Pathological Gambling in Parkinson's Disease: An Update on Medical Management

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Abstract: Pathological Gambling (PG) is characterized by "the failure to resist gambling impulses despite severe personal, family or occupational consequences". PG estimated prevalence ranges between 0.4% and 3.4% within the adult population. PG seems to be more common in patients with Parkinson's disease (PD) than in the general population. In the past few years, PG has been reported as a side effect of dopamine agonist (DA) therapy used in PD. This association has aroused great interest for the dramatic impact PG has on patients' quality of life. Management of PG in patients with PD could be demanding. It is based on patient and caregiver education, modification of dopamine replacement therapy, and in some cases psychoactive drug administration. This review describes possible pathogenesis of PG associated with DA therapy, available pharmacological treatments and management approaches that may increase the likelihood of satisfactory treatment outcomes in PD patients.

Keywords: Behavioural therapy, dopamine agonists, impulse control disorders, Parkinson's disease, pathological gambling, pharmacological therapy.

1. INTRODUCTION

Pathological Gambling (PG) is classified in the DSM-IV as an Impulse Control Disorder (ICD) [1]. ICDs are characterized by "the failure to resist an impulse, or temptation to perform an act that is harmful to the person or to others" [2]. PG is the most extensively studied ICD, in which patients fail to resist gambling impulses despite severe personal, family or occupational consequences. PG estimated prevalence ranges between 0.4% and 3.4% within the adult population, and it is often associated with other psychiatric disorders, such as substance use disorders, sharing with them several clinical features [3-5]. ICDs seem to be more common in patients with Parkinson's disease (PD) than in the general population [6]. In these patients, ICDs may be observed as PG, compulsive sexual behaviour, compulsive buying, binge eating, together with punding and the addiction-like compulsive use of dopamine replacement therapy, or dopamine dysregulation syndrome (DDS) [7]. In the past few years, ICDs have been reported as a side effect of dopamine agonist (DA) therapy used in PD [8, 9]. Less frequently, they have also been observed in subjects with restless leg syndrome (RLS) treated with DAs [10]. This association has aroused great interest for the dramatic impact ICDs have on life quality of patients and their families.

This review describes some aspects of PG classification in the upcoming DSM-V, possible ICD pathogenesis, specifically for PG associated with DA therapy, available pharmacological treatments and management approaches that may increase the likelihood of satisfactory treatment outcomes in PD patients.

2. PG AND THE UPCOMING DSM-V CLASSIFICATION

PG is currently classified as an ICD not otherwise specified according to DSM IV, in which comorbidity is common, particularly with substance abuse, obsessive-compulsive disorder (OCD) and mood disorders [1,11]. The serotoninergic dysfunction in PG may support a phenomenological link between this impulse control disorder and OCD [12, 13]. This connection has also been supported by the high rates of OCD among pathological gamblers and by several phenomenological similarities between the irresistible impulses and acts of ICD and the obsession and compulsions of OCD [14]. These analogies in psychopathology, neurobiology, and response to treatment have consequently motivated the conceptualization of PG as an obsessive-compulsive-spectrum disorder [11]. How disorders are grouped together in DSM has important implications. Disorders that are classified together in the same section of DSM are generally presumed to be related to one another and to have shared pathophysiology and etiology. Placing disorders in the same category can also enhance diagnosis and differential diagnosis [15]. Obsessive-compulsive (OC) spectrum refers to a group of disorders that are presumed to be distinct from, but related to, OCD, and which are characterized by repetitive thoughts and/or behaviours. This concept implies that such disorders might

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be grouped together in the same supraordinate category in DSM. DSM-IV does not include a category of OC spectrum disorders (OCSDs); in DSM-IV, candidates for inclusion in this new category are classified under anxiety disorders, somatoform disorders, ICDs not elsewhere classified, personality disorders, and disorders usually first diagnosed in infancy, childhood, or adolescence [15]. Whether there is utility to including a category of OCSDs in DSM-V, and, if so, which disorders might be included in this category is still a matter of debate [15]. A group of repetitive behaviours are classified in DSM-IV as ICDs not elsewhere classified, which have also been termed behavioural addictions. Substance addiction seems to be driven initially by brain reward systems and then becomes habitual in nature; this may also apply to some of the behavioural addictions. Whether these disorders should be construed as compulsive, impulsive, or impulsive-compulsive is controversial. There may be some overlap in the underlying psychobiology of OCD and certain behavioural addictions, although, a review of relevant research suggests more differences than similarities between these disorders and OCD. In addition, clinical approaches to assessment and treatment differ [15].

Based on presented evidence, it was recommended that ICDs not be considered OCSDs. Relatively few experts agreed with including ICDs in OCSDs in DSM-V [15-17].

PG shares many important features with substance use disorders, especially in terms of diagnostic criteria, clinical course, and treatment. Recently, the DSM-V Task Force has suggested that PG may be reclassified and included in a new category entitled "Addiction and Related Disorders". The category would include both substance-related and non-substance/behavioral addictions [18].

3. EPIDEMIOLOGY AND RISK FACTORS

Lifetime prevalence of PG in North America ranges from 0.4% to 1.9% within the adult population [8,19-21]. Cultural differences, advertising policy and the ease of access to gambling in an area are thought to have a significant impact on prevalence rates, being PG more common in the US (5.5%) compared with Canada (3.6%) [22].

ICDs prevalence in PD is debated, but evidence suggests that these behaviours are more frequent in patients with early disease onset, longer disease duration and high novelty-seeking personality traits [8,23,24]. Other features independently associated with ICDs include male sex, younger age, being unmarried, current cigarette smoking, prior personal/family history of alcohol addiction or gambling problems and impulse traits [22,25-27]. Isaias *et al.* observed that PD patients with elevated impulsivity had a high probability to have ICDs and only male subjects were positive to multiple ICDs [28].

In PD patients, PG lifetime prevalence is reported to be between 3.4% and 8%, with the higher frequency in patients treated with DAs [6,8,22,29,30,32]. PG was reported in 6% of patients using agonists and in 8% of male subjects with PD taking a DA [33]. This is far higher than general population risk, estimated at about 1% [3]. Some authors found that prevalence rates of ICDs in PD vary considerably, ranging from 6% in PD patients not receiving DA to 17% among those on DA treatment [34]. In PD patients taking a DA, concurrent levodopa use increases the risk to develop an ICD by approximately 50% [22]. In recent studies, the most common ICD observed in PD patients was PG (4-5%), followed by compulsive sexual behaviour, compulsive shopping and compulsive eating [22,35,36]. More than a quarter of patients with ICDs have two or more other behavioural addictions and it is not completely clear why a subgroup of PD patients develop these behavioural addictions. Age and sex differences could reflect differences in PD biology or a susceptibility to compulsivity independent of PD [37]. PG develop only in a subset of patients, suggesting an underlying susceptibility, mediated by PD-specific factors such as a dysregulation of dopaminergic system, which may also modulate underlying temperament traits. The psychological profile of PD patients may have a role as a risk factor, since impulse sensation seeking personality traits and addiction proneness characterized PD patients who develop PG.

In a prospective study, Voon *et al.* observed that PG was associated with DAs but not with agonist subtype or doses: both D1/D2 (pergolide) and D2/D3 (ropinirole and pramipexole) agonists were equally implicated [8,34]. However, the authors do not rule out D3 mechanisms, given that pergolide may have greater D3 than D1 receptor affinity [38]. Other authors confirmed these data, finding that agonist dose and duration were non-significant. Pramipexole, which has greater affinity for D3 receptors than ropinirole, did not differ in risk, and DA doses did not predict PG development [33]. Similarly, in a meta-analysis, Gallagher *et al.* did not find any significant difference between ergot and non-ergot derivatives, or between pramipexole and ropinirole administration [26]. On the other hand, retrospective reports suggest a different role of specific dopamine receptor agonists, considering their different dopamine receptor affinity [30, 31]. These authors found an increased prevalence of PG in PD patients treated with pramipexole, compared with other dopamine receptor agonists. In these patients, PG improved after switching to ropinirole or tapering pramipexole dose. So, in agreement with these authors, PD patients may develop PG for an excessive stimulation of D3 receptors. The role of DA dose in increasing PG risk is still not clear. Some authors found a relationship between higher doses and PG development, where others did not find any association [26, 39]. Whereas the greatest risk for ICDs development in PD patients is the use of DAs, it is controversial if higher DA doses represent a risk factor [22, 26].

Mood disorders are also considered powerful risk factors, and low performance in cognitive tasks requiring frontal function has recently been reported in association with PG [23, 40].

ICDs have also been observed in up to 7% of patients with RLS treated with either a DA or levodopa monotherapy. In subjects with RLS receiving dopaminergic treatment, predisposing factors for developing an ICD may be higher DA dose, younger onset age, female gender and a family history of gambling disorders [41]. There are few case reports of ICDs in patients with RLS treated with rotigotine, a non-ergot D3/D2/D1 dopamine agonist [42]. The authors observed ICD in 21% of RLS patients treated with this DA.

In these case series, even low doses of rotigotine (mean 3.8 mg/d) was associated with ICD development.

4. CLINICAL MANIFESTATIONS

PG is defined as the inability to resist gambling impulses despite severe repercussion on personal, family or professional life. This behaviour is often under-recognized in clinical practice. Most patients do not spontaneously give information about it, either because of shame or because they do not understand that it is related to PD treatment. Other ICDs observed in PD patients are compulsive sexual behaviour, compulsive shopping and compulsive eating [2]. Lives of patients affected by PG become dominated by gambling behaviour, leading to overwhelming financial burdens, inability to maintain a career, and eventually the disintegration of family relationships [43]. In this way, PG consequences may include a high rate of suicide attempts, increased rates of legal problems, and criminal behaviour [12]. The most frequent PG attitudes are slot machines, lottery scratch cards and bingo, and PG occurs more frequently during the "on" phase [44]. In Far Eastern countries, PG prevalence is higher than in Asia, so cultural differences are thought to have a significant impact on prevalence rates and on PG mode [45]. Furthermore, PG may be seen in association with other psychiatric disorders, such as mood disorders, anxiety disorders, personality disorders, other impulse-control disorders, and alcohol or other substance abuse and dependence [46].

5. ICDs PATHOPHYSIOLOGY

Pathophysiology of ICDs, and particularly PG, involves specific neurotransmitter systems, brain regions and neural circuitries. The main neural pathways seem to be cortico-striato-thalamo-cortical circuitry and mesocorticolimbic pathway for reward and reinforcement processes. Specific pathological changes occurring in PD probably do not play a major role since ICDs are described also in other diseases treated with DA, such as RLS [10, 41, 47].

Different hypotheses for the association between PG and dopaminergic stimulation in PD patients have been suggested. PD is characterized by a massive loss of dopaminergic neurons in the substantia nigra, with a pronounced depletion of dopamine in the nigrostriatal pathway and a decreased stimulation of the striatal D1 and D2 receptors [48]. This depletion leads to disturbance in the cognitive, limbic, and associative corticobasal ganglia-thalamo-cortical loops, and might predispose to the occurrence of ICDs in PD. PD patients, even in the absence of dementia or depression, are likely to show a range of clinically significant impairment in executive functions, most probably linked to degeneration in the basal ganglia-thalamocortical circuits (striatal-frontal tracts), secondary to cell loss within the substantia nigra (SN) (due to decreased dopaminergic transmission in fronto-striatal loops) [49,50]. Recently, some authors showed that medication impaired PD patients' ability to learn from negative decision outcomes, a psychological deficit that also may have relevance to the maintenance of ICD behaviours [51]. There is also some evidence that DA, but not L-dopa, treatment may worsen executive functions in patients affected by early/mild PD [52]. DAs, compared with L-dopa, have significantly greater D3:D2 and D3:D1 striatal receptor activation ratios [38]. The activation of D1 and D2 receptors, located in the dorsal striatum, is associated mainly with the motor effects of the medications. In contrast, the D3 receptor is localized to limbic areas of the brain, including the ventral striatum, and it seems to mediate psychiatric manifestations of dopamine receptor stimulation [53]. Neurodegeneration, and consequently dopamine depletion, in the earliest stages of PD, is most severe in the dorsal striatum and progresses only later to the ventral striatum. L-dopa, in this stage of disease, may improve certain cognitive functions that are associated with the severely depleted dorsal striatum, while at the same time impairing (by 'over-dosing') other cognitive functions, associated with the relatively intact ventral striatum [54]. Thus, one explanation is that excessive, targeted dopamine stimulation of intact ventral striatal receptors in early or mild PD leads to an "overdose" of ventral striatal-cortical circuitry that can manifest itself in the clinical phenomenon of impulsive-compulsive behaviours, such as PG. These behaviours are maintained by ongoing dopaminergic stimulation of a sensitized ventral striatal system, which is manifested clinically as an increased drive for certain behaviours and maintained by an inability to learn from negative decision outcomes [55].

The role of dopaminergic stimulation in ICDs development has been confirmed by several lines of evidence. An increased dopamine release in the brain of pathological gamblers has been suggested, and changes in cerebrospinal fluid (CSF) concentration of monoamines and their metabolites have been described in patients compared to normal controls [56].

Non-ergot dopamine agonists ropinirole and especially pramipexole are relatively selective for D3 receptor subtype. The highest concentration of D3 receptors is found in mesolimbic pathways and in areas such as nucleus accumbens and olfactory tubercle. All these areas are involved in motivation and reward behaviours. PG may be due to an excessive stimulation of this receptor subtype [31,57,58]. When D3 receptor subtype is stimulated too strongly, ICDs may occur [59]. No differences were observed between pramipexole, ropinirole, and pergolide in their association with ICDs [60].

Several functional imaging studies provided further evidences about the involvement of specific brain regions in PG behaviours. Areas such as prefrontal cortex (ventromedial and orbitofrontal areas), ventral striatum (nucleus accumbens) and amygdala showed a reduced activation in pathological gamblers during fMRI studies, suggesting a relationship with aberrant reward and response inhibition [61]. In another fMRI study about motivational and emotional states in men with and without PG, subjects with PG reported stronger gambling urges and showed relatively reduced activation of frontal cortical, basal ganglionic and thalamic brain regions while viewing gambling tapes, during the period prior to the onset of subjective motivational or emotional response [62]. In a [11C] raclopride positron emission tomography (PET) study, Steeves *et al.* assessed dopaminergic functions during gambling in PD patients. PG patients demonstrated a greater reduction in binding potential in the ventral striatum during

gambling compared with control subjects, reflecting greater dopaminergic release. Similar findings are reported in subjects with chemical addictions [63]. In a recent study, the authors found that PD patients with PG have abnormal resting state dysfunction of the mesocortico-limbic network on SPECT imaging, possibly associated with a drug-induced overstimulation of relatively preserved reward-related neuronal systems [64]. All these findings, based on different functional imaging studies, show that PG shares many features with drugs addiction such as the relation with a deficiency of the mesolimbic dopaminergic reward system. Similarly to what has been observed in drugs addicts and in impaired ICDs, a reduced activation in prefrontal cortex (ventromedial area) has been observed in pathological gamblers. These data support the view of PG within the spectrum of behavioural addictive disorder.

All these evidences underline the role of dopaminergic mechanisms in ICDs development. However, not all patients taking DA treatment develop these behaviours and ICDs are probably the result of an interaction between pharmacologic and nonpharmacologic predisposing factors, such as young age, male sex and personality traits [65].

The development of ICDs in patients receiving low doses of dopaminergic drugs suggests that a genetic predisposition may play a role in some cases. Genetic polymorphisms have been reported as possible contributors to ICD susceptibility in PD [66]. Recently, Lee *et al.* described a variant of the serotonin 2A receptor gene (HTR2A) associated with ICDs in PD patients receiving dopamine replacement therapy, mainly those taking low doses of dopaminergic drugs [67].

Other neurotransmitters may have a role in ICDs pathophysiology. Serotonin (5-HT) has been implicated in control over motivated behaviours. Abnormalities in 5-HT function have been described in subjects with PG [68]. Dopamine has been implicated in reinforcing and rewarding behaviours. It has long been associated with these processes in drug addiction, but its role in PG is less clear [4]. Norepinephrine (NE) system has been involved in drug relapse, reward and sensitization, and high NE levels have been observed in CSF and urine samples of subjects with PG as compared to controls [69, 70].

5.1. Serotoninergic and Dopaminergic Systems

Non-motor symptoms in PD, such as PG, are modulated by various neurotransmitter systems. Abnormalities of dopamine receptors and reward pathways, as well as serotoninergic (5-HT) dysfunction, are probably involved [12]. 5-HT levels appear lower in certain brain areas in PD, including the caudate nucleus, putamen, globus pallidus, SN, hypothalamus and thalamus [71, 72]. In these areas, the percentage of 5-HT loss can be as high as 85% in some PD patients [73]. The caudate nucleus appears to be more denervated than the putamen [72,74]. Interestingly, this pattern of 5-HT denervation is the opposite of dopamine denervation in PD, where the loss is more severe in the putamen than the caudate nucleus [73]. Dopamine function, particularly within the mesocorticolimbic pathways, is critical in the mediation of reward and reinforcement behaviours. Basic science research has shown that 5-HT receptors modulate dopaminergic function. Thus, the clinical efficacy of psychotherapeutic drugs that act on 5-HT systems may be due in part to their effects on dopaminergic systems. Most of the effects of 5-HT on dopamine neurons may be indirect, mediated *via* actions on complex neuronal circuitry, rather than direct effects on dopamine terminals.

There are three major dopamine pathways in the brain [74]. The nigrostriatal pathway connects the substantia nigra pars compacta (SNpc) to the dorsal striatum (caudate-putamen). Degeneration of these neurons results in the subsequent motor deficits of PD. The mesolimbic pathway originates in the ventral tegmental area (VTA) and terminates in the nucleus accumbens (NA); one function of this system is the mediation of natural and drug-induced reward [75]. The mesocortical dopamine pathway, which also originates in the VTA but terminates in the prefrontal cortex (PFC), regulates complex cognitive processes such as selective attention and working memory.

The cell bodies and terminal regions of all three dopamine pathways are innervated by 5-HT neurons originating in the medial and dorsal raphe nuclei. There are direct synaptic contacts between 5-HT terminals and dopamine cells in the midbrain [76]. Thus, 5-HT could potentially regulate the function of dopamine neurons *via* actions on midbrain dopamine cell bodies and/or dopamine terminals.

There are seven main types of 5-HT receptors with subtypes of most of these, for a total of at least 14 different receptors [77]. With the exception of the constitutively active 5-HT2C receptor, the other 5-HT receptor subtypes do not appear to tonically modulate dopaminergic activity, as evidenced by the lack of effect of antagonist treatments alone. On the other hand, 5-HT receptors are, nearly all, capable of regulating dopamine activity when 5-HT tone is elevated, or when they are stimulated by exogenous agonists. These effects are often indirect and mediated by complex neuronal circuitry involving other transmitters. 5-HT2A and 5-HT1A receptors are thought to be localized to pyramidal glutamatergic neurons in the medial PFC, and to regulate dopamine function through 'long-loop' feedback to the VTA. 5-HT2A receptors could play a role in PG and impulsive-compulsive behaviours in PD. The single nucleotide polymorphism His452Tyr has been described to be associated with PG in PD, whereas the T102C variant of the allele T102 might predispose to impulsive compulsive behaviour in PD patients taking low-dose dopaminergic drugs [78, 79].

There is evidence that 5-HT2C and 5-HT1B receptors in the VTA regulate mesocorticolimbic dopamine neurons indirectly by influencing GABA release from their host cells [74, 80].

6. MANAGEMENT OF ICDs IN PD

Management of ICDs in patients with PD is complex. It could be demanding and it has long been based on case reports, with limited data to support any particular therapeutic strategy. The association of DA therapy and ICDs suggests that modifications in dopaminergic treatment may be effective. In agreement with empirical data, compulsive behaviours often resolve after DA tapering, switching to a different agonist or discontinuing DA entirely

[30, 31, 81]. In a recent publication on long-term clinical outcomes of ICDs in patients with PD, the authors reported that 80% of patients discontinuing or significantly decreasing DA doses, or switching to a different agonist, experienced full or partial remission of ICD symptoms [31, 82]. The effectiveness of changing agonists is not entirely clear and some patients do not experience remission of ICD symptoms with these strategies, suggesting a complex aetiology. Many PD patients are reluctant to discontinue DA treatment because of the motor benefits associated with their use. Moreover, when reducing DA doses, a withdrawal syndrome (DAWS) may occur in a subset of patients, causing profound disability. Symptoms such as anxiety, dysphoria, diaphoresis, fatigue, pain, and drug cravings could develop. So physicians should monitor patients carefully. In a retrospective study of PD patients, all subjects with DAWS had baseline DA-related ICDs [83].

An important first step in ICDs management is to minimize the risk of their development by preventing them. Before starting dopaminergic treatment, risk factors such as male sex, young age and a history of drug abuse should be taken into consideration. Another aspect is to identify subjects with ICDs, also involving partners or other family members. There is only very limited data supporting the use of psychiatric drugs for ICDs in PD. Given the neurobiological similarities between PG and substance use disorders, it has been suggested that specific pharmacotherapies may be helpful in treating PG. A range of psychiatric treatments, such as atypical antipsychotics, antidepressants, mood stabilizers and various psychosocial interventions have been proposed to treat PD patients with ICDs [30, 84]. The role of these various agents in the management of ICDs is not well established as the data are primarily case reports [7]. There is only empirical evidence to support their use for this indication in non-PD subjects, and no empirical evidence has been reported in PD patients [85, 86].

6.1. Serotonin Reuptake Inhibitors (SSRIs)

Serotonin system has long been associated with impulse control and different studies support its role in PG [61, 85]. Decreased serotonin function within ventral medial prefrontal cortex may cause disinhibition and contribute to PG development. In this way, drugs affecting serotonin neurotransmission may represent potential treatment for PG. Various clinical trials have investigated SSRI role in ICDs treatment [87, 88]. SSRI, though effective in obsessive-compulsive disorders, provide questionable benefit in ICDs, since they may facilitate dopaminergic transmission and could worsen ICDs. In a randomize, double-blind, crossover trial on fluvoxamine versus placebo for PG treatment, fluvoxamine was associated with a statistically significant improvement in PG symptoms [89]. Another study on the same drug failed to demonstrate its efficacy in treating PG [90]. Two studies analyzed paroxetine effects on PG symptoms. The first one, a randomized, double-blind, placebo-controlled trial, showed a significant improvements in Gambling Symptoms Assessment Scale scores in patients taking paroxetine [91]. The other one failed to demonstrate a statistically significant improvement on PG between active drug and placebo groups [92]. Sertraline, another SSRI, did not prove to be superior to placebo, without any significant effect on PG, in a double-blind, placebo-controlled trial [93]. Citalopram seems to be an effective treatment for PG in the general population [94]. All these studies show some short-term efficacy of SSRIs in PG treatment in the general population, suggesting that they may be helpful in subgroups of patients (those with co-occurring anxiety or mood disorders). Moreover, these drugs seem to be effective on PG at higher doses compared to that used in depressive disorders.

Existing reports on the efficacy of SSRI for ICDs treatment in patients with PD have not been encouraging [95]. Moreover, among patients with PD, SSRIs may worsen tremor in about 5% of cases and occasionally they may induce an increase in akinesia and rigidity or a decline in gait [96,97].

6.2. Mood Stabilizers and Antipsychotics

Lithium carbonate was studied in a placebo controlled trial in patients with PG and bipolar disorders. Lithium showed a greater effectiveness on gambling and manic symptoms compared to placebo [98]. Lithium and valproate have been reported to be useful in ICDs control [84].

The role of atypical antipsychotics in PG treatment is not well established, since data are basically case reports. The efficacy of low-dose risperidone in controlling PG behaviour in PD patients has been reported [9, 31, 58]. Sevincok *et al*. observed a favourable effect of high-dose quetiapine in controlling gambling behaviour in a patient with PD [99]. Emerging evidence indicates that N-desmethylclozapine, the major active plasma metabolite of the atypical antipsychotic clozapine, which has been safely used in the treatment of Levodopa-induced psychosis in PD, has a potent partial agonist activity on dopamine D2/D3 receptors [100,101]. In a series of three cases, Rotondo *et al.* report the effectiveness of clozapine treatment on persistent PG following discontinuation of DA therapy [102]. All cases had a life-time history of major depressive disorder and/or alcohol abuse, confirming that predisposition for mood and addiction disorders is a risk factor for PG development in PD patients taking DA, and it unmasks the pre-existing disorder after DA discontinuation [25]. Only a few other studies report clozapine effectiveness on compulsive behaviours in PD patients treated with DA [95,103]. The use of clozapine requires careful monitoring because of potential risk of agranulocytosis [100].

The only controlled studies of an atypical antipsychotic drug for PG in non-PD subjects were performed on olanzapine, a dopamine and 5-HT2A antagonist. These studies showed that olanzapine is not effective in PG treatment [85,104,105].

Recently, some authors found that partial dopamine D2/D3 receptor agonists, such as aripiprazole, may be effective, probably more than D2/D3 antagonists, in treating impulsive/compulsive and addictive behaviours *via* regulation of reward pathway circuitries [106,107]. However, the use of aripiprazole in PD is controversial and recent findings show that this drug may be associated with an exacerbation of motor symptoms [108].

A randomized, double-blind, placebo-controlled trial failed to demonstrate a positive effect of bupropion, a drug with monoamine reuptake inhibition and nicotinic receptor antagonism properties, on PG symptoms compared with placebo [109].

An efficacy of glutamatergic therapies (such as riluzole) in ICDs treatment is suggested only by preliminary evidence of a beneficial effect of riluzole on a patient with trichotillomania [110,111].

Topiramate may have a role in the field of ICDs treatment. It has been known to have a positive effect on binge eating disorder associated with obesity, PG and compulsive impulsive sexual behaviours in patients with psychiatric disorders [112,113]. Topiramate has multiple mechanisms of action, and recently it has been shown to inhibit levodopa-induced dyskinesia in animal models, suggesting a possible inhibitory effect on dopaminergic drugs [114]. In a recent case report, the authors suggest that topiramate may be an effective therapy in PD patients with PG [115].

In a controlled study on PG in subjects with PD, amantadine was shown to be effective for PG symptom control in all patients [116]. However, it is worth noting that, in a cross-sectional study, amantadine administration was associated with one or more ICDs development, such as compulsive gambling, sexual behavior, and shopping [22].

An open non-randomized trial on zonisamide in fifteen PD patients with ICDs demonstrated a marked reduction in impulsive behaviour severity, without clinically significant side effects [117]. To be confirmed, these preliminary observations need additional corroboration.

6.3. Opioid Antagonists

Dopaminergic systems that influence rewarding and reinforcing behaviours have been implicated in PG. Gambling triggers dopamine release, which in turn may reinforce the pathological behaviour [118]. Opioid antagonists are thought to decrease dopamine neurotransimission in the nucleus accumbens and in the motivational neurocircuitry. Opioid receptor antagonist efficacy have been studied in PG treatment for their indirect modulation of mesolimbic dopamine circuitry and their role in alcohol and opiate dependence treatment [118]. In non-PD patients, a positive effect of naltrexone in PG treatment was demonstrated in a double-blind, placebo-controlled trial, with a statistically and clinically significant difference. Naltrexone was more effective in gamblers with more severe urges than in those who describe their urges to gamble as moderate [119]. An open-label study suggested naltrexone efficacy in reducing urge intensity to gamble when given in high doses (50 to 250 mg/day) [120]. These data were confirmed in another study in which naltrexone was administered at doses typically used in alcohol or opiate dependence, with a good safety profile [121]. However, clinical use of naltrexone is limited by its side effects. In a case report series, Bosco *et al.* observed that naltrexone could be an effective option for PG treatment in PD patients who develop PG after DA therapy. In this series, PG did not improve after reduction or discontinuation of DA. Patients responded poorly to SSRI, while treatment with opioid antagonist naltrexone resulted in PG remission [122].

Nalmefene, another opioid antagonist, has been found to be effective in non-PD subjects with PG. It was studied in a multicentre, double-blind, placebo-controlled trial, showing a positive effect of nalmefene on achieving PG symptom control, but its efficacy is connected with dosage [123]. Another multicentre randomized controlled trial demonstrated that low dose nalmefene (25 mg/day) is effective on PG symptoms in the short-term, with few adverse events and without the dose-dependent hepatotoxicity of naltrexone [124]. Additional studies are required to evaluate its long-term efficacy and tolerability.

6.4. Behavioural Therapies

When pharmacological treatments fail or in addition to them, psychosocial interventions may be considered in ICD management. Involving patient's partner or other family members in the management of PG may be useful. Counselling and limiting access to money and medications in conjunction with tapering DA treatment have been effective in some patients [2]. Several non-pharmacological treatments have been studied in PG, such as behavioural, cognitive, and psychoanalytic therapy. Cognitive behavioural therapy or attendance at Gamblers Anonymous meetings may play a role in selected groups of patients with PG, having been associated with better outcome in non-PD subjects [125]. They were seen effective on gambling severity and frequency, and these effects were maintained over time [126,127]. However, their effectiveness has not been examined in subjects with PD.

6.5. Deep brain Stimulation

Deep brain stimulation (DBS) surgery of the subthalamic nucleus (STN) or globus pallidus internus may markedly improve "off"-medication motor symptoms, and STN DBS has the potential to allow significant reduction in drug dose [128]. Therefore, STN DBS could be seen as a treatment option for patient with dopaminergic drug related behaviours. However, the relationship between DBS and ICDs seems to be complex. The efficacy of STN stimulation for ICDs in PD patients has not been fully clarified. Existing data are contradictory. Some case series suggest that bilateral DBS of STN may improve ICDs, allowing a decrease in levodopa dose or DA discontinuation [129]. Other evidence shows that ICDs may begin in the early postoperative period, and 71% of patients with pre-operative ICDs remained unimproved or worsened post-operatively [130-133]. Up to date, ICDs should not be considered an indication for DBS.

7. CONCLUSIONS

Management of ICDs, and particularly PG, in patients with PD taking DA, is based on patient and caregiver education, modification of dopamine replacement therapy, and in some cases administration of psychoactive drugs such as mood stabilizers, atypical antipsychotics, and opioid antagonists (see Fig. **1**). If an ICD has been identified, the treatment of choice is DA tapering to the lowest effective daily dose, with an improvement in ICD symptoms over time. In addition, switching dopamine agonist therapies and

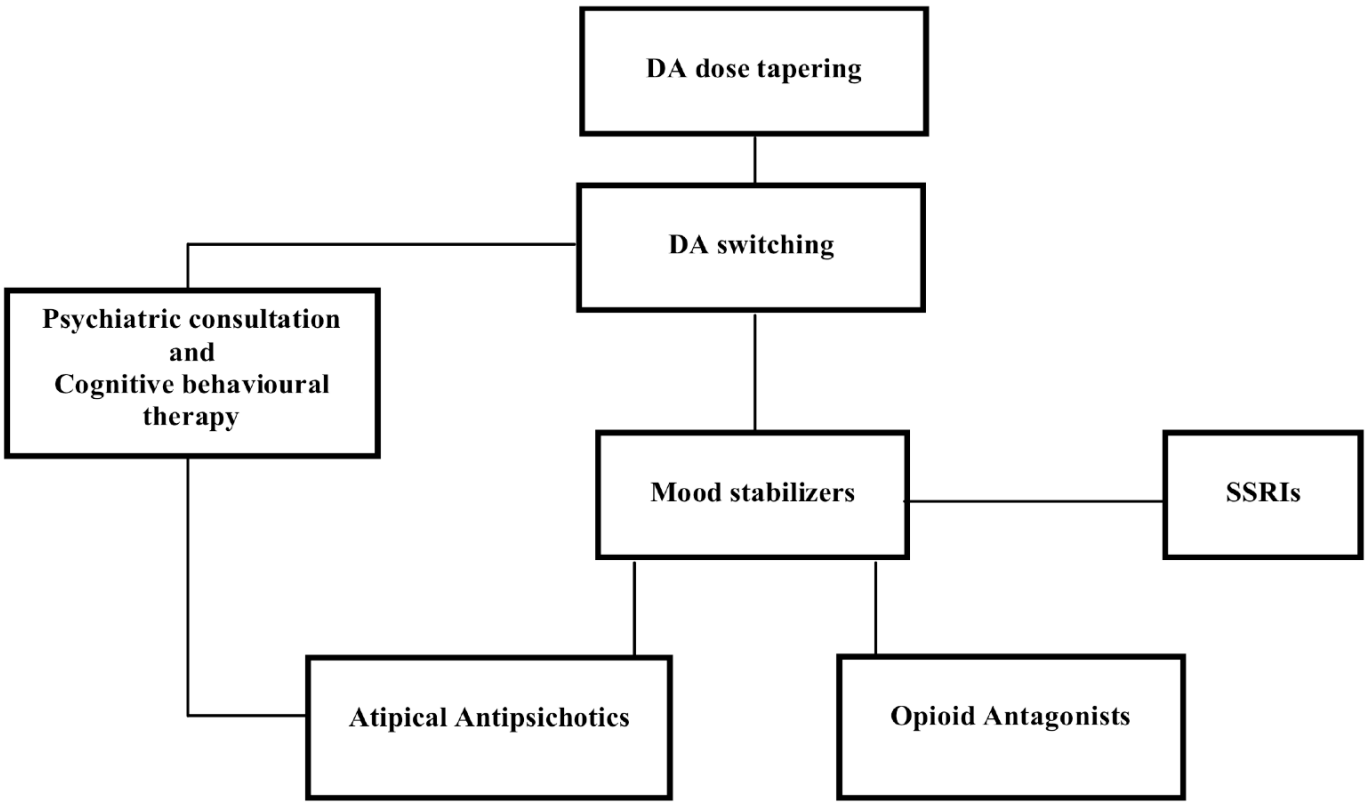

Fig. (1). Clinical management of pathological gambling in Parkinson's disease. Proposed scheme for clinical management of PG in patients with PD. DA tapering to the lowest effective daily dose is the first step. If symptoms do not improve over time, switching dopamine agonist therapies and a concomitant increase in L-dopa treatment may be considered. Mood stabilizers, atypical antipsychotics, opioid antagonists and SSRIs represent a secondary line of therapy. Psychosocial interventions, such as counselling and cognitive behavioural therapy, can be useful as an adjunctive treatment. Most of these interventions are used for impulse control disorders in populations without PD and limited data support their use in PD (see text). DA: dopamine agonist; SSRIs: serotonin reuptake inhibitors.

a concomitant increase in L-dopa treatment may be considered. Psychoactive drugs represent a secondary line of therapy, although there is no empirical evidence supporting their role in PD. Finally psychosocial interventions, such as counselling and cognitive behavioural therapy, can be useful as an adjunctive treatment.

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CONFLICT OF INTEREST

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