MANAGEMENT OF ENDOCRINE DISEASE

Impulse control disorders in patients with hyperprolactinemia treated with dopamine agonists: how much should we worry?

Maya Barake¹, Anne Klibanski² and Nicholas A Tritos²
¹Clemenceau Medical Center, Beirut, Lebanon and ²Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Abstract

Dopamine agonists (DAs) represent a cornerstone in the management of patients with hyperprolactinemia and have an important role in the treatment of neurologic disorders, including Parkinson’s disease and restless legs syndrome. A growing body of evidence has identified impulse control disorders (ICDs) as possible adverse effects of DA therapy. A variety of ICDs may occur in patients treated with DA, including compulsive shopping, pathologic gambling, stealing, hypersexuality and punding (repetitive performance of tasks, such as collecting, sorting, disassembling and assembling objects). These behaviors can have devastating effects on patients’ life and family. In the present review article, we summarize available data on ICDs in patients with hyperprolactinemia as well as other disorders. Possible risk factors for the emergence of ICDs in patients treated with DA are discussed and the putative pathophysiologic mechanisms underlying the development of ICDs in this setting are reviewed. In addition, strategies for the early identification and management of ICDs in patients on DA are discussed. In conclusion, a wide variety of ICDs can occur in patients treated with DA, including those with hyperprolactinemia. The development of ICDs can have serious implications for patients’ well-being and family. Endocrinologists and other physicians involved in the care of patients on DA therapy must be aware of this potential adverse effect, counsel patients regarding pertinent symptoms and regularly evaluate treated patients for the development of ICDs. Early detection of ICDs and discontinuation of DA therapy can mitigate the potential harms associated with ICDs in these patients.

Introduction

Dopamine agonists (DAs) constitute the primary therapy of prolactinomas, which are the most common type of functioning pituitary tumors (1). Treatment is indicated for all macroprolactinomas and for symptomatic microprolactinomas resulting in oligomenorrhea, amenorrhea, infertility, testosterone deficiency in men or bothersome galactorrhea (2).

Dopamine agonists exert their therapeutic effect through binding and activation of D2 receptors, resulting in decrease in prolactin levels, tumor shrinkage and restoration of gonadal function in the majority of treated patients. Available DA include cabergoline, bromocriptine and quinagolide (the last one is not available in the United States) (1). Treatment with DA is often prolonged. When prolactin levels remain normal for at least 2 years and the tumor is no longer visible on scan or shrinks by more than 50% over baseline is >5 mm away from the optic chiasm, gradual treatment withdrawal may be considered. However, this is often not possible in many patients with macroprolactinomas or a subset of patients...
with microadenomas who do not normalize prolactin levels despite small tumor size (2, 3).

Dopamine agonists generally have a favorable side-effect profile. However, with the potential for a prolonged treatment period, concern for long-term safety arises. The most common treatment-related adverse events are gastrointestinal (nausea), thought to be mediated through the 5-HT1 receptor and orthostasis, through interaction with the D1 receptor (4). In the past decade, the potential for some ergot-derived dopamine agonists to increase the risk of cardiac-valve regurgitation was raised following the publication of data in patients with Parkinson’s disease (PD) (5, 6). However, the daily cabergoline dose used in patients with this adverse effect exceeded 3 mg and the treatment duration was at least 6 months (5). The proposed mechanism for this effect is drug interaction with the 5-HT2B receptor (7). In the usual doses used for the treatment of hyperprolactinemia, most evidence from echocardiographic studies did not suggest an increased risk of clinically significant valvular disease in association with dopamine agonists (8, 9).

Throughout the years, concerns regarding an association between DA and psychiatric manifestations, namely increased impulsivity and impulse control disorders (ICDs) became recognized (10). In contrast to PD patients, who may experience psychiatric symptomatology (anxiety, depression, apathy, psychosis) in the absence of therapy, hyperprolactinemia has not been associated with ICDs in the absence of dopamine agonist therapy (11).

The aims of the present article are to review data on impulsivity and ICDs in patients receiving DA therapy, with emphasis on data in patients treated for hyperprolactinemia.

Methods

A review of available literature was performed using the electronic databases PubMed and MEDLINE from their inception up until July 2018. We used the keywords impulsivity, impulse control disorders, dopamine agonists, hyperprolactinemia, prolactinomas. We included relevant articles with no language limitation.

Impulsivity and impulse control disorders

Impulsivity has been defined as the urge experienced by an individual to perform certain behaviors like shopping or gambling, with low regard for their potential negative consequences (12). Impulse control disorders are a class of psychiatric disorders characterized by failure to resist an impulse to perform a certain activity with the potential for an immediate reward, disregarding the future potential harms for the individual, whether financial, social or health related. As in other psychiatric derangements, the condition becomes a disorder when it interferes with the person’s daily living, interpersonal relations and social wellbeing (13). Indeed, ICDs have the potential to result in significant and lasting social, financial and interpersonal problems for the patient and his or her family.

Depending on the pursued impulse, ICDs may include compulsive shopping, pathologic gambling, hypersexuality, stealing (kleptomania), hair pulling (trichotillomania), punding (repetitive performance of tasks, such as collecting, sorting, disassembling and assembling objects). In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), ICDs have been classified as psychiatric conditions among the ‘Disruptive, Impulse Control, and Conduct Disorders’ (13). Pathologic gambling has been classified as part of addictive disorders (13). Formal definitions for the different ICDs do exist, however, due to the potential for subjectivity in the evaluation of such disorders, there may be substantial heterogeneity in the available literature addressing this problem. Impulsivity can be better quantified using self-report questionnaires and through more objective psychometric tests. Available questionnaires measure responses to reward, punishment, attention, planning and subdivide impulsivity into different domains. Examples of existing questionnaires include the Behavioral Inhibition/Activation system and the Barratt Impulsiveness Scale (14, 15, 16). Psychometric tests also include computerized validated instruments with actual risk-taking behavior or choice between immediate or delayed rewards, including the Balloon Analog Risk Task and the Experiential Discounting Task (17, 18).

While ICDs may have different clinical presentations, they all share the same biologic substrate within the mesocorticolimbic pathway. With cell bodies located in the ventral tegmental area, the pathway involves neurons projecting to the limbic system and the frontal cortex (19). This dopaminergic pathway has been implicated in mediating reward-related behavior. And as such, increasing dopamine levels or stimulating dopamine receptors within the mesocorticolimbic system is postulated to promote behaviors with the possibility of immediate reward and increase impulsive choices (20, 21). Dopamine agonists used for the treatment of PD or restless leg syndrome, while designed for the stimulation...
of the nigrostriatal dopaminergic pathway involved in control of motor function, may also stimulate dopamine receptors within the reward mesolimbic tract, resulting in ICDs. Similarly, DA used to treat hyperprolactinemia through activation of the tuberoinfundibular pathway may also increase impulsivity through stimulation of the reward system (19, 20, 21).

Dopamine action in diverse available pathways is mediated through binding to dopamine receptors, namely D2 and D3. D2 receptors are localized within the caudate nucleus, the putamen, the nucleus accumbens and the substantia nigra. Anti-Parkinsonian effect is mediated through D2 receptor activation (22). Similarly, the dopamine receptor responsible for inhibiting prolactin release from the pituitary is the D2 receptor (23). D3 receptors are present in the regions containing D2 receptors, but are also highly expressed within the limbic system, in the frontal cortex and the thalamus. It is postulated that the development of ICDs with dopamine agonist treatment occurs via excessive stimulation of D3 receptors (22, 24, 25).

Impulse control disorders in Parkinson’s disease and disorders other than hyperprolactinemia

Prevalence

Impulse control disorders were reported as early as dopamine agonists were approved for the treatment of PD. In the largest cross-sectional Dominion study conducted in the USA and Canada, the prevalence of one or more ICDs in PD patients was 13.6% (26). The most commonly reported ICD was compulsive shopping (5.7%) followed by gambling (5%), compulsive eating (4.3%) and hypersexuality (3.5%). Of note, 3.9% of patients had more than one ICD (26). A comparable overall ICD prevalence was reported in a large Asian study (27). In a case–control study evaluating ICDs in restless legs syndrome (RLS), the prevalence of any ICD was 17%, while the frequencies of specific ICDs were as follows: 9% compulsive shopping, 5% pathologic gambling, 11% compulsive eating, 3% hypersexuality and 7% punding (28). Results were statistically significant when compared to a control population, except for hypersexuality and compulsive eating (28). In a recent systematic review, the prevalence of ICDs in PD treated with a DA ranged between 2.6 and 34.8% (19). In RLS, a typically lower prevalence of ICDs was reported, ranging between 7.1 and 11.4% (19). In a retrospective analysis of data from the FDA Adverse Event Reporting System, collected between 2003 and 2012, 61.7% of ICDs reported among patients on DA occurred in Parkinson’s disease, while 23.8% were seen in patients with restless legs syndrome (25).

Up until recently, epidemiologic data regarding ICDs were derived from cross-sectional and retrospective studies. In a newly published longitudinal study, 411 patients with PD were followed annually for up to 5 years and were formally evaluated yearly using semistructured interviews for the occurrence of an ICD. ICD prevalence increased from 19.7% at baseline to 32.8% at 5 years of therapy (29). Among the 306 patients without an ICD at baseline, the 5-year cumulative incidence of ICDs was 46.1%. In patients who ever used a DA in the follow-up period, the ICD prevalence was 51.5%, while in those who were never treated with a DA, the prevalence was 12.4% (29).

Although ICDs are not rare in PD, they may go undetected unless physicians specifically inquire about their presence during discussions with patients, as well as with their families. Even when physicians are aware of this adverse event, it may remain unknown in more than 50% of patients who suffer from an ICD; due to the personal nature of some of the symptoms of these disorders (including changes in sexual behavior or tendency to gamble), individuals may not spontaneously disclose them. In the series by Weiss et al., the detection of an ICD would have been missed in more than half of cases if physicians had not interviewed caregivers (30).

Screening instruments may be helpful to objectively determine the presence of an ICD. In PD, a specific questionnaire, named the Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease-Rating Scale (QUIP-RS), has been studied and validated to diagnose and measure the severity of ICD symptoms (31).

Risk factors

Patient related In the Dominion study, PD patients developing ICDs were compared to PD patients who remained free of this adverse effect. Significant demographic factors observed more frequently in the ICD group were younger age, smoking and single status (26). Hypersexuality and compulsive gambling occurred more commonly in men, while compulsive shopping and eating were more frequent in women (26). Similarly, in a published series of 15 PD patients developing hypersexuality on DA, all were men (24). Male gender was also an independent predictor for developing an ICD in general (19).

The presence of a mental illness or of certain psychological traits were found to correlate with the
prevalence of an ICD in several studies (19). Namely, the prevalence of a depressive or anxiety disorder or of depressive or anxiety traits on psychological surveys was significantly higher in PD patients who developed an ICD, as compared to those who did not (19, 21, 26). Other traits potentially related to ICD development include obsessive-compulsive symptoms, novelty seeking, ineffective coping skills and inability to perform well in decision-making tasks (19, 21). When looking at subtypes of ICDs, certain personality traits were more commonly related to specific ICDs but not to others, including the specific association of novelty seeking with compulsive shopping and gambling (21).

Disease related Different studies concluded that a younger age at onset of PD and a longer disease duration are linked to ICD prevalence (19). Certain studies, but not others, related the occurrence of an ICD to those patients with higher frequency of motor complications and a more substantial functional impairment (19).

Treatment related

Type of DA In the FDA report, the strongest safety signal for an ICD was for the DA pramipexole, followed by ropinirole (25). Both drugs share a preferential affinity for the D3 dopamine receptor and are commonly prescribed in PD (25). Indeed, the affinity of both dopamine agonists for the D3 receptor, primarily localized within the limbic system, is at least 100 times more than for D2, which likely explains their more frequent implication in ICDs (24). Similarly, in the systematic review by Grall-Bronnec, all FDA-approved DAs (pramipexole, ropinirole, cabergoline, bromocriptine, rotigotine and apomorphine) were associated with ICDs, but the strongest association was for pramipexole and ropinirole (19).

Dose and duration of DA In a multicenter cross-sectional survey conducted among 1167 PD patients, a positive dose–response relationship was observed between the dose of the DA and the odds ratio for developing compulsive shopping, gambling and hypersexuality but not for compulsive eating (27). In another survey investigating ICDs among PD patients, individuals who developed ICDs were exposed to higher cumulative DA doses than those free of an ICD (32). A positive non-linear dose–response relationship was obtained between DA and frequency of ICDs (32). Such a relationship was not observed in the Dominion study (26). The influence of treatment duration on the risk of an ICD was inconsistent among retrieved trials included in a systematic review, with some studies showing a relation between longer treatment duration and ICD occurrence, while others did not find a significant correlation (19). While the findings of cross-sectional studies were inconsistent, a recent longitudinal follow-up of PD patients on DAs clarified this association. Both treatment dose and treatment duration were independently positively associated with ICD prevalence, with a significant dose–effect relationship but no clearcut threshold (29).

Management

Prevention of the occurrence of an ICD can be considered as the best first step in management. In patients with higher predisposition to develop an ICD, including individuals with affective disorders, DAs should be used with caution and with close follow-up by the patients’ psychiatrist. It has been proposed that all patients who are prescribed a DA as well as their families (if possible) be counseled about this potential side effect, in order to allow early detection before the occurrence of significant financial and social problems (30).

In the event that an ICD occurs in a PD patient, the first consideration would be to decrease the dose of the DA or stop it. This has been associated, in certain studies, with remission or significant symptomatic improvement of the ICD (21, 33). In the longitudinal follow-up study on ICDs in PD, ICDs resolved in 50% of patients 1 year after treatment discontinuation (29). However, this may come at the expense of motor function deterioration and the occurrence of DA withdrawal syndrome (19).

Attempts at resorting to subthalamic deep brain stimulation to treat PD while cutting back on DA therapy to help with ICD control yielded controversial results. Initial case reports suggested that this method may be a suitable solution, mainly by allowing reduction or discontinuation of DA therapy post-operatively (34). However, more recent reports had inconsistent results with possible exacerbation of the ICD (35).

Other potential therapeutic options include cognitive behavioral therapy and specific pharmacological options (19). Medications administered to PD patients who developed an ICD comprise certain anti-epileptic drugs, including valproic acid and topiramate, as well as antidepressant drugs, including serotonin reuptake inhibitors and atypical antipsychotics. Effects from the use of these specific medications have been inconsistent, and each medication is associated with its own possible adverse effects (19, 21, 30).
Impulse control disorders in hyperprolactinemia

Prevalence

An association between DA use and impulsivity in hyperprolactinemia was first published in 2007. Davie et al. reported on a 38-year-old woman with a microprolactinoma who developed pathologic gambling 1 year after starting cabergoline (36). Her symptoms resolved 2 months after stopping the medication (36). In 2009, Falhammar reported a second case of ICD in a patient with pathologic gambling and hypersexuality despite low testosterone levels; this was a 50-year-old man with a microprolactinoma treated with cabergoline (37). Similarly, his behavior returned to baseline after withdrawal of the DA (37). A few other cases were reported thereafter, in both men and women, both with bromocriptine as well as with cabergoline use (38, 39, 40, 41). Interestingly, Almanzar reported on a middle-aged woman who developed compulsive shopping while treated with bromocriptine, and subsequently, compulsive gambling when switched to cabergoline (38).

Accurate epidemiologic surveys on the prevalence of ICDs in DA-treated hyperprolactinemic individuals are still lacking. Current evidence is mostly derived from retrospective reviews, case reports and cross-sectional studies. In 2014, a retrospective analysis of 1580 events of DA-associated ICDs reported to the FDA found that 3.5% of these events occurred in patients treated for hyperprolactinemia (25). In 2011, Martinkova et al. used a structured interview to screen for ICDs in twenty consecutive patients with prolactinomas treated with DAs (42) (Table 1). Two patients (10%) were diagnosed with an ICD (42). In 2014, we formally screened 30 individuals for impulsivity, including 10 hyperprolactinemic patients on DAs compared to two control groups, one with untreated hyperprolactinemia (n=10) and a second one with pituitary lesions and normoprolactinemia (n=10) in a cross-sectional pilot study (43). We used validated psychometric tests, including both self-report questionnaires and computer-based tasks. Patients treated with DAs had a higher score in one measure of impulsivity, the attention subscale of the Barratt Impulsiveness Scale, despite the lack of evident ICDs (43). In parallel, in a postal survey, Bancos et al. evaluated impulsivity in 77 patients with prolactinomas with current or past use of DAs (mean age 54.6 years), as compared to 70 patients with non-functioning adenomas (mean age 56.9 years) (44).

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Number of participants</th>
<th>Screening method for ICD</th>
<th>Number of patients with ICD (%)</th>
<th>DA type/dose</th>
<th>ICD type</th>
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<tbody>
<tr>
<td>Martinkova et al., 2011 (42)</td>
<td>Cross-sectional</td>
<td>20</td>
<td>Screening questionnaire (MIDI)</td>
<td>2 (10%)</td>
<td>Cabergoline 4 mg/week</td>
<td>Compulsive eating</td>
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<td>Bromocriptine 7.5–15 mg/day</td>
<td>Pathologic gambling</td>
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<td>Quinagolide 150 µg/day</td>
<td>Hypersexuality</td>
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<td>Barake et al., 2014 (43)</td>
<td>Cross-sectional (2 control groups)</td>
<td>30</td>
<td>Self-report questionnaires (BIS/BAS, BIS 11) + computer-based tests (BART/EDT)</td>
<td>NA</td>
<td>All patients except 1 on CAB (mean dose 1.1 mg)</td>
<td>Higher score in the attention subscale of BIS 11</td>
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<tr>
<td>Bancos et al., 2014 (44)</td>
<td>Cross-sectional (1 control group)</td>
<td>147</td>
<td>Four-part screening questionnaire sent by postal survey* + telephone interview of patients with positive answers</td>
<td>ICD prevalence on DA vs not on DA (24.68% vs 17.1% P=0.03) In subgroup analysis, ICD prevalence in men on DA vs not on DA (27.7% vs 3.7% P=0.01)</td>
<td>53% on CAB (median dose 1 mg/week), 29% on BRC (median dose 26.25 mg/week)</td>
<td>Hypersexuality significantly more with DA vs not on DA</td>
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*Four-part questionnaire including: Modified hypersexuality questionnaire, MIDI, modified South Oaks Gambling Screen, modified punding questionnaire. BART, Balloon Analog Risk Take; BIS 11, Barratt Impulsiveness Scale; BIS/BAS, Behavioral Inhibition/Activation System; BRC, bromocriptine; CAB, cabergoline; EDT, Experiential Discounting Task; MIDI, Minnesota Impulse Disorder Interview.
The median weekly dose of the DA was 1 mg for cabergoline and 26.25 mg for bromocriptine. The prevalence of ICDs was non-significantly higher in DA-treated patients (24.68%) than in the control group (17.1%). When studied according to the type of ICD, hypersexuality was associated with DA use (P=0.03). In subgroup analysis, men, but not women, had a higher ICD frequency in association with the use of a DA (44).

A variety of ICD types were reported in patients with prolactinomas treated with DAs, including compulsive gambling, shopping, eating, punding and hypersexuality. Case reports mainly described compulsive gambling and hypersexuality. Whether these particular ICDs are more commonly induced by DAs in prolactinoma patients cannot be definitively established. In the study by Bancos et al., hypersexuality was the most commonly reported ICD and the only type whose prevalence was significantly different from the non-functioning adenoma group (44). Only one out of the ten patients reporting hypersexuality had hypogonadism, which was appropriately treated with testosterone replacement (44). Patients can develop one or more ICDs, as suggested in the literature (37, 38, 41).

Risk factors

Patient related A striking gender effect on the occurrence of an ICD in association with DAs was recounted by Bancos et al. (44). In their survey, men with prolactinomas treated with a DA were 9.9 times more likely to develop an ICD than men with non-functioning adenomas. Concurrently, no difference in ICD prevalence was found between women in both groups (44).

A potential association between a specific type of ICD, hypersexuality and male gender has been hypothesized by De Sousa et al. (45). In a case series, the authors recently reported on eight men with prolactinomas who were treated with a DA and subsequent development of disruptive hypersexuality (45). The authors hypothesized that the relatively rapid increase and restoration of testosterone levels to normal, along with stimulation of reward pathways by the DA might have induced hypersexuality. This observed effect was termed ‘dopa-testotoxicosis’ (45). It was also suggested that a decrease in prolactin levels induced by DA therapy may contribute to improvement in erectile function, which could also potentially contribute to the higher hypersexuality in this patient population (45, 46). On the other hand, despite a similar increase in testosterone levels through either testosterone replacement or surgical resection of the prolactinoma, four patients in the same study showed no evidence of hypersexuality, suggesting that the causative factor for the ICD was likely exposure to the DA. Moreover, two patients who developed this ICD did not have hypogonadism at baseline and had normal testosterone levels. It should be noted that there has been no evidence of hypersexuality developing in patients with hypogonadism who receive testosterone replacement (47).

Whether ICDs occur more commonly in patients with certain predisposing psychologic traits or psychiatric disorders is not clear. Almanzar reported on a middle-aged woman with history of depression who initially developed compulsive shopping, then compulsive gambling on DAs (38). Other reported cases in the literature did not have a known psychiatric background. Similarly, in the cross-sectional observational study by Bancos et al., no difference in the prevalence of psychiatric disorders was observed between patients treated with DAs and the control group (44). Some prolactinoma patients, however, are newly diagnosed with a psychiatric problem alongside with the ICD. Whether they already had an undiagnosed disease or a predisposition to develop one that was unmasked by the DA therapy is not clear. The patient reported by Davie was diagnosed with both pathologic gambling, major depression and paranoid delusions after starting cabergoline (36).

Disease related ICDs have been reported in patients with either macro- or microprolactinomas and variable prolactin levels without an evident relationship between tumor size or prolactin level and ICD risk.

Treatment related In many countries, DA used in the treatment of hyperprolactinemia include bromocriptine and cabergoline, with a general preferential use of cabergoline due to higher efficacy, easier dosing schedule and fewer side effects (1). In certain countries outside the United States, quinagolide, a non-ergot dopamine agonist, is also used in the treatment of hyperprolactinemia. Whether ICDs are induced more frequently by one DA versus another and at a specific dose threshold or certain treatment duration has not been clearly established. It has been postulated that higher affinity to D3 receptors, as compared to D2 receptors, is associated with a higher prevalence of ICDs. Both cabergoline and bromocriptine are relatively selective D2 agonists, which might partly explain the lower ICD prevalence in hyperprolactinemia, as compared to PD, wherein DAs commonly used
(pramipexole and ropinirole) have preferential affinity for D3 receptors (19, 25). However, both bromocriptine and cabergoline also bind D3 receptors with substantial affinity and have lower affinity for other dopamine receptor subtypes (D1, D4, D5) (48). Case reports on DA-induced impulsivity in prolactinoma patients are available with both cabergoline and bromocriptine. In one case study, two different ICDs were induced sequentially with the successive use of both drugs (38). Pathologic gambling and hypersexuality have also been reported with quinagolide (42, 45).

ICDs seem to occur across the therapeutic dose range of DAs used in hyperprolactinemia. Indeed, in the literature, increased impulsivity was reported at the commonly used doses of DAs. Among the ten patients who developed hypersexuality in the Bancos study, six were on a relatively low dose of cabergoline (0.5–1 mg weekly) (44). Similarly, in the case series of men with hypersexuality on DAs, patients were on cabergoline (0.5–2.25 mg weekly), with most patients being on 0.5–1 mg weekly (5 out of 12 men). Men who were taking bromocriptine were on 15–25 mg daily (45). Whether the risk of developing an ICD increases with dose escalation is not clear. In our pilot study, a negative correlation was obtained between performance in the Experiential Discounting Task (EDT) test and cabergoline dose, indicating higher impulsivity with higher treatment dose (43). In the Bancos study, no relationship was found between treatment dose and risk of ICD (44). On the same matter, decreasing the therapeutic dose may help alleviate increased impulsivity (40). Four out of eight men had a decrease or resolution of their hypersexuality with DA dose reduction (45).

In available studies, no relation was observed between treatment duration and impulsivity scores or ICD occurrence (43, 44). ICDs were both reported soon after treatment initiation (45) (De Sousa 2017) or months to years thereafter (36, 37, 38, 40, 45).

Implications

In many instances, DA-induced impulsivity results in behaviors that could be detrimental to the patient’s personal and/or professional life. Compulsive shopping or gambling are often associated with significant financial burdens, including major financial losses, debts and bankruptcy (36, 37, 38, 41). Similarly, the social implications of hypersexuality are many. Six out of the eight men reported with this ICD on dopaminergic therapy developed problems in their personal relationships, including marital discord (45). They often had financial losses from reduced work performance and sometimes online dating. Few patients also had illicit activities incited by high risk sexual behavior, including illegal drug use and gambling (37, 45).

Management

There are no published treatment guidelines for the management of patients with DA-induced impulsivity. However, the next best step, once the condition is recognized is to stop or at least decrease the DA dose. The success of this management strategy is consistent with cases reported in the literature, wherein patients had dramatic behavioral changes and cessation of impulsive behavior several (up to 3) months after stopping the dopamine agonist (36, 37, 45). Similarly, a decrease in impulsivity or complete resolution of the ICD may be possible with DA dose reduction, as reported in a few cases, including two patients with hypersexuality (40, 45). However, dose reduction alone may not be sufficient in other cases, as ICDs may persist in some patients taking low doses of the DA (45). Switching from one DA to another does not seem beneficial, as ICDs have been reported with both cabergoline and bromocriptine (38, 42). Thus, cessation of DA therapy appears to be the most effective strategy in the management of patients who develop ICDs.

However, the beneficial effects of DA dose reduction or cessation on ICDs have to be balanced against the consequences of recurrent hyperprolactinemia or potential increase in size of a prolactin-secreting pituitary adenoma after withdrawal of DA therapy. Alternative treatment strategies should then be considered while planning for DA withdrawal (36, 37, 40). Such measures may include transsphenoidal pituitary surgery or hormone replacement (including oral contraceptives or androgen replacement), depending on the clinical scenario (1, 2, 3).

Additional non-pharmacologic therapies might help in the management of DA-induced impulsivity. These include psychotherapy and cognitive behavioral therapy (CBT) (40). Family interventions may also be needed due to the significant psychosocial burden of the condition (40). Specific psychotropic therapies are not uniformly effective. Escitalopram was temporarily used by Davie alongside to stopping cabergoline; his patient, however, had additional affective symptoms (36). Specific pharmacologic therapies targeting impulsivity have not been used in hyperprolactinemic patients. In PD patients developing impulsivity, few medications have been tried and appeared to be beneficial in case studies, including naltrexone, topiramate, valproate and zonisamide (19, 40).
Selected anti-psychotics and anti-depressants were also used with variable results (19). Whether these therapies can be considered in patients with hyperprolactinemia is not known; however, the use of most dopamine antagonists would be counterproductive with regards to prolactin secretion. Of note, however, aripiprazole is an antipsychotic that has partial DA activity and may often mitigate hyperprolactinemia (1).

**Awareness and prevention (implications for practice)**

The potentially devastating, yet reversible, effects of developing an ICD on DA therapy can only be prevented or at least mitigated if both clinicians and patients are aware of this possible adverse event.

In practice, physicians should routinely counsel both patients and their families about possible behaviors related to impulsivity prior to initiation of a DA. They should then regularly question patients about this potential adverse effect during follow-up. The use of written questionnaires to screen for heightened impulsivity during clinic visits may even be considered and could reduce communication deficits arising from the personal and sensitive nature of some ICDs, such as hypersexuality, and the possible reluctance of patients to openly address them with their physicians (45). The currently available questionnaire for ICD screening in PD could be validated for use in hyperprolactinemia (31). Emerging ICDs would then be promptly detected and reported to the treating physician, hopefully resulting in early intervention and prevention of serious consequences.

Current guidelines on the treatment and management of prolactinomas do not address ICDs as potential adverse events with dopaminergic therapy (2, 3). Similarly, DA package inserts do not contain a warning on the possibility to develop an ICD within their prescribing information. Updating these important references would help raise awareness among patients and providers of this recently identified problem.

**Future directions**

Longitudinal, prospective studies of larger sample size and variable treatment doses are needed to better understand the occurrence of impulsivity and ICDs in patients with hyperprolactinemia. Establishing risk factors predisposing to the development of this adverse event would help caregivers to identify patients at risk and follow them more closely. In addition, longitudinal follow-up is required to identify the best treatment strategy for an ICD once it occurs.

**Conclusions**

The use of DA in the treatment of hyperprolactinemia is associated with the potential for development of heightened impulsivity and ICDs. The prevalence of this adverse event seems lower than in patients with neurologic disorders, potentially due to the different dopamine receptor selectivity of DAs used in hyperprolactinemia and to the lower therapeutic doses needed as well as phenotypic differences between patients with hyperprolactinemia and PD.

In the case of hyperprolactinemic patients, the primary evidence comes from case reports, retrospective and cross-sectional studies. While these types of studies are methodologically considered to be of lower quality than prospective, randomized controlled trials, nevertheless the presence of consistent findings regarding the association between DA and ICDs in several studies strengthens the putative association between DA therapy and ICDs in hyperprolactinemic patients.

Awareness of this problem is likely low in the endocrine community, possibly related to underreporting of manifestations of ICDs among hyperprolactinemic patients. A variety of ICDs have been reported in patients on DA therapy for prolactinomas, most commonly compulsive gambling and hypersexuality. The latter has been mostly reported in men. Occurrence of an ICD has been associated with variable, but potentially devastating, social and financial consequences. ICDs have been described both in patients on standard cabergoline and bromocriptine treatment doses and among those receiving higher doses, either shortly after treatment initiation or several years into therapy. Whether individual predisposing factors do exist in hyperprolactinemic patients is still not clear. Management of ICDs in this population, though apparently straightforward (treatment cessation), can be challenging due to the undoubted benefits of DA therapy in hyperprolactinemia and the potential risks of more invasive surgical alternatives. Increasing awareness of this potential adverse event is critical among endocrinologists in order to facilitate early detection. Longitudinal, prospective studies are needed to better identify patients at risk of developing ICDs as well as devise effective screening and treatment strategies.
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References
23 Chang A, Shin SH & Pang SC. Dopamine D2 receptor mediates both inhibitory and stimulatory actions on prolactin release. Endocrine 1997 7 177–182. (https://doi.org/10.1007/BF02278139)
pseud.2012.10.002)

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