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# Management of Impulse Control and Related Disorders in Parkinson's Disease: An Expert Consensus

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Please see Members of the ICBD in PD Management Consensus Group in Appendix A.

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**ABSTRACT: Background:** Impulse-control and related behavioral disorders (ICBDs) significantly impact the lives of Parkinson's disease (PD) patients and caregivers, with lasting consequences if undiagnosed and untreated. While ICBD pathophysiology and risk factors are well-studied, a standardized severity definition and treatment evidence remain elusive.
**Objective:** This work aimed to establish international expert consensus on ICBD treatment strategies. To comprehensively address diverse treatment availabilities, experts from various continents were included.
**Methods:** From 2021 to 2023, global movement disorders specialists engaged in a Delphi process. A core expert group initiated surveys, involving a larger panel in three iterations, leading to refined severity definitions and treatment pathways.
**Results:** Experts achieved consensus on defining ICBD severity, emphasizing regular PD patient screenings for early detection. General treatment recommendations focused on continuous monitoring, collaboration with significant others, and seeking specialist advice for legal or financial challenges. For mild to severe ICBDs, gradual reduction in dopamine agonists was endorsed, followed by reductions in other PD medications. Second-line treatment strategies included diverse approaches like reversing the last medication change, cognitive behavior therapy, subthalamic nucleus deep brain stimulation, and specific medications like quetiapine, clozapine, and antidepressants. The panel reached consensus on distinct treatment pathways for punding and dopamine dysregulation syndrome, formulating therapy recommendations. Comprehensive discussions addressed management strategies for the exacerbation of either motor or non-motor symptoms following the proposed treatments.
**Conclusion:** The consensus offers in-depth insights into ICBD management, presenting clear severity criteria and expert consensus treatment recommendations. The study highlights the critical need for further research to enhance ICBD management. © 2024 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

**Key Words:** Parkinson's disease; deep brain stimulation; impulse-control and related behavioral disorders

## Introduction

Impulse-control and related behavioral disorders (ICBDs) occur in up to 20% of Parkinson's disease (PD) population at some point across the disease course and include pathological gambling, compulsive sexual behavior, binge eating, compulsive shopping, compulsive hobbyism, punding, and overuse of dopaminergic medication (also known as dopamine dysregulation syndrome [DDS]).[1-4] The prevalence of ICBDs is even higher when subsyndromal ICBDs are considered,[1] and it is common for PD patients to suffer from multiple ICBDs at the same time.[5] ICBDs also affect healthy controls and drug-naive PD patients, but PD patients under dopaminergic treatment are more likely to develop ICBDs.[6,7] In particular, if unrecognized and untreated, ICBDs can have a devastating impact on the life of patients and caregivers.[8] Dopamine agonists (DA) that preferentially bind to the D3 receptors in the mesolimbic pathways are the main risk factor for the development of ICBDs, although ICBDs can also occur in patients who are treated with high doses of levodopa (L-dopa) or apomorphine.[9-11] This is in line with studies from the field of addiction, which show that most drugs with addictive properties bind to the D3 receptors in the mesolimbic pathway.[12-14] One longitudinal study showed that 52% of DA ever users developed ICBDs within 5 years compared to 12% of DA never users.[15] The more severe the dopaminergic sensitization and the dopaminergic denervation, the more likely a patient is to develop ICBDs.[10,16-18] Additional risk factors for ICBDs in PD include younger age at disease onset, longer disease duration, motor fluctuations, male gender, apathy, depression, cognitive impairment, personal history of smoking, personal or family history of gambling and alcoholism, mutations in β-glucocerebrosidase (GBA), parkin genes, other poorly to date-defined genetic risk factors, and personality traits such as novelty obsessionality, novelty seeking, and impulsivity.[1,8,19-24]

DDS and punding exhibit distinct clinical and pathophysiological characteristics when compared to the other ICBDs.[11,25-27] Punding is defined as stereotyped



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behavior characterized by excessive nongoal-oriented, repetitive activities such as sorting things, tidying, taking objects apart, or collecting objects.[28,29] Individuals with punding typically consume higher-than-average doses of L-dopa, exhibit more dyskinesia, and are more prone to overuse dopaminergic drugs.[11] In DDS, patients initiate the use of dopaminergic medication beyond the necessity of controlling motor symptoms.[30] Some patients may experience withdrawal symptoms reminiscent of those observed in addiction, exerting pressure on their neurologists to obtain "on-demand" medications and request further increases in their drug regimen, even when motor control remains satisfactory. In rare instances, some individuals may resort to obtaining drugs illegally or obtain multiple prescriptions. However, for many patients the symptoms of DDS may be less severe, and distinguishing overuse of dopaminergic medication from adaptive increase in medication due to insufficient control of L-dopa responsive motor and nonmotor symptoms can be challenging.[31] Additionally, many patients with DDS have other ICBDs at the same time and may overuse their dopaminergic medication to engage in activities related to their ICBDs.

In contrast to the "classical" ICBDs, where the use of DA with high D3-receptor binding affinity is the primary risk factor, DDS and punding are more frequently observed in patients on high doses of L-dopa, which likely results in a pulsatile stimulation of dopaminergic D1 and D2 receptor families. The underlying pathophysiological mechanisms of DDS and punding are most likely a sensitization of the associative-limbic dopaminergic system.[30,32] Furthermore, imaging studies have demonstrated a reduction in prefrontal top-down behavioral control and upregulation of dopaminergic release in the ventral striatum in these conditions.[11,33,34] In particular, rapid-acting rescue doses of L-dopa or subcutaneous injections of the short-acting D1/D2 agonist apomorphine have been associated to DDS and punding.[35] Given these differences, treatment strategies for DDS and punding should be distinct from those for other ICBDs.

In this consensus paper, available studies on the management of ICBDs are reviewed, and management recommendations reached in an international expert consensus are presented.

## Definition of Impulse-Control and Related Disorders

Most of the definitions of ICBDs share the following three aspects[36-38]:

1. A failure to resist the impulse or temptation to perform a certain behavior (impulsivity)
2. Repetitive execution with a lack of self-control (compulsivity)
3. Negative consequences for the individual or his or her environment (functional impact)

Although both ICBDs and compulsive behaviors are defined by an inability to resist certain activities that are performed repeatedly despite negative long-term consequences, their underlying motivations differ. Unlike obsessive-compulsive disorders, ICBDs are typically perceived by individuals for their immediate pleasurable and rewarding qualities, whereas compulsive behaviors are driven by an effort to avoid or reduce anxiety.[36,39] ICBDs are often nonpathological at the outset. Whereas in some patients ICBDs remain mild and do not have harmful consequences (eg, slightly increased activity with hobbyism), others experience gradual worsening of ICBDs with a negative impact on different aspects of life. Typically, as ICBDs become more severe, they may start to get compulsive in character, with the avoidance of anxiety or dysphoria becoming the driving factor rather than the experience of reward or pleasure associated with it (ie, needing vs. wanting).[38,40-43] This is in line with other research on substance abuse, which shows that as the addiction becomes more severe, craving rather than pleasure becomes the driving factor for consumption.[42,43] Therefore, behavioral changes have to be understood as a continuum ranging from normal behavior to pathological impulsive-compulsive behavior, with the evolution of one to the other occurring gradually over weeks or months.[44] Moreover, ICBDs are culture dependent and should always be evaluated in the respective cultural context.[45] A trivial increase in pleasurable behaviors in an individual PD patient on dopaminergic treatment may be interpreted as a shift toward hyperdopaminergic behaviors foreshadowing ICBDs and thus deserves the attention of the prescribing physician.[46] Thus far, there is no severity definition reflecting this spectrum, which complicates the treatment process and research on the respective interventions. One aim of this expert consensus was therefore to define severity grades of ICBDs.

## Diagnosis of Impulse-Control and Related Disorders

The *Diagnostic and Statistical Manual for Psychiatric Disorders* (*DSM-5-TR*)[47] lists ICBDs under the chapter "Disruptive, Impulse-Control, and Conduct Disorders." However, pathological gambling is listed in the chapter "Substance-Related and Addictive Disorders," and compulsive eating is listed in the chapter "Feeding and Eating Disorders" under binge eating. The most frequently observed ICBDs in PD are thus not classified under the same umbrella in the *DSM-5-TR*, and several ICBDs lack specific mention (eg, compulsive buying and sexual behavior), making clinical diagnosis difficult. In general, ICBDs are assessed in clinical practice with interview questions. Additionally, different questionnaires have been developed and used to screen for ICBDs in



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clinical practice. For a comprehensive assessment of ICBDs in PD, in their latest commissioned review of 2019 the International Parkinson and Movement Disorder Society recommends the use of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, and the Ardouin Scale of Behavior in Parkinson's Disease.[48-51] In line with the *DSM-5-TR*, all the recommended questionnaires for ICBDs in PD require a minimum symptom duration of 4 weeks. Less common or underrecognized impulse-control disorders such as kleptomania,[52] excessive partaking in religious practices,[45] aimless walking about, excessive computer or smartphone use, and reckless generosity[53] are not included in all the questionnaires highlighting the relevance of careful inquisitiveness regarding behavioral changes in history taking. The assessment of ICBDs is further complicated by the fact that patients may sometimes feel embarrassed and, as a result, intentionally conceal these behaviors. Additionally, they may lack awareness of the problematic behavior. In some cases, their significant others are more likely to report these behaviors than the patients themselves.[54]

Therefore, screening should not be limited to questionnaires; it should also include a clinical interview that involves the patients and, if possible, their significant others.

## Management of Impulse-Control and Related Disorders

### *General Treatment Recommendations*

Research on management strategies for ICBDs in the context of PD is largely lacking. In the 2017 National Institute for Health and Care Excellence (NICE) guidelines,[55] only four studies met the criteria (ie, prospective trial with control group) to be included in the review.[56-59] The official recommendations in the 2017 NICE guidelines[55] for the management of ICBDs are to (1) seek advice from a health-care professional with specialist expertise in PD, (2) discuss the impact of ICBDs on the patient's life with the patient and his or her family members or care partners, (3) modify dopaminergic therapy by first gradually reducing any DA while monitoring for dopamine agonist withdrawal syndrome (DAWS), and (4) to offer specialist cognitive behavior therapy (CBT) targeted at ICBDs if modifying dopaminergic treatment is not effective.

In the most recent evidence-based medicine review for treatments of nonmotor symptoms in PD of the International Movement Disorders Society, only three studies[57-59] met the criteria to be mentioned. Only CBT was recommended as possibly useful in clinical practice.[60]

### *Management of Dopamine Reduction*

The management of ICBDs is further complicated by the fact that approximately 19% of patients[61] experience DAWS, which is defined as the occurrence or significant worsening of one or more nonmotor symptoms such as anxiety, panic attacks, depression, agitation, irritability, drug craving, insomnia, daytime fatigue, diaphoresis, nausea, vomiting, flushing, orthostasis, and generalized pain on discontinuation or tapering of DA.[62-65] Based on available studies, DAWS can occur at any time of the tapering process and even during slow tapering.[66,67] In some patients it may last only a few days, whereas in others it can be a persisting complication that negatively impacts the quality of life. The main risk factors for DAWS are the presence of ICBDs and higher doses of DA.[65-67] In most patients, DAWS improved on a reintroduction of small doses of DA.[62,66,67] Other management strategies for DAWS such as antidepressants, anxiolytics, opiates, antiepileptic drugs, and CBT have not shown any promising results so far,[67] but research is largely lacking.

Although DAWS typically develops within days, there can also be more long-term behavioral effects as a result of tapering dopaminergic medication. For instance, a gradual development of apathy after withdrawal of dopaminergic medication in the context of subthalamic nucleus deep brain stimulation (STN-DBS) has been well documented.[68] In the context of STN-DBS, a reintroduction of low-dose DA might be a helpful strategy to avoid apathy, but in some patients this might not always be possible due to the severity of ICBDs.

When employing different management strategies, it is therefore important to consider the possibility of DAWS or long-term apathy in mind and to closely monitor the patient.

### *Specific Treatments for Impulse-Control and Related Behavioral Disorders*

Involvement of significant others and psychosocial interventions. In line with the NICE guidelines, one study that observed the long-term outcomes of DDS identified the presence of involved caregivers as the most important positive predictor for remission.[3] Other studies on psychosocial and caregiver interventions (eg, blocking credit cards, restricting access to casinos, medication management by a significant other, or mobile nursing services) are unfortunately lacking but are often recommended in clinical practice.

Reduction in DAs. Several prospective studies have confirmed that DA use is the main risk factor for the development of ICBDs,[15,69] but only one controlled prospective study[56] provided evidence that reduction or discontinuation of DA improves ICBDs. Since then, it



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has become common clinical practice among neurologists to reduce or discontinue DA in ICBDs.

CBT. Okai et al showed in a randomized-controlled study that CBT adapted for ICBDs considerably reduces them.[57]

Other adjunctive medication. As for adjunct medication, only naltrexone and amantadine have been studied in randomized-controlled trials (RCT).[58] Papay et al provided mixed evidence that naltrexone decreases ICBDs, but naltrexone is not recommended in the NICE guidelines because this is the only RCT conducted so far and because of frequent adverse effects reported in the study that included nausea, dizziness, and changes in blood pressure.[58]

Thomas et al provided evidence that amantadine improves ICBDs in an RCT.[59] On the contrary, higher doses of amantadine correlated with more severe ICBDs in a large epidemiological study,[70] suggesting that amantadine could actually be a driving factor for ICBDs. A case report described the onset of multiple simultaneous ICBDs within 3 months of introducing amantadine for dyskinesia, and resolution of ICBDs 1 month after stopping amantadine, supporting a causal link between ICBD and amantadine in this patient.[71] The authors emphasized that insufficient evidence exists to support the use of amantadine as a treatment for ICBDs, and patients with a history of ICBDs should be cautioned about the use of the drug.

A few case reports have shown improvements in ICBDs under clozapine and quetiapine.[72-77]

Selective serotonin reuptake inhibitors (SSRI) have shown some efficacy in treating ICBDs in non-PD patients with compulsive gambling[78] and trichotillomania, but no trials have been conducted to assess the effectiveness of antidepressants in ICBDs in the context of PD. However, some recent studies point out that ICBDs are more prevalent in patients who take SSRIs, but further research controlling for confounding variables is needed to investigate if this is a correlative or a causal association.[79]

Switching from short-acting to long-acting DAs. To date, no studies have specifically evaluated the switch from short-acting to long-acting DAs as a treatment strategy for ICBDs. However, this could be a possible management strategy because observational studies report a lower incidence of ICBDs in patients treated with long-acting DA compared to short-acting DA.[80-82]

DBS. Several prospective studies showed a reduction in ICBDs after bilateral STN-DBS.[5,83,84] However, some studies, including not only STN-DBS patients but also patients with unilateral STN-DBS and DBS of the globus pallidus internus (GPi), showed worsening of ICBDs in some patients (eg, Lim et al[92]) or overall-stable ICBDs.[85] In this context, it is important to mention that a decrease in dopaminergic medication, which might be the main driving factor for a decrease in ICBDs after bilateral STN-DBS, is less pronounced in patients with unilateral STN-DBS or GPi-DBS. Another factor influencing the results of these studies is the baseline occurrence of ICBDs (eg, low incidence of ICBDs at baseline leading to less overall improvement). Regarding a direct effect of DBS on ICBDs, a few studies have demonstrated that a stimulation of the ventral parts of the STN can lead to (hypo-)manic symptoms and that steering of the stimulation toward more dorsal contacts can resolve postoperative (hypo-)mania.[86,87]

To resolve the controversy if ICBDs improve after DBS, prospective long-term follow-up studies have been conducted and confirmed a reduction in ICBDs several years after DBS for bilateral STN-DBS.[88,89] Finally, one randomized-controlled study[90] showed that both neuropsychiatric fluctuations and overall hyperappetitive behavior, measured using the Ardouin Scale of Behavior, decreased significantly after STN-DBS in the context of postoperative reduction in dopaminergic medication. However, no significant effects were observed for individual ICBDs, which might be explained by the fact that ICBDs were not the primary end point and that occurrence of baseline ICBDs was low compared to other DBS populations.[91]

In conclusion, the majority of studies conducted so far confirm that ICBDs tend to decrease after bilateral STN-DBS. In studies including patients with unilateral STN-DBS and GPi-DBS, the results are less clear,[85,92] but overall worsening of ICBDs is not common. However, further high-quality evidence is needed to confirm if ICBDs improve after DBS and to identify what role the postoperative reduction in medication and stimulation itself plays.

Pump therapies. A few prospective studies have focused on ICBDs under continuous apomorphine infusion pumps, indicating that in most patients ICBDs remain stable or improve; however, in a few patients they might worsen or occur for the first time.[19,93,94] In contrast, a special case relates to self-administered rescue injections of apomorphine, which are linked to DDS.[35]

Two prospective studies[94,95] showed an overall reduction in ICBDs after the initiation of levodopa–carbidopa intestinal gel. Interestingly, the improvement in ICBDs could not be explained by a reduction in DA, making it likely that the cause of the reduction in ICBDs was the replacement of pulsatile dopaminergic stimulation by continuous administration, leading to more stable blood plasma levels of L-dopa and synaptic dopamine levels in the brain compared to oral dopaminergic medication.

### Management of DDS

For DDS, no tailored management strategies have been studied yet. However, one retrospective case–control study reported that positive long-term outcomes



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of DDS were linked to effective caregiving and that sustained remission occurred more commonly on clozapine, duodenal L-dopa infusion, and STN-DBS.[3] A further possible strategy, which has been used by clinicians for decades to manage motor complications,[96] is to fractionate L-dopa. Fractionating L-dopa is a strategy in which lower individual dosages of L-dopa are used, but the frequency of intake is increased, with the aim of preventing both dyskinesia (with lower doses) and wearing-off of medication (with more frequent intake of the medication).[97] Thus far, there is no clinical evidence supporting this, but the possible underlying pathophysiological mechanisms and clinical correlation between dyskinesia and DDS[98] make this a promising strategy.

#### *Management of Punding*

Fasano et al showed an improvement in punding following a multistep management strategy, including stopping bedtime L-dopa and rescue L-dopa doses, followed by a reduction in L-dopa and/or DAs, introduction of catechol-O-methyltransferase (COMT)-inhibitors or other DAs in case of worsening of the motor condition, introduction of amantadine, and introduction of quetiapine or clozapine.[99] Other than this study, there is a lack of research regarding the management of punding, which often occurs in the absence of DA. As the pathophysiologies of DDS and punding are similar,[28] fractionation L-dopa might also be a possible treatment strategy here.

In summary, even though ICBDs occur frequently in the context of PD, there is still a lack of severity definition and specific treatment recommendations for ICBDs in this patient population. The aim of this work was therefore to establish an international expert consensus regarding treatment strategies for ICBDs. To take account of the varying availability of different treatments, we chose to include experts across continents.

## Patients and Methods

### Delphi Process

Movement disorders specialists with expertise in the field of ICBDs from 21 countries around the globe were involved in the project. The project was conducted from 2021 through 2023. The initial survey was drafted by a board of five movement disorders specialists (core expert group comprising manuscript authors I.D., S.P., D.A., P.K., and G.D.) after reviewing the current literature. After this, a meeting with a larger panel of 12 movement disorders specialists (large expert group further including authors F.C., J.-C.C., V.S.C.F., A.E.L., P.M.M., M.C.R.-O., and D.W.) was held to discuss the survey and get further input. The first expert panel online survey[100] was then sent to 53 panelists. In the subsequent surveys, only the 30 experts who replied in the first survey were readdressed. In the first survey, the goal was to obtain insight into how experts usually treat ICBDs. They answered different sociodemographic questions and questions regarding the use of different approaches depending on the severity of ICBDs. After this meeting, results were discussed in the core expert group, and a severity definition and treatment pathways were drafted. These were then discussed with the larger expert group, and consensus was obtained for each of the definitions and pathways. The severity definition and pathways were then modified further, and a second survey was sent to all panelists, with specific questions (*yes/no*) if they agreed to each of the proposed steps. Final issues were addressed, and on agreement with the larger expert group, a third survey was sent to all panelists to obtain a final consensus on all treatment pathways and specific recommendation strengths. The most important milestones are listed below (see supplementary material and Fig. S1 for a more detailed report).

## Results

Overall, 30 (73%) of the contacted specialists replied in the first survey, 25 in the second survey, and 26 in the last survey. The following countries were represented: Ghana, Nigeria, Egypt, Japan, Korea, France, Ireland, Italy, the Netherlands, Spain, Mexico, the United States, Australia, Argentina, Canada, Brazil, Germany, and Switzerland. Of the panelists (29% female), 87% were neurologists, 10% psychiatrists, and 3% psychologists, with 94% of the panelists having more than 10 years of experience in treating ICBDs in the context of PD. The panelists confirmed treating patients with ICBDs on a regular basis.

At the end of the third survey, a strong consensus was reached for the severity definitions and treatment pathways as follows.

### Severity Definition

The following definition (which applies to ICBDs, including DDS and punding) was determined within the expert panel based on the Movement Disorder Society-Unified Parkinson's Disease Rating Scale, as shown in Figure 1. Additional explanation and information on severity rating, as well as clinical examples, can be found in the Supplementary Material.

### General Treatment Recommendations

After establishing a definition of the severity of ICBDs, the different treatment options for ICBDs were discussed together with the large expert group in a meeting. In the second survey, 92% of the panelists agreed on the general management strategies (Fig. 2) that should always be followed regardless of the severity of the ICBDs.



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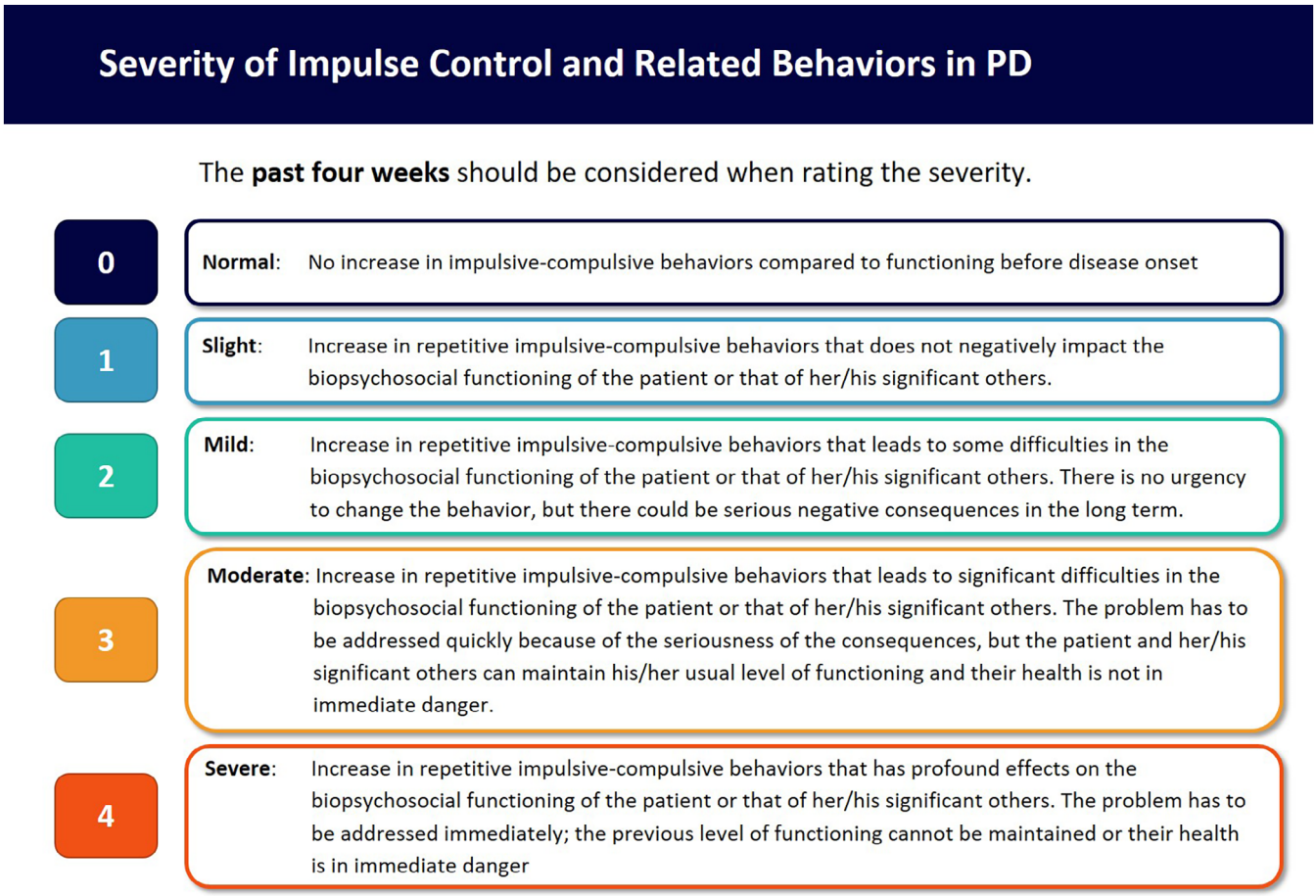


**Fig. 1.** Severity definition of ICBDs (impulse-control and related behavioral disorders) established by the expert panel. [Color figure can be viewed at wileyonlinelibrary.com]

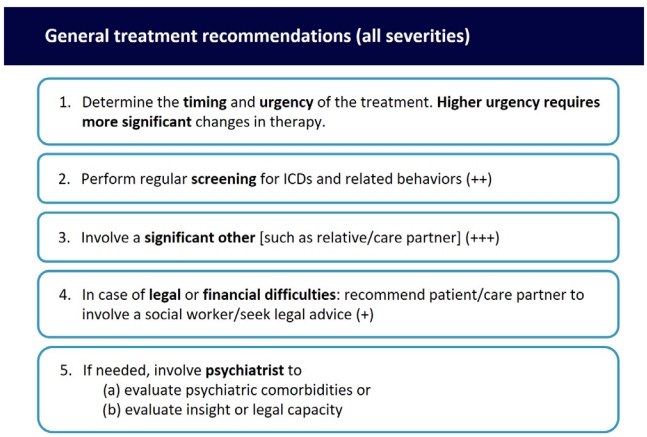


**Fig. 2.** General treatment recommendations of ICBDs (impulse-control and related behavioral disorders) established by the expert panel. Strength of recommendation based on expert opinion: +++, >90% experts; ++, between 75% and 90% of experts; +, 50% to 75% experts. [Color figure can be viewed at wileyonlinelibrary.com]

Based on the therapeutic strategies discussed in the current literature, the panelists were asked about the availability and use of different therapeutic strategies for ICBDs and to rank them according to the order they would use them in clinical practice (Fig. S2). Availability of all treatments ranged from 58% (apomorphine pump) to 100% (tapering of DA), with the majority of treatments being available for over 90% of the experts.

The most commonly used treatment strategy was tapering down of DA (used by 92% of experts in the third survey), followed by the reduction in total levodopa equivalent daily dose acting on L-dopa and/or Monoamine oxidase-B (MAO-B) inhibitors and/or COMT inhibitors (used by 89% of experts in the third survey). Treatments used by 50% to 75% of experts in the third survey were STN-DBS (73%), CBT (73%), reversal of last medication change before the onset of ICBDs (69%), quetiapine (69%), clozapine (69%), and antidepressant medications (especially SSRIs) (62%).

A total of 92% of the panelists agreed that only management strategies recommended by over 50% of the panelists should used in the treatment pathways and that strength of recommendation would be as follows: +++, more than 90% of experts would consider treatment option if available; ++, more than 75% to 90% of experts would consider treatment option if available; and +, 50% to 75% of experts would consider treatment



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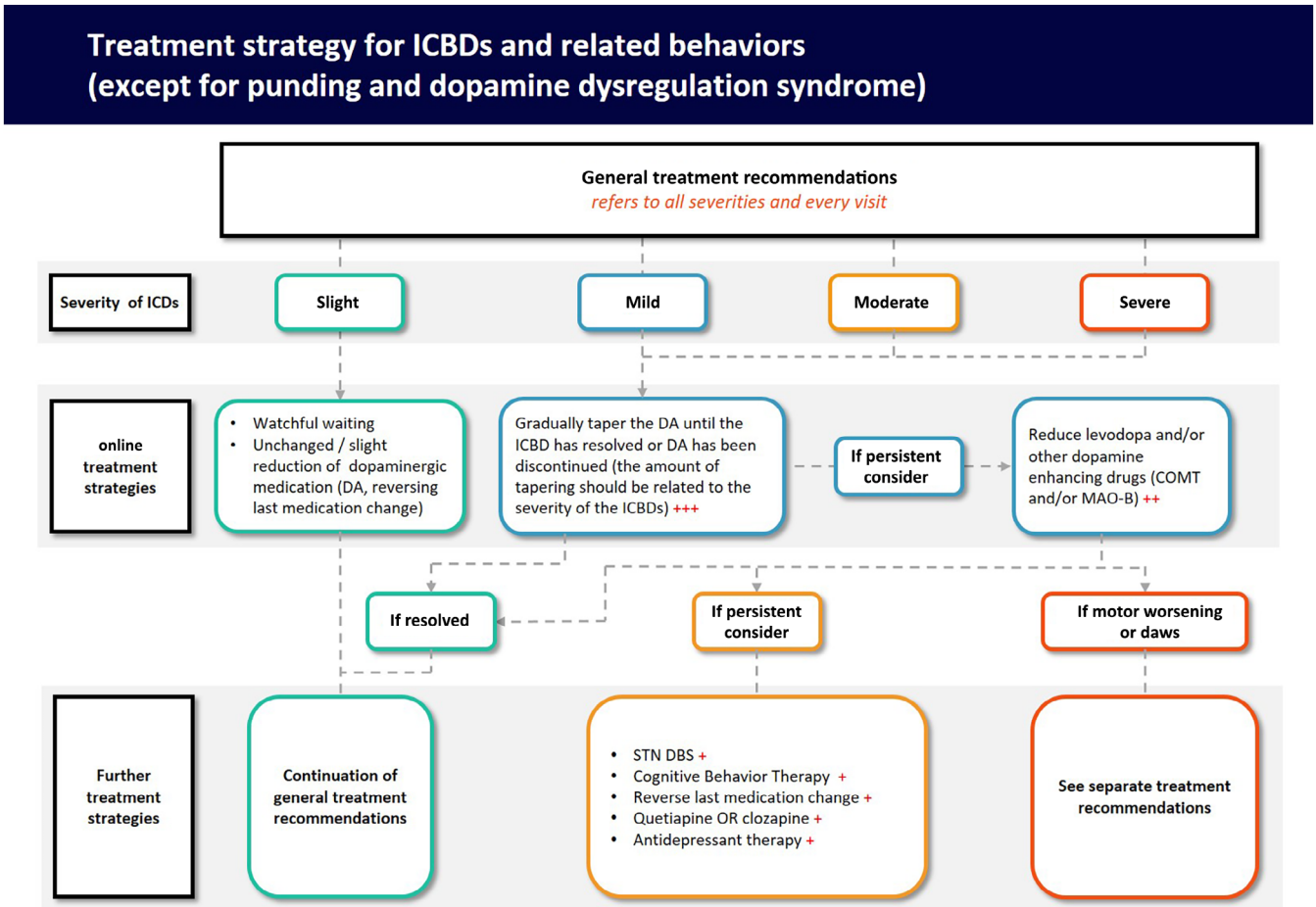


**Fig. 3.** Treatment strategies for ICBDs (impulse-control and related behavioral disorders) established by the expert panel based on the results of the online surveys. Strength of recommendation based on expert opinion: +++, >90% experts; ++, between 75% and 90% of experts; +, 50% to 75% experts. [Color figure can be viewed at wileyonlinelibrary.com]

option if available (these designations are applied in Figs. 3, 4).

Treatments that were excluded due to limited use in the second survey were pimavanserin (considered for use by 44%, only available in the United States) and naltrexone (considered for use by 36%). After the third survey, we also excluded the following treatments: L-dopa dose fractionating (used by 35%), amantadine (used by 31%), L-dopa pump treatment (used by 46%), apomorphine pump treatment (used by 27%), and switching to long-acting DA (used by 35%).

The following treatment pathway was drafted and continuously adapted based on the results of the panelist surveys (Fig. 3).

### Treatment Strategies for Punding and DDS

All the members of the large expert group agreed to include a separate treatment pathway for punding and DDS. A total of 76% of the panelists agreed in the second survey that stopping rescue doses of L-dopa and apomorphine followed by a reduction in L-dopa should be the first-line treatment strategies for punding and DDS. For second-line treatment strategies, an expert ranking was conducted (Fig. S3), and a related treatment algorithm was approved (Fig. 4).

### Complications Due to Tapering of Dopaminergic Medication (Worsening of Motor/Nonmotor Symptoms)

A total of 96% of panelists agreed with the consensus below for the treatment of complications related to tapering of dopaminergic medication (Fig. 5).

## Discussion

This international expert consensus proposes a severity definition and treatment pathways for ICBDs in the context of PD, which are urgently needed due to a lack of high-quality evidence and to facilitate future research.



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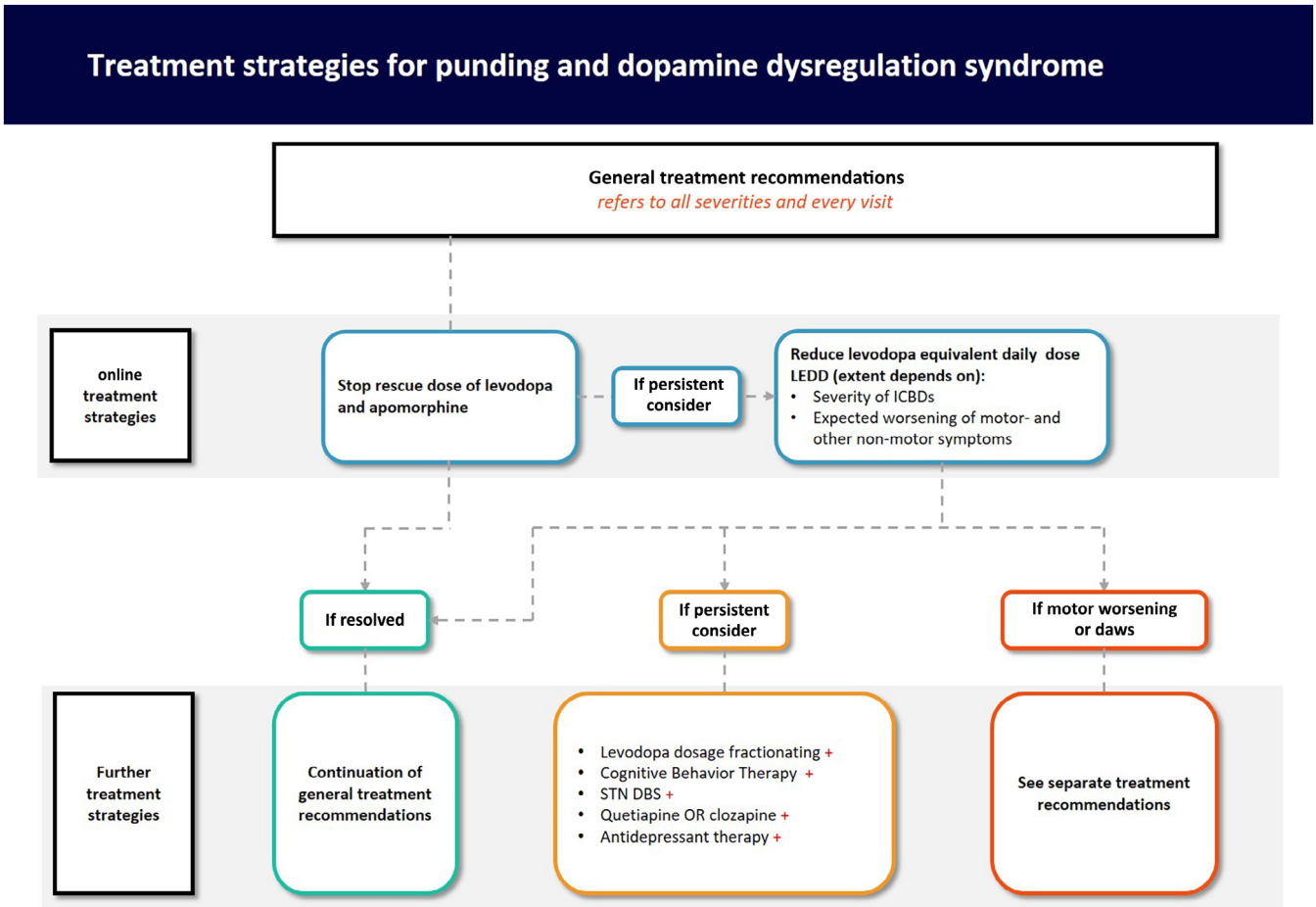


**Fig. 4.** Treatment strategies for punding and DDS (dopamine dysregulation syndrome) by the expert panel based on the results of the online surveys. Strength of recommendation based on expert opinion: +++, >90% experts; ++, between 75% and 90% of experts; +, 50% to 75% experts. [Color figure can be viewed at wileyonlinelibrary.com]

The panel first developed a severity definition as a basis of graded management strategies in which all the different treatment recommendations on expert basis are embedded. This severity definition also reflects the natural course of ICBDs usually worsening over time and increasingly impacting biopsychological functioning over time. The treatment strategy and urgency to treat ICBDs should always be based on their severity. Additionally, regular screening for ICBDs, involving a significant other, and getting specialist advice in case of legal or financial difficulties are further measures recommended by all experts. It is important to highlight that the role of significant others and specialists involved might depend on the culture and resources available in the respective country. For example, legal capacity (refers to the cognitive and mental capability of an individual to comprehend and render informed decisions pertaining to his or her medical situation; it also encompasses the patient's capacity to exercise his or her rights and fulfill his or her obligations within the framework of the law, as well as the patient's ability to make legal decisions such as entering contracts or obtaining loans in some countries) might be evaluated by a psychiatrist in some countries and by neurologists or neuropsychologists in other countries.

Even with multiple rounds of surveys and expert discussion, it remained difficult to establish a treatment pathway for ICBDs. This was mainly due to the fact that evidence regarding the management of ICBDs is largely lacking, and the management strategies used by experts are therefore very individualized and based mostly on clinical experience. Regarding treatment strategies, a ranking was difficult due to the lack of evidence and treatments not being available in all countries. To overcome this issue, the strength of recommendation, based on how many experts would use this strategy if available, was allocated to each treatment strategy. The panelists agreed that currently, a reduction in DA is the first and most important step in treating ICBDs. This recommendation is in line with the NICE guidelines and research showing a clear link and probable dose–relationship between DA and ICBDs.[15,55] Individual personalized tapering was proposed, with the amount of tapering depending on the



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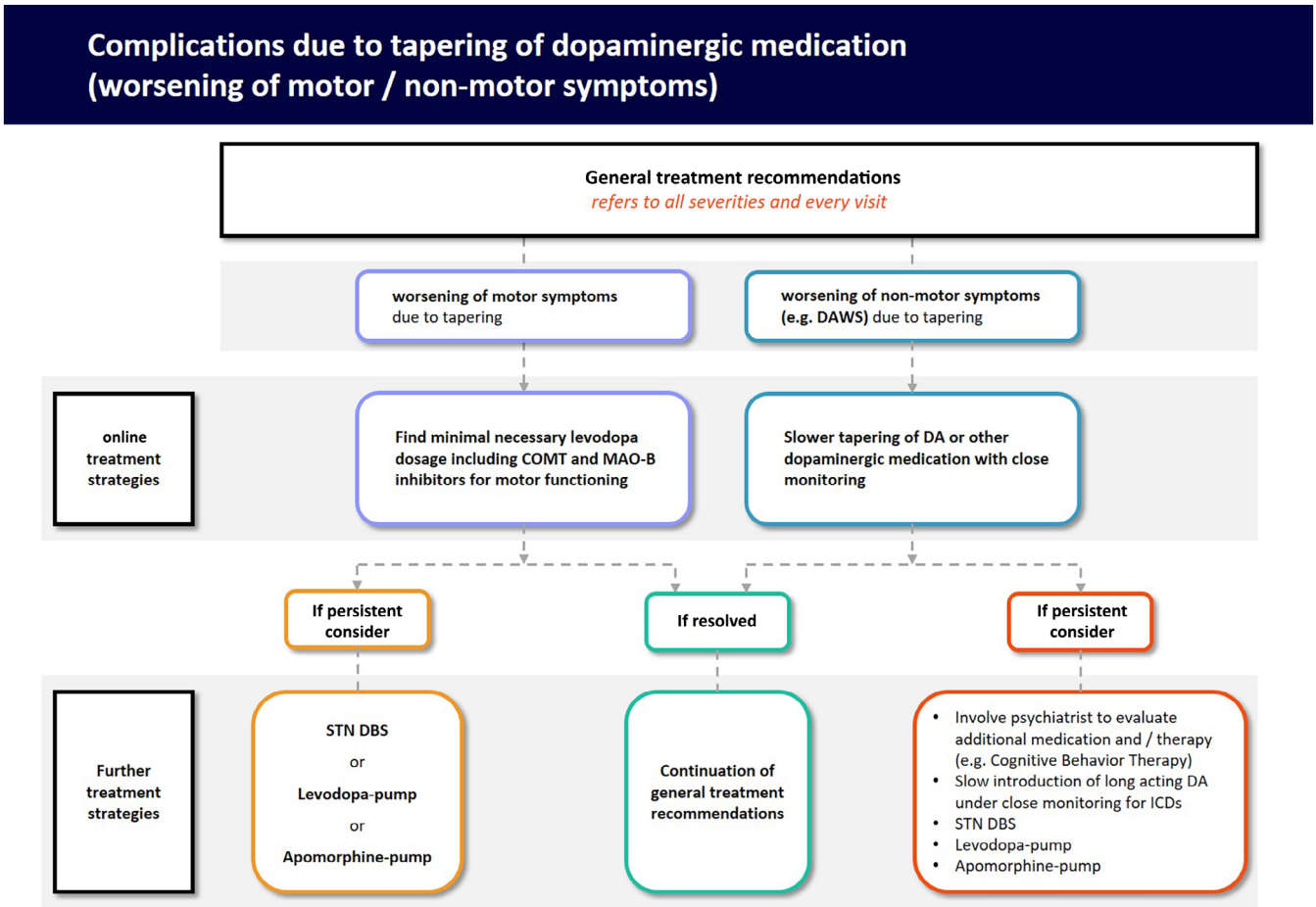


**Fig. 5.** Treatment strategies in the occurrence of tapering of dopaminergic medication (worsening of motor/nonmotor symptoms). [Color figure can be viewed at wileyonlinelibrary.com]

severity of the ICBDs and the current dosage of the medication. Importantly, immediate discontinuation of DA is discouraged due to the possibility of DAWS, and a total discontinuation of DA should be considered only in case ICBDs do not resolve despite tapering to avoid apathy and other hypodopaminergic symptoms. No time frame was defined for the individual steps of tapering, but experts agreed that changes in ICBDs may take several months to manifest, in line with the existing literature showing that desensitization of the mesolimbic pathways after DA reduction takes several months despite the ICBDs sometimes immediately improving after tapering.[68] This is an important message for clinicians treating ICBDs and again highlights the need for careful tapering and individual titration of low doses of DA, which also has implications for future study designs evaluating interventions for ICBDs.[97] In a significant proportion of patients, ICBDs persist after the reduction in DA, or the reduction in DA is not tolerated due to DAWS. To address this, further treatment strategies such as reducing L-dopa and/or other dopamine-enhancing drugs, STN-DBS, CBT, reversal of last medication change before onset of ICBD, use of clozapine or quetiapine, and antidepressant therapy were included in the recommendations. However, treatment strategies that were used by less than 50% of experts were excluded from the recommendations.

A different treatment pathway was established for DDS and punding. This decision was made considering the higher occurrence of punding and DDS in the absence of DA compared to other ICBDs. Furthermore, the pathophysiology of punding and DDS differs from that of other ICBDs, with the pulsatility of L-dopa in advanced-stage disease being recognized as a key risk factor.[11,25-27] It is important to mention that especially regarding DDS and punding, there is a lack of evidence-based studies which makes clinical decisions more dependent on clinical expertise. Most important in this context is the involvement of significant others[3] and supervised administration of medication alongside a multistep approach focusing first on stopping rescue doses of L-dopa and apomorphine, then reducing overall L-dopa dosage, and then applying second-line treatment strategies such as fractionation of L-dopa dosage, STN-DBS, CBT, clozapine, quetiapine, and antidepressants.



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A major risk of most of the medical therapeutic strategies of ICBDs is DAWS, which has therefore been particularly addressed in this consensus, and experts agreed that a slow individualized tapering of DA and other dopaminergic medication was the most important step. There is only limited evidence showing that this helps prevent DAWS,[67] but clinical experience of experts clearly indicated that this was the most helpful approach, especially to avoid severe withdrawal symptoms as well as long-term apathy as a downside of improving ICBDs.[97] Again, the involvement of a psychiatrist and psychologist for additional medication and/or therapy (eg, CBT) was dependent on the resources of the respective country but was generally viewed as useful and is supported by a randomized-controlled study.[57]

In case of worsening motor and nonmotor symptoms, advanced treatment strategies such as pump treatments and DBS were supported by all experts. Of course, advanced treatments should always be evaluated carefully and take disease progression, age, cognitive status, and comorbidities of a patient into account.

This expert consensus outlines the deficiencies of the current state of the art of ICBD treatments. Almost all therapies recommended here, based on the clinical experience of our experts, need adequate prospective RCTs with blinded outcomes. Acknowledging this, the expert team involved in the project will be committed to helping launch such attempts, encouraging research funders to support high-quality clinical studies as the significantly increased neurobiological understanding of this neuropsychiatric manifestation of PD now allows for targeted therapy research, with hypothesis-driven studies coming to a rapid clarification of the most important therapeutic interventions. The important knowledge that this is a disabling iatrogenically induced side effect of treatment should reinforce these efforts, supporting new RCTs, thereby replacing current expert consensus by evidence-based guidelines as soon as possible. ■

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## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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# APPENDIX

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## Supporting Data

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## Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript: A. Writing of first draft, B. Review and critique.

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