The Future of Parkinson’s Treatment – Personalised and Precision Medicine

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The modern concept of Parkinson’s disease (PD) has changed and evolved and we consider Parkinson’s to be a multi-neurotransmitter dysfunction-related disorder with central and peripheral nervous system involvement. The clinical expression is thus a mixture of the outwardly evident motor symptoms and a range of ‘hidden’ non-motor symptoms. The complex underlying neuropathology of PD calls for a reassessment of the treatment strategies currently used. Treatment of PD is guideline-driven and in most cases based on a dopamine replacement strategy or surgical manipulation of brain dopaminergic pathways. Treatment of many non-dopaminergic non-motor and some motor symptoms, which have major effects on quality of life, continue to remain a key unmet need. Like in other chronic conditions such as rheumatology, the role of personalised medicine in PD needs to be increasingly considered. Personalised medicine for PD is not just a genetic approach to treatment but encompasses various strands of treatment. These include pharmacogenetic, pharmacological, as well as socio-demographic and lifestyle-related issues. Once these ‘enablers’ of personalised medicine are considered then satisfactory treatment for our patients with Parkinson’s can be achieved in an individualised manner. Future therapy for PD should move in that direction.

Keywords
Parkinson’s disease, non-motor symptoms, quality of life, personalised medicine, precision medicine

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Personalised medicine
The concept of personalised medicine is subject to interpretation. The American Medical Association defines this ‘as each person’s unique clinical, genetic and environmental information’ while others consider personalised medicine purely from a genetic or pharmacogenetic ‘precision’ therapy standpoint. A more recent concept of the components that make up personalised medicine in PD as described recently by Titova and Chaudhuri is explained in Table 1.

The concept of personalised medicine is particularly relevant for PD, a condition with multiple pathology and neurotransmitter-linked syndromes.

For the development of new drugs relevant to the delivery of personalised medicine, robust animal models of PD are required. These models need to reflect the progressive pathology and multineurotransmitter defects that characterise PD. Such models based on toxin and/or genetic manipulation of rodents and primates remain elusive and represent an under-researched but key unmet need for the future of PD. Preliminary ‘bench’-based work has unravelled new potential targets for therapy which may help with aspects of non-motor symptoms (sleep dysfunction, cognition, pain and autonomic dysfunction) in PD, as well as some motor symptoms (gait freezing, dyskinesias). A combination of good animal model coupled with multiple non-dopaminergic target-based...
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Table 1: Personalised medicine in Parkinson’s disease

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<tr>
<th>Personalised Medicine Strategies</th>
<th>Pathways</th>
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<tr>
<td>Precision (genomic) medicine</td>
<td>Involves genomic principles such as clinical trial of gene therapy or HSP90 inhibitors for GBA positive/carriers at risk of developing PD.</td>
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<td>Pharmacogenetic medicine</td>
<td>Involves monitoring and/or adjusting dopamine replacement therapies in PD based on genetic susceptibility to side effects (dyskinesias, psychosis, levodopa response, impulse control disorder).</td>
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<td>Individualised medicine</td>
<td>Involves alteration or adjustment of therapeutic strategies based on racial differences/ethnicity, body weight, age.</td>
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<td>Personality medicine</td>
<td>Involves neuropsychologic input to delivery of personalised medicine driven by several strands of personality traits such as susceptibility to ICD, cognitive dysfunction, neuroticism, meta-cognitions, levodopa phobia.</td>
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<tr>
<td>Subtype-specific medicine</td>
<td>Involves modifications of therapeutic strategies based on clinically defined non-motor subtypes based on cholinergic, noradrenergic, serotonergic and mixed dysfunctions.</td>
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<td>Lifestyle-specific medicine</td>
<td>Involves adjustment, modification as well as alterations of treatment based on lifestyle (work, environment of work, pharmacoeconomics, exercise).</td>
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<tr>
<td>Target-driven medicine</td>
<td>Involves drugs being developed for new non-dopaminergic targets in PD. These include glucagon-like peptide 1 agonists, urate precursor agents or calcium channel antagonists as well as GABA, cannabinoid, purinergic and opioid target-driven drug developments.</td>
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GBA = glucocerebrosidase; HSP90 = heat shock protein 90; ICD = impulse control disorder; PD = Parkinson’s disease; Adapted from Titova N, Chaudhuri KR, Mov Disord, 2017.7

Other major factors involved in the delivery of personalised medicine include ageing and the concept of chronologic versus biologic age when increased life expectancy is taken into context. Therefore, it is possible that in the future, DBS of the subthalamic nucleus would be considered in ‘healthy aged’ PD patients even if they are older than 70 years. Currently, age remains a major limiting factor for offering DBS surgery to PD patients. Similarly, in younger patients depression and anxiety will have to be considered as such patients appear particularly susceptible to these non-motor symptoms.8 Non-motor and motor clinical subtypes of PD are an emerging and important clinical concept that will also determine treatment of PD.9 A cholinergic syndrome of PD would need a different treatment strategy to someone with a noradrenergic subtype of PD.10 Relevant clinical, imaging and genetic biomarkers may help define and drive these subtype-specific treatments. Other key issues are personality, lifestyle, body weight/body mass index, race and ethnicity as well as pharmacoeconomics.1 These are the ‘enablers’ of personalised medicine for future. Currently, our treatment strategies do not address these external but important variables that may determine the success of any therapy for PD. A ‘checklist’ of personalised medicine strategy supported by a strong multidisciplinary set-up should be the way forward to delivering successful treatment for PD in future. We need a combined holistic approach rather than a single target-focused dopaminergic treatment strategy which has failed to deliver cure, neuroprotection, neuromodulation or effective treatment of non-motor symptoms of PD in the past 50 years.1