Management of psychiatric and cognitive complications in Parkinson's disease

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Abstract

Neuropsychiatric symptoms (NPSs) such as affective disorders, psychosis, behavioral changes, and cognitive impairment are common in Parkinson's disease (PD). However, NPSs remain under-recognized and under-treated, often leading to adverse outcomes. Their epidemiology, presentation, risk factors, neural substrate, and management strategies are incompletely understood. While psychological and psychosocial factors may contribute, hallmark PD neuropathophysiological changes, plus the associations between exposure to dopaminergic medications and occurrence of some symptoms, suggest a neurobiological basis for many NPSs. A range of psychotropic medications, psychotherapeutic techniques, stimulation therapies, and other non-pharmacological treatments have been studied, are used clinically, and are beneficial for managing NPSs in PD. Appropriate management of NPSs is critical for comprehensive PD care, from recognizing their presentations and timing throughout the disease course, to the incorporation of different therapeutic strategies (ie, pharmacological and non-pharmacological) that utilize a multidisciplinary approach.

Introduction

The occurrence of neuropsychiatric symptoms (NPSs) in Parkinson's disease (PD), and non-motor symptoms more broadly,[1] has only recently gained recognition as being almost as common, and as disabling, as motor symptoms. However, it is clear that NPSs in PD are associated with poor long term outcomes and significant caregiver burden, and require special expertise for optimal management.[2] While PD is diagnosed based on the presence of motor signs and symptoms, the high prevalence of NPSs suggests that it could be considered as a prototypic neuropsychiatric disorder.[2] Common, clinically important NPSs include depression, anxiety, psychosis, impulse control disorders (ICDs), apathy, and cognitive impairment (both mild cognitive impairment (MCI) and dementia). Several factors explain the high cumulative prevalence of many NPSs in PD, including demographic characteristics, psychological and psychosocial factors, diffuse and multiple neurodegenerative disease pathologies, other neurobiological factors, and even PD treatments themselves.

Psychopharmacology (ie, psychiatric medications) remains the mainstay for many NPSs, with clinicians relying on both clinical experience and recommendations from specialists in the field, including the revised (2019) International Parkinson and Movement Disorder Society (IPMDS) Evidence-Based Medicine (EBM) Committee's review of treatments for non-motor symptoms[3] and the National Institute for Health and Care Excellence (NICE) guideline for the management of PD.[4] However, the evidence base for pharmacological treatment of many NPSs is limited and decisions about medication need to consider both potential benefit and adverse effects on parkinsonism and other PD related symptoms. In addition, some PD patients prefer and benefit from psychotherapy or combination approaches. The increased implementation and dissemination of evidence based psychotherapies has the potential to fill critical gaps in psychosocial care for people with PD.[5 6]

Therapeutic neuromodulation or stimulation strategies (eg, deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and electroconvulsive therapy (ECT)) are increasingly being studied and used clinically. There is growing interest in other non-pharmacological interventions for NPSs in PD, particularly for mood and cognition.[7] These interventions (eg, physical exercise, yoga, mindfulness and meditation, and cognitive training) are often complementary and adjunctive to pharmacological and psychosocial approaches. They may be appealing owing to their potentially lower risk profile, non-invasiveness, accessibility,

Table 1 | Psychopharmacology RCTs

Active treatment	Dose	Sample size	Duration	Primary outcome results summary	Reference or Clinicaltrials.gov ID
Depression					
Published					
Nortriptyline *v* paroxetine (*v* placebo)	Nortriptyline 25-75 mg/day; paroxetine 12.5-37.5 mg/day	52	8 weeks	Efficacious Nortriptyline (P<0.002 for HAM-D) Not efficacious Paroxetine	[10]
Pramipexole (*v* placebo)	0.125-1.0 mg 3 times/day	323	12 weeks	Efficacious (difference in BDI score=−1.9, 95% CI −3.4 to −0.5, P=0.01)	[11]
Venlafaxine XR *v* paroxetine (*v* placebo)	Venlafaxine up to 225 mg/day; paroxetine up to 40 mg/day	115	12 weeks	Efficacious (mean reductions in HAM-D score *v* placebo were 6.2 points (97.5% CI 2.2 to 10.3, P=0.0007) in the paroxetine group and 4.2 points (97.5% CI 0.1 to 8.4, P=0.02) in the venlafaxine XR group)	[12]
Rasagiline (*v* placebo)	1 mg/day	123	12 weeks	Not efficacious	[13]
Rotigotine (*v* placebo)	Transdermal patch 2-16 mg/day	380	8 weeks	Not efficacious	[14]
5-hydroxytryptophan (*v* placebo)	50 mg/day	25	4 weeks/treatment phase	Borderline efficacious (trend for significant treatment effect on HAM-D (F=4.19, df=1, P=0.05); not a significant effect on BDI)	[15]
Ongoing/unpublished					
Escitalopram *v* nortriptyline (*v* placebo)	Escitalopram up to 20 mg/day; nortriptyline up to 100 mg/day	408	8 weeks	Ongoing	NCT03652870
Anxiety					
Published					
Buspirone (*v* placebo)	7.5 mg twice/day	21	12 weeks	Poorly tolerated; unable to assess efficacy	[16]
Ongoing/unpublished					
Multi-strain probiotic (*v* placebo)	1 g twice/day	72	12 weeks	Ongoing	NCT03968133
Psychosis					
Published					
Donepezil (*v* placebo)	5 mg/day	145	96 weeks	No reduction in incidence rate of psychosis	[17]
Clozapine (*v* placebo)	6.25-50 mg/day	60	4 weeks	Efficacious (P=0.002 on the BPRS)	[18]
Clozapine (*v* placebo)	6.25-50 mg/day	60	4 weeks	Efficacious (P<0.001 on the positive symptoms subscore of the PANSS)	[19]
Olanzapine (*v* placebo)	2.5-15 mg/day	160	4 weeks	Not efficacious	[20]
Clozapine (*v* placebo)	12.5-50 mg/day	60	4 weeks	Efficacious (P<0.0001 on the positive symptoms subscore of the PANSS)	[21]
Quetiapine *v* clozapine	Quetiapine up to 200 mg/day; clozapine up to 50 mg/day	45	12 weeks	Efficacious (P<0.001 for both quetiapine and clozapine on the BPRS total score)	[22]
Quetiapine (*v* placebo)	25-150 mg/day	24	12 weeks	Not efficacious	[23]
Pimavanserin (*v* placebo)	34 mg/day	199	6 weeks	Efficacious (P=0.001; Cohen's d=0.50 on the SAPS-PD)	[24]
Ongoing/unpublished					
SEP-363856 (*v* placebo)	25-75 mg/day	36	6 weeks	Ongoing	NCT02969369
Cannabidiol (CBD) (*v* placebo)	Up to 1000 mg/day	120	12 weeks	Ongoing	ISRCTN87895237
Impulse control disorders					
Published					
Amantadine (*v* placebo)	200 mg/day	17	8 weeks/treatment phase	Efficacious (F=522.9, P<0.001 on the G-SAS; F=698.2;P<0.001 on the Y-BOCS)	[25]
Naltrexone (*v* placebo)	50-100 mg/day	50	8 weeks	Not efficacious Clinical Global Impression Efficacious QUIP-RS ICD score (P=0.04, regression coefficient for interaction term in linear mixed effects model=−7.37, F(df) 4.3 (1, 49))	[26]
Ongoing/unpublished					
Pimavanserin (*v* placebo)	34 mg/day	130	8 weeks	Ongoing	NCT03947216
Clonidine (*v* placebo)	75 µg twice/day	38	8 weeks	Ongoing	NCT03552068

(*Continued*)

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Table 1 | Continued

Active treatment	Dose	Sample size	Duration	Primary outcome results summary	Reference or Clinicaltrials.gov ID
Apathy					
Published					
Piribedil (*v* placebo)	maximum 300 mg/day	37	12 weeks	Efficacious (Apathy score reduced by 34.6% on piribedil *v* 3.2% on placebo, P=0.015)	27
Rivastigmine patch (*v* placebo)	9.5 mg/24 hours	30	26 weeks	Efficacious (rivastigmine improved LARS score *v* placebo (P=0.031; adjusted effect size=0.9)	28
Rotigotine patch (*v* placebo)	6 or 8 mg/24 hours	122	12 weeks	Not efficacious	29
5-hydroxytryptophan (*v* placebo)	50 mg/day	25	4 weeks/treatment phase	Not efficacious	15
Cognition					
Published					
Donepezil (*v* placebo)	5 mg/day	98	120 weeks	No reduction in dementia rate	30
PD-MCI					
Rivastigmine (*v* placebo)	9.5 mg/day	28	10 weeks/ treatment phase	Not efficacious	31
Rasagiline (*v* placebo)	1 mg/day	170	24 weeks	Not efficacious	32
Atomoxetine (*v* placebo)	80 mg/day	30	10 weeks	Not efficacious	33
PDD					
Rivastigmine (*v* placebo)	12 mg/day	541	24 weeks	Efficacious (P<0.001 on the ADAS-cog and P=0.007 on the ADCS-CGIC)	34
Memantine (*v* placebo)	20 mg/day	72 (40 PDD; 32 DLB)	24 weeks	Efficacious (P=0.03 on the CGIC, Cohen's d=0.52)	35
Memantine (*v* placebo)	20 mg/day	25	22 weeks	Not efficacious	36
Memantine (*v* placebo)	20 mg/day	175 (120 PDD; 75 DLB)	24 weeks	Not efficacious	128
Donepezil (*v* placebo)	5-10 mg/day	550	24 weeks	Not efficacious	129
Mevidalen (*v* placebo)	10, 30, or 75 mg/day	214	12 weeks	Not efficacious	130
Ongoing/unpublished					
Ambroxol (*v* placebo)	1350 mg/day	15	52 weeks	Ongoing	NCT04405596
Ceftriaxone (*v* placebo)	1 g IV days 1, 3, and 5/2 week cycle	106	17 weeks	Ongoing	NCT03413384
GRF6021 (human plasma fractions) (*v* placebo)	250 mL IV for 5 consecutive days at weeks 1 and 13	90	7 months	Ongoing	NCT03713957
Neflamapimod (*v* placebo)	80-120 mg/day	91	16 weeks	Ongoing	NCT04001517
SYN120 (5-HT6/5-HT2A antagonist) (*v* placebo)	100 mg/day	82	16 weeks	Not efficacious	NCT02258152
Intepirdine (*v* placebo)	35-70 mg/day	484	24 weeks	Ongoing	NCT02669433
Blarcamesine (*v* placebo)	30-50 mg/day	132	14 weeks	Ongoing	13th Clinical Trials on Alzheimer's Disease (CTAD) November 4-7, 2020
CST-103 (beta-2 adrenoreceptor agonist) (*v* placebo)	80 µg/day	40	2 weeks/treatment phase	Ongoing	NCT04739423
NYX-458 (*v* placebo)	30 mg/day	100	12 weeks	Ongoing	NCT04148391

ADAS-cog=cognitive subscale of the Alzheimer's disease assessment scale; ADCS-CGIC=Alzheimer's disease Cooperative Study-Clinical Global Impression of Change; BDI=Beck depression inventory; BPRS=Brief psychiatric rating scale; CGIC=Clinical global impression of change; CI=confidence interval; DLB=dementia with Lewy bodies; G-SAS=gambling-symptom assessment scale; HAM-D=Hamilton depression rating scale; IV=intravenous; LARS=Lille apathy rating scale; PANSS=positive and negative syndrome scale; PDD=Parkinson disease with dementia; PD-MCI=Parkinson disease-mild cognitive impairment; QUIP-RS ICD=questionnaire for impulsive-compulsive disorders in Parkinson's disease-rating scale ICD score; RCT=randomized controlled trial; SAPS-PD=Parkinson's disease-adapted scale for assessment of positive symptoms; Y-BOCS=Yale-Brown obsessive-compulsive Scale.

ease of use, social engagement, and perception as more "natural" or "less harmful."[8] Both stimulation strategies and other non-pharmacological interventions are posited to improve neuroplasticity through effects on neurotransmitters, glial activity, neurotrophic signaling, and inflammation.[9]

This review summarizes the epidemiology and neurobiology of NPS and management strategies for each of the major NPSs in PD, focusing on results from randomized controlled trials (RCTs), meta-analyses, expert consensus recommendations, and clinical experience.

Sources and selection criteria

To identify RCTs to include in this review, we performed a literature search (for Englishlanguage manuscripts) using an electronic database, PubMed, to access Medline for articles published between November 2018 and October 2021. We also systematically checked the references from review

Table 2 | Psychotherapy RCTs

Active treatment	Treatment description	Sample size	Duration	Primary outcome results summary	Reference or Clinicaltrials.gov ID
Depression					
Published					
CBT	In person *v* wait list (clinical monitoring+TAU)	80	4 months	Efficacious (HAM-D effect size*=1.59, BDI effect size*=1.1)	37
CBT	Telemedicine (audio only) *v* wait list (clinical monitoring+TAU)	72	9 months	Efficacious (HAM-D effect size*=1.69, BDI effect size*=0.88)	38
CBT	Telemedicine (audio-visual) *v* wait list (clinical monitoring+TAU)	90	9 months	Efficacious (HAM-D effect size*=1.27, BDI effect size*=0.80)	39
Anxiety					
Published					
CBT	In-person *v* CMO	48	9 months	Efficacious (PAS effect size*=0.74, LSAS effect size*=0.47)	40
Impulse control disorders					
Published					
CBT	In-person *v* wait list+SMC	45	10 months	Efficacious (CGI effect size†=0.21, NPI effect size†=0.12)	150

*Effect size reported as Cohen's d. †Effect size reported as partial n^2 BDI=Beck depression inventory; CBT=cognitive behavioral therapy; CGI=clinical global impression scale; CMO=clinical monitoring only; HAM-D=Hamilton depression rating scale; LSAS=Leibowitz social anxiety scale; NPI=neuropsychiatric inventory; PAS=Parkinson's anxiety scale; RCT=randomized controlled trial; SMC=standard medical care; TAU=treatment as usual.

articles, meta-analyses, and consensus guidelines. MeSH search terms were "Parkinson and depression" , "Parkinson and (psychosis or hallucination or delusion)", "Parkinson and anxiety", "Parkinson and (impulse control disorder or dopamine dysregulation syndrome)", "Parkinson and apathy", and "Parkinson and (mild cognitive impairment or dementia or cognition)." The RCT and meta-analysis filters were used to narrow the search. RCTs included in tables 1-4 had study designs that focused on an NPS of interest; had a primary outcome for that NPS; included a control group (blinding not required); had a sample size ≥20 (unless a crossover design); and had a treatment duration (treatment+observation period) ≥4 weeks (unless a stimulation study). The original search identified 315 potential articles and, after applying the criteria above, 100 articles were included for review. The key characteristics, including statistical details, of each study are shown in the tables and a summary and interpretation of the results are given in the main text.

Epidemiology and neurobiology

Depression

The frequency of major depression in PD is 5-20%, with subsyndromal forms of depression occurring in an additional 10-30% of patients.[52] Depression in PD (DPD) remains under-recognized and under-treated,[53] even in PD centers.[54 55] The cause is likely a complex interaction of psychosocial, psychological, and neurobiological factors. Supporting the contribution of neurobiological factors is the finding that depression can occur as a prodromal symptom in some PD patients,[56] at which time, neurodegeneration in dopaminergic, serotonergic, and noradrenergic neurons is already occurring. DPD has been linked with impairments in subcortical nuclei and the prefrontal cortex (PFC), striatal-thalamic-PFC and basotemporal limbic circuits, and brainstem monoamine and indolamine (ie, dopamine, serotonin, and norepinephrine) systems.[57-60]

Anxiety

Up to 40% of PD patients experience anxiety symptoms, including generalized anxiety disorder, panic attacks, and social phobia.[61-63] Clinically, anxiety and depression are highly comorbid; most patients with an anxiety disorder diagnosis also meet criteria for a depressive disorder, and vice versa.[64] Increasing anxiety and anxiety attacks have been associated with non-motor fluctuations (NMFs), particularly with dopaminergic medication wearing off (ie, "off" periods).[61 62] Similar to depression, an increased frequency of anxiety disorders occurs many years before PD motor symptom onset.[56] While the neurobiology of PD anxiety and depression overlap, the amygdala has emerged as the central hub of the fear circuit, and disease related changes in this region may contribute to the early and high rates of anxiety in PD. At the group level, pharmacological management for both depression and anxiety in PD is informed by the underlying monoaminergic deficits (eg, use of selective serotonin reuptake inhibitors).

Psychosis

Psychosis in PD (PPD) can present with misperceptions or illusions, and hallucinations (most commonly visual) and delusions, and occurs with increasing frequency as the disease progresses, particularly in those with cognitive impairment.[65] While PPD is uncommon in untreated PD patients, prospective studies report a long term cumulative prevalence of approximately 60%.[66] PPD is associated with both disease related pathological changes and PD medication use.[67] The underlying mechanisms of PPD may include hypersensitivity

Table 3 | Stimulation therapy RCTs

Active treatment	Treatment description	Sample size	Duration	Primary outcome results summary	Reference or Clinicaltrials.gov ID
Depression					
Published					
rTMS	rTMS *v* sham bilateral M1 (one sham DLPFC), DLPFC (one sham M1), M1 one DLPFC, or double sham; 2000 stimuli for the left DLPFC and 1000 stimuli for each M1	61	10 days	Not efficacious	[41]
rTMS	Bilateral M1 rTMS *v* sham	46	10 days	Efficacious (MADRS improved from a median of 17 points (IQR=12 to 20) to 7 points (IQR=5 to 12), Friedman test, P<0.001; BDI-II score improved from a median of 12 points (IQR 5 to 18) to 6 points (IQR 2 to10), Friedman test, P<0.001)	[42]
Anodal tDCS/sham tDCS+CCT	tDCS *v* placebo; 25 minutes/session during cognitive training in both groups	22	2 weeks daily treatment (5 day/week)	Efficacious (BDI-II: (F(1, 20)=5.46, P=0.030, n^2=0.21, 1-β=0.99). Anodal tDCS plus CCT: post-treatment=-22.6% (SD=7.4), follow-up=-28.5% (SD=5.6); Sham tDCS plus CCT: post-treatment=-4.5% (SD=2.9), follow-up=+16.2% (SD=7.7))	[43]
Ongoing/unpublished					
rTMS	rTMS for 45 minutes; 5 treatment sessions/week, 10 total sessions	252	2 weeks	Ongoing	NCT03552861
Navigated rTMS	Each rTMS session, 1200 pulses of stimuli at an intensity of 100 % RMT over left DLPFC; 20 minutes/session, 10 Hz stimulation trains (active) over left DLPFC	42	2 weeks	Ongoing	NCT04707378
rTMS	rTMS high frequency stimulation (25 Hz), with intensity of 80% of resting motor threshold detected from the hand motor area, total 2000 pulses on the left DLPFC	30	10 days	Unpublished	NCT04030923
tDCS	Active *v* sham tDCS	80	30 minutes over 10 treatment sessions	Ongoing	NCT03074812
tDCS	Active tDCS 2mA, 20 minutes/day, sham tDCS at 1 mA current, for 30 seconds	26	Sham tDCS at 1 mA current, for 30 seconds	Unpublished	NCT03227783
Psychosis					
Published					
Parietal anodal (P4) tDCS, and occipital cathodal (0z) tDCS	Two consecutive 20 minute sessions of active (0.048 mA/cm^2) or placebo tDCS, plus cognitive training separated by a 30 minute break	40 LBD (26 DLB, 14 PDD)	5 consecutive days	Not efficacious	[44]
Cognition					
Published					
rTMS	Bilateral DLPFC 20 Hz rTMS	46	2 weeks	Not efficacious	[45]
Anodal tDCS/sham tDCS+CCT	tDCS *v* placebo; 25 minutes/session during CCT in both groups	22	2 weeks daily treatment (5 days/week)	Not efficacious	[43]
Cognitive training+tDCS	Standard cognitive training, tailored cognitive training, tDCS, standard cognitive training+tDCS, tailored cognitive training+tDCS, or control group; tDCS of the left DLPFC	42	Cognitive training for 45 minutes, three times/week for 4 weeks; tDCS of the left DLPFC for 20 minutes, once/week for 4 weeks	Efficacious (overall improvement on various cognitive measures (executive function, working memory, memory, and language), mostly in groups receiving tDCS (Hedge's g range 0.01 to 1.75))	[46]
rTMS	iTBS over the left DLPFC, twice/day for 3 days with 1-2 days in between	28	3 days	Not efficacious	[47]
CVS	CVS *v* placebo; self-administered CVS, twice/day via pre-programmed TNM™ device	33	24 weeks	Efficacious (MoCA: therapeutic gain=2.2 (95% CI 1.0 to 3.5) at week 12 (P<0.05); therapeutic gain=3.0 (95% CI 1.5 to 4.5) at week 17 (P<0.05))	[220]
rTMS	rTMS (2000 pulses; 20 Hz; 90% RMT) 10 trains of 10 seconds with 25 seconds between each train over hand area of each motor cortex	33	10 days (5 days/week) followed by five booster sessions every month for 3 months	Not efficacious	[48]
iTBS	iTBS *v* sham; 6 sessions over the DLPFC for 1 week	41	1 week	Not efficacious	[49]
iTBS	iTBS *v* sham; applied over left DLPFC	35	10 days	Efficacious (total RBANS and MoCA scores immediately after intervention (P<0.001 for both) and at the 3-month follow-up (P=0.03 and P=0.05))	[50]

(*Continued*)

Table 3 | Continued

Active treatment	Treatment description	Sample size	Duration	Primary outcome results summary	Reference or Clinicaltrials.gov ID
Ongoing/unpublished					
rTMS	Real rTMS, real rTMS+cognitive training, sham; excitatory (>3 Hz) rTMS over the M1 and DLPFC	60	One session/day, for 10 days	Ongoing	NCT03059212
rTMS	rTMS *v* sham, each rTMS session will consist of 40 trains of 5 seconds each at 110% of resting motor threshold and 15 Hz provided at the left DLPFC	166	1 day	Ongoing	NCT03836950
rTMS	Real rTMS+high sensitivity infrared, sham rTMS, *v* high frequency rTMS; excitatory (>3Hz) rTMS over primary motor cortex or dorsolateral prefrontal gyrus; 10 sessions	150	12 weeks	Ongoing	NCT02006615
tDCS	Group 1: tDCS over M1+DLPFC; group 2: tDCS over M1+FPA; group 3: tDCS over M1	60	3 weeks	Ongoing	NCT04090385
tDCS	One session 2 mA tDCS of the primary motor cortex	36	One session	Ongoing	NCT04606979
tDCS	tDCS *v* sham tDCS at 4 mA	48	Duration of treatment not specified	Pending	NCT04762823
tDCS	tDCS *v* sham tDCS; tDCS to left DLPFC at 2 mA	40	20 minutes/day for 5 days	Ongoing	NCT03191916
tDCS	tDCS *v* sham tDCS, over the DLPFC, left anodal/right cathodal tDCS	26	10 sessions, twice/day for 5 days	Ongoing	NCT04171804
tDCS	tDCS on left and/or right DLPFC	36	Duration of treatment not specified	Ongoing	NCT03025334
RS-tDCS	Active *v* sham tDCS; bi-frontal 20 minute RS-tDCS 2 mA, F3-F4 montage, left anodal	31	10 daily, 20 minute sessions	Completed; unpublished	NCT03189472
DBS	DBS low frequency stimulation of the ventral STN *v* standard high frequency stimulation of the dorsal STN	20	Not specified	Ongoing	NCT04650932

BDI-II=Beck depression inventory-second edition; CCT=computerized cognitive training; CVS=caloric vestibular stimulation; DBS=deep brain stimulation; DLB=dementia with Lewy bodies; DLPFC=dorsolateral prefrontal cortex; FPA=frontal pursuit area; IQR=interquartile range; iTBS=intermittent theta-burst stimulation; LBD=Lewy body dementia; MADRS=Montgomery–Åsberg depression rating scale; MoCA=Montreal cognitive assessment; RBANS=repeatable battery for the assessment of neuropsychological status; RMT=resting motor threshold; RS-tDCS=remotely supervised transcranial direct current stimulation; rTMS=repetitive transcranial magnetic stimulation; SD=standard deviation; STN=subthalamic nucleus; tDCS=transcranial direct current stimulation; TNM™=ThermoNeuroModulation.

of mesocorticolimbic D2/D3 receptors, serotonin-dopaminergic imbalance, cholinergic deficits, limbic and pre-frontal neurodegeneration, and connectivity changes involving attentional, thalamic, and visual pathways.[68-77] The hypothesized underlying neurobiological mechanisms of PPD have led to studies of atypical antipsychotics with varying serotonin:dopamine receptor blocking properties and acetylcholinesterase inhibitors.

Impulse control disorders and related behaviors

Impulse control disorders (ICDs) in PD include compulsive gambling, shopping, sexual behaviors, and eating behaviors. Related disorders include dopamine dysregulation syndrome (DDS) (compulsive PD medication use with significant affective dysregulation and altered decision making) and punding (repetitive, non-goal directed activity). In the largest study to date, an ICD was identified in 14% of PD patients, and 29% of those with an ICD had more than one.[78] Recent national multi-site studies reported longitudinal cross-sectional prevalence rates of 25-30%[79] and a cumulative incidence rate of 46%.[80] Demographic correlates include male sex, younger age at PD onset, and longer PD duration.[81] Dopamine agonist (DA) treatment is the strongest ICD predictor[78 80]; higher dose levodopa,[78] amantadine,[82] and selective MAO-B inhibitors[83] have also been associated with ICD to a lesser extent. DDS is most associated with higher levodopa doses.[84] Onset of ICD symptoms may not occur until years after initiation of DA treatment.[85] Neurobiologically, both ICD and DDS are associated with sensitized dopamine receptors (D_2/D_3) in the midbrain[86 87] and extrastriatally (ie, anterior cingulate cortex),[88] and also decreased striatal dopamine transporter (DAT) availability.[89]

Apathy

Apathy occurs in approximately 40% of PD patients[90] and can be particularly challenging for care partners. It overlaps with both depression and cognitive impairment; studies have reported associations with executive and verbal memory impairments, and bradyphrenia.[91 92] Apathy in PD is associated with decreased cingulate and inferior frontal gyri volumes on imaging[93] and possibly multiple neurotransmitter deficits (ie, dopamine loss in mesolimbic and mesocortical circuits, and in serotonergic, noradrenergic, and cholinergic pathways).[94]

Cognitive impairment

Up to one third of PD patients will meet criteria for MCI at the time of diagnosis[95] and several longitudinal studies have shown that most patients will eventually progress to PD with dementia (PDD),[96] which is a much feared outcome. Initial impairments can occur in a range of cognitive domains, including

Table 4 | Other non-pharmacological treatment RCTs

Active treatment	Treatment description	Sample size	Duration	Primary outcome results summary	Reference or Clinicaltrials.gov ID
Depression					
Published					
Resistance training	Resistance training *v* no resistance training; 2 days/week, 30-40 minute sessions, under supervision of exercise specialist	33	20 weeks	Efficacious (HAM-D, Cohen's effect size*=-0.48)	51
Mindfulness yoga sessions	Mindfulness yoga 90 minutes, weekly+goal of 20 minutes home-based practice twice/week *v* SRTE 60 minutes, weekly+goal of 20 minutes home-based practice twice/week	138	8 weeks	Efficacious (HADS depressive symptoms (T1: β=-2.75 (95% CI −3.17 to −1.35), P<0.001; T2: β=-2.75 (95% CI −3.71 to −1.79), P<0.001)	148
Bright light therapy	Bright light (10K lux) *v* control light (200 lux), for 30 minutes, twice/day	83	3 months	Not efficacious	146
Anxiety					
Published					
Virtual reality training	Virtual reality training with BTS-Nirvana system *v* traditional cognitive training, 24 total sessions, 60 minute sessions, 3 times/week	20	8 weeks	Not efficacious	150
Mindfulness yoga	Mindfulness yoga 90 minutes, weekly; also with goal of 20 minutes home based practice twice/week *v* SRTE 60 minutes, weekly; also with goal of 20 minutes home-based practice twice/week	138	8 weeks	Efficacious (HADS anxiety symptoms (T1: β=−1.79 (95% CI −2.85 to −0.69), P=0.001; T2: β=-2.05 (95% CI −3.02 to −1.08); P<0.001)	148
SAFEx	SAFEx (internal focus of attention) *v* sham exercise (external focus of attention); 33 1 hour sessions; no exercise control	35	11 weeks	Efficacious (PAS total score: effect size†=0.17; PAS episodic score: effect size†=0.20)	151
Cognition					
Published					
Aerobic+SAFEx	Two treatments: (1) aerobic with recumbent ergometer and (2) goal based PD SAFEx (without eyes closed) walking, stretching, resistance training. Both 1 hour sessions, 3 times/week, and usual activities	76	12 weeks	Efficacious Aerobic exercise (Stroop Color-Word, P=0.04 (change in aerobic *v* goal based groups)) Not efficacious Goal based exercise	152
Virtual reality training	Virtual reality training with BTS-Nirvana system *v* traditional cognitive training, 24 total sessions, 60 minute sessions, 3 times/week	20	8 weeks	Efficacious Virtual reality resulted in greater improvement in executive and visuospatial abilities (MMSE (P=0.014); WEIGL (P<0.001); ACE-R (P<0.001))	150
Physiotherapy with cognitive training	Physiotherapy with cognitive training (motor-cognitive) *v* physiotherapy alone (motor); 32 sessions, 90 minutes, twice/week	58	4 months	Not efficacious (no added benefit from cognitive training)	153
Walking	Walking at a comfortable pace for 30 minutes/session, 4 times/week plus usual exercise	38	6 weeks	Not efficacious	154
Computerized working memory training	Computerized working memory training *v* wait-list control, 30 minutes/day, 5 days/week	76	5 weeks	Efficacious Verbal working memory (effect size=0.39 (95% CI 0.05 to 0.76))	155
Computerized working memory training	Computerized working memory training *v* active control (free online quiz task), 30 minute sessions, 3 times/week	52	5 weeks	Efficacious Working memory training (1-back effect size‡=0.69 (95% CI 0.11 to 1.27); 2-back effect size‡=0.98 (95% CI 0.39 to 1.58); SUST effect size‡=0.75 (95% CI 0.17-1.33))	156
Strategy training with ReSET Strategic Executive Treatment	Strategy training with ReSET Strategic Executive Treatment *v* computerized repetitive practice training for attention (Cogniplus), 14 1 hour sessions, 1-2 times/week	43	Up to 14 weeks	Not efficacious	157
Mediterranean diet	Mediterranean diet (individualized plan, monthly counseling) *v* health diet recommendation	80	10 weeks	Efficacious (MoCA total score (P<0.001))	158
CCT	Computerized multi-domain CT *v* active control, 45 minutes each, 24 sessions	136	8 weeks	Not efficacious	159
Ongoing/unpublished					
Interactive stepping exercise	Interactive stepping exercise *v* square stepping exercise; both two times/week for 16 sessions	40	8 weeks	Ongoing	NCT04494906
PDAE	PDAE twice weekly classes for first 3 months and then 1 lesson/week for 13 months *v* walking for 60 minutes followed by 30 minutes balance and stretching; both groups (unknown duration)	150	13 months	Ongoing	NCT04122690

(*Continued*)

Table 4 | Continued

Active treatment	Treatment description	Sample size	Duration	Primary outcome results summary	Reference or Clinicaltrials.gov ID
CRT BrainHQ	CRT Brain HQ *v* no intervention; 1 hour session, twice/week	26	10 weeks	Ongoing	NCT04955275
At home cognitive rehabilitation	Cognitive and memory strategy training *v* cognitive and memory strategy control training *v* active control for cognitive and memory strategy training; each group trains for, 30 minute session, 4 sessions/week	45	8 weeks	Ongoing	NCT03836963
COMPEX	CBCR *v* general computer based cognitive stimulation both groups will train 5 times/ week for 60 minutes	100 (PD)	8 weeks	Ongoing	NCT04229056

*Effect size reported as Cohen's d. †Effect size reported as partial n^2. ‡Effect size reported as Hedges' g. ACE-R=Addenbrooke's cognitive examination-revised; CBCR=computer based cognitive rehabilitation; CCT=computerized cognitive training; CT=cognitive training; COMPEX=COMPuter assisted self-training to improve executive function; CRT=cognitive remediation therapy; HADS=hospital anxiety and depression scale; HAM-D=Hamilton depression rating scale; MMSE=mini-mental state examination; MoCA=Montreal cognitive assessment; PAS=Parkinson's anxiety scale; PDAE=partnered dance aerobic exercise; SAFEx= sensory attention focused exercise; SRTE=stretching and resistance training exercise; SUST=selective updating of sentences training; WEIGL=Weigl color-form sorting test.

executive, memory, visuospatial, attentional, and even language abilities.[97-99] Predictors of cognitive impairment include older age and age at disease onset, greater disease severity, postural instability-gait disorder subtype, rapid eye movement sleep behavior disorder (RBD), psychosis, and depression and anxiety.[100] Neuropathological studies show that diffuse Lewy bodies are the major contributing pathology.[101 102] In addition, at least one third of PDD patients have Alzheimer's disease (AD) related neuropathological or neuroimaging changes.[103 104] The APOE ε4 genotype may also be a risk factor for PDD.[100] A range of neurotransmitter deficits in acetylcholinergic,[105] dopaminergic,[106 107] and norepinephrinergic[108 109] pathways are associated with PD cognitive impairment and provide substrates for pharmacological interventions. In addition, research has implicated diffuse gray and white matter neurodegeneration,[110-112] metabolic deficits,[57 113] and electrophysiological changes.[114 115]

Assessment

Significant advancements have been made in the assessment and diagnosis of NPSs in PD. Accomplishments spearheaded by the International Parkinson and Movement Disorder Society (IPMDS) task force and work groups include:

1. Recommendations for the use of depression rating scales in PD[116]
2. Proposed diagnostic criteria for PD psychosis (ie, hallucinations, delusions, and the "minor" phenomena of illusions and sense of presence that manifest themselves after the onset of PD)[117] and recommended psychosis rating scales.[118]
3. Recommendations for the use of ICD rating scales[119] and apathy rating scales in PD.[120]
4. Diagnostic criteria for both PDD (cognitive decline over time, cognitive impairment in multiple domains on testing, and significant cognitive functional impairment)[121] and Parkinson disease mild cognitive impairment (MCI; self-reported cognitive decline, some cognitive impairment on testing, but no significant cognitive functional impairment), including recommended cognitive testing,[122] a review of global cognitive assessment instruments for use in PD,[123] and determination of the relative sensitivity of commonly used cognitive tests in PD patients without dementia.[124]

In parallel work, a National Institutes of Health work group suggested provisional diagnostic criteria for PD depression, which differentiate between loss of pleasure and loss of interest, and also recommends an inclusive scoring approach for symptoms (ie, that does not attempt to determine if a given symptom is related to PD versus depression).[125] In addition, there is now a PD specific, validated anxiety rating scale—the Parkinson Anxiety Scale—which covers persistent anxiety, situational anxiety, and avoidance behavior.[126] Additional recommendations for assessment of NPS in PD can be found in the National Institute of Neurological Disorders and Stroke Common Data Elements (https://www.commondataelements.ninds.nih.gov).

Management

Depression

Psychopharmacology

Several RCTs of antidepressants have been conducted, with a meta-analysis[127] reporting evidence for efficacy and good tolerability of several antidepressant classes, specifically selective serotonin reuptake inhibitors (SSRIs) (standardized mean difference (SMD) −0.49, 95% CI −0.93 to −0.05), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) (SMD-0.83, 95% CI −1.53 to −0.13), with comparable effect sizes across these classes (table 1). The evidence for MAO-B inhibitors is mixed or secondary only.[127] In one study, nortriptyline (a TCA) was efficacious in treating depression, while paroxetine (an SSRI) was not.[10] In a subsequent 12 week study, venlafaxine (an SNRI) and paroxetine both significantly improved depression compared with placebo.[12] All three antidepressants were well tolerated in the aforementioned trials. In contrast, rasagiline (a selective MAO-B inhibitor) was superior to placebo after four weeks but not after 12 weeks.[13] In the largest study to date with more than 300 participants, Beck Depression Inventory (BDI) scores improved significantly more in the

pramipexole group (difference=1.9, 95% CI 0.5 to 3.4, P=0.01).[11] In addition, a recent 4 week trial of 5-hydroxytryptophan (a serotonin precursor) was reported to have a positive effect on depressive symptoms.[15]

Psychotherapy

Cognitive behavioral therapy (CBT) has received the most empirical support to date.[131-133] Multiple pilot studies and three RCTs have supported its efficacy for the treatment of DPD (table 2).[37-39] Two telemedicine RCTs found that a three month course of PD informed CBT (administered either by phone or web based video conferencing) was associated with significant reductions in depression compared with usual care.[38 39] Improvements were maintained for six months post-intervention, with results comparable with face-to-face trials. Meta-analytic findings further underscore the beneficial impact of CBT versus non-CBT control interventions (eg, standardized mean difference=−0.83, 95% CI −1.26 to −0.40[133]; standardized mean difference=−0.74, 95% CI −1.22 to −0.26[131]).

The application of mindfulness based psychotherapeutic approaches for the treatment of DPD is growing, and meta-analyses and systematic reviews suggest that mindfulness based cognitive therapy confers clinical benefit over time[132 133]; however, gains are more heterogeneous in nature and less consistently observed across studies. Smaller studies have provided preliminary support for psychodynamic therapy.[134] Positive psychology interventions that focus on strength, hope, and resilience warrant further exploration in people who are clinically depressed.[135]

Stimulation therapies

The results of studies of rTMS and tDCS for DPD are varied[3] but promising (table 3); a recent meta-analysis showed the overall benefit of rTMS when administered as high frequency to the left dorsolateral prefrontal cortex (DLPFC).[136 137] Of note, rTMS showed significant therapeutic effects on DPD (SMD=0.80, 95% CI 0.31 to 1.29, I^2=89.1%, P<0.001).

Studies of the effects of DBS on depression symptoms have shown conflicting results. A meta-analysis of three RCTs at 36 months' follow-up reported a significant reduction in depression scales scores, which were greater for globus pallidus interna (GPi) compared with subthalamic nucleus (STN) stimulation (weighted mean difference (WMD)=2.53, 95% CI 0.99 to 4.06, P=0.001).[138] It is unclear if the greater average postoperative decrease in PD medications and STN location play a role in reported differential mood outcomes (eg, loss of mood enhancing effects from DA use). Another random-effects meta-analysis of 48 studies including 1821 participants found a small-to-moderate, significant reduction in depressive symptoms after STN DBS (d=-0.31 (95% CI −0.46 to −0.15), Z=3.85, P<0.001).[139] Patients with severe depression and psychiatric symptoms are, however, generally excluded from DBS because they are considered high risk for poor outcomes. Changes in mood must therefore be considered in the context of relatively normal scores, pre-surgery. Suicidal ideation and behaviors post-DBS surgery have been reported,[140] although RCT evidence does not clearly suggest an increased risk.[141] Possible reasons for suicidal ideation or behavior post-DBS surgery include decline in social support and increased loneliness following improvement in motor control,[140] unrealistic expectations of improvement post-surgery, significant reduction in PD medications post-surgery,[142] and specific stimulation site in the case of the STN.[143]

A systematic review and meta-analysis found electroconvulsive therapy (ECT) is effective and well tolerated for pharmacotherapy resistant severe depression (six studies, n=51, SMD=1.33, 95% CI 0.42 to 2.24, P<0.001; heterogeneity: τ^2=1.26, I^2=97.8, Q=30.0, P<0.001) and for psychotic symptoms (five studies, n=50, SMD=1.64, 95% CI 0.90 to 2.38, P<0.001; heterogeneity: τ^2=0.64, I^2=96.6, Q=119.0, P<0.001) in patients with PD.[144] An open label pilot study has also shown the significant benefit of adopting modern ECT practices (right unilateral ultrabrief pulse).[145]

Other non-pharmacological

Non-pharmacological interventions for depression broadly encompass physical activity, exercise, yoga, dance, mindfulness, and bright light therapy (table 4).[146-149] A systematic review and meta-analysis of RCTs, five of which measured depression, did not demonstrate significant differences in favor of dance classes for depression (WMD=−0.39, 95% CI 4.10 to 3.31, P=0.84; Higgins I^2=78%, P=0.004).[149]

Depression has been studied alongside other comorbid NPSs in several studies. A systematic review on the effectiveness of physical activity on PD depression included 17 types of physical activity programs; results revealed variable effects but suggest that aerobic training can improve depression symptoms, as can agility exergaming, stationary cycling, and resistance training.[51 160 161] Meta-analytic findings support a medium effect of resistance exercise on quality of life (SMD=−0.41 (95% CI −0.72 to −0.09), P<0.01).[161] A small RCT found preliminary evidence of the benefit of Qigong exercise for a range of non-motor symptoms.[162] Mindfulness yoga may play a role in managing both depression and anxiety in PD, with one study showing greater improvement in these symptoms compared with stretching and resistance training exercises.[148] In a meta-analysis, dance therapy improved cognition (mean difference=1.50, 95% CI 0.52 to 2.48, P=0.0003, I^2=51%), but not depression, fatigue, or apathy; however, when excluding a small trial from the analysis, there was a suggested positive effect on depression.[163] Bright light therapy in the general population has positive clinical effects on mood and sleep, and underlying effects on the circadian

pacemaker. However, two RCTs of bright light therapy for DPD found no significant effect.[146 164]

Clinical practice

In the section "clinical practice" after each NPS we summarize the findings reported and make general treatment recommendations based on our interpretation of the literature and our clinical experience for each NPS.

Initial treatment of clinically significant depressive symptoms in PD is either with an antidepressant or a course of psychotherapy, and sometimes a combination of the two. First line antidepressants are either an SSRI or SNRI. Caution is indicated in prescribing a serotonergic antidepressant in patients also taking an MAO-B inhibitor because of the possible occurrence of serotonin syndrome, although this syndrome appears uncommon in PD.[165] Additional antidepressant safety concerns pertain to prolonged QTc interval with some agents (eg, citalopram), potential drug-drug interactions involving cytochrome P450 isoenzymes, and the anticholinergic properties of TCAs. For psychotherapy, treatment structure and content need to be flexibly tailored to meet the unique needs of each patient, with careful consideration to factors such as physical disability, cognitive impairment, motor/non-motor fluctuations, pain, learned helplessness, and limited disease awareness. Key targets for psychotherapeutic interventions in PD are varied (eg, social isolation, adaptive coping skills, healthy lifestyle choices, illness related beliefs and themes, pervasive patterns of avoidance and withdrawal, unrealistic expectations related to PD course and management, grief, loss, role transition, and perceptions of danger, self-efficacy, hope, resiliency, control, and empowerment).[6 39 135 166] Outcomes may be further enhanced via the participation of the caregiver in treatment.[167] For severe, treatment refractory depression, ECT remains an option. Studies of other non-pharmacological interventions for DPD are highly heterogeneous and yield varied results, although exercise, mindfulness yoga, and others may be considered as complementary therapies.

Anxiety

Psychopharmacology

Only one RCT for the treatment of anxiety in PD has been published: a small, safety and tolerability study of buspirone (a 5-HT_{1A} partial agonist). Nine of the 12 patients taking buspirone fulfilled responder criteria, although efficacy results were not reported for the four patients in the placebo group. Improvements in anxiety symptoms were offset by poor tolerability,[16] possibly related to its weak D2 receptor antagonism.

Psychotherapy

Extending the findings of smaller scale and uncontrolled investigations, the first RCT specifically targeting anxiety in PD found CBT was significantly superior to clinical monitoring in reducing situational anxiety, avoidance behavior, and social anxiety over nine months.[40] Modified mindfulness based cognitive therapy for the treatment of anxiety is a growing area of research; systematic reviews and small meta-analyses have shown mixed results,[132 133] and well designed RCTs are required to further evaluate benefit. Acceptance and commitment therapy may improve self-efficacy related to coping with NMFs and warrants further research as a primary intervention for anxiety.[168]

Other non-pharmacological

A variety of physical exercises, yoga, and dance have been studied, although not solely or specifically for anxiety.[148 151 162 164 169-172] Nordic walking demonstrated improvement in anxiety, but it was not superior to free walking.[169] Meta-analyses demonstrate the benefits of yoga in improving motor status, balance, functional mobility, anxiety, depression, and quality of life, although only a few studies included anxiety and depression measures.[171 173] Regarding anxiety, meta-analysis of four yoga studies in PD measuring anxiety demonstrated benefit compared with controls (SMD=−0.72, 95% CI −1.01 to −0.43, P<0.001, I^2=17%).[171] Bright light therapy did not significantly improve anxiety compared with a control group in a randomized, double blind, crossover study.[164]

Clinical practice

For anxiety, and to some extent depression, it is important to determine if symptoms are consistently present or are occurring as part of NMFs, as management strategies may differ depending on the clinical context. In general, first line psychopharmacology for anxiety in PD is typically an SSRI, as this medication class is also FDA approved for multiple anxiety disorders in the general population. The high comorbidity between anxiety and depression in PD also supports initial use of an SSRI for anxiety. Anxiety symptoms, including anxiety attacks occurring as part of NMFs, may be best managed with adjustments to the PD medications. As needed or scheduled low dose benzodiazepine (eg, lorazepam or alprazolam) may be used for NMFs or generalized anxiety symptoms, although careful monitoring for worsening cognition, sleepiness, and gait/balance is of utmost importance. Recent evidence suggests that CBT may also be beneficial for PD anxiety.[40] CBT strategies for anxiety occurring in the context of NMFs depend on the clinical state (eg, targeting anticipatory anxiety about and inability to cope with NMFs, use of exercise, and reframing while in the "on" state, and use of relaxation techniques and self-soothing behaviors during the "off" state).

Psychosis

Psychopharmacology

First line management for PPD involves a PD medication review and reducing dopaminergic medication dosages if possible, and excluding delirium, current infections, and other non-PD medication factors (eg, sensitivity to anticholinergic

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medications). Psychotic symptoms in the context of delirium are typically characterized by visual hallucinations and non-systematized delusions, in addition to significant alterations in attention and awareness. Strategies to prevent the development of PPD have not been developed, and a recent prophylactic placebo controlled double blind RCT evaluating donepezil (cholinesterase inhibitor) over a 48 week treatment period failed to reduce the incidence of psychosis.[17]

Symptomatic therapies for PPD have provided little evidence to support the use of mixed serotonin receptor and dopamine receptor blocking atypical antipsychotics (APs), such as olanzapine and risperidone.[20] In contrast, Level 1 efficacy (ie, through placebo controlled, double blind RCTs) has been demonstrated for serotonin receptor focused clozapine[18 19 21] (antagonist at the 5-HT_{2A}, 5-HT_{2C}, and D_4 receptors primarily) and pimavanserin (5-HT_{2A} receptor inverse agonist/antagonist).[24] There are no positive PPD RCTs for quetiapine, in spite of its favorable serotonin:dopamine receptor blocking profile.[22 23] Although clozapine and pimavanserin are both efficacious, safety monitoring is required for clozapine use (routine blood draws to monitor for agranulocytosis) and pimavanserin is currently available for use only in the US.

Both typical and atypical APs, including quetiapine, are associated with increased mortality[174] and morbidity risks in PD, as in AD, although this possible, slightly increased risk needs to be balanced against the risks of non-treatment.[175] Recent retrospective studies have probed the safety of pimavanserin with mixed outcomes. One study found that PD patients taking pimavanserin had an increased risk of 30 day hospitalization and higher mortality from 90 days to one year,[176] although other studies have found no excess death rate and have highlighted the possible confounds of greater disease severity and psychosis itself, both of which are also associated with increased mortality.[177 178]

Stimulation therapies

Well designed, adequately powered RCTs for the treatment of PPD are lacking. The results of an RCT for visual hallucinations in Lewy body dementia (both PDD and dementia with Lewy bodies (DLB)) that explored the efficacy of repeated consecutive sessions (five days) of parietal anodal tDCS and occipital cathodal tDCS, plus cognitive stimulation (attentional and visuoperceptual tasks), were negative.[44]

Clinical practice

Initial management of PPD includes ruling out delirium, infection, or other reasons for PPD, and minimizing anticholinergic and other potentially contributing medications (eg, medications with anticholinergic properties, benzodiazepines, and other central nervous system acting medications). After that, consideration should be given to decreasing the overall doses of PD medications starting with the medication classes that are thought to have the highest risk of inducing psychosis.[179] If a significant decrease in PD medications cannot be undertaken (eg, motor worsening) or is ineffective to reduce the PPD symptoms, an AP may be required. The only US FDA approved treatment is pimavanserin, although some clinicians often initiate quetiapine. Clozapine is typically reserved for treatment refractory patients and requires blood count monitoring. Whether APs increase the risk for mortality and morbidity in PD remains unclear. Caregiver support and education at every step is critical, given the burden that psychosis can place on the family. Although psychotherapy has yet to be studied as a primary intervention for PD related psychosis,[180] clinical experience suggests that applications of CBT techniques, such as stimulus control, caregiver skills training, family psychoeducation, and to a lesser extent cognitive reframing, may prove helpful. These CBT strategies may address modifiable risk factors such as healthy sleep habits, circadian rhythms, inaccurate beliefs about the meaning and cause of PD psychosis and the medications used to treat it, and provide caregiver management approaches (eg, helping the patient to reframe/reality test when insight is retained versus engaging in de-escalation techniques when insight is poor).

Impulse control disorders

Psychopharmacology

The mainstay of treatment for ICDs is a reduction in dose or discontinuation of the contributing dopaminergic medication(s), carefully reducing DAs, and monitoring for development of DA withdrawal syndrome (DAWS).[181] Similarly, the primary treatment for DDS is a decrease in total levodopa dose. While the primary outcome of a placebo controlled double blind RCT assessing naltrexone (an opioid antagonist FDA approved for the treatment of alcohol use disorder) was negative, this study did indicate support for the further evaluation of opioid antagonists given the positive findings using a PD specific ICD rating scale.[26] The results of epidemiological studies suggesting that amantadine (an N-methyl-D-aspartate antagonist that is also prodopaminergic) can trigger ICDs in PD[82] have superseded the suggestion that this may be useful as a treatment for compulsive gambling.[25]

Psychotherapy

Data from one RCT suggest that a three month course of CBT is superior to usual care in reducing the severity of ICD symptoms.[182] Improvement rates (as assessed by the Clinical global impression-improvement scale) were markedly larger in the CBT group (75% *v* 29%, P<0.001).

Stimulation therapies

STN DBS is considered a potential management strategy for ICDs. Findings from large prospective, observational studies have observed ICD remission after STN DBS, associated with DAT medication

reduction.[183-185] However, worsening, no change in, and development of incident ICD behaviors have also been reported in some patients after DBS surgery,[186] and may be more likely in those unable to undergo significant decreases in PD medications post-surgery. Moreover, it is possible that the site of stimulation (eg, dorsal versus ventral STN) may also be of relevance in the ICD course.[187]

Clinical practice

Education and routine monitoring are key when identifying ICD behaviors as soon as they develop. For ICDs that are having a significant impact, the initial management strategy is to decrease, and discontinue if necessary, DA treatment, being mindful that DAWS can occur. If that step is not sufficient, downward adjustments of other PD medications may be needed. Psychosocial support is critical and there is also a role for psychotherapy. Medications such as naltrexone can be used, although the evidence base for any pharmacological agents is very limited. Evidence suggests a beneficial role for DBS on ICDs, with preoperative ICDs usually improving and new onset ICDs uncommon.

Apathy

Psychopharmacology

Very few drug RCTs have taken place for apathy in PD. The IPMDS EBM review[3] concluded that there is some evidence for piribedil (a DA) in apathy occurring post-DBS surgery,[27] and for rivastigmine (an acetylcholinesterase inhibitor (ChEI)) in PD with apathy but without dementia and depression.[28] However, the results of an RCT of rotigotine (a DA) patches in patients with apathy were negative.[29] Subsequently, a crossover trial reported that four weeks of treatment with 5-hydroxytryptophan did not improve apathy.[15] In a 10 week open label randomized study, duloxetine (an SNRI) and paroxetine (an SSRI) improved depression but not apathy scores.[188]

Psychotherapy

Core components of CBT, such as exercise and behavioral activation, have been associated with significant improvements in apathy in a meta-analyses and one small pilot trial.[189 190] It was unclear, however, if noted improvements were secondary to gains in other associated NPS, such as depression and cognition, given the psychiatric complexity of the enrolled samples.

Stimulation therapies

There are no RCTs that have specifically investigated the role of neuromodulation on apathy in PD. Findings from meta-analyses and a scoping review are mixed. Results support both the critical role of post-DBS medication changes in worsening apathy (ie, decreases in dopamine agonist use, or concomitant antidepressant (SSRI) drug use which can improve depression but can also worsen apathy) (eight studies showing small detrimental effects of DBS on apathy, d=0.19, 95% CI 0.02 to 0.36, Z=2.18, P<0.05)[139] and the specific contribution of DBS itself regardless of dopaminergic medication change (33 studies, 1286 patients, overall apathy increased post-DBS compared with pre-DBS (g=0.34, 95% CI 0.19 to 0.48, P<0.001) or DBS compared with best medical therapy (g=0.36, 95% CI 0.03 to 0.65, P<0.004).[191] The poor quality of studies overall, high prevalence of comorbidities, and the lack of a gold standard for diagnosis may have contributed to heterogeneity in the results.[139 190 191]

Other non-pharmacological

Case studies and RCTs with exercise, dance, equine assisted interventions, mindfulness, cognitive training, and behavioral type strategies have been reported. A scoping review and realist review suggest that exercise interventions or mindfulness may be helpful for apathy, particularly in those individuals who do not have significant physical or cognitive impairment.[190 192]

Clinical practice

The treatment of apathy remains a major unmet need for PD patients, with limited evidence for both pharmacological and non-pharmacological approaches. Stimulant and stimulant-like medications, cholinesterase inhibitors, and DAs may have a role in management, and there is interest in exploring the use of mobile devices/apps for external motivation.

Cognitive impairment

Psychopharmacology

A Cochrane review that assessed data from 1236 randomized participants across six clinical trials has supported the general use of ChEIs in patients with PDD, with a positive impact on global assessment, cognitive function, behavioral symptoms, and activities of daily living.[193] However, only rivastigmine has shown significant, albeit modest, objective benefits on cognition in PDD,[34] with subsequent data suggesting similar efficacy for oral and transdermal formulations.[194] Donepezil appeared beneficial in DLB,[195] and showed mixed evidence for cognitive improvement in a large PDD study.[129] Preliminary evidence shows that discontinuation of ChEI treatment in PDD is associated with worse clinical outcomes.[196] Data from RCTs for memantine (an NMDA receptor antagonist that reduces brain glutamatergic neural transmission and glutamate toxicity) have not demonstrated objective cognitive improvements in PDD, and showed mixed results for Clinical Global Impression of Change scores.[35 36 128]

Currently, no medications have been approved for the symptomatic management of PD-MCI, with negative RCTs for rasagiline,[32] atomoxetine (a selective norepinephrine reuptake inhibitor),[33] and rivastigmine (a ChEI).[31]

Increasing evidence from prospective studies looking at newly diagnosed patients[197] and those with prodromal conditions such as idiopathic

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RBD,[198] suggests the existence of a therapeutic disease modifying window where progression to significant cognitive impairment could be halted or delayed. Utilizing a delayed versus early start design, investigators have tested whether administering the donepezil (a ChEI) in cognitively intact PD patients could preserve cognition, potentially by modulating neuroinflammation.[30] However, in this study, no significant differences were observed on the Mini-Mental State Examination scores between the early (120 weeks of treatment) and delayed start (24 weeks of treatment) groups.

Stimulation therapies

Evidence on neuromodulator treatments for PD-MCI or PDD is inconclusive; therefore, they cannot be recommended for clinical use,[199] although they are considered promising tools for cognitive impairment.[200] There are only two RCTs studying the potential benefit of rTMS on cognition in PD. One RCT that enrolled PDD patients assessed the efficacy of high frequency rTMS over each motor cortex and observed significant improvements in global cognition.[48] The other RCT, studying bilateral DLPFC rTMS in patients with PD-MCI, observed no significant cognitive improvement.[45] Three RCTs in PD-MCI investigated the efficacy of intermittent theta burst stimulation (iTBS; a faster and less painful technique than rTMS[201]) over the left DLPFC, and all reported benefits either acutely[50] or long term.[74 75]

Stimulation therapy is sometimes combined with cognitive training. Three tDCS RCTs[43 46 202] reported longlasting efficacy for combination treatments (tDCS over the DLPFC combined with cognitive training) and, in PD-MCI, mainly on frontal lobe based cognitive abilities.[203]

Regarding the impact of clinical DBS on cognitive outcomes, an early meta-analysis including 28 studies (612 patients) found significant, albeit small, declines in executive functions, and verbal learning and memory. Moderate declines were only reported in semantic (Cohen's d=0.73, 95% CI 0.41 to 1.04, effect size variance=0.03) and phonemic verbal fluency (Cohen's d=0.51, 95% CI -0.05 to 1.08, effect size variance=0.08).[204] Since then, two RCTs of DBS versus best medical therapy identified significant declines post-DBS in executive functions and verbal learning and memory.[205 206] This is not surprising given that DBS electrodes course through the PFC and subcortical white matter when implanted. Cortical point of entry during surgery, passage through the caudate nucleus, and stimulation of particular STN subregions may also increase risk of cognitive impairment post-DBS.[207]

Use of model based stimulation parameters to minimize the spread of current to non-motor portions of the STN reversed the cognitive decline that occurred post-DBS in one study,[208] and another study found that connectivity based heatmaps may identify patients at risk of cognitive decline preoperatively and help with DBS reprogramming postoperatively.[209] In addition, a more recent study of DBS in younger patients with shorter disease duration showed better cognitive tolerability.[210]

Other non-pharmacological

Non-pharmacological interventions for cognition in PD include physical exercise and cognitive training.[7 211 212] Meta-analytic review of physical exercise supports its superiority to treatment-as-usual for the cognitive domains of attention and working memory (effect size=0.24, P<0.009), executive functioning (effect size=0.15, P=0.013), memory (effect size=0.12, P=0.038), and psychomotor speed (effect size=0.23, P=0.003).[211] However, in a Cochrane database systematic review no clear evidence suggested that cognitive training improved global cognition (SMD=0.28, 95% CI −0.03 to 0.59; low certainty evidence), executive function (SMD=0.10, 95% CI −0.28 to 0.48; low certainty evidence), visual processing (SMD=0.30, 95% CI −0.21 to 0.81; low certainty evidence), although the evidence favored improvements in attention (SMD=0.36, 95% CI 0.03 to 0.68; low certainty evidence) and verbal memory (SMD=0.37, 95% CI 0.04 to 0.69; low certainty evidence).[212] These interventions have been studied in PD patients with and without cognitive impairment, either as a primary or secondary outcome measure.[152 213] Some studies focus on global cognition, whereas others examine specific cognitive domains (eg, attention and executive functioning). Generalizability of effects to additional cognitive domains, along with their sustainability, represent challenges. The effects of other lifestyle factors, such as nutrition, on cognition have not been studied widely to date.[158]

Exercise protocols vary widely (eg, individual versus group activities, home based versus fitness center, use of motivational techniques, supervision, different maximal heart rate targets, intensity, frequency, and duration). Several RCTs of physical exercise (ie, aerobic exercise) in PD failed to show significant improvement in cognitive outcomes.[154 214-216] In one RCT that included PD participants with cognitive impairment, aerobic exercise significantly improved executive abilities (inhibitory control).[152] Dance may improve global cognition and cognitive dual-tasking, with a meta-analysis indicating benefit on both the MoCA (two RCTs (SMD=0.52, 95% CI −0.00 to 1.04)) and dual-tasking tests (two RCTs (SMD=−0.85, 95% CI −1.5 to −0.21)), although only a few RCTs have been undertaken to date.[217] In a systematic review and meta-analysis of seven RCTs of dance therapy, there were significant differences in favor of dance on executive function (WMD=1.17, 95% CI 0.39 to 1.95, P=0.003; I^2=0%, P=0.45), but not in outcomes of global cognitive function, depression, and apathy.[149]

Cognitive training involves guided practice of different cognitive skills (eg, memory, attention, problem solving, and language). Two RCTs employed computerized working memory interventions in PD patients without cognitive impairment and found improvements in this domain, compared with the

control group.[155 156] Use of virtual reality in cognitive and motor rehabilitation improved global cognition in a small study and may provide interactive, "real-life" environments for therapies.[150] A Cochrane systematic review of cognitive training interventions for PD with cognitive impairment (MCI or dementia) included seven studies comparing cognitive training to a control intervention at 4-8 weeks, targeting either multiple or single cognitive domains.[212] No clear evidence suggested that cognitive training improved global cognition, executive function, or visual processing, although improved attention and verbal memory was suggested in some studies.

Clinical practice

Management of cognitive impairment in PD should begin with a careful review of medications, both PD and non-PD, with a particular focus on limiting or discontinuing medications with significant anticholinergic, sedating, or other central nervous system-acting properties (eg, benzodiazepines and opioid like pain medications). Of note, medications with anticholinergic properties are sometimes used in PD,[218] but are associated with long term cognitive decline[219] and should be avoided in older individuals with PD. Comorbid vascular diseases, other NPSs, obstructive sleep apnea and other sleep disorders,[220] and orthostatic hypotension, all associated with cognitive impairment in PD, should be treated. Cognitive training or fitness activities and exercise should be a mainstay of management. Regarding medication use, evidence suggests that ChEI treatment is effective, but less so for memantine. Neuromodulation as a potential treatment for cognitive impairment in PD is an exciting line of research, and multiple modalities show promise. In addition, physical exercise and cognitive training may have beneficial effects on cognitive functions in PD, although additional studies in cohorts with cognitive impairment are needed for the optimization of training protocols, generalizability, sustainability, and clinical application.

Emerging treatments

Psychiatric

An open label study of agomelatine (an agonist at melatonin (MT) 1 and MT2 receptors and neutral antagonist at serotonin 5-HT_{2C} receptors) showed a reduction in depression scores and improved sleep.[221] In addition, cannabinoids and probiotics are under investigation.[222] Exenatide, a glucagon-like peptide-1 receptor agonist, showed a positive effect on a "mood" item of a non-motor symptoms instrument in an RCT.[223] In addition to CBT, interpersonal psychotherapy is an area of active investigation for DPD (NCT02552836). Finally, one large, multi-site, well designed quadruple arm RCT is investigating the role of rTMS over the right and left DLPFC (comparing active left versus active right versus alternating left and right versus sham rTMS) (NCT03552861).

For anxiety, an RCT of a multi-strain probiotic (NCT03968133) is ongoing. In another recent study of non-motor symptoms in general, responders to open label nabilone (a synthetic analog of tetrahydrocannabinol) treatment had less anxiety worsening during the subsequent RCT.[222] Additional cognitive therapy approaches, such as interpretation bias training, are currently under study (NCT04007718).

Pre-clinical studies show that the trace amine associated receptor 1 (TAAR1; a G-protein coupled receptor) expressed in cortical, limbic, and midbrain monoaminergic regions can modulate dopaminergic, serotonergic, and glutamatergic activity. An RCT examining SEP-363856 (a TAAR1 and 5-HT_{1A} agonist) for the treatment of PD psychosis is currently under way (NCT02969369). A multi-center RCT exploring cannabidiol for PD psychosis is also ongoing (ISRCTN87895237).

An RCT of Sardinian dance therapy significantly improved apathy compared with usual care,[147 224] and an ongoing interventional study of dance with ballet (NCT04719468) includes apathy measures. Further treatment approaches are needed to tackle ICDs in PD, and current studies are evaluating the AP pimavanserin (NCT03947216) and clonidine (repurposed α-2 adrenergic agonist) (NCT03552068).

Cognition

Despite promising preclinical results, SYN120 (a 5-HT_6 and 5-HT_{2A} antagonist) failed to show any benefits in PDD (NCT02258152); similarly, no positive effects were reported for intepirdine (a 5-HT_6 antagonist) in patients with DLB (NCT02669433). The results of a recently published, large RCT of mevidalen (a selective positive allosteric modular (PAM) of the D1 receptor) in patients with Lewy body dementia (LBD; both PDD and DLB) were negative.[130] Recent unpublished work evaluating blarcamesine (an intracellular sigma-1 receptor agonist) improved episodic memory in a phase 2 study in PDD. A small safety study of IRL752 (a small molecule that selectively enhances norepinephrine, dopamine, and acetylcholine neurotransmission in the cerebral cortex) showed promise in a preliminary study.[225] Other ongoing studies investigating novel and repurposed agents for PDD include an RCT of CST-103 (a β-adrenoreceptor agonist administered with CST-107) targeting the locus coeruleus to improve noradrenergic tone (NCT04739423). Trials are ongoing to evaluate ambroxol (a repurposed expectorant that increases levels of the lysosomal enzyme glucocerebrosidase and reduces α-synuclein aggregation) to slow cognitive decline in PD dementia (NCT02914366) and LBD (NCT04405596).

Beyond symptomatic improvement, cognitive restoration or disease modification is also a goal. For example, it has been suggested that by inhibiting the α isoform of p38 mitogen activated protein kinase to reduce neuroinflammation and normalizing endosomal dysfunction through inhibition of rababptin (rab5; a small endosomal GTPase), the novel agent neflamapimod may not only slow disease progression but also rescue impaired

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synaptic function.[226] A recent 16 week RCT of this medication in patients with DLB, a synucleinopathy with similar clinical and pathophysiological features to PDD, reported improvements on a composite neuropsychological test battery score focused on executive function and attention (NCT04001517). Other ongoing trials with the goal of disease modification include the reduction of glutamatergic hyperactivity and excitotoxicity using the repurposed antibiotic ceftriaxone (NCT03413384) and the administration of a proprietary plasma fraction (GRF6021) that may enhance neurogenesis and reduce neuroinflammation (NCT03713957). Two NMDA receptor PAMs (SAGE-718 (NCT04476017) and NYX-458 (NCT04148391)) and E2027 (increases levels of cyclic guanosine monophosphate (NCT04764669)) are being studied for their cognitive effects. Given the overlap between AD and PD related neuropathological changes in PDD, any amyloid and tau modifying therapies found to be efficacious in AD would also warrant testing in PD.

Ongoing large RCTs are investigating the effect of rTMS over the DLPFC on executive abilities (NCT03836950 and NCT02006615), and the effect of tDCS on cognition in PD-MCI (NCT03191916 and NCT04171804) and PD without dementia (NCT03025334, NCT04090385, NCT04606979, and NCT04762823). An ongoing three-arm RCT (NCT03059212) is investigating the efficacy of combined treatment (rTMS combined with cognitive training) versus rTMS alone in facilitating working memory. Other ongoing studies are evaluating the feasibility of tele-monitored tDCS (NCT03189472) and transcutaneous auricular vagus nerve stimulation (NCT04157621).[227] Ongoing small RCTs using DBS as a neuromodulation tool for cognitive outcomes in PD patients without a defined cognitive disorder are investigating the impact of unilateral GPi versus unilateral STN DBS (NCT04255719) and theta versus gamma frequency STN DBS on verbal fluency function (NCT04383665). GPi DBS plus active versus sham nucleus basalis of Meynert DBS is being investigated specifically for PD-MCI (NCT04571112). Caloric vestibular stimulation delivered with an at-home solid state thermoneuromodulation device was associated with improved global cognition and overall non-motor symptoms compared with placebo treatment.[228] Ongoing studies are investigating interactive stepping exercises (NCT04494906), partnered dance aerobic exercise (adapted tango) (NCT04122690), and at-home computerized cognitive training programs (NCT04955275 and NCT03836963).

In addition, physical exercise interventions for cognition in PD encompass aerobic exercise, but also include resistance training, Tai Chi, dance, physical activity, and physical therapy with or without cognitive training.[152-154 170 214-216 229] Finally, although a recent Cochrane review suggested little benefit from combining memantine with ChEIs,[230] these data included mainly AD patients and there are plans to specifically evaluate this approach in PDD (NIHR129175).

Guidelines

Very few professional society guidelines exist for the management of psychiatric and cognitive disorders of PD, so it is not possible to compare them. The most recent are referenced.[3 4 193 212 230]

Conclusions

Prospective, longitudinal studies have shown that the cumulative prevalence of most NPS are far higher than earlier cross sectional studies had suggested, with many disorders having a cumulative frequency over 50%, and dementia likely affecting 80% of PD patients in the long term. NPSs are of high clinical significance, as they are associated overall with increased disability, worsened quality of life, poorer outcomes, and greater caregiver burden. There have been significant advances in the assessment (eg, questionnaires and rating scales) and diagnosis (ie, consensus diagnostic criteria) of disorders, which has led to more effective research and improved clinical management. Mounting evidence finds that the neural substrates of NPSs in PD are complex, involving a mixture of strategically placed PD and other neurodegenerative disease pathologies, dysfunction in multiple neurotransmitter systems, impairments in neural circuitry subserving mental functioning, and genetic influences. Interestingly, core PD treatments, in particular dopamine replacement therapy and DBS, have a complex and varied effect on NPS. The biggest unmet need is the availability of efficacious treatments; therefore, future research efforts need to focus on the development and testing of novel treatments, with the goal of improving the lives of PD patients and their care partners.

QUESTIONS FOR FUTURE RESEARCH

- How can research better address the clinical and neurobiological overlap of NPSs in PD (eg, examining interactions, identifying subtypes or profiles, and determining optimal assessments for them in treatment studies)?
- How can we improve our understanding of the neural substrates of NPSs, with an eye toward developing new treatments, through examination of neuropathology, disease specific biomarkers, neurotransmitters, brain structure, neural circuitry, and genetics?
- What measures can be taken to reach consensus on the optimal diagnostic criteria, screening questionnaires, rating scales, and cognitive tests to be applied in clinical research studies focused on NPSs in PD?
- Is it feasible to increase the number of large scale RCTs for NPSs to determine the efficacy of different interventions, including the use of disease modifying agents, when available?
- How can we increase the pool of and access to mental health providers with expertise in PD to improve the recognition and management of NPS in routine clinical care?

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The authors worked in collaboration with several people diagnosed with PD. The patients were asked to share in their words their specific experiences with the various NPSs of PD. All patients who participated signed a consent form before participation.

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