



Novel Treatment Opportunities Against Cognitive Impairment in Parkinson's Disease with an Emphasis on Diabetes-Related Pathways

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Abstract

Cognitive impairment is highly prevalent in patients with Parkinson's disease (PD) and causes adverse health outcomes. Novel procognitive therapies are needed to address this unmet need. It is now established that there is an increased risk of dementia in patients with type 2 diabetes mellitus (T2DM) and, moreover, T2DM and PD may have common underlying biological mechanisms. As such, T2DM medications are emerging as potential therapies in the context of PD dementia (PDD). In this review, we provide an update on pathophysiological mechanisms underlying cognitive impairments and PDD, focusing on diabetes-related pathways. Finally, we have conducted a review of ongoing clinical trials in PD patients with dementia, highlighting the multiple pharmacological mechanisms that are targeted to achieve cognitive enhancement.

Key Points

Mild cognitive impairment and Parkinson's disease (PD) dementia (PDD) are common disorders and are associated with severe morbidity and increased mortality.

PDD is treated with cholinesterase inhibitors (ChIs). Ongoing trials against PDD target glutamate, monoamines, kinases, glucocerebrosidase and glucagon-like peptide-1 alone or together with ChIs.

Type 2 diabetes mellitus shares pathophysiological mechanisms with PD and neurodegenerative dementias, such as central and peripheral insulin resistance that in turn results in altered autophagy, cell proliferation and increased inflammation.

Antidiabetic drugs have shown positive effects on cognitive outcomes in PD animal models, as well as in early-phase clinical trials.

1 Introduction

Parkinson's disease (PD) has traditionally been considered a movement disorder and its diagnosis relies on the presence of bradykinesia along with rigidity and/or rest tremor [1]. Non-motor symptoms have recently gained attention and quality-of-life studies have shown that PD patients are severely affected by its non-motor aspects. Indeed, increasing recognition has been given to non-motor manifestations; these are incorporated into both the latest Movement Disorder Society (MDS) criteria for PD [1] and particularly into separate MDS criteria for prodromal PD [2]. Among the non-motor symptoms, cognitive impairment and dementia are especially debilitating and they are the strongest component leading to nursing home placement of PD patients.

2 Prevalence of Cognitive Impairments in Parkinson's Disease (PD)

Cognitive deficits are common in PD, but vary in both quality and severity in different stages of the disease. The spectrum ranges from subjective cognitive decline [3] to mild

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cognitive impairment (MCI) [4] and PD dementia (PDD) [5]. Subjective cognitive decline does not have established criteria, but it is generally defined as a mild impairment noted by the patient, family or caregivers, although performance in formal cognitive testing is within normal range. Little is known about the occurrence of subjective cognitive decline in PD, but it is assumed to precede future progression to MCI and dementia [6, 7]. The main difference between PD–MCI and PDD is the degree to which the cognitive decline affects everyday life functioning, which is minimal in the case of PD–MCI but substantial in PDD [4, 5]. The cognitive decline often hides under more profound motor deficits and only detailed neurocognitive evaluation reveals the grade to which these deficits extend [8]. Among patients with PD, 25–30% have PD–MCI [4, 9], while an additional 30% have a PDD diagnosis [10]. An 8-year cumulative prevalence of 78% for getting a diagnosis of PDD has been reported in a Norwegian cohort [11] and a cumulative incidence of 83% 20 years after initial diagnosis was reported in the Sydney multicentre study of PD [12].

2.1 PD–Mild Cognitive Impairment (MCI)

MCI can affect one or more cognitive domains, and is further subdivided into amnesic MCI, when memory is the predominantly affected domain, and non-amnesic MCI, when domains other than memory are more impaired [13]. Previously, MCI diagnosis was based on subjective complaints from the patient and/or observations from a caregiver or clinician about cognitive difficulties that cannot be explained by age alone and do not interfere with everyday living [14]. However, recently, the MDS Task Force has redefined PD–MCI and established criteria to facilitate the use of a common definition, additionally stating that the deficits should be attributed to PD, excluding other conditions, and that detailed neuropsychological testing should confirm any subjective observation [4].

Older age, longer disease duration, concomitant depression and a higher motor burden are positively correlated with PD–MCI [9]. While MCI most often develops into PDD, amelioration and return to normal cognitive functioning is not uncommon [15]. Non-amnesic, single-domain PD–MCI is the most common according to some studies [9], while others report that multi-domain MCI is the most common [16]. Executive functioning, visuospatial abilities, verbal fluency, memory and language have all been reported to be affected [9, 15]. Accumulating evidence suggest that there are two distinct categories of cognitive dysfunction in PD with different prognoses. The first one is a frontal executive dysfunction that correlates with dopaminergic loss, which is affected by dopaminergic therapy and has a better prognosis. The second type is characterised by visuospatial and

semantic fluency deficits attributed to posterior and temporal dysfunction related to cholinergic loss. Prognosis in the latter is more severe, as the patients commonly progress to PDD [17, 18].

2.2 PD with Dementia

Dementia is the most severe cognitive syndrome, defined as acquired objective cognitive impairment affecting multiple cognitive domains that is severe enough to affect activities of daily life (ADL) [19]. PDD affects multiple cognitive domains, including attention, memory, executive and/or visuospatial ability [5]. In addition to this, PDD is characterised by neuropsychiatric features such as hallucinations and delusions, apathy, depression and anxiety [5]. PDD shares a lot of similarities with dementia with Lewy bodies (DLB), the latter presenting in close chronological proximity to the initiation of motor symptoms as opposed to PDD where parkinsonian semiology must precede cognitive deficits by at least 1 year [20]. Progression from PD or PD–MCI to PDD cannot be predicted but several risk factors have been identified [15]. These includes PD diagnosis at an older age, akinetic–rigid motor subtype, psychiatric manifestations, loss of postural control, dysautonomia, and rapid eye movement (REM) behaviour disorder (RBD) [5, 21].

Multiple mechanisms seem to be involved in the genesis of cognitive decline in PD. Limbic and cortical Lewy body pathology, as well as amyloid plaque and tau pathologies, are the most common contributors to PDD [22]. Additionally, the role of vascular disease [23] and neuroinflammation [24] has been emphasised. In order to explain the clinical heterogeneity between PDD patients, other mechanisms have also been examined such as the role of synaptic proteins [25], neurotransmitters [26] and genetic factors [26, 27].

Studies on glucosylceramidase beta (*GBA*) mutations have indeed highlighted a high risk for carriers to develop PD with a more rapid cognitive decline [27]. Moreover, several autosomal dominant α -synuclein mutations cause PD with a worse cognitive prognosis [28]. On the other hand, leucine-rich repeat kinase 2 (*LRRK2*) and parkin mutations have been described to lead to a milder PD phenotype with less cognitive decline [15, 28]. The role of polymorphisms in genes such as microtubule-associated protein tau (*MAPT*), apolipoprotein E (*APOE*) and catechol-*O*-methyltransferase (*COMT*) on cognitive outcomes has been examined, but results are not yet conclusive [15, 18, 28].

With regards to wet biomarkers, reduced cerebrospinal fluid (CSF) amyloid β 1–42 ($A\beta$ 1–42) concentration is consistently associated with cognitive impairment and predicts dementia development [29], while high levels of neurofilament (NFL) [30], inflammatory glycoprotein YKL-40 [31] and neurogranin [25] have been associated with cognitive

decline in PD. Furthermore, it has been reported that PDD patients have increased CSF levels of total and phosphorylated tau and α -synuclein; however, there are still inconsistencies between different studies [32].

In the field of neuroimaging, several modalities have been used to investigate PD–MCI and PDD. Magnetic resonance imaging (MRI) with various structural and functional techniques along with positron emission tomography (PET) and single-photon emission computerised tomography (SPECT) of various tracers (glucose metabolism, cholinergic, amyloid and tau PET) have mainly been used [15, 33, 34]. Structural MRI studies have shown that there is an early cortical thinning in PDD [35] and PD–MCI patients have parietal cortical thinning as well as lower left orbitofrontal cortex grey matter volume as compared to non-demented PD patients [36]. It has also been reported that PD patients have reduced glucose metabolism compared to controls in a range of regions including the parietal and prefrontal cortices [37–39]. Moreover, PD patients with cognitive impairment have reduced metabolism in the temporal, parietal and premotor cortices as compared to PD patients without cognitive decline [38, 39]. Additionally, electroencephalography and magnetoencephalography studies have shown promising results in terms of predicting cognitive deterioration in PD [40].

3 Role of Diabetes-Related Pathways and Antidiabetic Drugs in PD Dementia (PDD)

Various mechanisms are involved in the underlying pathology of cognitive decline in PD. These include limbic and cortical Lewy body pathology, amyloid plaque and tau pathology, neuroinflammation, synaptic plasticity dysregulation, neurotransmitter alterations as well as genetic factors [15, 18, 22–26, 28]. The complex roles of these in the underlying pathology of PDD has been previously reviewed in depth [41, 42]. There is accumulating evidence that diabetes-related pathways are involved in cognitive decline in PD and here we focus on these mechanisms.

3.1 PD and Diabetes

Although PD and diabetes are clinically different, an association between the two disorders was described in the 1960s, with the assessment of glucose tolerance in PD patients [43]. It was later suggested that alterations in similar pathways and common underlying mechanisms exist between the two disorders [44, 45].

Several epidemiological studies have demonstrated an association between type 2 diabetes mellitus (T2DM) and an

increased risk of developing PD [46–50]. More specifically, a large proportion of PD and PDD patients have impaired insulin signalling and insulin resistance [44, 51]. A prospective epidemiological study in a Finnish population found an association between T2DM and the risk of developing PD [46] and, furthermore, T2DM has been associated with a younger onset of PD and more severe symptoms [47, 48]. However, in contrast, some studies did not find diabetes to be a risk factor for PD and even reported a lower prevalence of diabetes in PD patients than in controls [45, 52–54]. Despite these conflicting reports, it has been suggested that the diseases may have common underlying biological mechanisms [44, 45]. Mitochondrial dysfunction, autophagy, inflammation and impaired insulin signalling deficits and resistance have all been associated with PD, PDD and diabetes [44]. In addition to shared biological pathways, whole-genome transcriptome profiling of the substantia nigra of PD patients has provided evidence of genetic links between PD and diabetes [55]. It was found that 892 dysregulated priority genes were altered, and various ‘hub’ genes with multiple interactions with other genes were identified, including those encoding glycogen synthase kinase-3 β (GSK-3 β) and insulin-like growth factor-1 (IGF-1) receptor (IGF-1R). Furthermore, diabetes was among the top three diseases showing the strongest probable relationship to the top upregulated priority genes [55]. Network-based approaches provide further evidence for a molecular link between diabetes and PD [56]. Interactome mapping revealed more than 400 genes linking both T2DM and PD and identified insulin receptor and lipid signalling, activation of the immune response, mitogen-activated protein (MAP) kinase (MAPK) cascade and protein serine–threonine kinase activity as convergent pathways [57].

3.2 PD, Diabetes and Dementia

The link between diabetes and PDD was noted back in 1992 when Sandyk and Awerbuch [58] reported an association between the two conditions in a small study of 12 PD patients. In their study, all five PD patients with diabetes also had dementia while the seven diabetes-free PD patients did not exhibit dementia at the time [58]. Since then the field investigating diabetes and PDD has grown. Bosco et al. [51] reported that PD patients with dementia are two times more likely to be insulin resistant than PD patients without dementia [51].

3.3 Diabetes and Dementia

In addition to lifestyle factors, such as obesity and physical inactivity, increased longevity and population aging are crucial factors contributing to the increasing prevalence

of T2DM worldwide [59]. Similar trends are observed in the prevalence of dementia, resulting in co-occurrence of the two diseases [60]. It is now established that there is an increased risk of dementia in patients with T2DM [61, 62]. Diabetes is also linked to less severe forms of cognitive dysfunction, including MCI [63, 64] and subtle cognitive changes reported under the term diabetes-associated cognitive decrements [65]. Diabetes-associated cognitive decrements in adults with T2DM are commonly subtle changes in cognitive function that may be bothersome, but do not affect ADL [65]. These cognitive decrements affect one or several domains, including processing speed, executive function, visual and verbal memory, as well as motor function [66]. It has been suggested that diabetes-associated cognitive decline develops during the pre-diabetic stages, and advances very slowly, over many years [67]. Cognitive decrements do not represent a pre-dementia stage in patients younger than 60 years, whereas older patients may progress to MCI and dementia [65].

An increasing body of evidence suggests that neurodegenerative and vascular dementias share some common underlying pathologies, such as insulin dysregulation, that act both through disease-specific and general mechanisms [68]. In a meta-analysis of 14 studies including over 2 million people, T2DM was associated with a 60% increased risk for dementia of all types, and for vascular dementia the additional risk was 19% higher in women than in men [69]. Radiological signs of vascular brain injury such as lacunes and white matter hyperintensities are common findings in patients with T2DM [70]; however, neuropathologic studies do not confirm increased occurrence of large artery infarcts or microinfarcts in these patients [71]. Also, although the risk for Alzheimer's dementia is increased in patients with T2DM, neither Alzheimer's pathology in the brain [72] nor in vivo biomarkers of amyloid β deposition and tau pathology [73, 74] are more common in patients with diabetes than in non-diabetic individuals. These findings may indicate that T2DM accelerates neurodegeneration by other, non-Alzheimer's-specific mechanisms, which may also contribute in other dementia syndromes, such as PDD. One such mechanism is insulin resistance, which appears in T2DM and neurodegenerative dementias including PD [75, 76]. Insulin resistance is a core sign of T2DM that, besides hyperglycaemia, also contributes in oxidative stress, inflammation, atherosclerosis and hyperlipidaemia. Brain insulin resistance has been defined as the failure of nerve cells to respond normally to insulin, with subsequent disturbances in synaptic, metabolic and immune response functions [77]. Systemic insulin resistance and T2DM are associated with brain insulin resistance and with neurodegeneration; however, it is unclear whether the inter-relation of these conditions depends on mechanistic links or co-occurrence of processes of aging [75].

3.4 Insulin, Insulin-Like Growth Factor (IGF)-1 and Insulin Resistance in Relation to PD

Insulin is thought to have neuroprotective functions in the central nervous system (CNS) [78]. Animal studies have shown that downregulating insulin receptor expression in the rat hippocampus impairs hippocampal plasticity, spatial learning and long-term potentiation [79]. Conversely, insulin treatment has been shown to improve memory and cognition in rats [80] and promote protective effects in rat models of PD [81]. IGF-1 is a neuronal survival factor and is closely related to insulin (Fig. 1). IGF-1 can bind to both the insulin receptor and IGF-1R with similar outcomes, and animal studies have demonstrated that IGF-1 can exert a neuroprotective effect on neurons in *in vitro* and *in vivo* models of PD and reduce α -synuclein aggregation [82–84]. IGF-1 levels are increased in the serum and CSF of PD patients [85–87], possibly as an endogenous neuroprotective response. Lower serum IGF-1 levels in PD patients have been associated with poor executive function [88] and found to predict poor verbal memory performance [89].

Peripheral insulin and IGF-1 can cross the blood–brain barrier (BBB) and animal studies have shown that they are also produced in regions of the CNS associated with cognition and dementia, including the hippocampus, cortex and olfactory bulb [76, 90–92]. The insulin receptor is widely expressed in the brain—in the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala [93] and substantia nigra [76, 94]. It is more concentrated in neurons than in glial cells and is present in post-synaptic neuron terminals [93]. To induce signalling, IGF-1 or insulin bind to the insulin receptor, causing autophosphorylation of the intracellular unit. This causes a signalling cascade resulting in the activation of either the mammalian MAPK/extracellular signal-regulated kinases (ERK) signalling pathway, resulting in cell growth, or the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signalling pathway for metabolic functions, resulting in cell proliferation and survival, and the synthesis of lipids and proteins [95] (Fig. 1). The activation of these pathways can modulate multiple downstream targets [76, 96] (Fig. 1). This results in the modulation of pathways in PD and PDD, such as apoptosis (mammalian target of rapamycin [mTOR], GSK-3 β and forkhead box O [FoxO]), autophagy (mTOR), inflammation (GSK-3 β and nuclear factor- κ B [NF κ B]) and synaptic plasticity (GSK-3 β , and cyclic adenosine monophosphate [cAMP] response element-binding protein [CREB]). GSK-3 β has been widely researched in neurodegenerative disorders, inflammation and cognition as well as diabetes, playing a role in each. Of note, α -synuclein, a key player in both PD and PDD can activate GSK-3 β directly and indirectly by inhibiting insulin receptor substrate 1, thereby altering insulin signalling [76, 97–99].

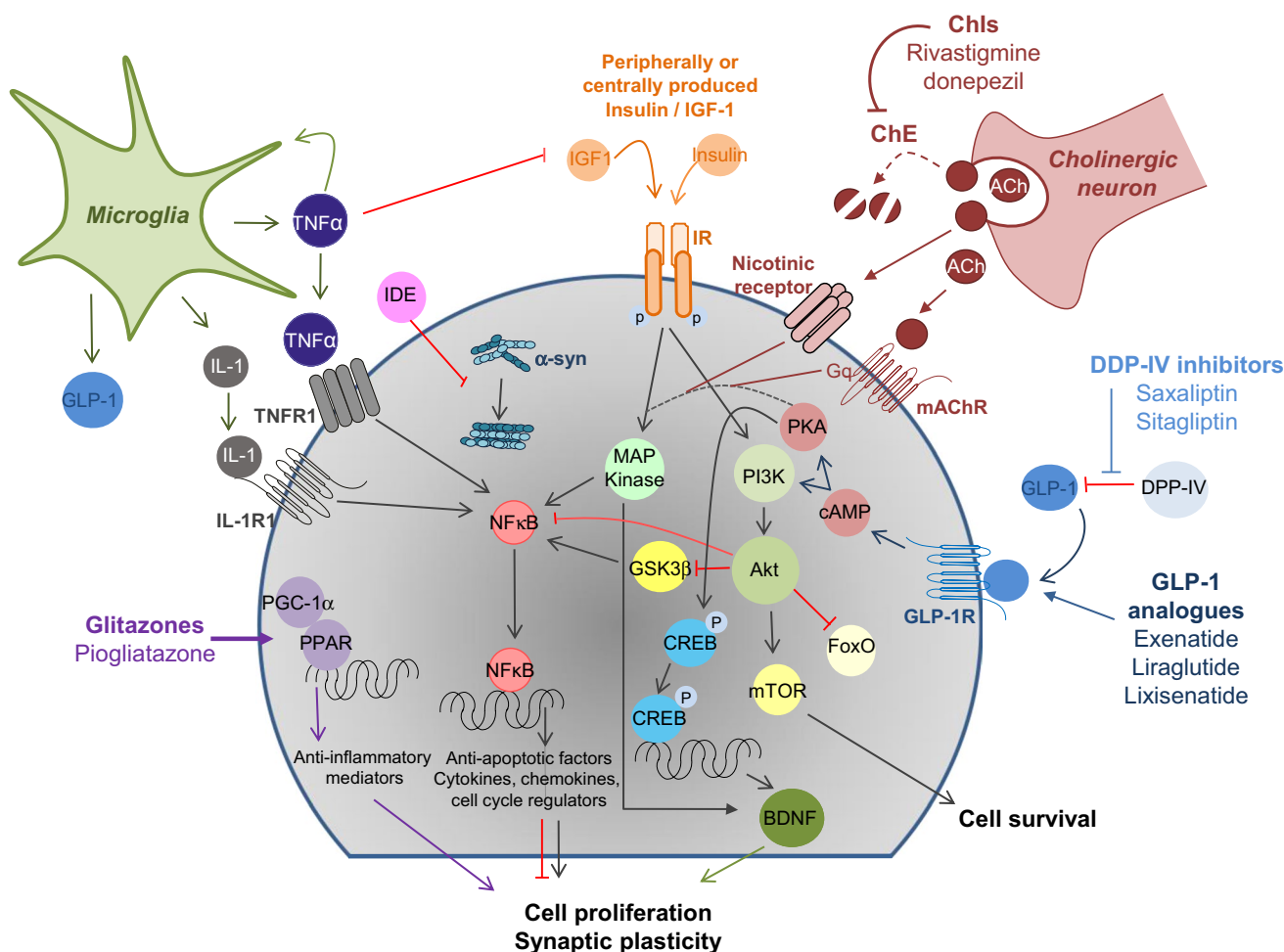


Fig. 1 Potential neuroprotective mechanisms of antidiabetic drugs in the context of Parkinson's disease dementia. ChIs block ACh degradation by ChE allowing ACh to bind to either the mAChR or nicotinic receptors resulting in MAP kinase signalling. IGF-1 or insulin bind to the IR activating MAP kinase signalling, promoting cell growth and synaptic plasticity via BDNF, or the PI3 K/AKT signalling pathway, resulting in cell proliferation and survival via modulating multiple downstream targets including mTOR, GSK-3β, FoxO and NFκB. DPP-IV inhibitors block the degradation of GLP-1 by DPP-IV, promoting signalling, while GLP-1 analogues directly promote GLP-1R signalling, which increases cAMP activating of the aforementioned signalling pathways and also activates the PKA signalling pathway resulting in the activation of CREB and resultant gene transcription. Proinflammatory cytokines, which are elevated in Parkinson's disease, such as TNFα and IL-1 promote pro-inflammatory cytokine release via NFκB signalling and can also inhibit insulin and IGF-1 signalling, resulting in the disruption of MAP kinase and PI3 K signalling. In contrast to this, glitazones can activate PPARγ,

resulting in gene transcription of neuroprotective mediators. PGC-1α can bind to various transcription factors including PPARγ and exerts a neuroprotective effect. The insulin degrading enzyme can target α-syn, binding to α-syn oligomers inhibiting the formation of fibrils. α-syn alpha-synuclein, ACh acetylcholine, AKT protein kinase B, ChE cholinesterase, ChI cholinesterase inhibitor, BDNF brain-derived neurotrophic factor, cAMP cyclic adenosine monophosphate, CREB cyclic adenosine monophosphate response element-binding protein, DPP-IV dipeptidyl peptidase IV, FoxO forkhead box O, GLP-1 glucagon-like peptide-1, GLP1R glucagon-like peptide-1 receptor, GSK3β glycogen synthase kinase-3β, IDE insulin degrading enzyme, IGF-1 insulin growth factor-1, IL-1 interleukin-1, IR insulin receptor, mAChR muscarinic acetylcholine receptors, MAP mitogen-activated protein, mTOR mammalian target of rapamycin, NFκB nuclear factor-κB, PI3 K phosphatidylinositol 3 kinase pathway, PGC-1α PPARγ coactivator 1α, PKA protein kinase A, PPARγ proliferator-activated receptor-γ, TNFα tumour necrosis factor-α

Dysfunctional insulin signalling due to insulin resistance, diabetes or excessive inflammation [100] may result in activated GSK-3β and NFκB and inactivated mTOR and CREB signalling, among others, resulting in altered autophagy, cell proliferation and increased inflammation (Fig. 1). Indeed, loss of insulin sensitivity centrally in animal models of

Alzheimer's disease (AD) has resulted in increased formation of AD-related pathology [101]. Willette et al. [102] have shown that insulin resistance is associated with higher frontal and temporal amyloid levels in normoglycaemic participants. In contrast, activation of the insulin degrading enzyme (IDE) results in degradation of amyloid β under

physiological conditions [103], which is of particular interest due to the fact that amyloid β levels have been associated with memory decline and cognitive impairment in PD [104–106]. Furthermore, upon activation, IDE can target α -synuclein, the main component of Lewy bodies, binding to α -synuclein oligomers, inhibiting the formation of fibrils [107].

In addition to the aforementioned pathways, it has been suggested that low concentrations of insulin together with reduced receptor levels, and thus reduced signalling, would result in decreased acetylcholine [108]. Reductions in cortical choline acetyltransferase correlate with cognitive impairment in PD [109] and there is widespread loss of cortical acetylcholine in PDD [110, 111]. Taken together, it is evident that insulin plays a role in many of the proposed pathological mechanisms in PDD, including autophagy, inflammation, apoptosis, synaptic plasticity and neurotransmitter alteration.

3.5 Glucagon-Like Peptide-1 (GLP-1), GLP-1 Analogues and Dipeptidyl Peptidase IV (DPP-IV) Inhibitors

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that maintains glucose homeostasis and facilitates insulin signalling by stimulating insulin secretion and biosynthesis as well as inhibiting glucagon secretion [112]. GLP-1 is primarily produced in the small intestine and is also thought to be produced in the CNS in the lower brainstem and in the axons of the hypothalamic nuclei as well as by microglia [113, 114]. GLP-1 binds to the G-protein coupled receptor (GPCR) GLP-1R, which has been shown to be expressed widely in the brain [115, 116]. In addition to its role in regulating glucose homeostasis, GLP-1 is also involved in cell proliferation, neuronal growth, inhibiting apoptosis and reducing oxidative stress in the CNS [117]. Interestingly, Kappe and colleagues [113] have demonstrated that GLP-1 expression is decreased in response to a lipopolysaccharide (LPS)-mediated inflammation challenge in vitro. The structure of GLP-1R in complex with a Gs protein has recently been revealed [118]. In general, this study has facilitated the integration of a large body of biochemical and biophysical data towards understanding the activation of GPCRs through peptide binding. GLP-1 binding to GLP-1R increases cAMP, and, similarly to IGF-1 and insulin signalling, activates the PI3K signalling pathway resulting in the activation of AKT signalling pathways [119] (Fig. 1). The dipeptidyl peptidase IV (DPP-IV) enzyme degrades GLP-1, thus inhibiting downstream signalling. As such, GLP-1 analogues and DPP-IV inhibitors have been developed as T2DM drugs, and have been found to have protective functions in PD animal models, protecting against cell death and having anti-inflammatory effects [112, 119]. Indeed, it has been suggested that

the protective effect of antidiabetic drugs observed in PD may partly be mediated by their anti-inflammatory effects [44]. GLP-1 analogues and DPP-IV inhibitors can cross the BBB, and affect neuroinflammation, mitochondrial function and cellular proliferation, among others. Moreover, because GLP-1R stimulation activates similar signalling pathways that are ‘de-activated’ as a consequence of insulin resistance, it has been suggested that the ability to restore brain insulin sensitivity also underlies the neuroprotective effect of GLP-1 analogues. Using a population-based register study, we have recently found that patients with T2DM treated with GLP-1R agonists or DPP-4 inhibitors have a lower incidence of future PD [120]. GLP-1 analogues, such as exenatide, liraglutide and lixisenatide, and DPP-IV inhibitors, including saxagliptin, vildagliptin and sitagliptin, have also been found to have neuroprotective effects in in vitro and in vivo animal models of both PD and AD. This has been comprehensively reviewed by Athauda and Foltynie [76, 112, 117] and by Hölscher [121, 122]. Of particular note here is that GLP-1R activation using exendin-4 has been shown to promote acetylcholine production in NSC-19 neuroblastoma cells in vitro [123], which has specific relevance in relation to the loss of cortical acetylcholine in PDD [110, 111]. Moreover, exendin-4 stimulates subventricular zone neurogenesis in the adult rodent brain and induces behavioural and histological recovery in an animal model of Parkinsonism [124].

3.6 Glitazones

Insulin-sensitizing thiazolidinediones (TZDs) are another group of antidiabetic drugs that have been investigated in relation to PD. TZDs increase insulin sensitivity by targeting peroxisome proliferator-activated receptor (PPAR)- γ . PPARs have been identified centrally in non-human primates in regions including the ventral tegmental nucleus, putamen and substantia nigra [125]. Furthermore, PPARs are expressed in adult human brain in an isotype- and cell-specific manner; PPAR γ is found in neurons and astrocytes but not in microglia in postmortem superior frontal gyrus [126]. However, PPAR γ is expressed in mouse microglia after an LPS challenge [126]. PPARs are ligand-dependent transcription factors and PPAR γ agonists inhibit proinflammatory cytokine production [127, 128]. As neuroinflammation plays a role in many neurodegenerative disorders, investigation of PPAR agonists has gained momentum. Indeed, pioglitazone has been found to have protective properties in rodent models of PD, reducing mediators of oxidative stress including nitric oxides and mitochondrial outer membrane protein [129], decreasing glial activation and NF κ B signalling, and protecting dopaminergic neurons [130, 131]. Furthermore, pioglitazone had neuroprotective effects in experimental parkinsonism in rhesus monkeys [132], and in a retrospective register study, Brauer and colleagues [133]

reported that diabetic patients also being treated with gli-tazones had a lower incidence of PD. However, a phase II multicentre double-blind randomized trial of pioglitazone with PD patients did not find protective effects of the drug (ClinicalTrials.gov identifier NCT01280123). This could be due to the relatively short follow-up time (44 weeks) of early diagnosed PD patients, which is not consistent with large changes in cognitive scores even in the natural course of the disease. In early PD patients the sensitivity to evaluate early and mild cognitive impairment is low [134]. It could also be attributed to inefficient penetration of the drug in the human brain, contrary to previous positive results in animal models [135]. Despite this, more recently pioglitazone was shown to protect against the risk of dementia in patients with T2DM [136]. Recently, attention has been drawn to the PPAR γ coactivator 1 α (PGC-1 α). PGC-1 α is involved in gluconeogenesis and mitochondrial biogenesis and, interestingly, GLP-1 has been found to increase PGC-1 α in rat pancreatic β cell lines [137]. Polymorphisms in PGC-1 α have been associated with the risk and age of onset of PD [138], while overexpression of PGC-1 α has a neuroprotective effect on dopaminergic neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD, while also protecting against α -synuclein-induced dopaminergic cell death [139, 140].

4 Current Treatment of PDD

Cholinergic dysfunction is one of the pathophysiological mechanisms that play a critical role in cognitive impairment in PD, and is targeted by cholinesterase inhibitors (ChIs) for the treatment of Lewy body disorders (PD, PD-MCI, PDD and DLB) [17, 141–148]. In a large meta-analysis assessing the efficacy and safety of 17 clinical trials for PDD and DLB, rivastigmine and donepezil were reported to have a beneficial effect on cognitive function, behavioural disturbances, ADL and global function. Furthermore, there were no detrimental effects on motor function compared with placebo [149]. There was, however, a higher rate of all-cause discontinuation of treatment and discontinuation due to adverse events (AEs) in the ChIs group than in controls. Nausea and tremor were common in all ChIs and vomiting and dizziness were more often associated with rivastigmine. It is concluded that ChIs are beneficial in the treatment of Lewy body disorders, including PDD.

An experimental medicine study [150] with a rivastigmine patch used functional MRI evaluations to assess pre-cognitive effectiveness. Despite a rather small number of participants, the study results implicate the use of rivastigmine with frontal function amelioration. Rivastigmine has also been tested against MCI in PD patients and had some

beneficial actions, but failed to meet its primary outcome on global clinical improvement [151].

Apart from ChIs, there have also been studies that evaluated the effect of *N*-methyl-D-aspartate (NMDA) receptor antagonists in PDD. Memantine affects the glutamatergic neuronal transmission and prevents toxicity from high concentrations of glutamate. Based on previous findings of altered glutamatergic markers in DLB, scientists have conducted studies on the effect of memantine on DLB and PDD [152–154]. The studies were multicentre and double-blind and medication was titrated to 20 mg. Pooled data presented in a meta-analysis confirmed a significant effect of memantine on the Clinician's Global Impression of Change scale and good safety outcomes. However, no effect on cognitive function, behavioural symptoms or ADL was reported [155].

5 Recent and Ongoing Drug Studies Against PD-MCI and PDD

The electronic databases ClinicalTrials.gov and the European Union Clinical Trials Register were searched using the terms "Parkinson's disease" and "dementia or cognitive impairment". Cross-references from the identified articles were also scrutinised for relevant studies. Litvan and colleagues [156] recently reviewed previous clinical trials in PD-MCI. As well as critically reviewing previous trials, they also highlight important factors to be considered for future PD-MCI trials including clarity on which cognitive syndrome investigators are addressing (for trial design), improved outcome measure choice and meaningful biomarkers [156]. As such, in this section we discuss ongoing trials.

5.1 Drugs Primarily Acting on Neurotransmitter Mechanisms

5.1.1 Glutamatergic Mechanisms

Sarcosine is a glycine transporter I inhibitor that blocks glycine uptake and enforces the function of the NMDA receptor. Glycine works as a potentiator via the NR1 subunit of the NMDA receptors. A placebo-controlled, double-blind study has shown that sarcosine has a positive effect on neuropsychiatric symptoms of PDD (NCT01785628) [157]. Patients received placebo or 2 mg of sarcosine daily for 8 weeks. Efficacy regarding neuropsychiatric symptoms and safety regarding AEs were the primary endpoints and the Unified Parkinson's Disease Rating Scale (UPDRS) and cognitive assessment were the secondary endpoints. Temporary dizziness was the only AE reported in the sarcosine group and temporary neuropsychiatric amelioration was achieved in the treatment group, but no differences in cognition or motor function were reported. The researchers indicate a possible

tolerance to sarcosine after a relatively short period of treatment and a need for larger studies.

Ceftriaxone is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic that has been shown to reduce glutamatergic hyperactivity and excitotoxicity and exert neuroprotective properties in preclinical PD models [158–160]. A phase II trial of ceftriaxone in PDD in which efficacy and safety are going to be investigated is ongoing in Taiwan (NCT03413384; Table 1). Patients will receive ceftriaxone 1 g or placebo on days 1, 3 and 5 per cycle on a 2-weekly cycle.

A phase I dose-finding clinical trial of NYX-458, a modulator of NMDA receptors, has been initiated. The aim is to optimize conditions for a phase II trial in PDD. A press release has reported that a preclinical study on a non-human primate model of PD-related cognitive impairment showed that NYX-458 significantly increased sustained attention, improved cognitive flexibility and enhanced working memory. These effects were present as early as 2 h following a single oral dose and remained 3 weeks post-dosing. NYX-458 resulted in complete reversal of cognitive impairment and performance back to baseline levels. No issues of tolerability were observed.

5.1.2 Cholinergic Mechanisms and their Interplay with Sigma 1 Receptors

ANAVEX2-73 (EudraCT: 2017-004335-36; Table 1) acts on the muscarinic M_1 receptors and reverses scopolamine-induced learning impairments in rodents. A phase II trial was recently initiated in Spain to evaluate the efficacy, tolerability and safety of ANAVEX2-73 for cognitive impairment in patients with PDD. ANAVEX2-73 is also a sigma-1 receptor agonist. The sigma-1 receptor is located on mitochondria-associated endoplasmic reticulum (ER) membranes and modulates the ER stress response and local calcium exchanges with the mitochondria. Previous preclinical studies on AD models have shown that ANAVEX2-73 acts synergistically on sigma-1 and muscarinic receptors and alleviates amyloid load in AD models [161]. ANAVEX2-73 has also been found to prevent learning impairment in mice injected with $A\beta_{25-35}$ by blocking hippocampal oxidative stress [162]. Finally, a synergistic protective effect between sigma-1 receptor agonists and donepezil on learning outcomes has been demonstrated in a non-transgenic mouse model of AD. This may be due to an inter-related mechanism involving $\alpha 7$ nicotinic acetylcholine receptors and sigma-1 receptor [163].

5.1.3 Monoaminergic Mechanisms

Atomoxetine is a selective norepinephrine reuptake inhibitor that affects dopaminergic and noradrenergic transmission in

frontal areas of the brain and is approved for the treatment of attention deficit disorder. It has also been investigated with positive results in non-demented PD patients with executive dysfunction in an 8-week, pilot, open-label, flexible-dose study [164]. The study reported improved executive dysfunction and only mild to moderate AEs, including sleep and gastrointestinal disturbances and hypomania. Another randomised, double-blind, placebo-controlled trial (NCT01738191; Table 1) on the potential benefit of atomoxetine on PD-MCI has just been completed, but the results are yet to be published.

Serotonin receptors have received increased attention in the context of non-motor symptoms in neurodegenerative disorders and the use of pimavanserin, a serotonin 5-HT_{2A} antagonist, has already been approved for PD psychosis [165]. Furthermore, 5-HT₆ and 5-HT₇ receptor antagonists have been shown to produce promnesic and anti-amnesic effects in preclinical models, as well as in humans with schizophrenia, PD or AD [166]; however, early results from phase III studies in AD have failed to demonstrate significant impact on cognition [167]. SYNAPSE is a proof-of-concept study that assessed the safety, tolerability and efficacy of a dual 5-HT₆/5-HT_{2A} antagonist (SYN120) in patients with PDD and ongoing treatment with ChI (NCT02258152; Table 1). Recruitment was completed in October 2017 but no results are available yet. Nelotanserin is a selective 5-HT_{2A} inverse agonist that can be administered orally and has been tested on sleep-maintenance insomnias [168]. There is an ongoing clinical trial on the effect of nelotanserin against RBD in patients with PDD and DLB (NCT02708186; Table 1). It is investigating the safety and efficacy of nelotanserin, based on motor scales and clinical evaluation of the REM sleep behaviours. Additionally, another study (NCT02871427; Table 1) is evaluating the long-term safety, tolerability and effectiveness of nelotanserin in DLB and PDD, targeting mainly psychiatric semiology and RBD.

The potentially beneficial role of intepirdine (RVT-101) in cognition has already been highlighted in AD [169]. It is a 5-HT₆ antagonist that has been implicated as playing an important role in multiple pathways. Intepirdine has also been investigated in DLB and there has been a study on AD, DLB and PDD (NCT02910102; Table 1) that assessed its effect on gait and balance. To date, no results have been published.

LY3154207 is an orally administered enhancer of dopamine D₁ receptors that is under investigation in a multicentre, phase II trial in the USA for patients with PDD (NCT03305809; Table 1). In addition, the pharmacokinetic properties of LY3154207 are going to be assessed in the Multiple-Ascending Dose, Safety, Tolerability, and Pharmacokinetic Study in healthy subjects and PD patients (NCT02562768; Table 1).

Table 1 Clinical trials investigating novel treatments for Parkinson's disease dementia

ClinicalTrials.gov/ EudraCT identifier	Study design	Estimated enrolment (n)	Agent	Mechanism of action	Comparison	Relevant outcome measures
NCT02415062	R, OL prospective, parallelled study	150	Donepezil	Ch1	Donepezil 25 mg (high dose) vs. donepezil 10 mg (standard dose)	General cognitive function assessed with Korean MMSE-2. Timeframe: change from base- line to week 24
NCT03413384	R, DB, PC, phase II study	106	Ceftriaxone	Cephalosporin antibiotic	Ceftriaxone vs. placebo	Assessment of memory, orienta- tion, language, and praxis meas- ured with ADAS-Cog. Time- frame: change from baseline to weeks 17 and 33
2017-004335-36	R, DB, PC, phase II study	120	ANAVEX2-73	Sigma-1 receptor agonist	ANAVEX2-73 vs. placebo	Continuity of attention measured by CDR computerised assess- ment system continuity of atten- tion test
NCT01738191	R, DB, PC	30	Atomoxetine	Norepinephrine reuptake inhibi- tor	Atomoxetine vs. placebo	Assessment of 7 atomoxetine-sen- sitive neuropsychological meas- ures of attention, set-shifting, information processing speed and working memory. Time- frame: change from baseline to 10 weeks
NCT02258152	R, DB, PC, POC	82	SYN120	Dual 5-HT ₆ /5-HT _{2A} antagonist	SYN120 vs. placebo	Assessment of CDR cognition battery continuity of attention. Timeframe: baseline to week 16
NCT02708186	R, DB, PC	20	Nelotanserin	Selective 5-HT _{2A} inverse agonist	Nelotanserin vs. placebo	Assessment of the frequency of REM sleep behaviours. Time- frame: baseline to day 28
NCT02871427	MC, OL long-term study	80	Nelotanserin	Selective 5-HT _{2A} inverse agonist	Nelotanserin 20, 40, 60 or 80 mg	Assessment of the frequency and severity of hallucinations, and REM sleep behaviours. Time- frame: 24 weeks
NCT02910102	R, DB, PC, phase II crossover study	38	Intepirdine	Selective 5-HT ₆ receptor antago- nist	Intepirdine vs. placebo	Quantitative gait measure- ments assessed by computerized gait assessment tools. Time- frame: baseline to week 12
NCT03305809	R, DB, PC, phase II study	340	LY3154207	Dopamine receptor D ₁ enhancer	LY3154207 vs. placebo	Assessment of Continuity of Attention measured by CDR computerized cognition battery continuity of attention composite score. Timeframe: baseline to week 12

Table 1 (continued)

ClinicalTrials.gov/ EudraCT identifier	Study design	Estimated enrolment (n)	Agent	Mechanism of action	Comparison	Relevant outcome measures
NCT02562768	R, DB, PC, multiple-ascending dose study	80	LY3154207	Dopamine receptor D ₁ enhancer	LY3154207 vs. placebo	Assessment of serious adverse events and pharmacokinetic properties. Timeframe: baseline through day 15
NCT01256905	OL	20	Armodafinil	Dopamine reuptake inhibitor	Armodafinil	Evaluation of striatal-thalamo- cortical network disturbances assessed with EEG. Timeframe: 2 h
2017-001673-17	R, DB, PC, MC, phase IIa study	40	IRL752	5-HT ₇ and α -adrenergic receptor antagonist	IRL752 vs. placebo	Safety, tolerability and efficacy on motor and non-motor symptoms including cognitive function measured with CANTAB and EEG pattern changes. Time- frame: baseline to day 28
2010-024424-26	Prospective, MC, R, DB, PC, parallel group, phase II study	45	Masitinib	Non-selective tyrosine kinase receptor inhibitor	Masitinib vs. placebo	Assessment of cognition with ADCS instruments. Timeframe: baseline to week 48
NCT02954978	R, DB, PC	75	Nilotinib	C-Abelson tyrosine kinase inhibitor	Nilotinib 300 mg vs. nilotinib 150 mg vs. placebo	Assessment of adverse events and pharmacokinetic properties and measurement of biomarker of dopamine metabolism in cerebrospinal fluid. Timeframe: baseline to 12 months
NCT02914366	R, DB, PC	75	Ambroxol	Chaperone, glucocerebrosidase stabiliser	Ambroxol 1050 mg vs. ambroxol 525 mg vs. placebo	Assessment of cognition with ADAS-Cog and ADCS-Clini- cian's Global Impression of Change. Timeframe: baseline to week 26 and week 52
NCT02906020	R, DB, PC	243	GZ/ SAR402671 (ibiglustat)	Glucosylceramide synthase inhibitor	GZ/SAR402671 vs. placebo	Assessment of MDS-UPDRS and Parkinson's disease Cognitive Rating Scale. Timeframe: base- line to week 8 and at week 52
NCT03456687	OL	20	Exenatide	GLP-1 receptor agonist	Exenatide	MRI and fMRI-based markers of free-water accumulation in substantia nigra, blood oxygen level-dependent signal in the posterior putamen, in M1 and in the supplementary motor areas. Timeframe: baseline to 1 year

Table 1 (continued)

ClinicalTrials.gov/ EudraCT identifier	Study design	Estimated enrolment (<i>n</i>)	Agent	Mechanism of action	Comparison	Relevant outcome measures
NCT03439943	MC, R, PC, DB parallel arm, POC	158	Lixisenatide	GLP-1 receptor agonist	Placebo	Assessment of MDS-UPDRS III motor score in the best ON condition. Timeframe: baseline to 12 months
NCT03659682	R, DB, PC	270 or 120	Semaglutide	GLP-1 analogue	Placebo	MDS-UPDRS III in OFF medication state, MoCA and MMSE scores. Timeframe: baseline and at 12, 24, 36 and 48 months

5-HT 5-hydroxytryptamine, *ADAS-Cog* Alzheimer's Disease Assessment Scale—Cognitive Subscale, *ADCS* Alzheimer's Disease Cooperative Study, *CANTAB* Cambridge Neuropsychological Test Automated Battery, *CDR* Cognitive Drug Research, *ChI* cholinesterase inhibitors, *DB* double-blind, *EEG* electroencephalography, *fMRI* functional magnetic resonance imaging, *GLP-1* glucagon-like peptide 1, *MC* multicentre, *MDS-UPDRS* Movement Disorder Society Unified Parkinson's Disease Rating Scale, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment, *MRI* magnetic resonance imaging, *OL* open-label, *PC* placebo-controlled, *POC* proof-of-concept, *R* randomised, *REM* rapid eye movements

Armodafinil is a dopamine reuptake inhibitor that acts as a wake-promoting agent, and has been shown to have positive effects on cognition, daytime sleepiness and visual hallucinations in patients with narcolepsy [170]. It has also been evaluated in a small, open-label, single-dose study in nine patients with DLB and PDD with positive results on attention and global mental status [171]. Another pilot study of 20 patients with PDD and DLB reported improvement in hypersomnia and wakefulness and reasonable safety and tolerability of armodafinil during 12 weeks of treatment [172]. In the next phase, a larger, open-label study (NCT01256905; Table 1) will evaluate the effect of armodafinil on attention modulation in PDD and DLB patients.

IRL752 belongs to a new class of CNS-active agents called psychomotor stabilisers. Such compounds modify psychomotor activity depending on the initial level of activity. In preclinical models, IRL752 potentiates cortical transmission of dopamine, noradrenaline and acetylcholine and has procognitive effects. This provided the rationale for developing IRL752 as a potential therapy against PDD. A multicentre phase IIa study evaluating the safety and tolerability of IRL752 in PDD patients is currently ongoing in Sweden and Finland (EudraCT: 2017-001673-17; Table 1). A press release has reported positive data on cognition and apathy, but no results have been published.

5.2 Drugs Primarily Acting on Intracellular Enzymes

5.2.1 Protein Kinase Inhibitors

Masitinib is a non-selective tyrosine kinase receptor (TKR) inhibitor currently being tested against cognitive impairment in PD in a phase II study assessing safety and efficacy (EudraCT: 2010-024424-26; Table 1). The primary target of masitinib is the TKR c-Kit, but it also exerts weak inhibitory activity in fibroblast growth factor receptor 3, lymphocyte-specific kinase (Lck), Lck/Yes-related protein, focal adhesion kinase and the Fyn TKR. It also targets platelet-derived growth factor receptor and is currently being used in the treatment of mast cell (MC) tumours in dogs, and in oncology for the treatment of unresectable or metastatic gastrointestinal stromal tumours [173]. Clinical use of masitinib in non-oncological applications seems reasonable, based on the involvement of c-Kit receptors in MC-mediated inflammatory pathogenesis.

Another biochemical pathway of increasing interest in PD is that of the C-Abelson (C-Abl) tyrosine kinase enzyme. C-Abl is phosphorylated and activated upon mitochondrial dysfunction, resulting in increased oxidative stress and dopamine neuron degeneration supposedly through parkin inactivation, α -synuclein aggregation and impaired autophagy of toxic elements [174]. The C-Abl inhibitor nilotinib, which is used in much higher doses in leukaemia treatment, has

been investigated in a small, open-label, proof-of-concept trial on 12 patients with advanced PD or DLB with good results on safety and tolerability during 24 weeks of treatment; however, one patient had a myocardial infarction and two had a corrected QT (QTc) interval prolongation on electrocardiogram [175]. Secondary objectives included the determination of the ability of nilotinib to cross the BBB, and to determine target engagement through measurements of phosphorylation of Abl in CSF. The study had very high coverage by the media when initially presented and a great impact on decision-making among patients and physicians. This led to a great escalation of off-label prescription of nilotinib, which in turn led to call for further, larger studies to include a control arm [176]. A larger phase II study is now underway (NCT02954978; Table 1) and is estimated to be completed by 2020.

5.2.2 Glucocerebrosidase Targeting

There are currently two clinical trials investigating drugs targeting glucocerebrosidase (GCase). Targeting the function of the *GBA*-encoded enzyme, GCase is a relatively new therapeutic approach in PDD. NCT02914366 is a currently recruiting study on the safety, tolerability and efficacy of ambroxol, a GCase chaperone, in PDD patients (Table 1). It is thought that as ambroxol will increase lysosomal function and has been shown to improve GCase functions it may reduce α -synuclein levels [177]. The study will investigate cognitive and motor scales as well as changes in GCase in lymphocytes and the pharmacokinetics of ambroxol. Another study on PD patients carrying a *GBA* mutation is also currently ongoing and aims to assess the drug dynamics, efficacy and safety of the substrate inhibitor GZ/SAR402671 (MOVES-PD, NCT02906020; Table 1).

5.2.3 GLP-1 Receptor Agonists

A phase II clinical trial is currently underway evaluating the GLP-1R agonist lixisenatide (NCT03439943; Table 1) as an add-on therapy for early-stage PD patients. However, the primary endpoint for this study is motor improvement with no specific interest in the cognitive aspects of the disease. In addition to this a phase II clinical trial with the GLP-1 analogue semaglutide and newly diagnosed PD patients is planned for early 2019 (NCT03659682; Table 1). In this trial cognitive assessment is also going to be examined among other parameters. Both of these drugs have demonstrated protective effects in preclinical studies [178, 179]. In addition to this the GLP-1 receptor agonist exenatide has been investigated in an open-label, randomised controlled trial of 45 patients with moderate PD [180]. In this study, exenatide was well-tolerated, although weight loss was a common concern. The single-blinded ratings of motor and cognitive

performance suggested clinically relevant improvements in the treatment group compared with control. Patients who had previously been exposed to exenatide showed persistent advantage in motor and cognitive performance 1 year after study completion [181]. Following these encouraging results, a phase II randomised, double-blind, placebo-controlled study was conducted including 60 patients with PD who were allocated to exenatide or placebo for 48 weeks, followed by 12 weeks of washout period [182]. The study reported positive results on practically defined off-medication motor scores, which were sustained after the exposure period. However, no significant differences were observed in cognitive performance between exenatide and placebo. This may be due to the short observation period, combined with the mixed population including both early and more advanced PD patients. The observation period may not have been long enough to show significant changes in cognitive outcome [134]. Interestingly, in a post hoc analysis of the Exenatide-PD trial, the authors report improvement in cognition in the subgroups of patients with insulin resistance and those with obesity [183]. Another open-label study of exenatide in PD is currently ongoing in the USA and aims to investigate how the brain and motor behaviour changes in response to treatment (NCT03456687; Table 1). It is also important to note that clinical trials are also evaluating GLP-1 analogues in AD, such as a randomised, placebo-controlled phase II trial that is assessing the safety and efficacy of liraglutide in 206 patients with early AD (NCT018430755). Another trial that aimed to evaluate exenatide in patients with AD or MCI (NCT01255163) was terminated due to insufficient recruitment.

6 Conclusions and Future Perspective

ChIs are being used for the treatment of PDD. However, there is a strong medical need for additional procognitive therapies. Several distinct pharmacological mechanisms are being targeted alone or together with ChIs to counteract MCI and PDD. T2DM appears to be associated with PD and neurodegenerative dementias, possibly through peripheral and cerebral insulin resistance that in turn results in altered autophagy, mitochondrial function, cell proliferation and increased inflammation. Drugs used in diabetes treatment have shown positive effects on neurodegenerative processes and on clinical outcome, regarding memory and cognition, and could, hopefully, be developed into novel therapies against PDD and related conditions. Since these drugs have primarily been developed for the treatment of T2DM, it is likely that a next generation of compounds with more BBB penetrance may be better neuroprotective agents. The fact that the structure of GLP-1R has been solved will likely facilitate the development of non-peptidergic GLP-1

compounds that may turn out to be favourable against neurodegeneration.

Compliance with Ethical Standards

Conflict of interest PS and PT are co-investigators on MOVES-PD and have been co-investigators in a clinical trial with IRL75 against dementia in Parkinson's disease. PS has also received grants from Servier and honoraria from IRLAB, AbbVie and Shire. DA has received research support and/or honoraria from AstraZeneca, H. Lundbeck, Novartis Pharmaceuticals and GE Health, and serves as a paid consultant for H. Lundbeck, Eisai and Heptares. HG and IM have no conflicts of interest directly relevant to the content of this article.

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