Novel approaches to the pharmacological treatment of Parkinson’s disease

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Disclosures and Disclaimers

- Speakers fees and consultancy fees have been received from Britannia Pharmaceuticals, UCB, Lundbeck, Teva, Worldwide Clinical Trials, Chronos Therapeutics, Kyowa Hakko, FP Pharmaceuticals, Adamas, Abbvie, BIAL and New β Innovation

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Objectives

• To discuss changing concepts on the nature of Parkinson’s disease
• To understand how this might impinge on clinical trial design
• To briefly discuss new approaches to treatment – dopaminergic and non-dopaminergic
• The dilemma of treating non-motor symptoms
Current drug treatment of Parkinson’s disease

- L-dopa
- Decarboxylase inhibitors – carbidopa, benserazide
- COMT inhibitors – entacapone, tolcapone
- MAO-B inhibitors – selegiline, rasagiline
- Combination forms – Stalevo
- Controlled release – Sinemet CR
- Dispersible – Madopar dispersible
- Liquid formulations – L-dopa methyl ester
- Intraduodenal administration - DuoDopa

- Ropinirole
- Pramipexole
- Pergolide
- Bromocriptine
- Cabergoline
- Extended release – Requip XL
- Transdermal administration – NeuPro
- Rescue therapy – Apokyn
- Subcutaneous infusion - apomorphine
# New levodopa formulations – overview

<table>
<thead>
<tr>
<th>Description</th>
<th>Route</th>
<th>Name</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended-release CD-LD</td>
<td>Oral</td>
<td>IPX066, Rytary, Numient</td>
<td>Impax</td>
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<tr>
<td>LD prodrug</td>
<td>Oral</td>
<td>XP21279(-CD)</td>
<td>XenoPort</td>
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<tr>
<td>Accordion pill CD/LD</td>
<td>Oral</td>
<td>AP-CD/LD</td>
<td>Intec Pharma</td>
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<tr>
<td>Microtablets LD/CD 5/1.25</td>
<td>Oral</td>
<td>LC-5, Flexilev</td>
<td>Sensidose</td>
</tr>
<tr>
<td>LD/CD oral device</td>
<td>Oral</td>
<td>DopaFuse</td>
<td>SynAgile</td>
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<tr>
<td>Metal coordinated LD</td>
<td>Oral</td>
<td>MCP-311 bismuth-levodopa</td>
<td>Synthonics</td>
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<tr>
<td>Liquid LD methylester+CD</td>
<td>Oral</td>
<td>Sirio, V1512, melevodopa</td>
<td>Chiesi</td>
</tr>
<tr>
<td>Inhaled LD</td>
<td>Pulmonary</td>
<td>CVT-301</td>
<td>Acorda</td>
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<tr>
<td>LD/CD for patch-pump</td>
<td>sc</td>
<td>ND0612L/H</td>
<td>Neuroderm</td>
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<tr>
<td>LD solution</td>
<td>sc/iv</td>
<td>Infudopa</td>
<td>Dizlin</td>
</tr>
<tr>
<td>LD/EN/CD intestinal gel</td>
<td>Intestinal</td>
<td>Lecigon</td>
<td>Lobsor</td>
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Device orientated drug delivery in Parkinson’s disease
APL-130277 – sublingual apomorphine

- APL-130277 is an apomorphine delivery system using a sublingual, thin film strip which rapidly dissolves when placed under the tongue.
- APL-130277 quickly produces blood levels in normal volunteers that in patients with PD are known to restore relatively normal motor function.
- Avoids first pass metabolism

Cynapsus Therapeutics
Hauser, R. et al., 2016
Pathology and biochemistry is wide and diverse

‘Parkinson’s disease (PD) is no longer considered a complex motor disorder characterized by extrapyramidal symptoms, but a progressive multisystem or — more correctly multi-organ disease with variegated neurological and non-motor deficiencies’

1. Parkinson’s is a multi-organ disorder: CNS and extra-CNS
2. Parkinson’s is a multi-peptide dysfunction related disorder
3. Non-DA involvement may be greater than DA involvement
Parkinson’s disease has a spreading but variable pathology

- Pathology sweeps through the brain
- No agreement on the origin or pattern
- Not just a basal ganglia disease

Braak et al, 2003; Halliday et al, 2011
Non-motor symptoms – early and late in the progression of Parkinson’s disease

Neuropsychiatric and Cognitive
  e.g. depression, anxiety, apathy and dementia

Autonomic dysfunction

Gastrointestinal disorders

Sleep disorders

Drug induced
  e.g. Hallucinations, ICD/DAWS

Sensory disorders
  e.g. pain, RLS, olfaction, vision

Fatigue, Sexual dysfunction

Urinary disorders

Chaudhuri et al. Lancet Neurology 2006;5:235-245

Chaudhuri and Schapira. Lancet Neurology 2009
Subtype based on phenotype

- PD - sleep
- PD - pain
- PD – depression
- PD-cognitive
- PD – fatigue
- PD - autonomic

- NMS - with ‘OFF’
- NMS – no effect of ‘OFF’

Chaudhuri et al., 2016
Parkinson’s disease as a syndrome

- Different clinical presentations
- Different genetic backgrounds
- Late versus early onset
- Slow versus rapid progression
- Akinetic-rigid versus tremor dominant
- Different response to drugs

### Table 1: Parkinson’s disease subtypes identified by data driven studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Subtypes identified</th>
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| Graham 1999 | Short duration (mean 5 years):  
1. Good motor control without cognitive impairment  
2. Good motor control, executive cognitive deficits  
3. Older age at onset, poor motor control +  
   complications, mild cognitive impairment  
Longer duration (mean 14 years):  
1. Poor motor control, no cognitive impairment  
2. Poor motor control, moderately severe cognitive impairment |
| Gasparoli 2002 | 1. Rapid progression  
2. Slow progression |
| Dujardin 2004 | 1. Mild motor impairment, relatively preserved cognition  
2. Reduced overall cognitive efficiency, subcortico-frontal  
   syndrome and more severe motor dysfunction |
| Lewis 2005 | 1. Young onset  
2. Non-tremor dominant, cognitive impairment and  
   depression  
3. Rapid progression without cognitive impairment  
4. Tremor dominant |
| Schrag 2006 | 1. Young onset  
2. Older onset, more rapid progression, less dyskinesias  
   and fluctuations |
| Post 2008 | 1. Young onset with slow progression  
2. Intermediate age onset with anxiety and depression  
3. Oldest onset |
| Reijnders 2009 | 1. Rapid progression  
2. Young onset with motor complications  
3. Non-tremor dominant and psychopathology  
4. Tremor dominant |
| Van Rooden 2011 | 1. Mild all domains, young  
2. Severe motor complications, sleep and depressive  
   symptoms, younger  
3. Medium severity, older  
4. Most severe, except mild tremor, prominent motor  
   complications, older |
| Liu 2011 | 1. Non-tremor dominant  
2. Rapid disease progression  
3. Young onset  
4. Tremor dominant |

Marras and Lang (2013)
Queen Square Brain Bank Diagnostic Criteria

- Commonly used to select patients for clinical trial
- Motor signs based diagnosis
- NMS may be an exclusion factor
Staging of Parkinson’s disease

**MODIFIED HOEHN AND YAHRI STAGING**

| Stage 0 | —No signs of disease. |
| Stage 1 | —Unilateral disease. |
| Stage 1.5 | —Unilateral plus axial involvement. |
| Stage 2 | —Bilateral disease, without impairment of balance. |
| Stage 2.5 | —Mild bilateral disease with recovery on pull test. |
| Stage 3 | —Mild to moderate bilateral disease; some postural instability; physically independent. |
| Stage 4 | —Severe disability; still able to walk or stand unassisted. |
| Stage 5 | —Wheelchair bound or bedridden unless aided. |

- PD staging is based on motor signs and disability
- Commonly used to select and balance patient groups in clinical trials

Goetz et al. Mov Disord. 2004;19:1010-8
UPDRS as a clinical tool

- UPDRS does not reflect the progression or severity of non-motor symptoms
- Individual patients may have a mild or low UPDRS score but high NMSS burden or vice versa

UPDRS is almost universally used to assess drug effect in clinical studies
NMSS: a grade rating scale

- The first comprehensive grade rating scale for PD
- Addresses 9 domains and 30 questions
- Complementary to NMSQuest
- To be administered by healthcare professional
- Good clinimetrics in two international studies and validated in over 600 patients\(^1,2\)
- Sensitive to change in clinical trials

New MDS Criteria

- Motor abnormalities remain central but increasing recognition has been given to non-motor manifestations.

- The new criteria represent the first step in the formal delineation of early stages of PD.
Non-dopaminergic targets in Parkinson’s disease

- Alterations in basal ganglia circuitry in non-dopaminergic neurones
- Widespread pathology throughout brain that affects non-dopaminergic neurones
Diverse pathological and biochemical effects offer opportunity

- Non-dopaminergic actions
- Multimodal drugs
- Motor and non-motor symptoms
- Repurposing of existing drugs
Istradefylline – the first in class A2a adenosine antagonist

Nouriast approved in Japan for treatment of Parkinson’s disease
Istradefylline and neuropsychiatric disturbance

- Istradefylline active in animal models of depression, anxiety and cognition.

- Potential use in treating motor and non-motor symptoms of PD
Clinical trials should reflect preclinical science

- Trials consistent with FDA Guidelines
- Effect in addition to optimised dopaminergic therapy
- Synergistic effect with low doses of L-dopa
- No additive effect with high doses of L-dopa
- Clinical trial design important
Zonisamide – a multifunctional drug for PD

- Adjunct to levodopa treatment with low incidence of dyskinesia and psychosis
- Inhibition of striatal GABAergic transmission
- Inhibition of sodium and calcium channels
- Inhibition of MAO-B
- Activation of dopamine synthesis and release
Non-dopaminergic nature of non-motor symptoms

- Some non-motor symptoms show some improvement to dopaminergic medication
- Related to motor state
- But clearly dopaminergic treatment is not the whole answer to non-motor symptoms
Non-dopaminergic drugs used to treat non-motor symptoms of PD

- Treat on a symptomatic basis using drugs already available for other indications eg. cholinesterase inhibitors, atypical antipsychotics, antidepressants

- Examine non-dopaminergic agents used in PD for effects on non-motor symptoms eg. adenosine A2a antagonists

- Test using classical models of other disease states eg. depression, anxiety, cognition

Differences between NMS in animal models and clinical PD

- Phenomenology not established
- Rating scales not established
- Relationship to progression of pathology not established
- Relationship to motor fluctuations not established
- Response to current dopaminergic treatment not established

- Relationship to pattern of pathological change and progression – limited by models used
Neuroprotection or disease modification is difficult

- 38 clinical trials reviewed
  - Dopamine agonists and L-dopa
  - Glutamate antagonists
  - Trophic factors
  - Antioxidants
  - Mitochondrial enhancers
  - Anti-apoptotic agents

- Nothing proven to be effective

Al Dakheel et al., 2014
Not a single approach to disease modification

- Parkinson’s disease is a syndrome
- Differing patterns of pathology and biochemical change
- Different subtypes of PD
- No single cause or pathogenic mechanism
- Classical clinical trial design ignore subtypes
- Unlikely to find that ‘one size’ drug fits all
Repositioning existing drugs from other therapeutic areas

- Development of neuroprotective drugs is a high risk strategy
- Long development time – 15 years from molecule to medicine
- Clinical trials complex and expensive
- Reposition drugs already used in man for other indications that may also be effective in PD – shorter time, less risk, less cost, side-effects known, rapidly explored hypothesis – e.g. anti-diabetics, anti-hypertensives, anti-cancer drugs
Conclusions

• Dopaminergic therapies remain the mainstay of the treatment of Parkinson’s disease
• New approaches are focused on delivery and devices

• The definition of Parkinson’s disease is under review
• This reflects on the assessment of Parkinson’s disease and the design of clinical trials

• New approaches to therapy are focussed on non-dopaminergic drugs and the treatment of non-motor symptoms

• Designing clinical trials for neuroprotective/disease modifying therapies may require sub-type selection of patients