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Clinical management model for impulse control disorders in Parkinson's disease

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Review

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Abstract

Over the last decade, we have gained a better understanding of impulse control disorder in Parkinson's disease (PD-ICD), a medication complication in PD. Researchers were aware of its complexity and took efforts to learn more about its diagnostic and treatment possibilities. Nevertheless, clinical management for it is currently neglected. We conducted a narrative overview of literature published from 2012 to October 2023 on various aspects of clinical management for PD-ICD. A potential "susceptibility-catalytic-stress" model in the development of PD-ICD was proposed and a profile encoding predictors for PD-ICD was created. Based on these predictors, some methods for prediction were recently developed for better prediction, such as the polymorphic dopamine genetic risk score and the clinic-genetic ICD-risk score. A variety of treatment options, including dose reduction of dopamine receptor agonists (DAs), DAs removal, DAs switch, and add-on therapy, are investigated with inconsistent reports. Based on current findings, we developed a clinical management model prototype centered on prevention, consisting of prediction, prevention, follow-up and monitoring, therapy, and recurrence prevention, for clinical reference, and further proposed 4 key clinical management principles, including standardization, prediction centered, persistence, and whole course.

Introduction

Impulse control disorders (ICDs/ICD) were defined as a series of repetitive, excessive, and compulsive behaviors driven by a strong desire with limited control.[1] With a 2.0–3.5-fold increased risk, ICDs can arise as non-motor side effects of chronic dopamine replacement treatment (DRT) in Parkinson's disease (PD),[2–5] a rapidly growing neurological disorder globally.[6] Owing to the variability in regions, diagnosis standards, and evaluation methods, the reported prevalence of ICDs in PD patients (PD-ICDs/ICD) range from 3.5% to 46.0%[2,4,5,7–11] and is higher in western countries than in Asian countries.[12] Some PD patients on the same treatment plan showed no or less tendency toward ICDs, implying underlying neurobiological differences in susceptibility to ICDs. Theis et al. proposed a "vulnerability-stress" model for the development of PD-ICDs. Specifically, the relative reduction of dopamine projection to the ventral striatum (VS) and the sensitization of postsynaptic neurons can promote the "vulnerability" to PD-ICDs, while DRT could cause a relative overdose of dopamine in the sensitive VS ("stress"), ultimately leading to PD-ICDs.[13]

PD-ICD can present numerous symptoms and suffers are likely to confront multiple ones, causing enormous suffering in daily life.[14–16] Binge eating, compulsive shopping, pathological gambling, and compulsive sexual behavior are 4 common symptoms. For several PD-ICD types, sex variations were observed (eg, compulsive sexual behavior is more prevalent in men, while binge eating is more prevalent in women).[2,16,17] Additionally, there are a few symptoms relevant to ICDs, such as punding (stereotypical, repetitive, and pointless behaviors),[18] dopamine dysregulation syndrome (compulsive drug overuse),[19] and hobbyism (eg, compulsive internet surfing, artistic endeavors, and writing).[20] These are collectively referred to as impulsive and compulsive behaviors (ICBs) when combined with ICDs.

Nevertheless, due to lack of awareness in clinical management of PD-ICDs, most suffers do not receive proper care.[21] Recent research has made some contributions to PD-ICDs' management. This review aimed to (a) review the PD-ICDs from all aspects of clinical management; (b) develop a clinical management model for clinical reference; (c) extract clinical management principles; and (d) explore future research directions and ideas.

Method

PubMed, Cochrane, and EMBASE were searched using the strategy below: (Parkinson) AND ((((((((impulse control) AND (binge eating)) OR (compulsive eating)) OR (compulsive shopping)) OR (pathological gambling)) OR (compulsive sexual behavior)) OR (hypersexual)) AND

(English), from 2012 to October, 2023. Studies involving at least 1 impulse control disorder in PD patients were included. Articles were excluded provided that they met one of the criteria below: (a) editorials or comments; (b) inconsistent theme; (c) review articles. The articles were selected by 2 experienced researchers, and any conflicts were settled by consensus in the review panel.

Results

We finally received 487 articles on PD-ICDs after searching and screening them by the methods above (see details in Supplementary Figure S1). In the articles screened, about 237 articles were on the PD-ICD management.

Subsequently, we tend to review the research advance of PD-ICD from the core aspects of clinical management, including prediction, prevention, evaluation, and therapy.

Prediction and prevention

Considering that there is no ideal treatment for PD-ICDs currently, prevention should be the priority, which is based on the prediction of high-risk groups. Quite a few factors have been reported as predictors, including some pharmaceutical factors, demographic factors, PD-related factors, and genetic factors. These predictive factors could play roles in the development of PD-ICDs. The genetic factors and pharmaceutical factors could play the "vulnerability" and "stress" roles respectively. Besides, the demographic and PD-related factors could play another significant role.

"Stress"

As a side effect of DRT, PD-ICD is undoubtedly a product of "stress" from DRT, particularly DAs.[11,22] The "stress" function can be explained by a "overdose theory," in which the comparatively intact ventral striatum (VS) and parts of the limbic system in dopaminergic projection degeneration can be overstimulated by the supplied DRT which efficiently counteracted dopamine shortage in the motion systems.[23–25] Furthermore, a larger lifelong mean daily dose and a longer cumulative duration of DAs were discovered to have significant dose-effect correlations with PD-ICDs.[11,26] The relationship between different DAs with variable receptor selectivity and ICDs is inconsistent, for instance, with a stronger dopamine receptor 3 (expressing preferentially in the limbic pathway) selectivity than bromocriptine, pramipexole is more likely to lead to PD-ICDs.[27] Less selective, levodopa exhibits more physiological receptor activation pattern, nevertheless, it is also associated with more ICDs, particularly at high doses,[2,28] and concurrent levodopa use in patients taking DAs can increase the risk of PD-ICDs.[2] Moreover, delivery route and pharmaceutical formulation could also make a difference, as evidenced by the higher association of PD-ICDs with oral short-lasting DAs than with oral long-lasting or transdermal DAs.[29,30] With stable plasma levels and elimination of pulsatile dopaminergic stimulation,[31] levodopa-carbidopa intestinal gel therapy can lead to a lower risk of ICDs onset.[32]

"Vulnerability"

As in the same condition, not all patients with PD on DRT would experience ICDs, indicating that potential genetic neurobiological substrates can contribute to them.[33] For instance, PD patients with ICDs were observed to have more preserved limbic-paralimbic connectivity than those without ICDs, and the stronger the preserved connectivity is, the heavier the ICD is.[34] Males with stronger connectivity[35–38] are more prone to PD-ICDs than females.[39]

No association was found between the ICDs and polygenic risk score of PD, which indicated that ICDs and PD don't share genetic susceptibility.[40] For ICDs' susceptibility, we found its correlations with variants in genes encoding enzymes or receptors from the dopamine, opioid, serotonin,[41] norepinephrine, and glutamate pathways in PD and a previous review tabulated the findings of 7 candidate gene associations.[42] Based on that, predictive roles of the polymorphisms in opioid receptor gene (OPRM1)[43,44] and β-glucocerebrosidase[45] also got attention. Besides, the signal channel relevant genes of G protein-coupled receptors (dopamine receptors acted by DAs) can also play a role.[46] Furthermore, decreased striatal dopamine transporter (DAT) concentrations in the VS were consistently found to predate and predict PD-ICDs with a positive connection with the severity.[47–51] A positive relationship between reduced DAT availability in the VS and reduced metabolism in several cortical limbic and associative pathways or functionally related areas was found to facilitate the vulnerability.[52] Furthermore, aid of a multi-polymorphism in genes implicated in glutamatergic, opioid, and monoaminergic signaling pathways was revealed to bring 11–16% increase in ICD predictability compared to assessing clinical factors alone.[44,53]

The variation of dopamine genes can affect impulse control[54] and further affect the response to DRT. Evidence revealed that ICD could be alleviated by DAs in the low dopamine genetic risk score (DGRS, including the dopamine receptor D1-3 (DRD1-3), Catechol-O-methyltransferase, and DAT) group and worsened in the high score group.[55] Hall et al. further revealed the association that patients with a low DGRS were more prone to ICBs during DRT, but the number of ICBs may decrease over time.[56,57]

"Catalysis"

Some certain demographic factors and PD-related factors could create an internal environment catalyzing the occurrence of PD-ICD.

For demographic factors, a younger age, pre-PD history of ICDs, history of substance abuse, and alcohol use have all been proposed to increase risk.[39,58–61] PD patients with ICDs have a more conserved brain metabolism environment than those without ICDs, thus, factors correlated with better metabolic environment, such as substance abuse[62] and a younger age,[2] could promote the occurrence of ICDs. Additionally, smoking,[2,39,63], caffeine usage,[64] poor education,[65] and unmarried status[2,66] have controversially been proposed.[39] Furthermore, some personality traits like irritability, impulsivity, and alexithymia were found to be predictive.[29,30,67–73]

For PD-related factors, to begin, the significant difference in dopaminergic fiber degeneration between the striatum and extrastriatum is an inherent condition predisposing to ICD in PD.[74] Moreover, a younger age of PD onset, longer PD duration,[65] and severe motor symptom,[60] may promote the occurrence of PD-ICD. Movement complications,[64] such as motor fluctuations[75] and dyskinesias,[76,77] as well as non-motor complications, such as depression,[78] anxiety,[79] and apathy[80] can also increase the risk.[65] PD-ICDs patients were found cognitive preservation[81] perhaps due to better metabolic preservation.[82] Sleep disorders, such as sleep disturbances and fragmentation, may increase the risk of PD-ICD which could promote or aggravate the sleep restriction and fragmentation, indicating a bidirectional link.[83] In addition, whether rapid eye movement sleep behavior disorder (RBD) can increase

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the risk of PD-ICDs remains debatable probably due to differences in evaluation methods or the unreliable results from a small number of patients.[39,84–86]

The "vulnerability-catalysis-stress" model

The predictors above can predict the occurrence of PD-ICDs from 3 perspectives: the genetic factors may help predict the intrinsic basal predisposing vulnerability; the PD-related factors and demographic factors may act as a "catalyst" for some potential internal changes to ICD susceptibility; and the drug-related factors may act as external "stimuli" leading to a "stress response" and thus to PD-ICDs. In short, under "catalyst" conditions, the "stimulus" may produce "stress reaction" in genetic susceptible individuals, and chronic "stress reaction" promotes the eventual incidence of PD-ICD (Figure 1). Therefore, even though DRT is closely related to development of PD-ICD, the full and sustained remission rate of PD-ICD is relatively low after stopping DRT.[81] DRT only plays a "stress" role, and other factors may be dominant and difficult to reverse. This "vulnerability-catalysis-stress" model can be an improvement on the "vulnerability-stress" model.[13]

From the 3 perspectives, Weintraub et al. developed a clinic-genetic tool, the ICD-risk score, with 7 easily obtained clinical variables (sex, age, ethnicity, disease duration, cohort, and DAs and levodopa therapies) and genotype for 2 single nucleotide polymorphisms (rs1800497 [in DRD2] and rs1799971 [in OPRM1]) to identify patients at high risk.[87] It can classify PD patients into groups with an ICD prevalence of 40% (highest risk quartile) and of 7% (lowest risk quartile),[87] so that clinicians could conduct a preliminary risk assessment for a better PD medication selection.

Considering the strong link between ICDs and DAs, it is critical for high-risk individuals to avoid or reduce the use of DAs. At the same time, the risk may be reduced by some interventions, such as promptly and effectively dealing with the PD-related complications (both motor and non-motor complications above), quitting smoking and drinking, avoiding substance abuse, improving the education level, improving marital status and receiving social satisfaction, which all deserve further investigations.

Predictors for progression

The qualitative research revealed that both internal factors (gene, mood, personal traits and coping methods) and external social factors (significant life events and social support networks) could influence the severity of PD-ICDs.[66,86,88,89]. For instance, *Parkin* mutations,[90] reduced DAT availability,[51,52] increased right-lateral fronto-striatal activation,[91] and stronger preserved limbic-paralimbic connectivity[34] have all been linked to increased severity of PD-ICD. Moreover, other factors like RBD[89] and high doses of DAs[77,92] were found to worsen the severity.

To summarize, we incorporated all these predictors and produced a profile for coding factors affecting occurrence and progression of PD-ICDs for future research reference (Figure 1).

Evaluation and monitoring

Scale evaluation remains the first option among the complementary diagnostic approaches. The International Parkinson and Movement Disorder Society has evaluated the clinometric properties and practicability of 50 currently available screening instruments and scales used for PD-ICBs and made some recommendations for selection.[7]

Notably, patients with PD-ICDs were actually under-reported and under-managed in clinical practice,[93] most likely due to a lack of awareness of their actions and suspicion of a possible link with PD medication, embarrassment, or alexithymia (specifically, difficulty describing feelings).[73] As a result, positive education on PD-ICDs for patients and caregivers, as well as incorporating caregivers' claims while accessing are required to raise awareness and ensure active cooperation and timely reporting.

Therapy

When PD-ICD occurs, active treatment ought to begin. Therapy options include DAs dose reducing, DAs removal, DAs switch, and add-on therapy.

DAs dose reducing or removal

Reducing or even withdrawing from DAs as the first-line therapy option can moderately relieve ICDs; a 40% remission rate was observed in 1 longitudinal study[94] and a 50% remission rate was reported in another with a longer follow-up period.[11] Meanwhile, levodopa dosage can be raised to prevent worsening motor symptoms.[95] There are certain limitations to its usefulness. Switching from DAs to sustained-release formulations of levodopa/carbidopa, for example, can alleviate ICDs behaviors in PD patients, but ICD-related neuropsychiatric problems persisted after the 12-wk therapy.[94] Patients with pre-existing obsessive compulsive disorder were more likely to experience paradoxical aggravation of ICDs after DAs removal, which may assist in predicting refractoriness of this treatment on PD-ICD.[96] Furthermore, patients who attempt to taper DAs may develop dopamine agonist withdrawal syndromes such as anxiety/panic, apathy, suicidality, diaphoresis, anorexia, and fatigue, complicating DA tapering.[97–99]

DAs switch

DA switch is a method of altering the type of DAs and delivery routes. Following a thorough assessment of pharmacological contraindications, temporary replacement of pramipexole with bromocriptine with lower DRD3 selectivity may relieve or reverse the ICDs while maintaining the DRD2 stimulation for easing motor symptoms.[27] Several studies have linked ICDs to pulsed dopaminergic treatment.[100] Levodopa-carbidopa intestinal gel therapy can lower the risk of ICDs development by providing stable plasma levels and elimination of pulsatile dopaminergic stimulation,[31,32] and is appropriate for all patients with long disease duration.[101] However, ICDs caused by this therapy may share a common mechanism with dopamine dysregulation syndrome.[102] Furthermore, long-acting or transdermal DAs were found to lower ICD morbidity.[29]

Add-on therapy

Aside from adjustments in DRT, other pharmacological and non-pharmacological methods were investigated.

For pharmacological methods, as reward-based decision-making and impulsivity in ICDs are mediated by a complex neural network involving the dopaminergic, noradrenergic, and serotonergic pathways, as well as dopaminergic network,[103,104] many psychotropic agents targeting different pathways can be investigated as interventions.

Several drugs were tested and suggested effective based on limited evidence. Continuous apomorphine infusion may improve pre-existing ICDs, but as a potent dopamine agonist, it may also result in new or more ICDs.[32] Amantadine, an anti-glutamatergic agent, may help with pathological gambling.[105] by reducing hypersensitivity to rewards and maintaining activation

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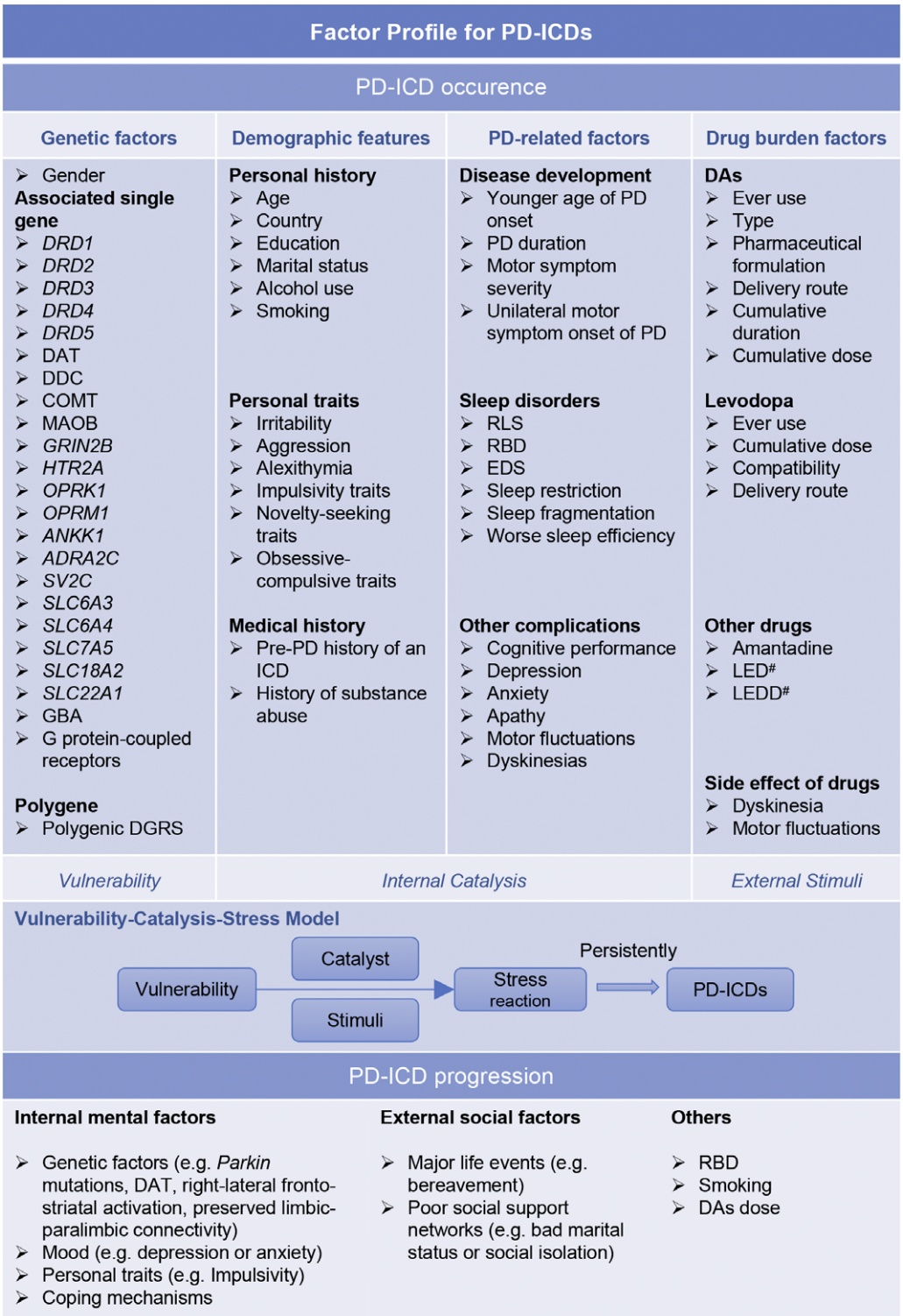

Figure 1. Factor profile for PD-ICDs. The profile summarizes the factors affecting occurrence and progression of PD-ICD. There are 70 factors affecting PD-ICD occurrence, including 25 genetic factors, 14 demographic factors, 16 PD-related factors, and 15 drug burden factors. These factors can be summarized to predict PD-ICDs from 3 aspects via a vulnerability-catalysis-stress model. Under "catalyst" conditions, the "stimulus" may produce "stress reaction" in individuals with genetic vulnerability, and chronic "stress reaction" leads eventual occurrence of PD-ICD. In addition, 9 factors are related to PD-ICD progression, including 4 internal mental factors, 2 external social factors, and 3 other factors.[39] Associated with PD-ICDs in the meta-analysis by Cao et al.[39] ICDs, impulse control disorders; PD, Parkinson's disease; DAs, dopamine receptor agonists; DGRS, dopamine genetic risk score; EDS, excessive daytime sleepiness; RLS, restless legs syndrome; RBD, rapid eye movement sleep behavior disorder; LED, levodopa equivalent dose; LEDD, levodopa equivalent daily doses; DRD1, dopamine receptor D1; DRD2, dopamine receptor D2; DRD3, dopamine receptor D3; DAT, dopamine transporter; DDC, dopamine decarboxylase; GRIN2B, glutamate receptor ionotropic *N*-Methyl-D-aspartic acid 2B; HTR2A, serotonin receptor 2A; OPRK1, opioid receptor kappa; ANKK1, ankyrin repeat and kinase domain containing 1; OPRM1, mu opioid receptor; SLC22A1, organic cation transporter 1; COMT, catechol-O-methyltransferase; MAOB, monoamine oxidase type B; ADRA2C, adrenergic alpha2C receptor; SV2C, synaptic vesicle 2 C; SLC6A3, dopamine transporter gene; SLC6A4, serotonin transporter gene; SLC7A5, L-type amino acid transporter 1 gene; SLC18A2, monoamine transporter gene; SLC22A1, organic cation transporter gene; GBA, β-glucocerebrosidase.

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toward uncertainty,[106] however, it has been linked to a higher risk of PD-ICDs.[107] Moreover, Safinamide is effective even at high doses. It can partially replace levodopa in treating motor symptoms while requiring less doses of other dopaminergic drugs and producing fewer side effects like ICDs.[108] As an opioid antagonist, Naltrexone was demonstrated to be effective in treating pathological gambling in general population[109] while ineffective in the PD-ICD population from clinical general impression of change assessed by clinicians, although it did lower the severity.[110] Other medications, such as citalopram, valproate, and clozapine, could be beneficial to ICDs as well.[111–114]

To summarize, research into other drugs is ongoing, and none of them has sufficient evidence to date for treatment of ICDs. More clinical trials are required to determine the precise functions of them on PD-ICDs.

For non-pharmacological treatments, repetitive transcranial magnetic stimulation, a non-invasive therapy, could suppress or stimulate brain neurons using magnetic fields to improve impaired brain function and has been shown to have therapeutic promise for ICDs.[115,116] Second, since psychological traits have been linked to PD-ICDs,[117] psychological therapies could be effective in treating PD-ICDs. Evidence suggested that integrating cognitive-behavioral therapy with routine medical care was more effective in reducing the severity of PD-ICDs than medical care alone.[118] Notably, patients with fewer ICDs and other psychiatric symptoms, better social functioning, and a lower dose of PD medication may benefit most from the cognitive-behavioral therapy.[118]

Last but not least, deep brain stimulation (DBS) on either the subthalamic nucleus (STN) involved in cognitive control,[119] or the globus pallidus internus[120] involved in reward expectation salience[119] can affect the reward processing and levels of impulsivity. Despite the fact that a prospective observational study found DBS could relieve PD-ICDs symptoms in the majority of patients,[121] its use as a treatment for PD-ICD remains disputed. The palliative impact of DBS on the STN in ICDs could be attributable to a decrease in dopaminergic medications or the specific effect of stimulation[121–123] as others have found that DBS could reduce the severity of PD-ICDs regardless of medication modifications.[124] Rarely, ICDs may deteriorate or appear as de novo ICDs after STN-DBS.[125,126] Moreover, significant changes in personality traits, such as increased apathy and harm avoidance, were observed, especially when DRT was drastically reduced.[127]

Given the disparity in DBS efficacy on PD-ICDs, factors influencing postoperative evolution of ICDs warranted investigation. First, studies have found that postoperative dopaminergic reduction in patients with mild PD (low dopaminergic drug doses, mild motor symptoms, and mild complications) was linked with ICDs remission[81,128]; nevertheless, these patients had a higher tendency to become apathetic postoperatively.[128] Moreover, younger age and personality traits such as irritability and compulsive behaviors have been linked to refractory ICDs.[96,129] Furthermore, the location of active contact within the STN may influence the result of postoperative ICD[130] with the ventral part of the STN favoring a rise in dysfunctional impulsivity.[131] Additionally, oscillatory activity in the theta-alpha band was found to impact dopaminergic side effects.[132] Thus, ICDs may be triggered, similar to dopaminergic treatment, when stimulation intensity is rapidly increased.[133] Consequently, more emphasis should be placed on electrode placement, parameter adjustment, and close monitoring during DBS surgery.

Current treatment status

One study preliminarily investigated the frequency and effects of these treatment options, and revealed that no-change was the most widely used treatment option (37.5%), followed by DAs removal (16.7%), DAs switch (12.5%) and DAs lowering (8.3%).[21] Fortunately, the majority achieved ICD remission regardless of treatment. Surprisingly, no change in the prevalence of PD-ICDs was observed throughout a 10-yr period before and after the screening and treatment methods were applied in clinical practice.[75] Some factors, such as the continued overdose of DAs despite decrease, as well as inadequate screening and treatment, may interpret this. This can serve as a reminder that much work remains to be done concerning clinical management.

Discussion

We generally reviewed current research advances of PD-ICD from the core aspects of its clinical management, including prediction, prevention, evaluation, and therapy. Based on these findings, we proceed to construct a clinical management model for PD-ICDs (Figure 2).

Construction of a clinical management model

The clinical management model primarily focuses on prediction, prevention, monitoring with follow-up, therapy, and recurrence prevention. Prevention can be central to management. Thus, predicting high-risk populations for PD-ICD is critical. The potential predictors can help predict from 3 aspects, indicating an effect model in the development of PD-ICD (vulnerability-catalysis-stress). The development of prediction tools, such as the DGRS and the ICD-risk score, may make some contributions. Second, high-risk individuals can be given better PD medication selection and advised taking relevant interventions against the changeable risk factors such as smoking and those PD-related complications to reduce risk. Third, positive education and regular monitoring using suggested scales are critical for early diagnosis and treatment. Fusaroli et al. provided an extended list of possible manifestations of ICBs that can be used as a reference.[134] Fourth, for patients diagnosed with PD-ICDs, therapy options, including DAs dose reducing, DAs removal, DAs switch, add-on therapy, and combined strategies, can be individually customized while ensuring an extent of control over motor symptoms. Fifth, when ICDs symptoms fade with active treatment and regular monitoring, recurrence prevention is essential. After all, history of PD-ICD can also be a risk factor. Therefore, active prevention is the primary emphasis of the clinical management, accounting for the majority of management efforts.

Implications of the clinical management model

On the one hand, this model offers a comprehensive management strategy based on current research and the existing scenario in which PD-ICD is difficult to treat and inadequately managed. Thus, this model can be refined further as research into PD-ICDs advances.

On the other hand, it suggests a prevention-focused management strategy that should be implemented throughout the whole course of PD management. Based on this model, 4 key management principles can be summarized: standardization, prediction-centered, persistence, and whole course. Specifically, a standardized clinical management is necessary for PD-ICDs patients, which

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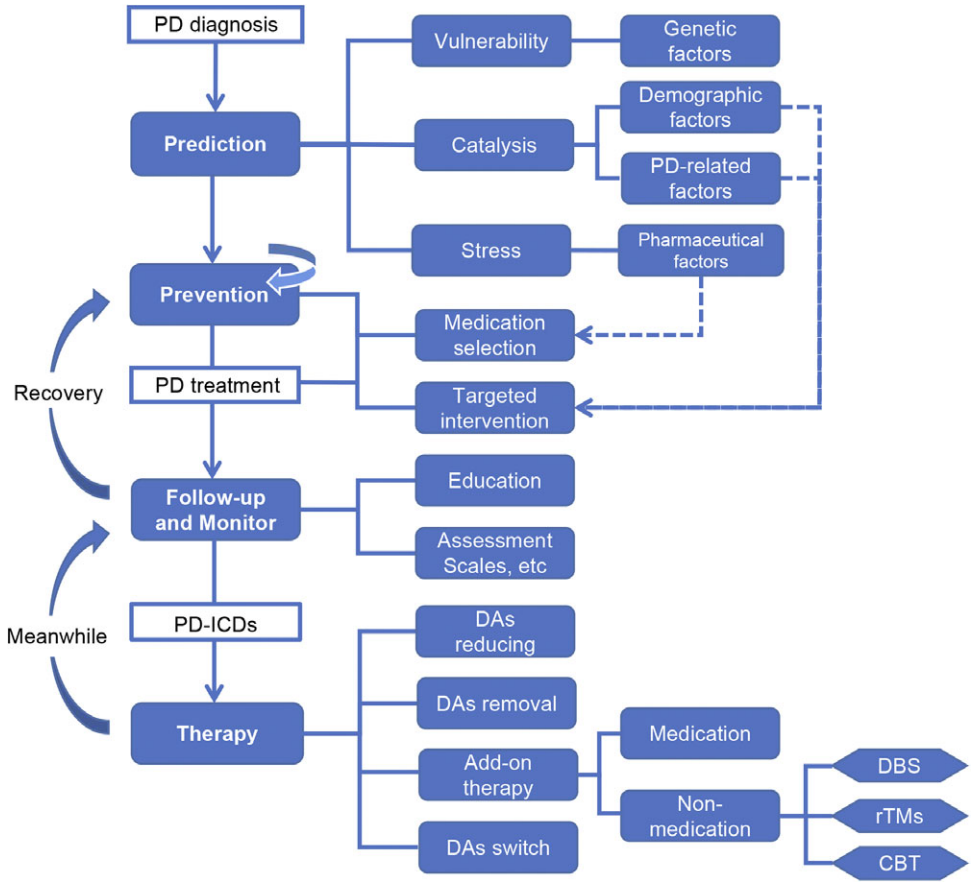

Figure 2. Prevention-centered clinical whole-course management model for PD-ICDs. The clinical management model prototype centered on prevention, focuses on prediction, prevention, follow-up and monitoring, therapy, and recurrence prevention. With prevention at the center stage, this model shows that PD-ICD management should be persistent and continuous through the whole process of PD treatment. The solid lines with arrows indicate the management process, and the solid lines without arrows prompt relevant contents of the process. Dashed lines with arrows indicate some contributions. The curved arrows imply the model's continuity and circularity. PD, Parkinson's disease; ICDs, impulse control disorders; PD-ICDs, impulse control disorders in Parkinson's disease; DAs, dopamine receptor agonists; DGRS, dopamine genetic risk score; ICD-RS, ICD-risk score; DBS, deep brain stimulation; rTMs, repetitive transcranial magnetic stimulation; CBT, cognitive-behavioral therapy.

ought to center on prediction and run throughout the entire PD treatment cycle with clinicians' constant attention.

Challenges and inspirations

Without a doubt, there are many challenges to the management model's successful implementation in clinical practice.

To begin with, the management model is actually built on 4 assumptions: (a) Predictive factors can aid in relatively accurate identification of high-risk populations for PD-ICDs. (b) Positive interventions to the corresponding controllable risk factors can reduce the risk of PD-ICDs. (c) Early diagnosis and intervention for PD-ICDs contribute to a good prognosis. (d) Personalized treatment options can be tailored to individual conditions. Thus, a series of large-scale longitudinal research, including clinical trials, are expected to validate these hypotheses in the future.

Second, a lack of awareness about PD-ICD among patients, family members, and even physicians can obstruct the implementation of the standardization and whole course principles. Thus, education is significant and imperative. Third, because the existing PD-ICD diagnosis is based primarily on scales, there is no gold standard, restricting the continuous monitoring and early diagnosis of PD-ICDs. Fourth, we lack robust and reliable methods for identifying high-risk individuals, and existing methods need to be validated and improved through large-scale studies. Fifth, given the unsatisfactory therapeutic effect, future efforts are warranted to improve the efficacy of existing therapies and investigate novel therapeutic targets.

Strengths and limitations

This review features the following strengths and implications: (a) achieving a comprehensive review of literature on various aspects of the clinical management course of PD-ICD over the last 10 yr; (b) compiling the predictors of PD-ICDs into a profile for reference of future research; (c) proposing a "susceptibility-catalysis-stress" model for the occurrence of PD-ICDs based on the profile; (d) creating a prevention-centered clinical management model for clinical reference; and (e) proposing 4 key clinical management principles.

However, as the management model was proposed based on existing research, its clinical use is limited due to a lack of knowledge about PD-ICD. The model requires ongoing improvement and supplementation during future research and clinical work. Moreover, the article concentrates mostly on the clinical management of PD-ICD with the research overview of PD-ICD pathogenesis and imaging limited.

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Conclusion

Currently, there is a lack of adequate understanding and standardized clinical management for PD-ICDs. Thus, we reviewed current research progress of PD-ICD from the core aspects of its clinical management. Subsequently, based on current research, we created a factor profile for PD-ICDs development and a "susceptibility-catalysis-stress" development model for future research reference, as well as proposed a clinical management model and 4 clinical management principles both for clinical reference.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S1092852924000403.

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Author contribution. Anmu Xie had the idea for the article, Han Li performed the literature search and data analysis, Yong Yang, Liying Yang, and Anmu Xie drafted and critically revised the work. All authors read and approved the manuscript.

Clinical implications.

a. This is a comprehensive review on PD-ICD clinical management.
b. A factor profile for PD-ICDs' development was created for research reference.
c. A "susceptibility-catalysis-stress" model was proposed for PD-ICDs occurrence.
d. A clinical management model was constructed based on current research for clinical reference.
e. Four management principles were proposed as follows: standardization, prediction-centered, persistence, and whole course.

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