Current Nondopaminergic Therapeutic Options for Motor Symptoms of Parkinson’s Disease

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Objective: The aim of this study was to summarize recent studies on nondopaminergic options for the treatment of motor symptoms in Parkinson’s disease (PD).

Data Sources: Papers in English published in PubMed, Cochrane, and Ovid Nursing databases between January 1988 and November 2016 were searched using the following keywords: PD, nondopaminergic therapy, adenosine, glutamatergic, adrenergic, serotoninergic, histaminic, and iron chelator. We also reviewed the ongoing clinical trials in the website of clinicaltrials.gov.

Study Selection: Articles related to the nondopaminergic treatment of motor symptoms in PD were selected for this review.

Results: PD is conventionally treated with dopamine replacement strategies, which are effective in the early stages of PD. Long-term use of levodopa could result in motor complications. Recent studies revealed that nondopaminergic systems such as adenosine, glutamatergic, adrenergic, serotoninergic, histaminic, and iron chelator pathways could include potential therapeutic targets for motor symptoms, including motor fluctuations, levodopa-induced dyskinesia, and gait disorders. Some nondopaminergic drugs, such as istradefylline and amantadine, are currently used clinically, while most such drugs are in preclinical testing stages. Transitioning of these agents into clinically beneficial strategies requires reliable evaluation since several agents have failed to show consistent results despite positive findings at the preclinical level.

Conclusions: Targeting nondopaminergic transmission could improve some motor symptoms in PD, especially the discomfort of dyskinesia. Although nondopaminergic treatments show great potential in PD treatment as an adjunct therapy to levodopa, further investigation is required to ensure their success.

Key words: Dyskinesias; Motor Fluctuations; Nondopaminergic Options; Parkinson Disease

Introduction
Parkinson’s disease (PD) is caused by neurodegeneration of nigrostriatal pathways and is characterized by a series of motor symptoms (bradykinesia, rigidity, postural instability, and static tremor), which are caused by progressive dopamine loss in the substantia nigra (SN) pars compacta. Dopamine replacement therapy, currently the most efficacious and gold standard treatment for PD, mainly comprises the use of the dopamine precursor levodopa (L-DOPA), dopamine agonists, monoamine oxidase B inhibitors, and catechol-O-methyltransferase inhibitors. Long-term use of L-DOPA may result in several complications, including motor fluctuations and levodopa-induced dyskinesia (LID), which cause serious distress to patients. Moreover, symptoms that appear at the later stages of PD are often not responsive to dopaminergic treatments. The development of these symptoms could involve the degeneration of nondopaminergic systems, leading to PD. The development of novel nondopaminergic treatments is therefore of great clinical interest. Continuous studies have shown that the mechanism of PD involves many nondopaminergic mechanisms including adenosine receptors (ARs), glutamatergic, adrenergic, serotoninergic, histaminic, and iron chelator pathways. Targeting nondopaminergic systems could prove an effective approach to treatments.
A Phase II trial, assessing istradefylline, is capable of reducing off time in the effects of istradefylline in patients with moderate-to-severe PD. Received. A subsequent 52-week Phase III trial to assess the efficacy and caused an obvious reduction in off time; administered at 40 mg/d. Moreover, istradefylline was well tolerated. Another Phase II trial of long-term (36-week) preladenant treatment (5 mg twice a day) yielded similar findings. However, in two Phase III and a Phase II trials, preladenant did not cause a clear reduction in off time compared with placebo. The failed results were attributed to inappropriate study design and execution. To the best of our knowledge, preladenant is no longer under study for the treatment of PD.

Tozadenant is another A2A antagonist that could alleviate motor fluctuation. The results of a small Phase IIa study suggested that tozadenant could cause an obvious decrease in thalamic cerebral blood flow following reduced pallidothalamic inhibition via the indirect pathway. In a Phase Ib trial, tozadenant administered at 120 mg or 180 mg twice daily was generally effective in reducing off time. A Phase III study is currently under way. Combination treatments with tozadenant and other drugs have been tested in animal models. The A2A/NR2B receptor antagonist combination (tozadenant/radiprodil) could ameliorate motor symptoms without the side effects associated with dopaminergic treatment.

Other A2A antagonists that have progressed to Phase I clinical trials include ST1535, ST4206, ST3932, V81444, and PBF-509.

A1/A2A receptor antagonists

Blocking of adenosine A1 receptors that are distributed throughout the cortex, hippocampus, and striatum has also resulted in motor activation in animal models. Combined targeted blockage of A1 and A2A receptors could therefore synergistically provide a potential alternative to conventional PD treatments. Several novel adenosine A1/A2A antagonists that have been effective in treating motor deficits are based on the common structure of the synthesized 2-aminopyrimidine motif, with potent adenosine A1/A2A affinity. Further studies on the physicochemical properties of these compounds are needed.

Nonspecific adenosine receptor antagonist

Caffeine is a nonspecific AR antagonist that has shown antiparkinsonian and neuroprotective effects in animal models of PD. Caffeine could possibly increase excitatory activity in the striatopallidal area and inhibit astrocyte-induced PD is currently ongoing. The improvement of motor function in early PD without provoking dyskinesia upon administration of istradefylline with low-dose dopaminergic drugs has been described in 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated common marmosets. Further istradefylline was reportedly safe and well tolerated as monotherapy for PD in a Phase II study, which showed great benefits based on the unified PD rating scale III (UPDRS III).

Preladenant, another adenosine A2A antagonist, improved motor ability without worsening dyskinesia in rodent and primate models of PD. A Phase II trial, assessing preladenant as an adjunct to levodopa in individuals with PD for 12 weeks, showed significant off time reduction upon treatment with 5 and 10 mg preladenant twice daily. Moreover, preladenant was well tolerated. Another Phase II trial of long-term (36-week) preladenant treatment (5 mg twice a day) yielded similar findings. However, in two Phase III and a Phase II trials, preladenant did not cause a clear reduction in off time compared with placebo. The failed results were attributed to inappropriate study design and execution. To the best of our knowledge, preladenant is no longer under study for the treatment of PD.

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| Mechanism                        | Drugs                          | Stage | n    | Dose            | Duration | Results                                                                 | Reference |
|---------------------------------|--------------------------------|-------|------|-----------------|----------|------------------------------------------------------------------------|-----------|
| Adenosine                       | Istradefylline                 | II    | 176  | 40 mg/d         | 12 weeks | Improvement in UPDRS III motor score                                   | [11]      |
|                                 |                                | II    | 363  | 20 or 40 mg/d   | 12 weeks | Reduction in off time                                                   | [12]      |
|                                 |                                | II    | 196  | 40 mg/d         | 12 weeks | Reduction in off time                                                   | [10]      |
|                                 |                                | II    | 395  | 20 or 60 mg/d   | 12 weeks | Reduction in off time                                                   | [13]      |
|                                 |                                | III   | 373  | 20 or 40 mg/d   | 12 weeks | Reduction in off time                                                   | [14]      |
|                                 |                                | III   | 308  | 20 or 40 mg/d   | 52 weeks | Sustained reduction in off time                                         | [15]      |
|                                 |                                | III   | 231  | 20 mg/d         | 12 weeks | Reduction in off time                                                   | [16]      |
|                                 |                                | III   | 584  | 10, 20, or 40 mg/d | 12 weeks | No reduction in off time, only improved motor score at 40 mg/d        | [17]      |
|                                 |                                | III   | 253  | 1, 2, 5, or 10 mg, bid | 12 weeks | Reduction in off time                                                   | [18]      |
|                                 |                                | II    | 106  | 5 mg, bid       | 36 weeks | Sustained reduction in off time                                         | [19]      |
|                                 |                                | II    | 450  | 2, 5, 10 mg, bid | 12 weeks | No reduction in off time                                                | [20]      |
|                                 |                                | III   | 778  | 2, 5, 10 mg, bid | 12 weeks | No obvious reduction in off time                                       | [21]      |
|                                 |                                | III   | 476  | 2 or 5 mg, bid  | 12 weeks | No obvious reduction in off time                                       | [22]      |
|                                 |                                | III   | 420  | 60, 120, 180, or 240 mg, bid | 12 weeks | Reduction in off time                                                   | [23]      |
|                                 |                                | III   | 450  | 60 or 120 mg, bid | 24 weeks | Ongoing                                                                | [24]      |
|                                 |                                | III   | 119  | 200 mg, bid     | 5 years  | Ongoing                                                                | [25]      |
|                                 | Caffeine                       | III   | 119  | 200 mg, bid     | 5 years  | Ongoing                                                                |           |
| Glutamate                       | ADS-5102 (extended-release)    | II    | 83   | 260, 340, or 420 mg/d | 8 weeks  | Reduction of LID, and increase in on time without troublesome LID | [26] (EASED study) |
|                                 |                                | III   | 77   | 260, 340, or 420 mg/d | 13 weeks | Completed waiting for a result                                        | [27] (EASE LID 3) |
|                                 | Amantadine HCL (extended-release) | III   | 126  | 240 or 320 mg/d | 25 weeks | Completed without results                                              | [28] (EASE LID) |
|                                 |                                | III   | 162  | 240 or 320 mg/d | 16 weeks | Ongoing                                                                | [29] (ALLAY-LID I) |
|                                 |                                | IV    | 80   | 200 mg/d        | 12 weeks | Reduction in severity of LID                                          | [30] (ALLAY-LID II) |
|                                 | Mavoglurant                    | II    | 31   | 50–300 mg/d     | 16 days  | Reduction in severity of dyskinesia                                    | [31]      |
|                                 |                                | II    | 28   | 50–300 mg/d     | 16 days  | Reduction in severity of dyskinesia                                    | [32]      |
|                                 |                                | II    | 197  | 20, 50, 100, 150, or 200 mg/d | 13 weeks | Reduction in severity of dyskinesia without worsening underlying motor symptoms | [33] |
|                                 |                                | II    | 78   | 100 mg/d        | 12 weeks | No significant change in LID                                          | [34]      |
|                                 |                                | II    | 154  | 150 or 200 mg/d | 12 weeks | No significant change in LID                                          | [35]      |
|                                 |                                | II    | 66   | 3.5 years       | Completed without results                                             | [36]      |

Contd...
inflammation in PD. A 4-year observational cohort study revealed that caffeine consumption played a pivotal role in reducing accrual of disability in PD. However, there have been inconsistencies in the conclusions obtained from some clinical trials. A clinical study demonstrated that caffeine could reduce the likelihood of developing dyskinesia. However, there were no significant changes in motor features except for reduced total UPDRS score and objective motor component in another randomized controlled trial. A Phase III trial to evaluate the efficacy of caffeine in PD is currently ongoing.

**Glutamatergic Options**

The role played by glutamate in the mechanism and progression of PD via various ionotropic and metabotropic receptor types in the basal ganglia motor loop has been extensively investigated. N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and metabotropic glutamate receptors (mGluRs) in particular have been extensively studied, not only to identify their role in the progression of PD but also as potential novel therapeutic options. Overactivity of the corticostriatal glutamatergic pathways and disinhibition of the subthalamic nucleus (STN) exacerbate the pathogenesis of PD by further activating the indirect striatopallidal pathway by weakening of normal dopamine D2-like receptor-mediated inhibition.

Enhanced cell excitotoxicity to the SN also underpins the appearance of motor symptoms in PD. Increased glutamate transmission from corticostriatal projections by long-term volatile stimulation of dopamine receptors at the affected striatal synapses could play a key role in LID; however, the mechanisms involved remain unclear. The appearance of LID is accompanied by the excessive synaptic plasticity, known as long-term potentiation (LTP), which could promote the development of LID.

**N-methyl-D-aspartate receptor antagonists**

The appearance of LID is accompanied by the excessive activation of NMDA receptors, a type of ionotropic glutamate receptor expressed in the striatum and STN. Dopaminergic and glutamatergic receptors are located in mutual striatal projection spiny neurons. Activation of D1 receptors results in the phosphorylation of NMDA receptors via protein phosphatase-1 and Fyn protein tyrosine kinase and consequently triggers a rapid redistribution of NMDA receptors via trafficking from synaptic to extrasynaptic compartments. Over time, this functional link between D1 and NMDA receptors results in a change of corticostriatal synaptic plasticity, known as long-term potentiation (LTP), which could promote the development of LID.

Most conventional nonselective NMDA receptor antagonists, however, have been implicated in adverse effects including psychotomimetic effects, impairments of learning, memory, and dissociative anesthesia. Thus, more selective antagonists targeting specific subtypes of NMDA receptors, especially...
NR2A and NR2B receptors that seem to be alternatively expressed in the striatum, have been explored.[73,78] A favorable antidyskinetic outcome was reported in a study using a NR2B-selective NMDA glutamate antagonist, CP-101, 606; however, adverse cognitive effects were observed.[79] The clinical efficacy of NR2B subtype-selective antagonists in alleviating PD symptoms could not be confirmed following a randomized controlled trial, which failed to show any motor improvements after treatment with the NR2B-selective antagonist MK-0657.[80] Studies on NR2A subunits revealed that a cell-permeable peptide blocking NR2A subunits caused a reduction of LID in parkinsonian rats.[81,82] Currently, nonselective NMDA antagonists are still preferred for clinical use.

There have been several reports on the antidyskinetic effects of amantadine, a nonselective NMDA receptor antagonist.[31,83,84] Amantadine has been approved for the treatment of LID despite its side effects such as confusion, constipation, and visual hallucinations. ADS-5102, a long-lasting sustained-release capsule of amantadine HCl, administered once daily at night, has been described in an 8-week Phase II study in patients with obvious dyskinesia.[26] The 340 mg/d dosage of amantadine caused significant improvement of dyskinesia versus placebo and increased “on” time without aggravating dyskinesia. Two Phase III trials by the same sponsor on the use of ADS-5102 for the treatment of LID were recently completed, and the results are awaited.[27,28] Two Phase III studies testing another long-lasting sustained-release formulation of amantadine for 16 and 26 weeks are currently ongoing.[29,30]

Memantine is another conventional nonselective NMDA antagonist used for the treatment of dementia. Unexpected improvements in LID and On-Off appearance in PD were recorded after administration of memantine in five cases.[95,96] Memantine could be effective against LID despite transient tolerance in 6-OHDA-lesioned rat models.[97] However, recent studies on memantine (20 mg) revealed no significant improvement in dyskinesia ratings. Further, no serious side effects were observed in a small crossover clinical study in 15 patients with PD.[32]

α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonists

AMPAs are ionotropic glutamate receptors expressed in the striatum and SN. The potential use of AMPA antagonists in the improvement of LID has been demonstrated in preclinical studies.[73,88] Perampanel, a selective AMPA receptor antagonist, however, failed to effect statistically significant improvement in motor symptoms and motor fluctuations of levodopa-treated patients with moderately advanced PD in clinical trials.[33-35] Topiramate is an antiepileptic drug that functions via inhibition of voltage-gated sodium and calcium currents. Topiramate is also a potent AMPA receptor antagonist and triggers AMPA receptor dephosphorylation. Studies in animal models have suggested applications for topiramate as a potential antidyskinetic treatment.[89,90] However, contrary to the results of preclinical studies, topiramate tended to worsen dyskinesia in patients with PD and was poorly tolerated.[91] The use of topiramate as an adjunct to amantadine is being evaluated in a Phase II trial.[36]

Metabotropic glutamate receptor antagonists

The mGluRs are eight G-protein-coupled receptors, consisting of three groups (Groups I, II, and III), which are localized in the basal ganglia. They are involved in synaptic transmission and plasticity in progression of LIDs.[92] Studies on Group I mGluRs, particularly subgroup mGluR5, showed that mGluR5 antagonists are highly efficient in ameliorating motor symptoms and LIDs in animal models.[93,94] Enhanced density of postsynaptic metabotropic glutamate 5 (mGlu5) receptor and specific combination with the striatum and posterior putamen observed in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned macaque models could contribute to the pathogenesis of LIDs in PD.[95-97] These results formed the basis of several clinical trials evaluating the potential of two mGlu5 receptor negative allosteric modulators (NAMs) — mavoglurant and dipraglurant. In previous studies, mavoglurant (AFQ056) demonstrated relevant antidyskinetic effects;[98,99] however, further clinical trials did not reveal obvious antidyskinetic efficacy.[40,98,99] A recent Phase II trial has been concluded without results being published.[40] Dipraglurant (ADX48621) is another mGluR5 antagonist that was proven to reduce LID in an MPTP-lesioned macaque model.[100] Results of a new Phase IIa study showed safety and well tolerability of dipraglurant.[41]

Activation of Group II mGluRs (mGluR2/3) could also be used to treat parkinsonian motor symptoms because of decreased excitatory glutamate transmission at corticostratial synapses. However, there is no significant evidence from studies on animal models of PD that Group II mGluRs could reverse dyskinesia.[101,102] Group III mGluRs consist of mGlu4, 6, 7, and 8 receptors. Activation of mGlu4 receptors, especially localized at GABAergic and glutamatergic synapses in the indirect pathway of basal ganglia circuitry, was tested using positive allosteric modulators (PAMs) for reducing synapse transmission at GABAergic and glutamatergic synapses.[103] Several animal studies had revealed that mGlu4 PAMs (VU0364770, VU0400195, Lu AF21934, and VU0418506) have good efficacy in antiparkinsonian clinical use.[104-107]

Adrenergic Options

The degeneration of the locus coeruleus that can produce noradrenaline plays a major role in subcortical neuronal loss in PD.[108] Dramatic reductions in noradrenergic levels in the extensive brain regions, including the frontal cortex, striatum, hippocampus, and amygdala, have been detected in postmortem PD brains, and could contribute to motor dysfunction.[109] Noradrenaline deficiency is believed to

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be involved in the pathogenesis of LID and freezing of gait (FOG). However, the detailed mechanisms remain unclear. Growing evidence supports the development of strategies to enhance NE neurotransmission for the treatment of LID and FOG in animal models and clinical trials of PD [Table 1].

**Noradrenergic reuptake inhibitor**

Methylphenidate is a central stimulant, conventionally used for treating attention-deficit hyperactivity disorder. It elevates noradrenaline and dopamine levels by inhibiting the presynaptic dopamine and noradrenaline transporters in the striatum and prefrontal cortex. In a 3-month crossover study by Moreau et al., gait hypokinesia and freezing was improved in the methylphenidate group in 69 patients with advanced PD despite optimized dopamine treatment and subthalamic stimulation. Side effects were also reported in this group, including weight loss, increased heart rate, sleeplessness, and transient confusion. Further, dopamine transporter type 1-encoding gene (SLC6A3) variants played a vital role in the efficacy of methylphenidate treatment for gait disorders in the same population. Another 6-month randomized trial (n = 27) did not show a significant improvement in gait, although a double-blind assessment was also conducted. Thus, longer follow-up studies in patients with PD who have not received surgery are needed. A case report of isolated FOG in PKN (pantothenate kinase-associated neurodegeneration) revealed dramatic responsiveness with an increased dosage of methylphenidate. These findings suggest that the association between methylphenidate and FOG merits further exploration.

**Adrenergic receptor antagonist**

Fipamezole, an α2-adrenergic receptor antagonist, was previously reported to reduce LID and improve the quality of levodopa action in animal models. In a 1-month crossover study conducted in the USA (n = 115) and India (n = 64), no significant outcome was reported, only a subgroup analysis of subjects in the USA revealed obvious LID reduction under fipamezole treatment, because of the difference in demographic characteristics between the USA and India.

**Serotonergic Agents**

In the brain, serotonergic receptors are localized in the raphe nuclei of the brainstem which provides 5-HT innervation to the entire brain. Depletion of serotonergic neurons and accumulation of Lewy bodies in PD were observed in previous studies. Abnormality in the serotonin system responsible for LID could be due to aberrant processing of exogenous levodopa and dysregulated dopamine release in striatal serotonergic terminals. Furthermore, an increased serotonin-to-dopamine transporter binding ratio accelerates PD progression. Several clinically available drugs have been assessed recently in this context [Table 1]. Buspirone is a combined 5-hydroxytryptamine-1A (5-HT1A) and α1 adrenergic receptor agonist with antidyskinetic potential. Results of a dose-finding study suggested the suitability of buspirone for use as antidyskinetic agent in PD. A Phase I study assessing the efficacy of buspirone (in combination with amantadine) and a Phase III (monotherapy) are actively ongoing.

Eltoprazine is a mixed 5-HT1B and 5-HT1A agonist, which exerts antidyskinetic effects by reducing striatal glutamate transmission. Eltoprazine (5 mg/d) showed antidyskinetic effects without reducing normal motor responses to levodopa through the restoration of LTP and synaptic depotentiation in a subset of striatal spiny projection neurons. However, in another rat model study, reduced levodopa-induced mobility was observed despite the antidyskinesia properties of eltoprazine. A combination of eltoprazine and preladenant reduced dyskinesia and maintained the full therapeutic effects of a low dose of levodopa. A Phase II study is currently active.

A retrospective investigation on the effects of selective serotonin reuptake inhibitors (SSRIs) during dopaminergic treatment revealed that SSRIs did not prevent dyskinesias. However, SSRIs exposure could delay onset of dyskinesia and reduce the severity, suggesting potential anti-PD applications for the serotonergic system in the future.

**Histamine Pathways**

Histamine receptors are classified into four subtypes (H1, H2, H3, and H4). H2 receptors are mainly distributed in basal ganglia, particularly in the major input nucleus of the striatum indicating that histamine can affect direct pathways. In addition, cholinergic interneurons activated in LID were attenuated by inhibition of H2 histaminergic transmission in mouse models. Furthermore, histamine modulates the microglial activity in PD, which is accompanied by microglia-induced neuroinflammation. Famotidine, a selective histamine H2 antagonist, could enhance the antiparkinsonian effects and duration of levodopa action in a macaque model. However, a Phase II trial evaluating famotidine 80, 120, 160 mg/d failed to demonstrate efficacy in reducing dyskinesia severity [Table 1].

**Iron Chelators**

A normal SN has a higher density of iron linked to ferritin and neuromelanin. Maintenance of iron homeostasis is important and involves several mechanisms. Mismanagement of iron homeostasis may lead to various neurological injuries observed in PD. Brain iron deposition could contribute to oxidative stress response in the SN and therefore exacerbate dopamine neuron degeneration. Iron chelators likely protect against reduction in striatal dopamine by combining with iron in the SN. This dopaminergic neuroprotection was proved in animal models, wherein the iron chelator desferrioxamine ameliorated iron accumulation. Desferrioxamine has long been clinically available. However, its obstruction of the blood–brain barrier has restricted its use in neurodegenerative disorders. The
chelator deferiprone has an advantage over desferrioxamine, a 12-month study in patients with early-stage PD revealed a meaningful reduction in iron levels and improvement in motor symptoms,\(^{[17]}\) and several Phase II clinical trials evaluating deferiprone are ongoing [Table 1].\(^{[50,51]}\)

**C-Abelson Tyrosine Kinase Inhibitor**

C-Abelson tyrosine kinase (c-Abl) is activated in the brain of patients with PD. Nilotinib, the c-Abl inhibitor, is clinically used for chronic myelogenous leukemia treatment. Recent studies revealed that nilotinib could degrade autophagy of α-synuclein, leading to protection of SN neurons and amelioration of motor symptoms.\(^{[118,119]}\) A new 6-month Phase I trial \((n = 12)\) showed that nilotinib had beneficial effects on clinical motor outcome and changed cerebrospinal fluid biomarkers which indicated reduction of toxicity to the brain.\(^{[52]}\) However, this small proof-of-concept study lacked a placebo group, and further studies with a greater sample size and control group are needed [Table 1].

**Conclusions**

Targeting nondopaminergic transmission could improve some motor symptoms in PD, especially the discomfort of dyskinesia. Some nondopaminergic drugs, such as istradefylline and amantadine, are currently used clinically, while most such drugs are in preclinical testing stages. Transitioning of these agents into clinically beneficial strategies requires reliable evaluation since several agents have failed to show consistent results despite positive findings at the preclinical level. In conclusion, although nondopaminergic treatments show great potential in PD treatment as an adjunct therapy to levodopa, further investigation is required to ensure their success.

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**Conflicts of interest**

There are no conflicts of interest.

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