Recent Perspectives on Impulse Control Disorder in Dopamine Agonist-Treated Patients in Endocrine Practice

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Introduction

Pituitary adenomas (PAs) are frequently encountered in clinical practice, with an estimated prevalence of ~1 in 1,000 persons.1 Prolactinomas and nonfunctioning pituitary adenomas (NFPAs) are the predominant types of PAs.2 Prolactinoma exhibits a higher prevalence in women; nearly half of all adenomas are more than 1 cm in size.1,2

Unlike other PAs, prolactinomas are very sensitive to dopamine agonist (DA) therapy (such as cabergoline and bromocriptine), resulting in the normalization of prolactin levels, reduction in tumor size, and improvement in vision.3 Although these drugs are typically well tolerated, DA treatment can be linked to undesirable effects. The most common adverse effects of DA therapy are nausea, vomiting, dizziness, headache, and orthostatic hypotension.4 These are usually managed with dose reduction, gradual titration, or by taking the tablet with a small snack at night. However, there are other less common but more serious side effects associated with DA use, such as valvular heart disease and impulse control disorders (ICDs).4
The correlation between the emergence of ICD in patients undergoing DA treatment is firmly established in individuals with Parkinson’s disease. Within this specific category of patients, DAs are commonly administered in large doses and for extended periods, accumulating high doses over time.

Impulse Control Disorder and Dopamine Agonist Therapy

- Fig. 1 illustrates the growing acknowledgment of an association between ICDs and DA in the medical literature. However, only a minority were detected when pituitary was used as an extra search term. The association between ICDs and DA therapy is relatively new in pituitary medicine, with studies documenting a widely variable frequency ranging between 0 and 61% of patients on DA therapy.

A recent cross-sectional study used questionnaires of 200 patients (52.5% female, 69.5% married) diagnosed with PAs (93.5% prolactinomas and 6.5% NFPAs) in four referral centers in the Kingdom of Saudi Arabia and the United Arab Emirates. The majority of patients (87%) were treated with cabergoline. The findings indicate that nearly half (52%) of the participants reported experiencing symptoms of ICD. In the context of multivariate analysis, it was found that being young and having a personal history of psychiatric problems were predictive factors for the occurrence of ICDs, but being single was found to have a protective effect.

- Fig. 2 illustrates the notably wide distribution in the observed frequency of ICDs across various published studies involving patients with PAs/disorders undergoing DA therapy. This variation can be attributed to many factors, as demonstrated in -Table 1. These factors include disparities in study demographics (patients with prolactinomas vs. other adenomas or pituitary disorders), sex distribution, study methodologies (cross-sectional vs. prospective designs), the inclusion or exclusion of well-matched control groups, and nuances in DA therapy (type, duration, dosage, current or prior usage, cumulative dosage). Furthermore, variations in assessment tools (both in quantity and type), whether assessments were self-reported or conducted by health care professionals or experts in ICDs and the presence of additional risk factors for ICD development (smoking, alcohol consumption, history of depression/mental illness, and family predisposition to mental health conditions) can all contribute to the frequency of ICD.

Two important findings from these studies deserve further attention. First, the predominant reliance on self-reported data for diagnosing ICD, including our study, may lead to an overestimation of its frequency not only in patients on DA therapy but also in the healthy control groups. Of note, in the study by Ozkaya et al, the reported frequency of ICD in 40 patients with prolactinomas was 62.5% when based on patient self-reports using Minnesota impulse disorders interview-Revised, but significantly reduced to 15% following an interview with a physician and finally dropped to 7.5% following assessment with a specialized psychiatrist. The same pattern with a 42.5% reduction in frequency was observed in the other group of patients with acromegaly, and none of the 18% patients with NFA was confirmed to have ICD following assessment with a specialized psychiatrist. Hence, while the ICD assessment tool serves well for screening, definitive diagnosis and confirmation necessitate expert involvement. Second, most published studies did not characterize the severity of ICD, its impact on the patient’s personal or professional life, and its associated financial, social, and legal consequences.

Implications for Endocrine Practice

Due to its efficacy, tolerability, availability, and affordability, DA remains the first line of treatment in most patients with prolactinoma. Nonetheless, the emerging data about ICDs associated with DA use warrant proper assessment, and weighing the risks and benefits of each treatment modality

Fig. 1  The increasingly recognized association between impulse control disorder and dopamine agonists as seen by the number of records in the PubMed database between 1982 and 2023. Courtesy of Dr Salem A Beshyah, Abu Dhabi, United Arab Emirates.)
becomes critical. Before commencing DA therapy, it is essential to educate patients and their families about possible behavioral adverse effects linked to these medications. In selected cases of microprolactinoma, exploring alternative options for surveillance or management with non-DA pharmacological therapy, such as oral contraceptive pills, could be considered. Additionally, when pregnancy is not planned shortly and when expert pituitary surgeons are available, surgery may emerge as a favorable treatment choice, particularly as it can offer a potential cure. Surgery's broader acceptance now positions it as a viable first-line therapy for patients with microprolactinoma and intrasellar macroprolactinoma, as highlighted in a recent consensus statement. This consideration might be particularly important in patients with mental illness or predisposing factors for ICDs. Nevertheless, it is essential to consider the possibility of patients encountering enduring surgical complications, especially if an experienced neurosurgeon does not perform the procedure. Therefore, engaging in comprehensive discussions with the patient and the multidisciplinary team (MDT) is essential for informed decision-making.

During follow-up visits, it is advisable to routinely inquire from the patient and accompanying relatives about symptoms of ICDs and related behaviors. Periodic administration (once or twice yearly) of one of the impulsivity questionnaires utilized in the literature is recommended. Upon the emergence of ICD symptoms, it becomes paramount to assess their severity and societal impact through open discussion thoroughly. Treating physicians should contemplate dose reduction or discontinuation of DA therapy in line with recent consensus management statements and positive outcomes reported in the literature. Furthermore, a psychiatrist experienced in ICD management is crucial for comprehensive assessment and support. Decision-making regarding the discontinuation of DA treatment should weigh the benefits against the potential risks of relapsing hyperprolactinemia or tumor enlargement upon DA withdrawal. Prior to discontinuation, alternative approaches such as pituitary surgery, radiation therapy, or nonpharmacological interventions such as psychotherapy and cognitive behavioral therapy should be considered, ideally in an MDT setting. Regular follow-up and evaluation to document and monitor improvements or resolution of ICDs are essential. Table 2 outlines a practical approach for identifying and managing ICDs in patients undergoing DA therapy.

**Conclusion**

DA stands as the primary treatment for patients with prolactinoma and hyperprolactinemia. Nevertheless, it is crucial to be aware of the potential risks of ICDs, particularly in those with predisposing factors. Early recognition is paramount, and dose reduction or medication discontinuation often resolves the issue. In certain cases, it may be required to consider a different approach, such as surgery, particularly when dealing with microprolactinoma or intrasellar macroprolactinoma and when an experienced pituitary neurosurgeon is available.

Future studies should address confounding risk factors associated with ICD development, ensuring confirmation of ICD presence by psychiatrists, documenting the severity of ICD, and providing guidance on optimal management strategies upon ICD detection.
<table>
<thead>
<tr>
<th>Authors (Ref.)</th>
<th>Year</th>
<th>Region</th>
<th>Study type</th>
<th>Sample size</th>
<th>Frequency&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cohort details</th>
<th>Limitations</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>AlMalki et al&lt;sup&gt;8&lt;/sup&gt;</td>
<td>2024</td>
<td>KSA and UAE</td>
<td>Cross-sectional survey</td>
<td>200</td>
<td>52%</td>
<td>93.5% PRLoma, 6.5% NFA</td>
<td>No control group, Not all ICD RFs assessed</td>
<td>RFs: FHx or personal Hx of psychiatric illness, younger age</td>
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<tr>
<td>Bancos et al&lt;sup&gt;7&lt;/sup&gt;</td>
<td>2014</td>
<td>United States</td>
<td>Cross-sectional survey</td>
<td>77</td>
<td>24.7% PRL, 17.1% NFA</td>
<td>77 PRLoma, 70 NFA</td>
<td>A small number of patients</td>
<td></td>
</tr>
<tr>
<td>Celik et al&lt;sup&gt;9&lt;/sup&gt;</td>
<td>2018</td>
<td>Turkey</td>
<td>Prospective</td>
<td>25</td>
<td>8%</td>
<td>25 PRLoma, 32 NFA, 32 controls</td>
<td>Small cohort, short-term FU (1 y), Patients with a Hx of current ICD or major psychiatric disorders were excluded; 29% (10/35) of DA Rx patients dropped out</td>
<td>ICD Dx made by an expert physician, ICD reversed or decreased with d/c DA</td>
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<td>Dogansen et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>2019</td>
<td>Turkey</td>
<td>Cross-sectional multicenter survey</td>
<td>308</td>
<td>17%</td>
<td>PRLoma on DA Rx for at least 3 mo</td>
<td>No control group</td>
<td>RFs: current smoking, ETOH, gambling</td>
</tr>
<tr>
<td>Hinojosa-Amaya et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>2020</td>
<td>United States</td>
<td>Cross-sectional single-center survey</td>
<td>76</td>
<td>26.5% in DA +; 23.1% in controls</td>
<td>76 PAs (73 PRLoma)</td>
<td>Small cohort excluded patients with depression and psychiatric illness</td>
<td></td>
</tr>
<tr>
<td>De Souza et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>2020</td>
<td>Australia</td>
<td>Cross-sectional multicenter survey</td>
<td>113</td>
<td>61.1%</td>
<td>113 (95% PRLoma), 99 control</td>
<td>High rate of unemployment, retirement, and smoking c/t control group</td>
<td>42% of ICD in controls, Male sex, psychiatric comorbidity, age, Hardy tumor classification, hypogonadism, 37% are only aware of ICD risk with DA use, age, male, hypersexuality; dose and duration, not RF? increased risk in the elderly; DA increased risk by two–three folds; high baseline risk of ICD in nonexposed cohort</td>
</tr>
<tr>
<td>Beccuti et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>2021</td>
<td>Italy</td>
<td>Cross-sectional, single-center survey; QUIP</td>
<td>132</td>
<td>46% DA+, 24% DA-</td>
<td>132 patients on DA 58, no DA</td>
<td>Heterogenous cohort (functional hyperPRL and PAs), Excluded patients with psychiatric illneses; 81% current use of DA</td>
<td>DA use, age, male, hypersexuality; dose and duration, not RF? increased risk in the elderly; DA increased risk by two–three folds; high baseline risk of ICD in nonexposed cohort</td>
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<tr>
<td>Ozdeniz Varan and Gurvit&lt;sup&gt;19&lt;/sup&gt;</td>
<td>2023</td>
<td>Turkey</td>
<td>Cross-sectional, multicenter</td>
<td>31</td>
<td>25.8% DA+, 15% DA- (16.7% controls)</td>
<td>31 PRLoma DA + 20 PRLoma DA - 30 controls</td>
<td>Excluded patients with RFs for ICDs</td>
<td>No significant difference in ICD prevalence among DA Rx patients</td>
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<tr>
<td>Sanjan et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>2023</td>
<td>India</td>
<td>Prospective, single-center questionnaire</td>
<td>15</td>
<td>0% (incidence)</td>
<td>15 PRLoma (Macro) 15 NFA</td>
<td>Small cohort, short FU (3 mo), excluded patients with Hx of psychiatric disorders, single center</td>
<td>No patients developed ICD, but the impulsivity score increased in the DA-treated patient’s c/t baseline</td>
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<tr>
<td>Ozkaya et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>2020</td>
<td>Turkey</td>
<td>Cross-sectional questionnaire interview</td>
<td>80</td>
<td>6.3% (all) 7.5% PRLoma; 5% ACRO</td>
<td>40 ACRO 40 PRLoma 38 NFA 32 controls</td>
<td>Single center</td>
<td>All patients’ symptoms resolved after DA discontinuation; ICD with self-report &gt; psychiatrist assessment</td>
</tr>
<tr>
<td>Martinkova et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>2011</td>
<td>Slovakia</td>
<td>Retrospective, single-center, structured interview focused on ICDs</td>
<td>20</td>
<td>20%</td>
<td>18 PRLoma</td>
<td>Small study, No controls</td>
<td>Dx made by expert, Compulsive eating developed in one patient in addition to pathologic gambling, Switching to other DAs did not help</td>
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Authors

K.A. conceived the article’s concept, coordinated its design, and performed the literature search. M.A. reviewed the data and edited the manuscript. Both authors read and approved the final manuscript.

Conflict of Interest
None declared.

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