

Dyskinesia – Advances in the Understanding of Pathophysiology and Possible Treatment Options

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Abstract

The degeneration of nigrostriatal dopaminergic neurons in Parkinson's disease gives rise to tremor and slowness of movement, cardinal motor symptoms of the disease that can be alleviated by the dopamine precursor L-DOPA. Despite this, long-term L-DOPA treatment is hampered by the development of abnormal involuntary movements, i.e. dyskinesia, in the majority of patients. The pathophysiology of dyskinesia is complex and multifactorial, but excessive swings in extracellular dopamine causing aberrant plasticity in dopaminergic neurons are attributed a primary role. To date there are few effective treatment alternatives for patients with Parkinson's disease experiencing dyskinesia, representing an unmet therapeutic need in the treatment strategy of the disease. This article reviews recent findings from both clinical and pre-clinical studies and their impact on the search for novel therapeutic approaches to levodopa-induced dyskinesia.

Keywords

L-3,4-dihydroxyphenylalanine (L-DOPA), dopamine replacement therapy, dyskinesia, animal models, plasticity, basal ganglia, dopamine, serotonin, noradrenalin, glutamate

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Since its introduction in the 1960s, dopamine replacement therapy with its metabolic precursor L-3,4-dihydroxyphenylalanine (L-DOPA) has remained the most effective pharmacotherapy for Parkinson's disease (PD).¹ Particularly in early disease, it is efficiently converted into dopamine, replacing that which is lost through the degeneration of nigrostriatal dopaminergic neurons. In doing so, L-DOPA alleviates bradykinesia and rigidity, helping, for example, to restore gait and arm swing.² However, its utility is limited by the development of motor complications that become increasingly evident as the disease progresses. These include:

- The development of 'on-off' fluctuations;
- periods in which the beneficial effects of L-DOPA are rapidly lost;
- a reduction in the effective duration of L-DOPA response; and
- the most troubling – choreic and dystonic abnormal involuntary movements, collectively termed L-DOPA-induced dyskinesia (LID).

The movements are present predominantly during the beneficial activity of L-DOPA,³ most commonly occurring as 'peak dose' dyskinesia but also occurring as dopamine levels decline as 'end-of-dose' LID. The reported incidence of LID varies between studies and patient groups, but can affect up to 40% of PD patients after only four to six years of L-DOPA therapy.⁴

Given that L-DOPA is still the most efficacious antiparkinsonian medication, providing therapy that circumvents LID remains a major unmet therapeutic need in the treatment strategy of PD. Currently, pharmacological interventions are limited to short-term

treatment with the antiviral and weak NMDA (N-methyl-D-aspartic acid) antagonist amantadine or invasive neurosurgical intervention targeting the deep basal ganglia nuclei with deep brain stimulation (DBS). DBS stands alone as the only therapeutic option for severe LID and is both expensive and associated with acute and ongoing risks.^{5–7} The criteria for patient selection for this treatment is quite stringent and, critically, DBS is not offered to patients suffering from cognitive impairment, which affects as many as one-third of PD patients.⁸

Although the precise mechanisms underlying LID have remained elusive, three main risk factors for this condition have been conclusively identified in clinical studies. These are a young age of disease onset, disease severity (reflecting the extent of putaminal dopamine denervation) and high doses of L-DOPA.^{9,10} The latter two factors are readily reproduced in both non-human primates and rodents by the administration of neurotoxins, which ablate the nigrostriatal pathway, followed by daily treatment with L-DOPA at a sufficient dosage.^{11–16} The animals develop abnormal involuntary movements of hyperkinetic and/or dystonic phenotypes during the treatment period. These movements will gradually replace normal motor behaviour¹⁵ and overshadow the beneficial effect of L-DOPA.

Not all patients with PD develop dyskinesia and, similarly, a proportion of animals do not develop abnormal involuntary movements after chronic L-DOPA treatment. Thus, the animal models provide a valuable tool whereby molecular and neurochemical changes can be specifically correlated with dyskinesia rather than to

a general effect of L-DOPA treatment. This article will provide a summary of the most important findings from these experimental models and their impact on the search for novel therapeutic options for LID.

Maladaptive Plasticity in L-DOPA-induced Dyskinesia Pre-synaptic Plasticity

Generally, therapeutic doses of L-DOPA given to rodent or primate models of PD typically require a substantial dopaminergic depletion before LID can be established. Even so, some animals with extensive dopamine denervation remain non-dyskinetic after chronic L-DOPA treatment. Therefore, the extent of LID cannot be solely predicted by the degree or pattern of dopaminergic depletion.¹⁷ Dopaminergic depletion is a significant risk factor but additional, thus far undetermined factors, must also be key to the development of LID.

Large and rapid fluctuations in extracellular levels of dopamine have been regarded as the prime trigger of the motor complications associated with L-DOPA therapy.¹⁸ Accordingly, recent positron emission tomography studies in PD patients have demonstrated large increases in putaminal dopamine release after L-DOPA administration, which correlate positively with the severity of dyskinesia.^{19,20}

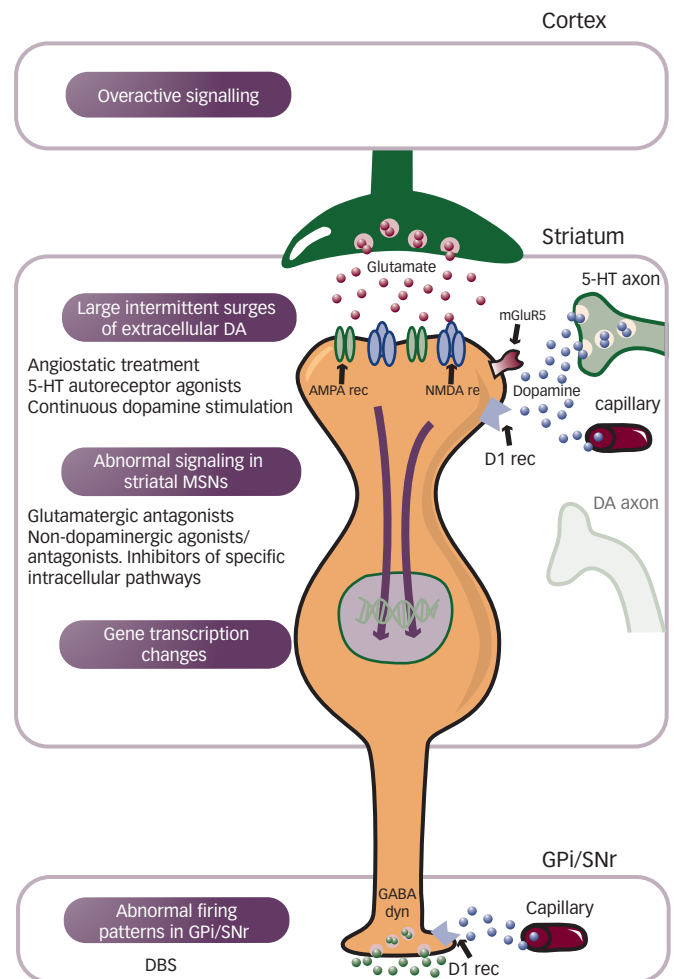
In line with the clinical findings, high striatal levels of dopamine have been reported in L-DOPA-treated dyskinetic rats.^{21–23} The fluctuations were originally thought to be due to the loss of dopamine neurons. However, more recently it has been suggested that a reduced expression/dysfunction of the dopamine transporter in the remaining nigrostriatal terminals^{21,24} and a higher density of striatal serotonergic fibres²⁵ may be critical contributors to changes in dopamine levels.

As the number of dopaminergic neurons decreases, the ability of the remaining terminals to convert L-DOPA into dopamine is reduced. Eventually, serotonergic neurons become the main site of L-DOPA decarboxylation in the brain. The lack of both dopamine autoreceptors and high-affinity reuptake capacity for dopamine, however, provides a source of unregulated dopamine efflux following exogenous L-DOPA administration.¹⁷

A causal link between the serotonin system and LID has recently been demonstrated in which LID was abolished by lesions of ascending 5-HT projections and greatly reduced by agonists of the serotonin autoreceptors 5-HT_{1A} and 5-HT_{1B}.²⁶ These drugs were later found to blunt the surge of striatal extracellular dopamine following L-DOPA administration.²² Clinical trials with the 5-HT_{1A} agonist sarizotan have demonstrated some improvements in dyskinesia, although the dopamine antagonist activity of this drug may have influenced the overall unimpressive clinical outcome.^{27,28} Pardoprunox (SLV308) is also being evaluated as a 5HT_{1A} agonist with additional dopamine D_{2/3}-receptor partial agonist activity. It has already shown some success as a *de novo* treatment in early PD.²⁹

Dysregulated dopamine release may contribute substantially to the pulsatile levels of dopamine caused by intermittent L-DOPA administration.¹⁸ As these pulsatile events are closely correlated with LID, current pharmaceutical strategy has moved towards the concept of continuous dopaminergic stimulation (CDS). CDS aims to prolong

Figure 1: Pathophysiological Findings in L-DOPA-induced Dyskinesia and New Pharmacological Targets and Strategies Under Investigation



Fluctuating dopamine (DA) (filled blue circles) levels after peripheral L-DOPA administration are considered the prime trigger of L-DOPA-induced dyskinesia (LID). Both unregulated DA release from serotonergic neurons and increased blood-brain barrier permeability may further exacerbate these fluctuating levels of DA. The expression of LID is also associated with an overactive signalling in cortical motor areas as well as supersensitised D₁ dopamine receptors (D₁ rec), causing abnormal signalling in striatal medium spiny neurons (MSNs) and long-term alternations in gene and protein expression. Overactive γ -Aminobutyric acid (GABA)ergic projections from striatum to the output nuclei of the basal ganglia leads to a large amount of GABA (green circles) being released in the output structures following L-DOPA administration. This neurochemical imbalance gives rise to abnormal firing patterns in GPi/SNr, which most likely represent the neural code for dyskinesia. DBS = deep brain stimulation; GPi = globus pallidus interna; SNr = substantia nigra pars reticulata.

the effects of L-DOPA, with the dual benefit of increases in 'on-time' and (hopefully) a reduction in dyskinesia. This approach is reportedly successful with the use of slow-release formulations of L-DOPA and adjuvant catechol-o-methyltransferase inhibitors improving 'on' time³⁰ but two meta-analyses suggest that the consequence is significantly worse dyskinesia.^{31,32}

The delivery of CDS moved forward significantly with the introduction of devices such as the duodenal L-DOPA pump (DuoDopa) and dopamine receptor-agonist patches. New gene therapy approaches should also assist in this endeavour, utilising viral vector-mediated delivery of coding sequences for essential enzymes in the synthesis of dopamine.³³ The enzymes involved are tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, L-amino acid decarboxylase, which converts L-DOPA into dopamine, and guanosine 5'-triphosphate cyclohydrolase 1, which synthesises

the co-factor bipterin necessary for tyrosine hydroxylase function.³³ Gene therapy provides striatal neurons with the machinery to produce dopamine, obviating the need for exogenous L-DOPA delivery and providing a continuous supply of dopamine. This has been successfully demonstrated to protect against LID development in rodent and primate models of advanced PD^{34,35} and clinical trials are in progress.

Post-synaptic Plasticity

As dopaminergic innervation is lost, plastic changes occur at the post-synaptic membranes of striatal medium spiny neurons expressing D1 or D2 receptors. These are differentially altered again by the repeated pulsatile administration of L-DOPA.³⁶ There are substantial data pointing towards a close correlation between the severity of LID and post-synaptic changes at the receptor level, downstream kinases, at gene regulation and transcription, largely focused around the D1 receptor subtype.^{11,12,37-40} Pre-clinical studies with dopamine D1 receptor agonists show both good antiparkinsonian and pro-dyskinetic effects, part of which may be attributed to their short half-lives, but also to the biochemical changes occurring at this receptor. D1 receptors are in fact G-protein-coupled receptors linked to G proteins, stimulating adenylate cyclase and activating gene transcription. With dopaminergic denervation and administration of L-DOPA, dopamine D1 receptors become more highly expressed and increasingly sensitive, the G-protein levels increasing, thereby altering activity through the whole signalling cascade.

Long-term dopamine D1 receptor sensitisation is controlled in part by G-protein receptor kinases (GRKs), which normally trigger receptor internalisation and halt the receptor response. GRK6, for example, is upregulated by MPTP administration to non-human primates and normalised by L-DOPA treatment.⁴¹ Reversing this normalisation significantly reduces LID, probably through the process of increasing internalisation of the D1 receptor.⁴²

Further down the receptor cascade, components of the RAS/ERK signalling pathway become hyperactive in response to D1 supersensitivity and inhibitors of ERK, or an intermediary in this pathway, significantly reduce the severity of LID.⁴³⁻⁴⁵ The importance of these pathways is also that they are a point of convergence at which dopaminergic nigrostriatal and glutamatergic corticostriatal inputs to the medium spiny neurons are acting through co-localised dopaminergic and glutamatergic metabotropic receptors. Activation of the RAS/ERK pathway leads to phosphorylation of the GluR1 subunit on AMPA receptors located at the synapse promoting glutamatergic transmission.⁴⁶

Further still down the cascade, the acetylation and phosphorylation states of histones H3 and H4 are altered (although reports are inconsistent as to the details).⁴⁷⁻⁴⁹ Nevertheless, this is indicative of chromatin rearrangements and thereby changes in transcriptional control. An example of these transcriptional changes is the persistent upregulation of the immediate early gene Δ FosB in the striatum of dyskinetic rodent and non-human primates.^{11,50,51} This is indicative of the long-term changes that cause the priming phenomena, meaning that dyskinesia can still be evoked after prolonged L-DOPA withdrawal. Experimental evidence suggests that it may be possible to 'deprime' the L-DOPA-treated striatum through suppression of these proteins.^{11,51}

Dopamine D3 receptors that are co-expressed with D1 receptors on the direct pathway are increased in animal models of LID and may directly interact with them through intramembrane crosstalk.⁵² Nevertheless, *in vivo* reports are conflicting, suggesting either no effect or significant improvement on the effect of manipulating activity at the D3 receptor in LID, which may or may not be at the expense of the antiparkinsonian effect of L-DOPA.⁵³⁻⁵⁷

Dopamine D2 receptor agonists are effective at alleviating some of the symptoms of the motor disorder in early stages of the disease, partly because *de novo* therapies do not commonly induce significant levels of dyskinesia.^{58,59} Before concluding that D1 receptors are the LID culprits, however, it must be considered that D2 receptor agonists can produce motor sensitisation⁶⁰ and are capable of inducing dyskinesia expression if L-DOPA priming has already taken place.⁶¹ Therefore, D2 receptors are not innocent bystanders concerning LID generation or expression.

Whether there are direct changes in D2 receptor expression in response to chronic L-DOPA administration is unclear,⁶² but there are indications that D2 receptor mechanisms are altered and as such could be potential therapeutic targets. D2 receptors are negatively coupled through G-protein Gi/o to adenylate cyclase, the activity of the G-protein being controlled by the speed at which guanosine triphosphate is converted back into guanosine diphosphate. Regulators of G-protein signalling (RGS) are GTPases, which mediate this conversion, effectively influencing the speed of inactivation of the active α G-protein subunit. RGS9 is upregulated following chronic L-DOPA administration⁶³ and is thought to reflect an intrinsic compensation to the increase in D2 receptor activity. Despite this, further upregulation compromised the beneficial effects of L-DOPA.⁶³

Microvascular Changes in L-DOPA-induced Dyskinesia

Maladaptive plasticity in LID is not restricted to neuronal activity but also includes the structural microenvironment of the basal ganglia. There is accumulating evidence of changes to the essential microvasculature in PD, accompanying both the progressive dopamine degeneration and the development of LID. Post-mortem studies of human PD brains have demonstrated pathological microvascular changes and altered levels of angiogenic cytokines in the basal ganglia.⁶⁴⁻⁶⁷

Recent experiments in rodents suggest that the microvascular changes may be attributable to dyskinesiogenic D1-receptor stimulation and activation of ERK1/2.^{43,68} These angiogenic vessels may represent areas with blood-brain barrier leakage and thus local foci of high L-DOPA concentration that may further exacerbate the fluctuations of dopamine. Interestingly, drugs with well-known effects on vascular physiology, such as α_2 -adrenergic receptor antagonists and nicotine, have well-documented antidyskinetic efficacy in animal models of PD.⁶⁹⁻⁷¹ This suggests that possible effects on the microvasculature need to be taken into consideration when novel treatments for PD are evaluated.

Non-dopaminergic Modulators of Dyskinesia

As mentioned above, striatal function is not only modulated by nigrostriatal dopaminergic inputs. Indeed glutamatergic, corticostriatal and acetylcholine interneurons also have modulatory influences and

post-synaptic dopamine receptors co-localise with other receptors (adenosine, glutamatergic). The activity of the striatum can also be modulated by monoamines apart from dopamine, such as noradrenaline and serotonin. It may also be possible to interfere with signalling in other nuclei of the basal ganglia circuitry, such as the globus pallidus, subthalamic nucleus and substantia nigra pars reticulata (cannabinoids and opioids). Using non-dopaminergic systems to regulate the activity of the basal ganglia is likely to be highly useful in the search for antidyskinetic agents that allow the maintenance of L-DOPA efficacy on motor function.

Glutamate

Both clinical and pre-clinical data point to the importance of the glutamate system in the pathophysiology of dyskinesia.⁷² Currently, the most commonly used drug for the treatment of dyskinesia is amantadine, a weak glutamatergic antagonist.⁷³

Pre-clinical studies have demonstrated striatal changes in glutamate receptor expression, phosphorylation and synaptic organisation in LID.^{36,74} Picconi and co-workers recently showed defective corticostriatal synaptic plasticity in dyskinetic 6-OHDA-lesioned rats.⁷⁵ It was demonstrated that the corticostriatal neurons recorded from rats with LID lost the capability to depotentiate the long-term potentiation previously induced by high-frequency stimulation.⁷⁵ Lately, changes in the density of NMDA-receptor subunits due to altered trafficking in striatal neurons in LID versus non-dyskinetic rats have been demonstrated. Biochemical analysis of the post-synaptic density revealed increased expression of the NR2B subunit, whereas the levels of NR2A were decreased.⁷⁶ The reduced expression of NR2B was discovered to be parallel to altered anchoring to the membrane-associated-guanylate kinase (MAGUK) protein family. Treatment of non-dyskinetic rats with a synthetic peptide that disrupted the binding between the NR2B subunit and the MAGUK protein resulted in the expression of abnormal involuntary movements.⁷⁶

The fast glutamatergic transmission in the striatum from the cortex is also mediated by metabotropic glutamate receptors (mGluR). Among the different classes of mGluR, the mGluR5 receptor has repeatedly been shown to have antidyskinetic properties.⁷⁷⁻⁸¹ Antagonising the receptor blocks the maladaptive post-synaptic changes associated with LID, such as upregulation of Δ FosB,⁷⁷ prodynorphin mRNA^{78,81} and PERK1/2.⁸¹

Abstract overactivity of striatal alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors has also been implicated in the expression of LID. Radioligand binding studies in primate models of LID have shown both upregulation⁸² and no change in striatal AMPA binding.⁸³ A more complex subcellular alteration of striatal AMPA receptor localisation was recently demonstrated by Silverdale and co-workers. AMPA receptors were redistributed from the vesicular fraction and into the post-synaptic membrane during LID.⁸⁴ Antagonising AMPA receptors attenuated the expression of LID in both MPTP-treated monkeys and 6-OHDA-lesioned rats, as well as blocking the associated molecular correlates of LID.⁸⁵⁻⁸⁷

Opioids

The striatal output neurons are GABAergic but also co-release the opioid peptides enkephalin and dynorphin, which act at the mu, delta

and kappa opioid receptors. The synthesis of these peptides, dynorphin in particular, is enhanced in dyskinetic states,^{12,88} while receptor binding and sensitivity is significantly altered.

Conflicting pre-clinical studies report that non-selective opioid receptor antagonists can improve or worsen LID,^{89,90} while a clinical trial illustrated their potential use as antidyskinetic agents.⁹¹ Mu- and delta-specific antagonists showed clear anti-dyskinesia activity in the MPTP-treated marmoset without compromising L-DOPA efficacy, while the kappa antagonist nor-binaltorphimine failed to show any effects.⁸⁹ In the rodent model, infusion of the kappa receptor antagonist prevented behavioural sensitisation to apomorphine,⁹² while the kappa-receptor agonist TRK-820 reduced L-DOPA-mediated dyskinesia generation and LID expression in primed animals.⁹³

Adenosine

The neural activity of the basal ganglia can also be modulated by adenosine, acting on adenosine A2A receptors that are abundantly expressed in several basal ganglia nuclei.⁹⁴ The adenosine A2A receptors located on the dendritic spines of the striato-pallidal GABA neurons form functional complexes with dopamine D2 and metabotropic glutamate 5 (mGlu5) receptors⁹⁵ and can modulate dopamine-mediated motor functions.

Antagonists of the A2A receptor have been put forward as potential targets for anti-parkinsonian drugs.⁹⁴ Evidence from the use these antagonists as antidyskinetic agents is less convincing, as are the clinical trial data obtained thus far. Pharmacological antagonism of the A2A receptor alleviated apomorphine-induced dyskinesia in MPTP-lesioned monkeys⁹⁶ but the same pharmacological agent had no effect on LID in 6-OHDA-lesioned rats.⁹⁷ Moreover, clinical trials with the A2A receptor-antagonist istradefylline actually produced a significant worsening of LID when given in conjunction with dopaminergic treatments.⁹⁸ More recent studies suggest that the addition of an adenosine agonist may lower the dose of L-DOPA required to produce functional efficacy, which may as a consequence reduce LID.^{99,100}

Noradrenaline

It has long been suggested that the effects of L-DOPA in PD are mediated by both the noradrenergic and dopamine systems.¹⁰¹⁻¹⁰³ The noradrenergic system has also been implicated in LID.¹⁰⁴ The α_2 -adrenoreceptor antagonists reduce LID in both the MPTP-primate model,^{70,105,106} and in 6-OHDA-lesioned rats.^{15,107,108} Unfortunately the antidyskinetic effect in patients with PD is somewhat disputable, with data showing both a reduction of LID¹⁰⁹ and no effect on LID.¹¹⁰ Recently, Buck and co-workers showed that the attenuation of LID by the α_2 -adrenoreceptor antagonist idazoxan in 6-OHDA-lesioned rats was associated with a reduction in striatal extracellular levels of dopamine,¹¹¹ thus providing a possible mechanistic insight into the antidyskinetic effect of these noradrenergic drugs. New findings from the same investigators suggest that antagonists of the α_1 -adrenoreceptor could also work as potential targets for new antidyskinetic drugs.¹⁰⁷

Cannabinoids

The precise contribution of the cannabinoid (CB) system in LID has been difficult to define, since both agonists and antagonists of the CB1-receptor seem to alleviate LID.¹¹² The attenuating effect on LID is well-documented in both animal models of PD¹¹³⁻¹¹⁶ and in patients,¹¹⁷

but mechanistic insights have been lacking. A recent study by Morgese and co-workers demonstrated that treatment with a CB1-receptor agonist alleviated LID in 6-OHDA-lesioned rats.^{114,115} The improvement in symptoms was inversely correlated with extracellular glutamate levels in the denervated striatum.¹¹⁵ Additionally, pharmacological elevation of endocannabinoid levels only attenuated LID when the transient receptor-potential vanilloid subtype (TRPV1) was blocked, suggesting that stimulation of the CB-receptors and TRPV1 have opposing effects on LID.¹¹⁴

The Translational Significance of Basic Experimental Data

The translation of antiparkinsonian and antidyskinetic agents into clinically successful drugs has been limited in recent years. As highlighted here, neither sarizotan nor istradefylline – both promising in pre-clinical studies – produced the anticipated results in clinical trials. It has been beyond the scope of this article to analyse why in detail, but key factors that may influence this translation are reviewed in detail elsewhere.^{118,119}

While the animal models, in general, accord with each other and clinical post-mortem evaluations, there are issues with both clinical and pre-clinical investigative tools. A recent study of clinical dyskinesia rating scales raised concerns over their reliability and relevance and has recommended only two out of eight rating scales as having excellent clinometric properties in PD.¹²⁰ There are also examples of conflicting findings using the same pharmacological approaches in pre-clinical studies. These discrepancies may be based on the precise animal model used, the strain, species or extent and selectivity of dopaminergic denervation.

The concept of lesion extent is similarly problematic in clinical trials. This is because patients may have variable degrees of degeneration and particular pharmacological approaches may only be effective at certain stages of the disease, thus only being appropriate for subgroups of patients.

Clinical trials need to take all of these issues into account to fully evaluate the true potential of new agents.

Conclusion

There are new pharmacological targets and strategies under investigation, at the receptor and downstream signalling cascade levels. Furthermore, is also looking towards how non-neural mechanisms influence the microenvironment of the striatum.

There are many proposed targets for treating dyskinesia, but where treatment strategies may require invasive procedures, such as neurosurgery, or risks, such as the use of viral vectors, the clinical benefit of alleviating PD symptoms through the same procedure should be a primary consideration.

Hopefully, advances in treatment will move the field into a new era of dyskinesia management, whether that be treating the dyskinesia or finding ways to avoid its development. ■



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