



PD Academy Report

Expert Perspectives – Parkinson's Disease Pathophysiology and Management

Highlights of a Zambon-sponsored
PD Academy meeting held in Barcelona,
1–2 February 2018

Expert reviewers: David J Brooks,
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Expert Reviewers: David J Brooks,¹ Paolo Calabresi,² Susan Fox,³ Thomas Müller,⁴ Werner Poewe,⁵ Oliver Rascol,⁶ Fabrizio Stocchi,⁷

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The Fourth Edition of the PD Academy, sponsored by Zambon, was held in Barcelona on 1–2 February 2018. During the pan-European event, world-renowned experts in Parkinson’s disease (PD) presented the latest findings in the pathophysiology and management of the disease. Delegates attended a series of lectures by specialists that largely focused on non-dopaminergic dysfunction in PD. These were explored in terms of pathophysiology and imaging, as well as in-depth discussion of the clinical consequences in terms of non-dopaminergic dysfunction on the serotonin, acetylcholine, adenosine and glutamate systems. The effects of non-dopaminergic dysfunction on PD symptoms is now known to play a role in motor and non-motor functions (pain and mood) as well as in motor fluctuations and dyskinesia. The experts also showed the latest findings in these areas. Of interest, safinamide is a relatively new player in the PD spectrum of therapeutics, but it now appears consolidated that it affects multiple systems and as a consequence, has an array of activities that are not associated with other drugs used to treat non-dopaminergic dysfunction in patients with PD. Indeed, safinamide was held to be a highly promising adjunct therapy to treat a variety of motor and non-motor symptoms in PD, potentially improving efficacy and removing the need for further increases in levodopa dose. Safinamide, one name, two actions, four benefits. The experts considered the meeting to be a success and discussed possible topics and new avenues to explore for the future.

Keywords

Safinamide, dopaminergic, glutamatergic, levodopa adjunct, motor symptoms, dyskinesia, motor complications, non-motor symptoms, add-on

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Optimising the effect of dopaminergic treatment in Parkinson’s disease

Presented by: Werner Poewe

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In considering dopaminergic treatment of Parkinson’s disease (PD), one must consider dopaminergic drug targets, effect sizes of dopaminergic approaches, management of motor and non-motor complications,¹ impact of non-motor symptoms and lastly the role of non-dopaminergic mechanisms. From recent evidence-based reviews, the most efficacious drugs include levodopa, dopamine agonists (pergolide, pramipexole, ropinirole, pramipexole, rotigotine) and monoamine oxidase B (MAO-B) inhibitors (selegiline, rasagiline).²⁻⁷ Among these, following levodopa, pergolide is considered to have the largest effect size, followed by pramipexole (measured by Unified Parkinson’s Disease Rating Scale [UPDRS] total score versus placebo). The results of the ADAGIO study highlighted the need for additional antiparkinsonian therapy during the placebo-controlled phase: the likelihood of needing additional antiparkinsonian treatment was about 60% less in the rasagiline group than in the placebo group.⁸ Several early studies have also clearly shown that levodopa consistently provides better symptom control than the dopamine agonists pramipexole or ropinirole.^{9,10} These results were later confirmed in a Cochrane review involving 29 trials with 5,247 participants.¹¹ Although dopamine agonists have been proven to be effective as monotherapy in early PD, it is clear that they are less efficacious than levodopa. Therefore, in practice, the majority of patients initiated on dopamine-agonist therapy require levodopa within the first 2 years of treatment in order to reach a symptomatic control. Indeed, levodopa is still considered the “gold standard” for symptomatic efficacy and its antiparkinsonian efficacy has been documented by decades of clinical use. Moreover, it has a large and robust effect size and is well tolerated.

Considering a broad literature analysis, motor complication rates (referring to motor fluctuations and dyskinesias) vary somewhat, but broadly range around 50% after about 5 years in community-based and uncontrolled studies.¹²⁻¹⁴ The established risk factors for motor complications include the dose of levodopa (a major risk factor) and other factors such as younger age, female gender and lower body weight. It has implications for treatment since the dose of levodopa must be adjusted for a lower body weight, using the lowest dose that provides satisfactory clinical control. Early consideration to adjunct therapies should also be given. Adjunct therapies have been categorised according to their symptomatic effects and reduction of motor fluctuations.¹⁵ Safinamide is a new chemical entity that has been widely studied and is used as an

adjunct to levodopa. It can lead to an increase in motor function as well as ON-time without dyskinesia or non-troublesome dyskinesia in both the short- and long-term (24 months),^{16,17} and can be considered as a valuable addition to the therapeutic armamentarium.

There are several novel methods under study to optimise delivery of levodopa (reviewed by Aquilonius and Nyholm¹⁸). Such techniques include the continuous infusion of a levodopa-carbidopa intestinal gel, which has shown a significantly reduced ON-time without dyskinesia versus an immediate-release levodopa-carbidopa formulation.¹⁹ These aspects are important, as from the patient’s perspective, fluctuating response to medication is considered to be the most bothersome symptom. Moreover, psychotic non-motor symptoms fluctuate frequently and severely.²⁰ One such system of continuous subcutaneous levodopa infusion is NDO612, a proprietary liquid formulation that enables subcutaneous administration of levodopa-carbidopa. A randomised clinical study is ongoing with the device, which is showing promising results (NCT02782481). Another novel formulation for delivery of levodopa is CVT-301, a self-administered, inhaled formulation of levodopa that is being studied for the treatment of symptoms of OFF periods in patients taking an oral levodopa/carbidopa regimen. The formulation is currently under study and the initial results are encouraging.^{21,22} Other novel formulations under investigation are shown in *Table 1*.

Conclusions

- Levodopa is still the most effective drug to control motor symptoms and some non-motor symptoms
- Multiple options are available to treat motor fluctuations:
 - Catechol-O-methyltransferase (COMT) and MAO-B inhibitors
 - Long-acting dopamine agonists
 - Pump delivery for refractory patients (apomorphine, duodopa)
 - Multiple new approaches in development (novel formulations of levodopa and apomorphine, D₁-dopamine agonists, A_{2A} antagonists)
- Continuous drug delivery may prevent motor complications
- Non-motor symptoms remain a major therapeutic need
- Non-dopaminergic drug targets hold potential in improving motor and non-motor symptoms in addition to the control of motor complications □

Table 1: Novel formulations of levodopa currently being studied

Drug	Mechanism	Status
IPX 066 (Rytary, Numient)	LD-ER	FDA and EMA approval 2015
LD/CD intestinal gel	Continuous jejunal delivery	FDA approval 2015
NDO612/NDO611	Subcutaneous LD/CD delivery	Phase II (NCT02726386/ NCT01229332)
XP21279	ER LD-prodrug	Phase II (NCT0117131)
AP CD/LD	Prolonged gastric retention	Phase III (NCT02615873)
CVT-301	Inhaled levodopa (dry powder aerosol)	Phase III (NCT02242487)
IPX203	LD-ER	Phase II (NCT03007888)
ODM-101	Novel LD/CD/ENT combination	Phase II, completed (NCT01766258)

CD = carbidopa; EMA = European Medicines Agency; ENT = entacapone; ER = extended release; FDA = US Food and Drug Administration; LD = levodopa.

Non-dopaminergic dysfunction in Parkinson's disease – pathophysiology

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Aspects on non-dopaminergic dysfunction in non-motor symptoms focus on cognition, motor symptoms with a focus on tremor and freezing of gait, and the role of glutamate.²³ Non-dopaminergic systems are important since Braak stages reflect the involvement of multiple networks, not only the dopaminergic one.²⁴ In addition, non-motor symptoms may be prodromal, but are present throughout all stages of PD, and can be related to non-dopaminergic dysfunction. These are relevant aspects since non-dopaminergic features have significant impact on the course of PD and correlate with disease duration (Figure 1).²⁴ These include issues such as sleep problems, cognitive impairment, depression, autonomic disturbances and psychic symptoms.

The effects of non-dopaminergic dysfunction on cognition are complex, and involve brainstem pathology (nigrostriatal pathway), cholinergic neuronal loss (Meynert nucleus) and limbic and cortical Lewy body-type degeneration (direct cortical impairment). In fact, deficit in cognitive domains depends on multiple pathways, and involves the interplay of dopamine and acetylcholine during the induction and reversal of the main forms of synaptic plasticity as shown in Figure 2.²⁵

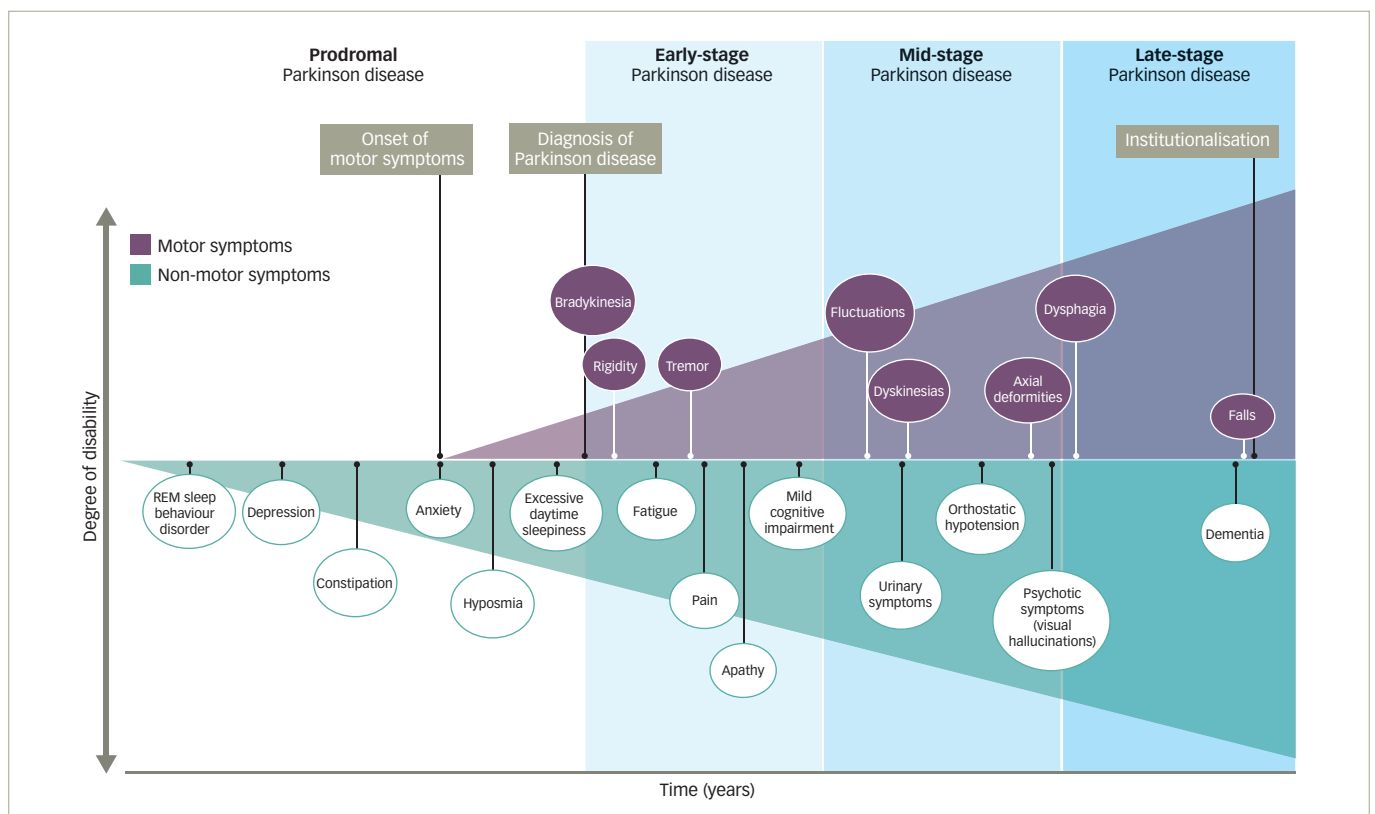
Considering non-dopaminergic dysfunction in motor symptoms, tremor is defined as involuntary, rhythmic and alternating movements of one or more body parts; resting tremor is "typical" in PD and present in about 75% of patients with the disease.²⁶ Importantly, tremor-dominant patients follow a more benign course.

Parkinsonian tremor is caused mainly by central, rather than peripheral mechanisms.

Pathophysiologically, tremor is linked to altered activity in not one, but two distinct circuits: the basal ganglia, which are primarily affected by dopamine depletion in PD, and the cerebello-thalamo-cortical circuit, which is also involved in many other tremors. As such, peripheral deafferentation has no effect on it, while levodopa and anti-acetylcholine agents have a beneficial effect as does deep-brain stimulation.^{27,28} Serotonergic dysfunction in PD has been associated with the development of both motor and non-motor symptoms and complications.²⁹ Indeed, 5-hydroxytryptamine (5-HT) transmission has shown to be involved in basal ganglia in tremor-dominant patients.³⁰ 5-HT transmission has also been shown to be crucial in freezing of gait as the pedunculopontine nuclei and locus coeruleus are highly involved in locomotor control and modulation of spinal network. Freezing of gait in PD has been associated with reduced 6-[¹⁸F]fluoro-L-m-tyrosine uptake in the locus coeruleus.³¹

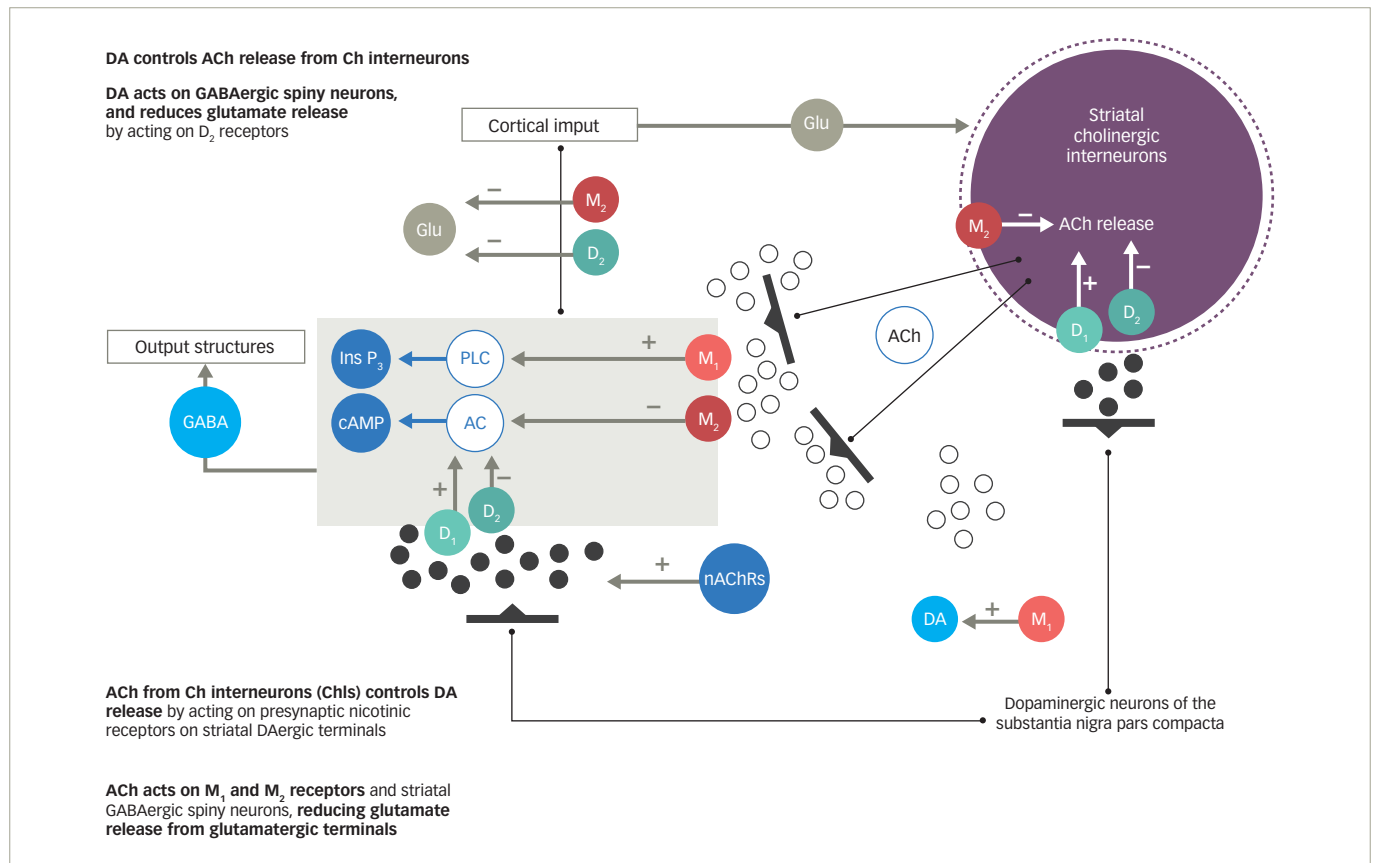
Lastly, the available information is strongly suggestive that glutamate is also implicated in the pathophysiology of PD.^{32,33} Correct glutamatergic activity and physiological signal-to-noise ratio of excitatory drive in the striatum is essential for synaptic plasticity and motor learning. In PD, this balanced transmission is disrupted by an increased presynaptic glutamatergic activity and by altered postsynaptic N-methyl-D-aspartate (NMDA)-mediated function.

Figure 1: Summary of Parkinson's disease stage and motor and non-motor symptoms that predominate at each stage²⁴



REM = rapid eye movement. Adapted with permission from Poewe et al., 2017.²⁴

Figure 2: Biological interactions of dopamine-acetylcholine in the striatum²⁵



AC = adenylate cyclase; ACh = acetylcholine; Ch = cholinergic; D_{1/2} = dopamine receptor subtypes; DA = dopamine; GABA = gamma-aminobutyrate; Glu = glutamate; InsP₃ = inositol-3-phosphate; M_{1/2} = muscarinic receptor subtypes; nAChRs = nicotinic acetylcholine receptors; PLC = phospholipase C. Adapted with permission from Calabresi et al., 2006.²⁵

Conclusions

- Multiple non-dopaminergic systems are implicated in non-motor symptoms of PD patients
- Cognitive deficits in PD are caused by dysfunctions of dopaminergic as well as non-dopaminergic systems such as the cholinergic and noradrenergic pathways
- Non-dopaminergic dysfunctions also participate in motor symptoms, and in tremor and freezing of gait in particular
- Alpha-synuclein leads to several motor and cognitive dysfunctions by interacting with both dopaminergic and glutamatergic mechanisms □

Non-dopaminergic dysfunction in Parkinson’s disease – neuroimaging

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An important aspect in the pathophysiology of peripheral dysfunction in PD is the finding that there is loss of myocardial sympathetic function. In fact, there appears to be a reduction in postganglionic presynaptic cardiac sympathetic innervation, which is suggestive of cardiac sympathetic dysfunction early in patients with PD.³⁴ Medulla and hippocampal diffusivity is also increased in PD and correlates with both cardiac and breathing abnormalities.³⁵ Moreover, in PD, the dorsal motor nucleus of the vagus undergoes severe degeneration, and pathological α -synuclein aggregations are also seen in nerve fibres innervating the gastrointestinal tract. The small intestine and pancreas show decreased cholinergic function in patients with PD, but there are no correlations with disease duration, severity of constipation, gastric emptying time or heart rate variability.³⁶

A number of studies have shown that there are cortical changes in PD. These include cortical thinning and subclinical cortical glucose hypometabolism.³⁷ Indeed, reductions in cortical fluorodeoxyglucose (FDG) metabolism are present in newly diagnosed PD, and correlate with performance on neuropsychological tests such as impaired paired-associate learning and impaired attention.³⁸ Cognitive dysfunction has also been seen to correlate with reduced glucose uptake.³⁹ Studies on network connectivity and cognition in PD have shown that reduced attentional network connectivity correlates with poor performance of Stroop and Trail making B tests, and that higher default mode connectivity correlates with poor performance in visual perception tests.⁴⁰ It is believed that the changes in differential connectivity affecting the different networks evaluated are related to

the pathophysiological basis of different types of cognitive impairment in PD.

Amyloid deposition has also been examined by positron-emission tomography (PET) imaging. Global cortical amyloid burden is high in dementia with Lewy bodies (DLB), but low in PD dementia.⁴¹ These data suggest that beta-amyloid may contribute selectively to the cognitive impairment of DLB and may contribute to the timing of dementia relative to the motor signs of parkinsonism. Indeed, amyloid may be linked to cognitive decline in patients with PD without dementia.⁴²

Regarding non-dopaminergic central transmitter loss and dysfunction, acetylcholinesterase (¹¹C]PMP) PET imaging has been used to show that cortical cholinergic loss correlates to cognitive assessment scores, while thalamic cholinergic loss leads to gait and balance disorders.⁴³ As such, assessment of clinical indices of cholinergic denervation may be useful for identifying suitable subjects for trials of targeted cholinergic drug treatments in PD. Acetylcholine levels have also been linked to depression,⁴⁴ and depressive symptomatology is associated with cortical cholinergic denervation in PD that tends to be more prominent when dementia is present. Similarly, serotonin levels in the brain have been associated with fatigue in PD.^{45,46} This is relevant as there is evidence of decreased 5-HT_{1A} receptor number or affinity in chronic fatigue syndrome.⁴⁷ This may be a primary feature of the disorder, related to the underlying pathophysiology, or a finding secondary to other processes, such as previous depression, other biological changes or the behavioural consequences of chronic fatigue. Fewer serotonin transporters in the rostral raphe have also been linked to excessive daytime somnolence in PD.

Another important aspect to consider is noradrenergic function in PD. In a PET/magnetic resonance imaging (MRI) study, PD patients with rapid eye movement sleep behaviour disorder (RBD) showed a decreased

locus coeruleus neuromelanin signal on MRI and widespread reduced binding of ¹¹C]MeNER, which correlated with amount of REM sleep without atonia.⁴⁸ PD with RBD was further associated with a higher incidence of cognitive impairment, slowed electroencephalogram activity and orthostatic hypotension. Thus, reduced noradrenergic function in PD is linked to the presence of RBD and associated with cognitive deterioration and orthostatic hypotension. Noradrenergic impairment may contribute to the high prevalence of these non-motor symptoms in PD and may be of relevance when treating these conditions.

Lastly, overactive glutamate ion channels in PD have also been associated with levodopa-induced dyskinesias.⁴⁹ In the 'OFF' state withdrawn from levodopa, dyskinetic and non-dyskinetic patients had similar levels of tracer uptake in basal ganglia and motor cortex. However, when PET imaging was performed in the 'ON' condition, dyskinetic patients had higher ¹¹C]CNS 5161 uptake in caudate, putamen and precentral gyrus compared with the patients without dyskinesias, suggesting that dyskinetic patients may have abnormal glutamatergic transmission in motor areas following levodopa administration.

Conclusions

- Both peripheral sympathetic and parasympathetic dysfunction can be imaged in PD
- Cortical thinning and loss of metabolism can be detected at clinical onset of PD
- Dementia is multifactorial involving Lewy body pathology, loss of acetylcholine, and amyloid deposition
- Central fatigue is associated with limbic serotonergic loss
- Impaired sleep regulation involves loss of both serotonergic and noradrenergic function
- Levodopa-induced dyskinesias are associated with overactive glutamate NMDA ion channels □

Clinical consequences of non-dopaminergic dysfunction

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Both motor and non-motor dysfunction may be consequent to non-dopaminergic dysfunction in PD. The motor consequences may be the result of aberrant signalling with several neurotransmitters (Table 2).⁵⁰⁻⁷⁴

Preclinical studies have shown enhanced glutamatergic neurotransmission underlying parkinsonism and following chronic levodopa therapy resulting in levodopa-induced fluctuations, including dyskinesia.^{50,51} Several subtypes of glutamate receptor are involved, including NMDA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and metabotropic. In patients with PD, glutamate antagonists may increase 'good-ON time' i.e., ON time without troublesome/disabling levodopa-induced dyskinesia.

A number of glutamatergic targets are under investigation for levodopa-induced fluctuations (Table 3).^{17,52-57} Adenosine A_{2A} receptors have a selective location on the indirect D₂ pathway.⁵⁸ Dopamine D₂ activation (with levodopa) and adenosine A_{2A} antagonism is known to reduce overactive glutamate transmission (and over-activity of indirect D₂-mediated pathway) resulting in improved PD motor symptoms. While several adenosine A_{2A} antagonists have been evaluated in PD, none show

Table 2: Motor symptoms in Parkinson's disease that may be a result of non-dopaminergic dysfunction⁵⁰⁻⁷⁴

Motor symptoms	Non-dopaminergic receptor dysfunction
Levodopa-induced fluctuations	Multiple: glutamatergic/adenosine/serotonin
Gait and balance	Acetylcholine/noradrenaline
Tremor	Acetylcholine/serotonin

any significant benefits as monotherapy, and appear to be of variable benefit as adjunct therapy.^{59,60} Dyskinesia is one of the most important side effects of these drugs.

Several serotonergic agents have also been evaluated in PD (Table 4).⁶¹⁻⁶⁷ The relationship is that dopamine release from 5-HT terminals is the cause of levodopa-induced dyskinesia in parkinsonian rats.⁶⁸ Several serotonergic agents have been evaluated for use in PD patients (reviewed by Huot et al.⁶⁹). Additionally, several drugs have been evaluated for non-dopaminergic treatments for gait and balance in PD.

Table 3: Glutamatergic targets under investigation for levodopa-induced fluctuations^{17,52–57}

Drug	Target	Phase of development	Results
ADS-5102 extended-release amantadine	NMDA antagonist	FDA approved	Significant increased ON time without troublesome LID ⁵²
Amantadine HCl extended release	NMDA antagonist	Phase III	Ongoing (ALLAY-LID I; ALLAY-LID II) – over 16–28 weeks (NCT02153645; NCT02153632)
Safinamide	MAO-B-I/channel blocker	EMA/FDA approved	Significant improvement of ON time without troublesome LID ¹⁷
Dextromethorphan/quinidine (AVP-923)	NMDA antagonist/ CYP2D6 inhibitor	Clinically available Phase II	Reduced UDysRS III (during acute levodopa infusion) by approximately 20%; no significant AEs ⁵³
Memantine	NMDA antagonist	Clinically available Phase III	Non-significant 35% reduction in day spent with LID (diary) ⁵⁴
Mavoglurant	mGluR5 antagonist	Phase II (no further development)	Non-significant ^{55,56}
Dipraglurant	mGluR5 antagonist	Phase II (no further development)	Non-significant ⁵⁷

AEs = adverse events; EMA = European Medicines Agency; FDA = US Food and Drug Administration; LID = levodopa-induced dyskinesia; MAO-B = monoamine oxidase B; mGluR = metabotropic glutamate receptor; NMDA = N-methyl-D-aspartate; UDysRS = Unified Dyskinesia Rating Scale.

Table 4: Serotonergic agents evaluated in Parkinson’s disease for dyskinesia^{61–67}

5-HT receptor properties	Drug	Study
SSRI/5-HT _{1A} agonist	Fluoxetine	Phase II (n=7), reduced LID by 47% after 11 days (20 mg BID) ⁶¹
5-HT _{1A} agonist	Sarizotan	Phase III: no benefit versus placebo (AE worsening PD motor) ^{62,63}
5-HT _{1A} agonist	Buspirone	Acute dosing reduced LID in levodopa challenge. ⁶⁴ Two ongoing trials: DBRCT 20–30 mg (NCT02617017); buspirone (30 mg) as add on to amantadine (NCT02589340)
5-HT _{1A/1B} agonist	Etoprozine	Phase IIa: acute dosing (7.5 mg) reduced dyskinesia. No worsening of PD. ⁶⁵ Ongoing phase IIb DBRCT 2.5–7.5 mg/day (NCT02439125)
5-HT _{2A/2C} antagonist	Clozapine	Phase II (n=64) 25–50 mg/day improved on time with LID after 10 weeks ⁶⁶
5-HT _{2A/2C} antagonist	Quetiapine	Phase II (n=9) no benefit with 25–50 mg for 2 weeks ⁶⁷

AE = adverse event; BID = twice daily; DBRCT = double-blind randomised controlled trial; LID = levodopa-induced dyskinesia; PD = Parkinson’s disease.

Tremor-dominant PD is also an important clinical phenotype, and in these patients, striatal dopamine depletion may not correlate with tremor symptoms. Moreover, these patients may not respond to levodopa or may need higher doses of levodopa. Non-dopaminergic targets such as cholinergic antagonists (muscarinic M₁) and serotonergic antagonists (5-HT_{2A}) have been investigated, although the results are not conclusive.⁵⁹ Cholinergic interneurons are modulated through dopamine receptors and loss of nigrostriatal dopaminergic input results in an increase in cholinergic activity that is controlled by both nicotinic and muscarinic receptors. Cholinergic interneurons linked to the indirect pathway markedly increase in PD. The anticholinergic drugs in clinical use include benzhexol, orphenadrine, benztropine and parsitan. Mixed 5-HT_{2A/2C} antagonists together with an anti-cholinergic have also been preliminarily investigated, including mirtazapine and clozapine,^{59,60} although these drugs are not approved for this indication.

Changes in non-dopaminergic neurotransmitters may also have clinical consequences on non-motor symptoms, and many non-motor symptoms may not adequately respond to dopamine.⁷⁰ Among these, PD-related psychosis is characterised by illusions, hallucinations, delusions and paranoia. These may be disease-related (particularly with duration of disease) or drug-related that may first occur on starting dopaminergic drugs and may improve with reducing or stopping the drug. There is now good evidence that 5-HT_{2A} receptors in the temporal cortex underlie pathophysiology of visual hallucinations in PD.^{71,72} In this case, clozapine, as a 5-HT_{2A/2C} antagonist, may be the most effective agent in reducing

PD psychosis. Indeed, targeting the 5-HT_{2A} receptor appears to be a valid way to treat PD psychosis.^{73,74} In addition to clozapine, quetiapine and pimavanserin may also be considered. This latter drug was approved by the FDA in 2016 for PD psychosis.

In PD dementia, a combination of Lewy bodies and neurites in cortical, limbic and brain stem areas, Alzheimer disease pathology (cortical and striatal amyloid and Braak tau) and vascular disease are believed to be its pathological basis. Non-dopaminergic drugs targeting acetylcholine and glutamate have been studied in these patients. These include donepezil, rivastigmine, galantamine and memantine.^{75,76}

Orthostatic hypotension is considered as the “triple whammy” of autonomic failure in patients with PD, and has three determinants: cardiac noradrenergic denervation, extra-cardiac noradrenergic denervation and arterial baroreflex failure. Orthostatic hypotension causes a syndrome that is composed of post-prandial hypotension, labile blood pressure, supine hypertension, fatigue and exercise intolerance and falls. Several drugs are currently under investigation for orthostatic hypotension.

Conclusions

- Non-dopaminergic neurotransmission is involved in the pathophysiology of many aspects of PD
- Targeting non-dopaminergic systems e.g., glutamate/acetylcholine or serotonin/noradrenaline can help both motor and non-motor symptoms in PD □

Role of non-dopaminergic dysfunctions in PD symptoms – clinical effects on dyskinesia

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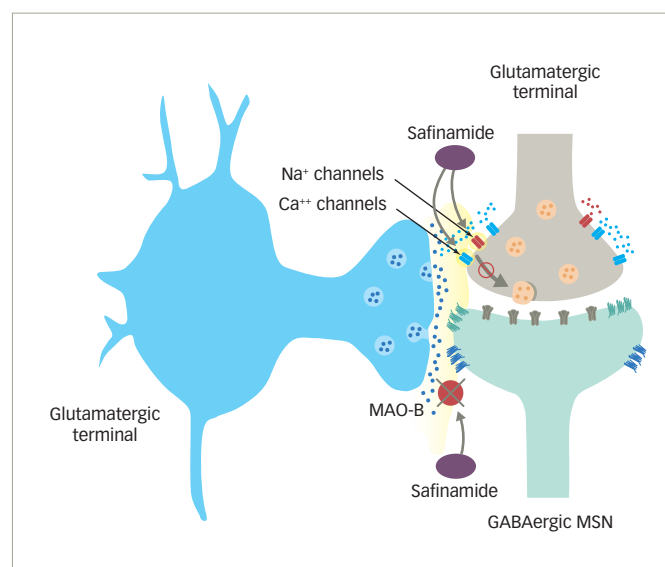
In considering the clinical impact of dyskinesia, it is worth bearing in mind that there are different types of dyskinesia, thus raising the question of whether diphasic dyskinesias are the expression of the same pathophysiology. In particular, dysphoric dyskinesia is more dependent on levels of levodopa and dopaminergic stimulation than other forms. It has been noted that the main factors leading to the development of dyskinesia include denervation of the dopaminergic system, disease duration and severity, dopaminergic treatment and pulsatile stimulation of post-synaptic DA receptors.^{77,78} Dyskinesia can also initiate when levodopa levels are stable. In some patients, this may be induced by continuous intraduodenal infusion of levodopa that ceases after about 15 minutes when the pump is disconnected.

Levodopa is metabolised by the serotonergic system, and patients with levodopa-induced dyskinesia have abnormal distribution of serotonergic terminals; serotonergic terminals try to compensate for the lack of dopaminergic terminals.⁷⁹ This suggests that it may be possible to target the serotonergic system, even though there have been several studies to date but little clinical success.^{64,80}

In an advanced stage of dopaminergic cell loss, the remaining serotonergic neurons in the basal ganglia complex can specifically take up levodopa and convert it to dopamine.⁸¹ In contrast to the normal situation, release of dopamine occurs in this setting when the serotonergic neurons are activated and dopamine functions as a false transmitter. This abnormally released dopamine stimulates postsynaptic dopamine receptors in an uncontrolled manner. Moreover, uncontrolled stimulation of super-sensitized dopamine D₁ receptors in the direct striatonigral pathway are thought to mediate levodopa-induced dyskinesia.^{82,83}

Both pre-clinical and clinical research has further supported the potential of modulating the 5-HT system for prevention and treatment of levodopa-induced dyskinesia.^{84–86} In this regard, eltopazine and trazadone have been studied.^{65,87} The latter does have some benefits for dyskinesia, although the drug is likely to be poorly tolerated, having a sedative effect. The opioid system has also been considered as a possible target.^{88–90} Various opioid compounds have been evaluated in levodopa-induced dyskinesia,^{88–90} and the available data indicate that mu antagonism has the most benefit,⁸⁸ with kappa-agonism also having desirable effects.⁹¹ Nalbuphine has been investigated for its antidyskinetic effects in animals.⁸⁹ However, no clinical studies have been carried out to date.

Figure 3: Pharmacological systems affected by safinamide



GABA = gamma-aminobutyrate; MSN = Medium spiny neurons. Adapted with permission from Reichmann et al., 2015.⁹⁵

In considering other modulators of dyskinesia, glutamate-related mechanisms are likely to be involved. Levodopa-induced dyskinesias are also consistently associated with abnormal glutamate transmission in the basal ganglia in rodent and primate models of PD.^{92,93} Extracellular glutamate levels are also markedly increased in the basal ganglia of dopamine-lesioned rats receiving levodopa. Promising results have been obtained in clinical trials with glutamate receptor modulators.⁹¹

Lastly, safinamide is another promising agent in treatment of levodopa-induced dyskinesia, and the molecule is likely to affect multiple systems as it has both dopaminergic and non-dopaminergic effects (Figure 3). The levodopa sparing effects of safinamide are of increasing interest in this regard, as well as its demonstrated benefits on dyskinesia.^{23,94,96,97}

Conclusions

- Development of dyskinesia is likely to be related to denervation of the dopaminergic system
- Drugs that modulate the glutamatergic system can improve dyskinesia
- Safinamide is a promising candidate also for the control of dyskinesia as it affects multiple systems □

Clinical effects on pain

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Pain is an important consideration in patients with PD, and non-dopaminergic dysfunctions play a substantial role in this symptom.⁹⁸ Indeed, pain is prevalent in patients with PD, and reported to be present in 40–85% of cases.⁹⁹ It is also one of the most prevalent non-motor symptoms. Importantly, quality of life scores are reduced by comorbid pain, and affect many aspects of life such as mobility, emotional wellbeing, stigma, social support and communication.¹⁰⁰ In reality, pain in PD is heterogeneous and characterised by many features.⁹⁸ This leads to difficulty in its classification, and there is thus an objective need for a unified taxonomy to assess pain in PD.¹⁰¹ In addition, at least 25% of PD patients suffer from three or more types of pain at the same time.¹⁰²

There are complex interactions between pain and mood in PD.¹⁰³ However, the use of antiparkinson medications is a common therapeutic approach employed for many types of pain present in PD. A frequent question is whether pain in PD is related to motor or non-motor fluctuations, although the available data seem to suggest that it is prevalently related to motor fluctuations.¹⁰⁴ As such, ON/OFF medications may be of value.

Several studies have also examined the benefits of rotigotine on pain in PD, although conflicting results have been reported,¹⁰⁵ including the use of a transdermal patch.¹⁰⁶ Notwithstanding, there are some safety concerns for the use of dopamine agonists such as rotigotine in PD, including intensification of daytime somnolence and impulse control disorders, in addition to oedema and hallucinations.^{107,108} In avoiding additional pharmacotherapy, deep brain stimulation may be an effective means of controlling pain and other non-motor symptoms in PD, although more studies are needed.

Prolonged-release oxycodone-naloxone has been studied for treatment of severe pain in patients with PD, in the PANDA trial which involved 202 patients.¹⁰⁹ However, the primary endpoint of average 24-hour pain score at 16 weeks, was not significant, even if the authors highlighted the possible efficacy of the combination in treatment of severe pain in PD.

Another question regarding pain in PD is whether central pain can be considered as a dopaminergic symptom. However, there are many possible pathophysiological mechanisms of pain in PD, which include degeneration of noradrenergic neurons in the locus coeruleus, nociceptor degeneration, pain processing at the spinal level, hypofunction of the striatal dopaminergic system and pain-induced activation in prefrontal and cingulate cortices.¹¹⁰

Pain thresholds are known to be altered in response to levodopa treatment. Interestingly, however, apomorphine does not modify the subjective and objective pain thresholds in PD patients with or without “central” pain and does not modify PET activation patterns in PD patients with or without pain.¹¹¹ While duloxetine has been used to treat pain in patients with PD, it is not likely to be significantly effective. It is also clear that pain medications are underused in patients with PD.¹¹² This is especially true for weak opiates, which may show significant benefits in pain for PD patients.

Safinamide has also been examined in terms of its effects on pain. Safinamide inhibits state- and use-dependent sodium channels,¹¹³ and sodium channel inhibitors are known to improve neuropathic pain.^{114,115} In

Figure 4: Pooled analysis of SETTLE and Trial 016 on concomitant use of pain treatments – proportions of patients not using/using concomitant pain drugs with safinamide or placebo⁹⁴

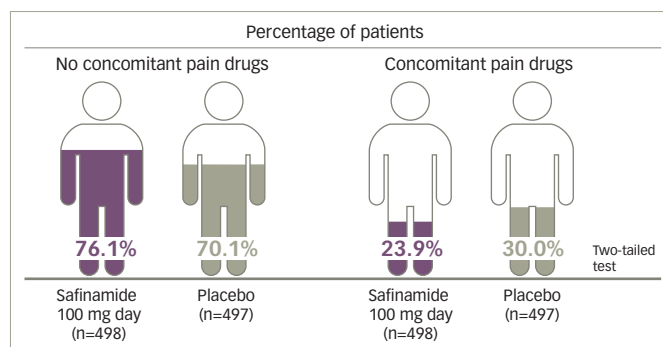
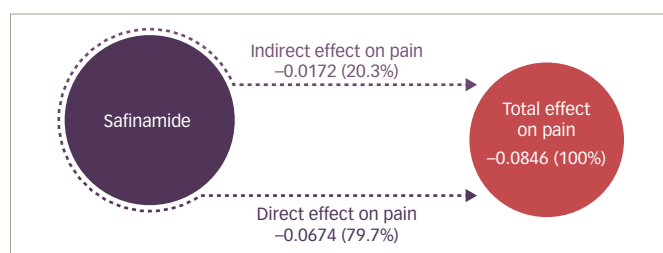


Figure 5: Pain reduction ascribed to safinamide⁹⁴



the 016 and SETTLE trials, there was a significant reduction in the number of concomitant pain treatments by 23.6% ($p=0.0421$) with safinamide compared with placebo (Figure 4).⁹⁴ Moreover, safinamide 100 mg/day significantly improved two of the three Parkinson’s Disease Questionnaire (PDQ)-39 items related to musculoskeletal and neuropathic pain.⁹⁴

Path analysis has shown that safinamide has both direct and indirect effects on pain; 79.7% of pain reduction ascribed to safinamide was attributable to a direct effect of the drug ($p=0.0076$), while the remaining 20.3% was an indirect effect mediated by the activity of safinamide on OFF time (10.1%), GRID Hamilton Rating Scale for Depression (GRID-HAMD) (5.4%) and UPDRS IV (4.5%) (Figure 5).⁹⁴

Conclusions

- Lots of uncertainty and empiricism
- Identify specific situations justifying specific interventions:
 - Dystonia
 - Orthostatic hypotension
 - Depression
- Adjust antiparkinsonian medications
 - Motor and non-motor fluctuations
 - Levodopa versus dual mechanism (safinamide) or other transmitters
- Consider pain killers
 - Nociceptive pain medications
 - Neuropathic pain medications
- Non-pharmacological interventions
 - Functional surgery
 - Other

Clinical effects on mood

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Mood alterations are an important issue when considering non-dopaminergic dysfunctions in patients with PD. Treatment of both motor impairment and non-motor symptoms is important. Improvement of non-motor symptoms results in improvement of motor behaviour and vice versa.^{116,117} As expected, the presence of non-motor symptoms reduces the quality of life, and fluctuations in motor behaviour also contribute to fluctuations in non-motor symptoms.^{116–118} Moreover, considering that PD has heterogeneous presentations, personalised approaches are needed.¹¹⁹

MAO-B inhibitors have been used in patients with PD; inhibition of MAO-B elevates biogenic amines such as serotonin, noradrenaline and dopamine, and thereby improves mood disturbances and mood fluctuations.^{120,121} Its inhibition also reduces MAO-B-triggered oxidative stress in contrast to antidepressants. Importantly, MAO-B inhibitors are also well tolerated and safe, and metabolites of MAO-B inhibitors may have some impact on efficacy and symptoms.^{120,121}

The most widely used MAO-B inhibitors in PD are selegiline and rasagiline, even if there are some differences between the two in terms of pharmacodynamics. The former is metabolised to metamphetamine which, at least in experimental studies, is toxic to dopaminergic neurons and may even be associated with cardiotoxicity and psychosis.^{122,123} The metabolite of rasagiline, R-1-aminoindan, on the other hand, is not a MAO-B inhibitor and is not associated with the negative effects that have been attributed to selegiline. Long-term studies with selegiline have suggested that it is actually associated with poor sleep quality, worsened mood and cognitive issues.^{124,125} Switching to rasagiline can lead to improvements in concentration, depression and sleep.¹²⁶

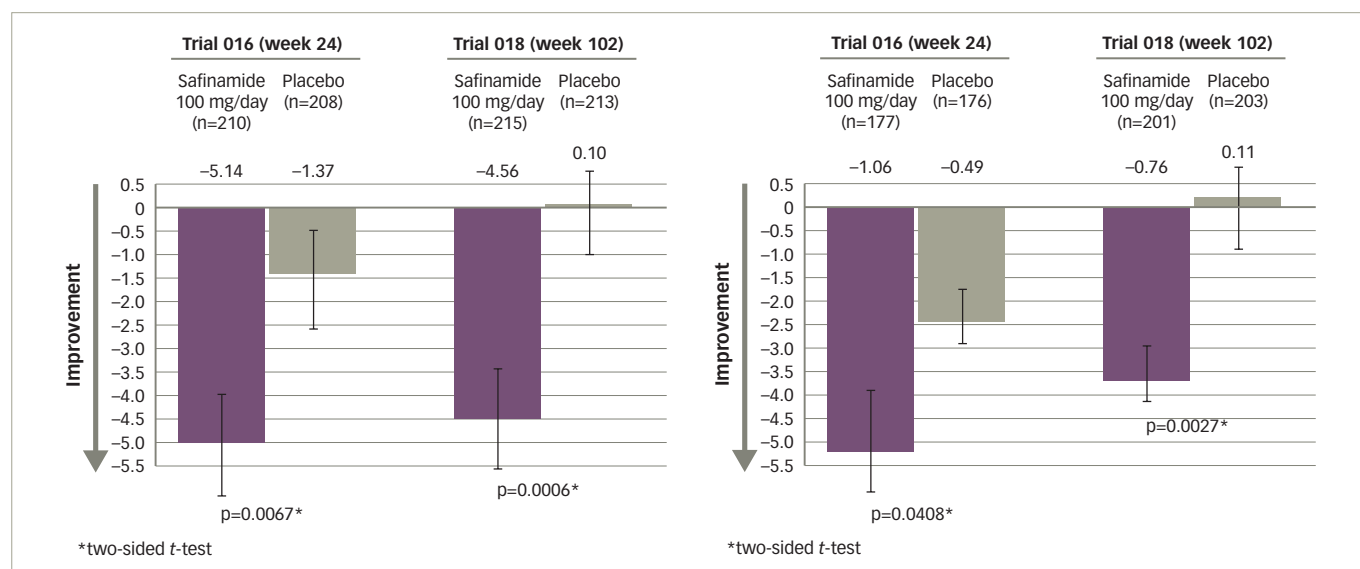
When examining the effects of safinamide, it has been stated that it is “not just another MAO-B inhibitor”.^{97,127} Firstly, MAO-A activity does not differ following treatment with rasagiline and safinamide versus

no MAO-B inhibitor.¹²⁷ Second, there is no difference between MAO-B inhibition between rasagiline and safinamide in PD patients in the long-term. Interestingly, in a post-hoc analysis of trials 016 and 018, significant changes were seen in PDQ-39 “Emotional well-being” domain scores and GRID-HAMD scores (*Figure 6*).⁹⁷ The study also reported that significantly fewer patients reported depression as an adverse event.

Conclusions

- Non-motor symptoms, such as mood disturbances and pain, play an important role in PD
- As dopaminergic dysfunction is not the only pathogenic mechanism involved in PD, it is important to target both dopaminergic and non-dopaminergic disease pathways
- Safinamide, a unique treatment modulating both dopaminergic and glutamatergic systems, has been shown to be effective as an add-on to levodopa therapy, prolonging levodopa efficacy, improving motor function and increasing ON time with no/non-troublesome dyskinesia
- Unlike other dopamine replacement therapies that improve motor function by acting solely on the dopaminergic pathway, safinamide does not worsen dyskinesia; this effect may be related to its dual mechanism of action which modulates dopaminergic and glutamatergic pathways
- Safinamide, compared with placebo, significantly improved the PDQ-39 “Emotional well-being” domain after 6-months ($p=0.0067$) and 2 years ($p=0.0006$), as well as the GRID-HAMD ($p=0.0408$ after 6 months and $p=0.0027$ after 2 years).
- Safinamide is an effective and well-tolerated once-daily drug for fluctuating PD, irrespective of concomitant medication
- The favourable effect of safinamide on mood may be explained by the improvement in wearing off and by its modulation of glutamatergic hyperactivity and reversible MAO-B inhibition. Prospective studies are warranted to investigate this potential benefit \square

Figure 6: Changes in PDQ-39 emotional well-being domain scores (left) and changes in GRID-HAMD scores (right) with safinamide and placebo.⁹⁷



GRID-HAMD = GRID Hamilton Rating Scale for Depression; PDQ = Parkinson’s Disease Questionnaire. Reproduced from Cattaneo et al.⁹⁷ with permission under the CC BY-NC 4.0 license.

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