as an add-on treatment for people with Parkinson's disease (PD) who are taking levodopa/carbidopa and experiencing "off" episodes.

• Safinimide is a reversible MAO-B inhibitor. It is taken once a day

• Advantages: convenient, low side effects

• Disadvantages: modest effect similar to rasagline and selegiline
Results from Settle trial (JAMA Neurology 2017)

Figure 2. Change in "On" Time Without Troublesome Dyskinesia During Double-blind Treatment in the Intention-to-Treat Population (Last Observation Carried Forward)

Results are based on patient diary data. "On" time indicates when patients experience relief of parkinsonian motor features. Error bars indicate SE.  

a $P < .001$ (unpaired, 2-sample t test).
Levodopa/carbidopa (Rytary)

- Approved 2015 for the management of Parkinson’s motor symptoms

- Rytary is a capsule that contains both immediate release and extended release carbidopa/levodopa

- Advantages: Rytary may allow few daily doses and less “off” time

- Disadvantages: Has the same side effects as levodopa/carbidopa
Impact of Rytary in early PD

Mean change from baseline\textsuperscript{4} in sum of UPDRS\textsuperscript{5} Parts II and III scores at Week 30 or early termination.\textsuperscript{1}

- In clinical trials, patients did not take additional carbidopa-levodopa products.\textsuperscript{1}

\begin{itemize}
\item *3 times daily.
\item \(P<.05\) vs placebo.
\item Values collected immediately prior to first study treatment administration.
\item Unified Parkinson's Disease Rating Scale.
\end{itemize}
Effect of Rytary in advanced PD

-1.0 HOUR

5.9
4.9

-2.2 HOURS

6.1
3.9†

2X the reduction in “off” time during waking hours

<table>
<thead>
<tr>
<th>Immediate-release carbidopa-levodopa</th>
<th>RYTARY</th>
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<tr>
<td>Baseline*</td>
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<tr>
<td>RYTARY End of Study (EOS)‡</td>
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<tr>
<td>Immediate-release carbidopa-levodopa EOS‡</td>
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*Values collected immediately prior to first study treatment administration.
†P<.05 vs immediate-release carbidopa-levodopa.
‡Week 22 or early termination.
Levodopa/carbidopa (Duopa)

• Approved in 2015 for treatment of PD motor symptoms

• It is a gel formulation of carbidopa/levodopa that is designed for continuous infusion into the small intestine, usually infused for 16 hours per day

• Advantages: may be an alternative to deep brain stimulation

• Disadvantages: similar side effects to levodopa; tube and pack can be cumbersome
Duopa tubing and dispensing pump
Effect of Duopa on motor fluctuations

**Primary efficacy endpoint:**
mean change in daily "off" time

- Duopa (n=35): ~1.9 hours (P=0.0015)
- Oral carbidopa/levodopa IR (n=31): -4.0 hours

**Secondary efficacy endpoint:**
mean change in daily "on" time without troublesome dyskinesia

- Duopa (n=35): +4.1 hours
- Oral carbidopa/levodopa IR (n=31): +2.2 hours
Droxidopa (Northera)

- Was approved in 2014 to treat orthostatic hypotension

- Droxidopa is converted to norepinephrine (nor-adrenaline) which works to raise blood pressure

- Advantages: may lessen lightheadedness that results from low blood pressure

- Disadvantages: can cause high blood pressure, particularly when lying down
Pimavanserin (Nuplazid)

• Pimavanserin was approved in 2016 for the treatment of hallucinations due to Parkinson’s disease psychosis

• Pimavanserin does not work on the dopamine system and therefore should not worsen Parkinson’s motor symptoms

• Advantages: May also improve sleep

• Disadvantages: most common side effects are leg swelling, nausea and confusion. May not work as well as clozaril
Pimavanserin for PD Psychosis
(Pimavanserin - 5HT-2A inverse agonist)

Focused ultrasound

Man's hands stop shaking for first time in 15 years after doctors zap his brain with pioneering ultrasound treatment

• Doctors used MRI scans to find rogue brain cells causing the tremor
• Ultrasound killed cells by heating them
• Patient was awake and aware throughout the five-hour procedure and didn't need anaesthetic
• Experts say it could help patients with other conditions such as Parkinson's or brain tumours

• By Claire Bates


Read more: http://www.dailymail.co.uk/health/article-2250513/Man-stops-shaking-time-15-years-brain-zapped-ultrasound-pioneering-surgery-free-treatment.html#ixzz4k1y2Je4O
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Results of focused ultrasound compared to sham procedure

What causes Parkinson’s disease?

- Genes and environment
- Synuclein aggregation in Lewy Bodies
- Dopamine loss
- Tremors etc.
Gene therapy to improve the effects of levodopa
Treatments to remove alpha-synuclein

- Affiris: alpha synuclein vaccine
- Roache/Prothena: anti-alpha-synuclein antibody
- Biogen: anti-alpha synuclein antibody
Treatments aimed as specific genetic abnormalities

- GBA mutations: Sanofi phase 2 trial of a drug designed to replace missing GCase activity

- LRRK2 mutations: multiple companies with kinase inhibitors
Nilotinib

• Repurposed cancer drug

• A lot of excitement around early results

• MJFF sponsored study planned for late 2018
Others

• Isradipine

• Inosine
CVT-301 (levodopa)

• Self-administered, inhaled formulation of levodopa

• Developed by Acorda Pharmaceuticals

• Positive results from Phase III trial announced June 2017. Improved UPDRS III by approximately 4 points during “off” episodes

• Planned NDA (New Drug Application to FDA) later in 2017. Indication will probably be for rescue from “off” episodes (like apomorphine) If approved, would be available 2018-2019
Summary

• Newly approved medications focus on better delivery of old drugs and treatment of non-motor features

• Focused ultrasound is new, but not necessarily better than traditional DBS for Parkinson disease

• The pipeline of experimental medicines offers real promise for disease modification than