2019

Impulse control disorders in dopamine agonist-treated hyperprolactinemia: Prevalence and risk factors

Sunita M.C De Sousa

John Baranoff

R Louise Rushworth
The University of Notre Dame Australia, louise.rushworth@nd.edu.au

Jessica Butler

Jane Sorbello

See next page for additional authors

This article was originally published as:
De Sousa, S. M., Baranoff, J., Rushworth, R. L., Butler, J., Sorbello, J., Vorster, J., Thompson, T., McCormack, A. I., Inder, W. J., & Torpy, D. J. (2019). Impulse control disorders in dopamine agonist-treated hyperprolactinemia: Prevalence and risk factors. *Journal of Clinical Endocrinology and Metabolism, Early View (Online First)*.

Original article available here:
https://doi.org/10.1210/clinem/dgz076

Impulse control disorders in dopamine agonist-treated hyperprolactinemia: prevalence and risk factors

Sunita M.C. De Sousa[1-4], John Baranoff[5,6], R. Louise Rushworth[7], Jessica Butler[1], Jane Sorbello[8], Juanita Vorster[8], Tanya Thompson[9], Ann I. McCormack[9,10], Warrick J. Inder[8,11], David J. Torpy[1,4]

[1]Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, Australia;

[2]Department of Genetics and Molecular Pathology, Centre for Cancer Biology, an SA Pathology and University of South Australia alliance, Adelaide, Australia;

[3]Adult Genetics Unit, Royal Adelaide Hospital, Adelaide, Australia;

[4]School of Medicine, University of Adelaide, Adelaide, Australia;

[5]Centre for Treatment of Anxiety and Depression, Mental Health Directorate, Central Adelaide Local Health Network, Adelaide, Australia;

[6]School of Psychology, University of Adelaide, Adelaide, Australia;

[7]School of Medicine, Sydney, The University of Notre Dame, Australia;

[8]Department of Diabetes and Endocrinology, Princess Alexandra Hospital, Brisbane, Australia;

[9]Hormones and Cancer, Garvan Institute of Medical Research, Sydney, Australia;

[10]St Vincent's Clinical School, Faculty of Medicine, UNSW Sydney, Sydney, Australia

[11]Princess Alexandra-Southside Clinical Unit, The University of Queensland, Brisbane, Australia.

Keywords: dopamine agonists, hyperprolactinemia, hypersexuality, impulse control disorders, prolactinoma

Corresponding author and whom reprint requests should be addressed: Sunita M.C. De Sousa, A: Area 8G-480 Royal Adelaide Hospital Port Rd Adelaide Australia 5000, Ph: +61 8 7074 2673, E: Sunita.DeSousa@sa.gov.au

Support: SMCD is supported by a Royal Adelaide Hospital A. R. Clarkson Scholarship.

Disclosure statement: The authors have nothing to disclose.

ABSTRACT

Context: There are growing reports of dopamine agonist (DA)-induced impulse control disorders (ICDs) in hyperprolactinemic patients. However, the magnitude of this risk and predictive factors remain uncertain.

Objective: To determine ICD prevalence and risk factors in DA-treated hyperprolactinemic patients compared to community controls.

Design, Setting and Participants: Multicenter cross-sectional analysis of 113 patients and 99 healthy controls.

Main Outcome Measures: Participants completed a neuropsychological questionnaire consisting of the Depression Anxiety Stress Scale (DASS21), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease (QUIP-S), Hypersexual Behavior Inventory (HBI), Hypersexual Behavior Consequences Scale and Social Desirability Response Set Scale. Demographic and clinical data were collated to determine ICD risk factors. Patients testing positive for an ICD were offered a semi-structured psychological interview.

Results: Patients were more likely than controls to test positive by QUIP-S for any ICD (61.1 *vs* 42.4%, *P*=0.01), hypersexuality (22.1 *vs* 8.1%, *P*=0.009), compulsive buying (15.9 *vs* 6.1%, *P*=0.041) and punding (18.6 *vs* 6.1%, *P*=0.012), and by HBI for hypersexuality (8.0 *vs* 0.0%, *P*=0.004). Independent risk factors were male sex (OR 13.85), eugonadism (OR 7.85), Hardy's tumor score, and psychiatric comorbidity (OR 6.86) for hypersexuality; and age (OR 0.95) for compulsive buying. DASS21 subset scores were higher in patients *vs* controls, and in patients with *vs* without different ICDs. Only 19/51 (37.3%) interviewed patients were aware of the relationship between DAs and ICDs before the study.

Conclusions: DA therapy poses a high, previously underestimated risk of ICDs, especially in the form of hypersexuality in eugonadal men.

PRÉCIS

Dopamine agonist therapy for hyperprolactinemia increases the risk of impulse control disorders, especially hypersexuality in men with normal testosterone.

Introduction

Dopamine agonist (DA) therapy is used in hyperprolactinemic patients to stop galactorrhoea, restore eugonadism and/or shrink causative tumors, particularly prolactinomas where DAs are the first-line treatment. As prolactinomas are the commonest clinically evident pituitary adenoma (1,2) and typically occur at a young age, often leading to prolonged treatment, DAs are the most frequent anti-tumor agent employed in pituitary endocrinology. DAs are highly effective in prolactinomas, but common side effects include nausea and postural hypotension (3). Rare risks include psychosis (4) and cardiac valvulopathy (5,6).

When used at high doses in Parkinson's disease and restless legs syndrome, DAs have been recognized to induce impulse control disorders (ICDs). The mechanism appears to involve reward system activation via D3 dopamine receptors in the mesocorticolimbic dopaminergic pathway (7). ICDs have been considered rare in hyperprolactinemic patients due to lower DA doses and use of agents with low D3 receptor affinity. Current hyperprolactinemia guidelines do not warn against this risk (8,9), but there are now several case reports (10-15), a case series (16) and recent studies (17-20) of ICDs developing in hyperprolactinemic patients.

The defining feature of ICDs is failure to resist impulses to engage in a pleasurable activity that is harmful to self or others (21). However, there is no uniform approach to diagnosing the various ICDs in the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (22). The ICD diagnostic tool, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP), encompasses pathological gambling, hypersexuality, compulsive buying, and compulsive eating, as well as compulsive behaviors relating to medication use, punding (preoocupation with meaningless motor activities e.g arranging objects), hobbyism (preoccupation with specific activities e.g. repairing machinery), and walkabout (excessive wandering without purpose) (23).

In hyperprolactinemic patients, DA treatment results in prolactin suppression and restoration of sex steroid secretion. Hence, sex steroids, especially testosterone, may have a role in the development of

hypersexuality (16,20). We hypothesized that ICDs in patients treated with DAs would be more common than in community controls, and that demographic and clinical characteristics of patients would be associated with ICD risk. The primary aim of our study was to determine the prevalence of ICDs in DA-treated hyperprolactinemic patients compared to healthy controls. Secondary aims were to identify ICD risk factors, and to quantify the impact of hypersexuality given the apparent predominance of this ICD in hyperprolactinemic patients (16,18).

Materials and Methods

Patients and controls

This was a multicenter cross-sectional study of DA-treated hyperprolactinemic patients in three Australian tertiary referral centers (*n*=113) and healthy volunteers serving as controls (*n*=99). The study was approved by the Royal Adelaide Hospital Research Ethics Committee (HREC/16/RAH/494). All participants provided written informed consent.

Patients were recruited from April 2017 to December 2018. Inclusion criteria were diagnosis of pathological hyperprolactinemia after exclusion of physiological and drug-induced hyperprolactinemia, and current DA treatment for ≥1 month. Exclusion criteria were age <18 yr, current antipsychotic medication use, prior brain or pituitary radiotherapy, and inability to consent or engage in neuropsychological assessment due to intellectual impairment, mental illness, non-English speaking background or any other reason. Eligible patients were identified using local pituitary clinic databases and contacted by telephone and mail. Of 51 eligible patients at the primary site, 42 (82.4%) completed the study, whilst four (7.8%) were uncontactable, four (7.8%) declined participation, and two (3.9%) did not return the required paperwork. Additional patients were consecutively recruited during clinics and admissions with similarly high acceptance rates. Clinical data were collated using medical records and information from patient questionnaires. Eugonadism was defined as regular menses in women and normal serum testosterone in men. As this was an observational study with various hormone assays employed as in usual clinical practice, prolactin levels were compared by

dividing absolute values by the upper limit of normal for a given assay. Weekly cabergoline equivalent dose was calculated as cabergoline 1 mg weekly = quinagolide 75 mcg daily as previously defined (24). Cumulative cabergoline equivalent dose was calculated by weekly cabergoline equivalent dose multiplied by duration of DA therapy in weeks.

Healthy controls were selected as the comparator arm because of the frequent medical comorbidity, older age and difficulty in controlling for gender when non-functioning pituitary adenoma (NFPA) controls have been employed in other studies (18,19). Volunteers were recruited by hospital and laboratory staff email asking for participation in an anonymized study relating to mood, wellbeing and behavior. Exclusion criteria specific to the control group were active medical problems (other than asthma, allergic rhinitis and minor joint problems), use of prescription medications (other than asthma inhalers, intranasal sprays and non-steroidal anti-inflammatory drugs) and previous medical attention for an ICD.

Neuropsychological assessment

Patients completed a written questionnaire (*questionnaire and scoring sheet to be deposited in a public data repository*) consisting of summary demographic and medical history questions, and five validated neuropsychological tools:

1. Depression Anxiety Stress Scale, DASS21: a 21-item questionnaire with three subscales assessing the severity of depression, anxiety and stress symptoms (25), with good reliability and validity in clinical and community samples (26,27).

2. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – Shortened version, QUIP-S: a comprehensive instrument validated for the diagnosis of DA-induced ICDs in patients with Parkinson's disease. Sensitivity is similar between the 13-item QUIP-S and the full QUIP (94 *vs* 96%, respectively) (23).

3. Hypersexual Behavior Inventory, HBI: a 19-item questionnaire regarding the control, consequences and coping associated with sexual thoughts, feelings and behaviors. It has high internal consistency and shows reliability over time, with scores ≥53 diagnostic of hypersexuality (28).

4. Hypersexual Behavior Consequences Scale, HBCS: a detailed questionnaire assessing hypersexuality consequences in affected patients. This complements the HBI, with high internal consistency and reliability over time. Comparison of the HBCS between hypersexual and non-hypersexual psychiatric patients and the HBCS against other hypersexuality assessment tools has shown discriminant and convergent validity, respectively (29).

5. Social Desirability Response Set Scale, SDRS5: a 5-item measure indicating a participant's tendency to give socially desirable responses (30). This measure was included to screen for confounding as prolactinoma patients have been shown to respond in a more socially desirable manner compared to healthy controls (31), possibly reflecting the evolutionary functions of prolactin in promoting parental behaviors as observed in animal and human studies (32).

Controls completed an anonymized online version of the demographic questions and five-part neuropsychological questionnaire.

Semi-structured psychological interview

Patients who tested positive for an ICD by QUIP-S or HBI were offered a follow-up semi-structured telephone interview with a clinical psychologist (JB) to assess patient knowledge of the risk of DA-induced ICDs prior to study participation and to identify any relationships between ICD symptoms and DA dosing/cessation.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 25.0. Missing data were coded as negative where appropriate, e.g., GH deficiency was defined as the presence of a low IGF1 level or requirement for GH treatment and patients without available data to the contrary were considered to be GH sufficient. Cases were excluded where missing data could not be assumed to be negative. Categorical variables were defined by frequency expressed as percentages, and continuous variables by mean ± standard deviation (*SD*) unless otherwise stated. Chi-square tests with continuity corrections and unpaired t-tests were employed for categorical and continuous variables, respectively, for comparisons between all patients and controls and for comparisons between patients with and without ICDs. The Chi-square test was substituted for the 2-tailed Fisher's exact test when ≥20% of expected cell counts were <5. Statistical significance was set at $P<0.05$. Risk factors for the ICDs shown to be more frequent in patients than controls were first assessed by univariate analysis comparing patients with and without ICDs. Logistic regression models were developed to assess the relationship between patient characteristics and screening positive for any IDC, hypersexuality by QUIP-S, hypersexuality by HBI, compulsive buying and punding. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated.

Results

General characteristics

Demographic and clinical data of the 113 patients (56 males, 57 females, age 38.1±15.9 yr) are outlined in Table 1. The cause of hyperprolactinemia was a prolactinoma in 107/113 (95%) patients and other sellar masses in the remainder. Most patients had hypogonadotrophic hypogonadism at diagnosis; a minority demonstrated other pituitary hormone deficiencies. At the time of neuropsychological assessment, 109/113 (96.5%) patients were taking cabergoline and four (3.5%) were taking quinagolide; no patients were taking bromocriptine.

Compared to patients, controls were more likely to be employed full-time, less likely to be current/former smokers, and more likely to drink alcohol. Controls were slightly younger (41.2±10.1 *vs* 45.5±16.5 yr, *P*=0.020) and there was no difference in sex ratio.

Neuropsychological dysfunction

Neuropsychological dysfunction in patients and controls was determined by the composite questionnaire as shown in Fig 1. DA-treated hyperprolactinemic patients were more likely than controls to test positive by QUIP-S for any ICD (61.1 *vs* 42.4%, *P*=0.01), hypersexuality (22.1 *vs* 8.1%, *P*=0.009), compulsive buying (15.9 *vs* 6.1%, *P*=0.041) and punding (18.6 *vs* 6.1%, *P*=0.012). Hypersexuality as defined by the more stringent HBI tool was also more common in patients (8.0 *vs* 0.0%, *P*=0.004), with all HBI-positive patients also scoring positive by QUIP-S. Multiple ICDs were found in 32.7% of patients and 15.2% of controls (*P*=0.005). Patients scored higher than controls for depression (4.7±4.4 *vs* 3.1±4.0, *P*=0.005) and anxiety (3.4±3.2 *vs* 2.2±2.7, *P*=0.005) by DASS21. Trends towards higher patient scores were observed for stress by DASS21 (6.1±4.2 *vs* 5.1±4.0, *P*=0.080) and for hypersexuality consequences by HBCS (25.9±10.4 *vs* 23.9±5.4, *P*=0.072).

Because of the gender dimorphism in ICD risk previously observed by us (16) and others (18,20), we analyzed patients and controls stratified by gender (Fig 1). In female patients *vs* female controls, there were trends towards higher frequencies of hypersexuality by QUIP-S (8.8 *vs* 0.0%, *P*=0.058) and punding (15.8 *vs* 3.8%, *P*=0.075), with no differences in other ICD frequencies or depression, anxiety, stress or hypersexuality consequences scores. Men showed greater divergence, with male patients *vs* male controls showing higher frequencies of any ICD (73.2 *vs* 45.7%, *P*=0.008) and hypersexuality by HBI (16.1 *vs* 0.0%, *P*=0.004), as well as higher depression (5.4±4.8 *vs* 2.6±3.1, *P*=0.001), anxiety (3.7±3.3 *vs* 1.7±2.2, *P*=0.000), stress (6.8±4.2 *vs* 4.7±3.7, *P*=0.009) and hypersexuality consequences (28.9±13.8 *vs* 23.4±3.2, *P*=0.005) scores. A trend towards more frequent hypersexuality by QUIP-S was apparent in male patients *vs* controls (35.7 *vs* 17.4%, *P*=0.066).

ICD risk factors in DA-treated patients

We analyzed risk factors for each of the ICDs shown to be more common in patients compared to controls (i.e. any ICD, hypersexuality by QUIP-S or HBI, compulsive buying and punding), postulating that different risk factors may pertain to different ICDs. This was first performed by univariate analysis. Compared to patients screening negative for all ICDs, patients screening positive for at least one ICD had a higher proportion of men, greater alcohol use, and higher depression, anxiety, stress and hypersexuality consequences scores (Table 2). Hypersexuality by QUIP-S was associated with male gender, having children, lower Hardy's tumor score at diagnosis, higher testosterone at assessment in men, eugonadism at assessment in men and women, and higher hypersexuality scores by HBI and HBCS. Hypersexuality by HBI was associated with male gender, divorce, full-time employment, comorbid mental illness, higher testosterone at diagnosis in men, lower agreeableness by SDRS5, and higher scores for depression, stress and hypersexuality consequences. Compulsive buying was associated with younger age at diagnosis and at assessment, growth hormone deficiency at diagnosis, and higher depression, anxiety and stress scores. Punding was only associated with higher anxiety and stress scores.

Statistically significant differences were not observed in other employment/marital status, smoking history, cause of hyperprolactinemia, other pituitary hypersecretion, DA or pituitary tumor duration, DA type, weekly or cumulative CBG equivalent dose, degree of hyperprolactinemia or other pituitary hormone perturbations at diagnosis or at assessment, degree of prolactin fall or testosterone rise between diagnosis and assessment, tumor diameter or cerebrovascular change on MRI at diagnosis or at assessment, visual field deficits at diagnosis or at assessment, previous pituitary surgery, sex steroid or antidepressant use at assessment, or central nervous system comorbidity.

In addition to the male bias in any ICD and hypersexuality by QUIP-S and HBI (Table 2), we found that the proportion of men was greater in patients screening positive *vs* negative for gambling (100.0 *vs*

46.2%, *P*=0.006). No sex difference was seen in patients with and without compulsive eating, hobbyism, walkabout or compulsive medication use.

Logistic regression analysis

Logistic regression models were generated to identify predictive factors that remained independent upon multivariate analysis. This showed that screening positive for any ICD was significantly associated with an increase in stress score (OR 1.23, 95% CI 1.10-1.37). Hypersexuality by QUIP-S (*n*=80) was significantly associated with male gender (OR 13.85, 95% CI 2.89-66.49), eugonadism at assessment (OR 7.85, 95% CI 1.45-42.42), and lower Hardy's tumor score at diagnosis (OR 11.60, 95% CI 1.87-71.88 for I *vs* III; OR 4.59, 95% CI 1.03-20.47 for II *vs* III). Hypersexuality by HBI was significantly associated with mental illness (OR 6.86, 95% CI 1.28-36.72) and higher stress score (OR 1.22, 95% CI 1.02-1.48). Compulsive buying was significantly associated with younger age at assessment (OR 0.95, 95% CI 0.91-0.99 for each increasing year of age) and higher stress score (OR 1.26, 95% CI 1.10-1.46). Punding was significantly associated with a higher stress score (OR 1.26, 95% CI 1.11-1.45).

Separate logistic regression models were created for men with available testosterone levels. Hypersexuality by QUIP-S in applicable men (*n*=45) showed a trend towards a higher risk of hypersexuality with higher testosterone at assessment (OR 1.11, 95% CI 1.00-1.23). Hypersexuality by HBI, which was found in 6/48 applicable men, showed a weak trend towards higher testosterone at diagnosis (OR 1.25, 95% CI 0.97-1.61).

Patient insights

Free prose responses in patient questionnaires illustrated the extremity of the impact of DA-induced side effects (Table 3).

Semi-structured psychological interview

Of 69 patients who screened positive for an ICD by the questionnaire, 51 (73.9%) participated in the psychological interview. 17/51 (33.3%) patients reported ICD symptom fluctuation with dose changes and/or worsening ICD symptoms on the day of or the day after cabergoline dosing. Of 11 patients who interrupted DA treatment, 8 (72.8%) experienced resolution or improvement of ICD symptoms. Amongst all interviewees, 19/51 (37.3%) knew about the relationship between DAs and ICDs before participating in the study. 30/51 (58.8%) had the opportunity to discuss their ICD symptoms with their treating endocrinologist – 18/30 (60.0%) found this to be helpful.

Discussion

This study represents the largest cross-sectional analysis of the risk of ICDs in hyperprolactinemic patients compared to controls, demonstrating significantly higher rates of any ICD, multiple ICDs, hypersexuality, compulsive buying and punding in DA-treated patients. Risk factors that remained predictive after logistic regression were male gender, eugonadism at assessment, lower Hardy's tumor score at diagnosis and psychiatric comorbidity for hypersexuality; and younger age for compulsive buying. DA dose was not predictive of ICD risk. Higher testosterone at assessment appeared to have a permissive effect on the development of hypersexuality as diagnosed by QUIP-S. The burden of hypersexuality consequences was substantial, with significantly higher HBCS scores in patients screening positive *vs* negative for hypersexuality. This is noteworthy as increased sexual thoughts and behaviors following DA treatment of hyperprolactinemia could otherwise simply reflect a normal return of libido with reversal of hypogonadism.

The prevalence of ICDs in DA-treated hyperprolactinemic patients was much higher than the few previously published studies (Table 4). The low ICD rates in other studies may be explained by the exclusion of patients with a psychiatric history (19,20,33), short follow-up times following DA commencement (19), the inclusion of patients who have ceased DA treatment and may not accurately recall their experiences during treatment (18), and the use of more focused tools in screening for ICDs

(18-20). The known inverse association between age and impulsivity (22) could partly explain the high ICD prevalence in our study where patient age was 46±16 yr compared to the study by Bancos *et al* (18) where patient age was 55±14 yr. However, our patients were older than patients in other studies (17,19,20). In addition, two studies were undertaken in Turkey (19,20), where gambling is prohibited (20), although all of the tested ICD subsets were more frequent in our patients. Cultural differences in reporting impulsivity could be contributory, particularly given the high ICD prevalence in our controls. The male bias in developing ICDs and our relatively high proportion of men at 49.6% of study patients is also noteworthy. However, tertiary endocrine centers typically show female-to-male prolactinoma ratios that are much lower than the community ratio of 10:1 because of the greater invasiveness of prolactinomas in men and consequent referral bias (2,31). We found that men similarly comprised 51.0% of eligible patients in our primary site 30-year pituitary database.

Though not encompassing the overall DA-induced ICD risk, we previously proposed the term 'dopa-testotoxicosis' to highlight the male predilection and hypersexuality predominance in hyperprolactinemic patients, putatively due to synergy between restoration of eugonadism and D3 receptor stimulation (16). The present study found no association between hypersexuality and testosterone rise, although statistical power was limited by only 41/48 men with available testosterone levels exhibiting a DA-induced rise. Testosterone appears to be permissive in the development of any ICD and hypersexuality based on the male predominance shown here and by others (16,18,20,34,35). Whilst DA-treated hyperprolactinemic patients do not reach supraphysiological testosterone levels (16,18), we and Dogansen *et al* (20) have shown greater ICD risks with relative testosterone increases into the normal range. Though not significant upon multivariate analysis, Dogansen *et al* (20) found a higher testosterone percentage rise at the preceding visit in hypersexual men. We found an independent trend towards higher testosterone at assessment in hypersexual men, and eugonadism at assessment was one of the few predictive factors in logistic regression modeling. The trend towards increased hypersexuality in female patients *vs* controls in our study does not refute the concept of dopa-testotoxicosis as testosterone also contributes to female

libido. Nonetheless, testosterone is not sufficient for the development of hypersexuality as it only occurs in a minority of hyperprolactinemic men rendered eugonadal by DA therapy, and hypersexuality is not associated with androgen replacement in post-pubertal males (16,36). Testosterone is also not necessary for the development of hypersexuality as it frequently occurs in the neurology setting (34) where DA therapy is not expected to cause testosterone fluctuations. Notably, DA therapy is also neither necessary nor sufficient as ICDs may occur in healthy controls and not all DA-treated patients develop ICDs.

Other factors contribute to the risk of DA-induced ICDs (Table 4). The independent inverse association between age and compulsive buying is especially pertinent as hyperprolactinemic patients tend to be younger than patients with Parkinson's disease or restless legs syndrome. This is a new association in the hyperprolactinemia setting and there are other differences in ICD risk factors between this and previous studies, which may partly have a sociocultural basis. Smoking was predictive of the risks of any ICD and of hypersexuality in the study by Dogansen *et al* (20) that had a high proportion of current smokers (24%), whereas only 8% of our patients were current smokers and we did not find a statistically significant association between current/former smoking and ICD risk. Alcohol use was common in our patients (58%) and we found a higher ICD risk only when grouping patients who consumed ≥2 standard drinks of alcohol daily, whilst Dogansen *et al* (20) found an association with any alcohol use, which reflected a small minority (5%) of their patients. We also observed an association between a lower Hardy's tumor score and increased ICD risk; the reason for this is unclear.

We found higher DASS21 subset scores in patients *vs* controls, and in patients with *vs* without different ICDs. We also found a higher prevalence of mental illness in patients who tested positive *vs* negative for hypersexuality by HBI. Parkinson's disease studies have similarly reported higher rates of depression and anxiety in patients with *vs* without DA-induced ICDs (34,35). It is possible that depression, anxiety and stress leads to ICDs as a method of coping with these negative affective states. Alternatively, ICDs may induce hyper-emotionality and consequent stress.

The present study was not a formal prevalence study as it used a convenience sample, had limited size, and there may be some recruitment biases due to referral patterns to tertiary centers. Nevertheless, the study is likely to be representative of ICD patterns in patients typically treated in tertiary endocrine clinics. Investigation of rare ICDs and some associations may need a large registry DA study. With respect to our control group, there appeared to be a higher ICD rate amongst hospital and laboratory staff compared to other control groups (37,38), which might have underestimated differences in ICD prevalence between patients and controls. Our reliance on healthy controls rather than a diseased population may also be considered a weakness of our study as the presence of a pituitary adenoma may influence DA responses. Our method of recruiting controls via hospital and laboratory staff email may have introduced an additional selection bias. However, healthy controls were intentionally selected to better approximate the demographics and general health status of prolactinoma patients compared to NFPA patients. As in previous studies (18-20), another limitation of our study is that we relied on neuropsychological tools validated outside of the hyperprolactinemia setting. QUIP-S was designed for patients with Parkinson's disease. The present study and that by Dogansen *et al* (20) broadens the experience of this tool in hyperprolactinemic patients, but further data are required to validate it in distinguishing between patients with disruptive hypersexuality *vs* those with a normal return in libido with DA treatment. We were able to compare hypersexuality diagnosis by QUIP-S and HBI, finding that fewer patients tested positive by HBI but with greater impact as determined by mean HBCS score (56.8±14.1 in HBI-positive *vs* 37.0±17.8 in QUIP-positive). In addition to validating neuropsychological tools in hyperprolactinemic patients, it may be illuminating to study other impulsive activity that may apply to the younger hyperprolactinemic population compared to the neurology setting – for example, exercise, caffeine consumption and video game use. Prospective studies will be valuable in capturing patients who, because of the development of ICDs or other side effects, cease DA therapy, leading to exclusion in cross-sectional studies of only currently treated patients. In addition, prospective prolactin and testosterone measurement by standardized assays will better evaluate the possible relationships between ICD risk and hormone levels. Other

directions of future research should include recruitment of prolactinoma patients beyond tertiary centers and comparison of prolactinoma patients with both healthy and diseased controls. Given the lack of interaction between ICD risk and DA dose and duration, future research should also consider whether DA-induced psychological side effects relate to the underlying psychological structure of individual patients. Screening tools that identify such at-risk patients may in turn guide a personalized approach to prolactinoma management with avoidance of DA therapy as the usual first-line treatment in susceptible individuals.

In conclusion, we have shown a significantly higher prevalence of ICDs in DA-treated hyperprolactinemic patients compared to healthy controls. The greatest risk appears to be hypersexuality with a strong male bias and a permissive effect from normal testosterone. The risk of DA-induced ICDs is not addressed in hyperprolactinemia guidelines (8,9). Only 37% of patients were aware of the relationship between DAs and ICDs before their involvement in the present study and patient awareness may be lower outside of tertiary pituitary centers. Increased awareness is required amongst endocrinologists and patients, especially in view of successful class actions against pharmaceutical companies for failing to warn patients of ICD risks in the setting of Parkinson's disease and restless legs syndrome. We recommend considering all DA-treated hyperprolactinemic patients to be at risk of developing ICDs, educating patients regarding this risk at the time of DA commencement, directly asking patients about ICD symptoms at follow-up, and potentially using written questionnaires as in the current study to overcome communication barriers in this sensitive area. If a DA-induced ICD develops, patients should be assessed for concurrent ICDs, depression and anxiety, and DA therapy should be ceased with consideration of treatment alternatives. We recommend caution if following a wait-and-see approach given the severe, long-lasting consequences that may occur with transient ICDs (16). Reducing or switching DA agents should also be performed cautiously as this is not substantiated by current and previous evidence showing ICD development regardless of DA doses (18-20) and agents (16,17). Heightened awareness of DA-induced ICDs should improve treatment safety.

REFERENCES

1. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J Clin Endocrinol Metab 2006; 91:4769-4775

2. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol (Oxf) 2010; 72:377-382

3. Barake M, Klibanski A, Tritos NA. MANAGEMENT OF ENDOCRINE DISEASE: Impulse control disorders in patients with hyperpolactinemia treated with dopamine agonists: how much should we worry? Eur J Endocrinol 2018; 179:R287-r296

4. Ioachimescu AG, Fleseriu M, Hoffman AR, Vaughan Iii TB, Katznelson L. Psychological effects of dopamine agonist treatment in patients with hyperprolactinemia and prolactin-secreting adenomas. Eur J Endocrinol 2019; 180:31-40

5. Caputo C, Prior D, Inder WJ. The need for annual echocardiography to detect cabergoline-associated valvulopathy in patients with prolactinoma: a systematic review and additional clinical data. Lancet Diabetes Endocrinol 2015; 3:906-913

6. Elenkova A, Shabani R, Kalinov K, Zacharieva S. Increased prevalence of subclinical cardiac valve fibrosis in patients with prolactinomas on long-term bromocriptine and cabergoline treatment. Eur J Endocrinol 2012; 167:17-25

7. Moore TJ, Glenmullen J, Mattison DR. Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. JAMA Intern Med 2014; 174:1930-1933

8. Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, Colao A, Fahlbusch R, Fideleff H, Hadani M, Kelly P, Kleinberg D, Laws E, Marek J, Scanlon M, Sobrinho LG, Wass JA, Giustina A. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf) 2006; 65:265-273

9. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96:273-288

10. Falhammar H, Yarker JY. Pathological gambling and hypersexuality in cabergoline-treated prolactinoma. Med J Aust 2009; 190:97

11. Bulwer C, Conn R, Shankar A, Ferrau F, Kapur S, Ederies A, Korbonits M, Spoudeas HA. Cabergoline-related impulse control disorder in an adolescent with a giant prolactinoma. Clin Endocrinol (Oxf) 2017; 86:862-864

12. Athanasoulia-Kaspar AP, Popp KH, Stalla GK. Neuropsychiatric and metabolic aspects of dopaminergic therapy: perspectives from an endocrinologist and a psychiatrist. Endocrine Connect 2018; 7:R88-R94

13. Gahr M, Connemann BJ, Schonfeldt-Lecuona CJ. [Pathological gambling induced by dopamine agonists]. Fortschr Neurol Psychiatr 2011; 79:470-474

14. Thondam SK, Alusi S, O'Driscoll K, Gilkes CE, Cuthbertson DJ, Daousi C. Impulse control disorder in a patient on long-term treatment with bromocriptine for a macroprolactinoma. Clin Neuropharmacol 2013; 36:170-172

15. Premaratne VS, Saeger I, Macdonald BK. Lesson of the month (1): cabergoline - 'i eat funny on that'. Clin Med (Lond) 2014; 14:205-207

16. De Sousa SM, Chapman IM, Falhammar H, Torpy DJ. Dopa-testotoxicosis: disruptive hypersexuality in hypogonadal men with prolactinomas treated with dopamine agonists. Endocrine 2017; 55:618-624

17. Martinkova J, Trejbalova L, Sasikova M, Benetin J, Valkovic P. Impulse control disorders associated with dopaminergic medication in patients with pituitary adenomas. Clin Neuropharmacol 2011; 34:179-181

18. Bancos I, Nannenga MR, Bostwick JM, Silber MH, Erickson D, Nippoldt TB. Impulse control disorders in patients with dopamine agonist- treated prolactinomas and nonfunctioning pituitary adenomas: a case–control study. Clin Endocrinol (Oxf) 2014; 80:863-868

19. Celik E, Ozkaya HM, Poyraz BC, Saglam T, Kadioglu P. Impulse control disorders in patients with prolactinoma receiving dopamine agonist therapy: a prospective study with 1 year follow-up. Endocrine 2018; 62:692-700

20. Dogansen SC, Cikrikcili U, Oruk G, Kutbay NO, Tanrikulu S, Hekimsoy Z, Hadzalic A, Gorar S, Omma T, Mert M, Akbaba G, Yalin GY, Bayram F, Ozkan M, Yarman S. Dopamine Agonist-Induced Impulse Control Disorders in Patients With Prolactinoma: A Cross-Sectional Multicenter Study. J Clin Endocrinol Metab 2019; 104:2527-2534

21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th (Text Revision) ed. Washington, DC: American Psychiatric Association.

22. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association.

23. Weintraub D, Hoops S, Shea JA, Lyons KE, Pahwa R, Driver-Dunckley ED, Adler CH, Potenza MN, Miyasaki J, Siderowf AD, Duda JE, Hurtig HI, Colcher A, Horn SS, Stern MB, Voon V. Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. Mov Disord 2009; 24:1461-1467

24. Primeau V, Raftopoulos C, Maiter D. Outcomes of transsphenoidal surgery in prolactinomas: improvement of hormonal control in dopamine agonist-resistant patients. Eur J Endocrinol 2012; 166:779-786

25. Lovibond SH, Lovibond PF. Manual for the Depression Anxiety Stress Scales. 2nd ed. Sydney: Psychology Foundation.

26. Antony MM, Bieling PJ, Cox BJ, Enns MW, Swinson RP. Psychometric properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical groups and a community sample. Psychol Assessment 1998; 10:176-181

27. Henry JD, Crawford JR. The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. Br J Clin Psychol 2005; 44:227-239

28. Reid RC, Garos S, Carpenter BN. Reliability, validity, and psychometric development of the Hypersexual Behavior Inventory in an outpatient sample of men. Sex Addict Compulsivity 2011; 18:30-51

29. Reid RC, Garos S, Fong T. Psychometric development of the hypersexual behavior consequences scale. J Behav Addict 2012; 1:115-122

30. Hays RD, Hayashi T, Stewart AL. A five-item measure of socially desirable response set. Educ Psychol Measur 1989; 49:629-636

31. Athanasoulia AP, Ising M, Pfister H, Mantzoros CS, Stalla GK, Sievers C. Distinct dopaminergic personality patterns in patients with prolactinomas: a comparison with nonfunctioning pituitary adenoma patients and age- and gender-matched controls. Neuroendocrinology 2012; 96:204-211

32. Grattan DR. 60 YEARS OF NEUROENDOCRINOLOGY: The hypothalamo-prolactin axis. J Endocrinol 2015; 226:T101-122

33. Barake M, Evins AE, Stoeckel L, Pachas GN, Nachtigall LB, Miller KK, Biller BM, Tritos NA, Klibanski A. Investigation of impulsivity in patients on dopamine agonist therapy for hyperprolactinemia: a pilot study. Pituitary 2014; 17:150-156

34. Grall-Bronnec M, Victorri-Vigneau C, Donnio Y, Leboucher J, Rousselet M, Thiabaud E, Zreika N, Derkinderen P, Challet-Bouju G. Dopamine Agonists and Impulse Control Disorders: A Complex Association. Drug Saf 2018; 41:19-75

35. Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, Whetteckey J, Wunderlich GR, Lang AE. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol 2010; 67:589-595

36. Bancos I, Nippoldt TB, Erickson D. Hypersexuality in men with prolactinomas treated with dopamine agonists. Endocrine 2017; 56:456-457

37. Valenca GT, Glass PG, Negreiros NN, Duarte MB, Ventura LM, Mueller M, Oliveira-Filho J. Past smoking and current dopamine agonist use show an independent and dose-dependent association with impulse control disorders in Parkinson's disease. Parkinsonism Relat Disord 2013; 19:698-700

38. Napier TC, Persons AL. Pharmacological insights into impulsive-compulsive spectrum disorders associated with dopaminergic therapy. Eur J Neurosci 2018; doi: 10.1111/ejn.14177. [Epub ahead of print]

FIGURE LEGENDS

Fig 1. ICD frequency and mean HBCS and DASS21 scores in all patients *vs* controls **(a)**, and in patients *vs* controls stratified by female **(b)** and male **(c)** gender.

Abbreviations: A, anxiety score by DASS21; D, depression score by DASS21; HBCS, Hypersexual Behavior Consequences Scale; HBI, Hypersexual Behavior Inventory; ICD, impulse control disorder; QUIP-S, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Shortened Version; S, stress score by DASS21.

Table 1. Demographic and clinical data of study participants.

	Patients (*n*=113)	Controls (*n*=99)	*P*
Gender, % male	49.6	46.5	ns
AT DIAGNOSIS			
Age, yr	38.1±15.9		
Tumor diameter, mm	20.8±17.0		
Hardy's score, %			
0	0.9		
I	27.4		
II	27.4		
III	31.0		
IV	0.0		
Unknown	13.3		
Tumor consistency, %			
Solid	57.5		
Cystic	8.0		
Mixed	16.8		
Unknown	17.7		
Visual field defects, %	15.9		
PRL, xULN*	56.4±144.3		
Testosterone, nmol/L*	5.2±3.7		
Pituitary hormone deficiency, %			
LH/FSH	78.8		
GH	6.2		
TSH	3.5		
ACTH	1.8		
AT ASSESSMENT			
Age, yr	45.5±16.5	41.2±10.1	0.020
Employment status, %			
Full-time	54.9	73.7	0.007
Part-time	15.0	26.3	ns
Home duties	7.1	0.0	0.008
Retired	15.0	0.0	0.000
Unemployed	8.0	0.0	0.004
Marital status, %			
Single	20.4	15.2	ns
Married	73.5	79.8	ns
Divorced	4.4	5.1	ns
Widowed	1.8	0.0	ns
Has children, %	61.1	62.6	ns
Current/former smoker, %	31.9	12.1	0.001
Any alcohol consumption, %	57.5	78.8	0.002
Tumor duration, yr	7.5±7.3		
DA duration, yr	6.5±7.1		
Non-ICD DA side effects, %	24.8		
Wkly CBG equivalent dose, mg	969.0±1100.5		
Cumulative CBG equivalent dose, g	307.3±419.1		
On sex hormone replacement, %	27.4		
PRL, xULN	0.8±1.8		
Testosterone, nmol/L	13.7±8.4		
PRL fall^, xULN (median, IQR)	11.2, 4.5-38.6		

Testosterone rise^, nmol/L	8.3±7.6
Prior pituitary surgery, %	15.9

*Abbreviations: ACTH, adrenocorticotrophin hormone; CBG, cabergoline; DA, dopamine agonist; FSH, follicle stimulating hormone; GH, growth hormone; ICD, impulse control disorder; LH, luteinising hormone; ns, non-significant; PRL, prolactin; TSH, thyroid stimulating hormone; ULN, upper limit of normal; * various normal ranges due to observational nature of study with different hormone assays employed depending on the referring clinician; ^ since time of diagnosis.*

Table 2. Significant differences on univariate analysis in patients screening positive *vs* patients screening negative for the ICDs shown to be higher in patients compared to controls.

Parameter^	Any ICD	Hypersexuality by QUIP-S	Hypersexuality by HBI	Buying by QUIP-S	Punding by QUIP-S
n positive/negative	69/44	25/88	9/104	18/95	10/103
Male, %	59.4 *vs* 34.1, *P*=0.015*	80.0 *vs* 40.9, *P*=0.001	100.0 *vs* 45.2, *P*=0.001	ns	ns
Divorced, %	ns	ns	22.2 *vs* 2.9, *P*=0.050	ns	ns
Has children, %	ns	80.0 *vs* 55.7, *P*=0.049	ns	ns	ns
Employed full-time, %	ns	ns	88.9 *vs* 51.9, *P*=0.039	ns	ns
≥2 SD/d alcohol, %	15.9 *vs* 2.3, *P*=0.027	ns	ns	ns	ns
Alcohol, SD/d	1.0±1.0 *vs* 0.5±0.5, *P*=0.027	ns	ns	ns	ns
Has mental illness, %	ns	ns	33.3 *vs* 6.7, *P*=0.032	ns	ns
Age at Dx	ns	ns	ns	30.9±12.7 *vs* 39.5±1.1, *P*=0.018	ns
Testosterone at Dx, nmol/L (*n*=48)	ns	ns	8.4±4.8 *vs* 4.8±3.3, *P*=0.026	ns	ns
Hardy's score at Dx (*n*=98)	ns	1.7±0.8 *vs* 2.1±0.8, *P*=0.035	ns	ns	ns
GH deficient at Dx, %	ns	ns	ns	22.2 *vs* 3.2, *P*=0.012	ns
Age at Ax	ns	ns	ns	36.5±12.5 *vs* 47.3±16.6, *P*=0.004	ns
Testosterone at Ax, nmol/L (*n*=55)	ns	17.3±8.9 *vs* 11.8±7.5, *P*=0.018	ns	ns	ns
Hypogonadism at Ax, % (*n*=95)	ns	12.5 *vs* 40.8, *P*=0.022	ns	ns	ns
SDRS5 score (*n*=111)	ns	ns	0.9±0.8 *vs* 1.9±1.5, *P*=0.005	ns	ns
D score	5.6±3.9 *vs* 3.4±4.9, *P*=0.010	ns	7.6±4.8 *vs* 4.5±4.3, *P*=0.022	7.4±4.2 *vs* 4.2±4.3, *P*=.004	ns
A score	4.1±3.2 *vs* 2.3±2.8, *P*=0.003	ns	ns	5.6±3.3 *vs* 3.0±3.0, *P*=0.001	5.7±3.7 *vs* 2.9±2.8, *P*=0.000
S score	7.3±4.0 *vs* 4.2±3.8, *P*=0.000	ns	9.3±3.4 *vs* 5.8±4.1, *P*=0.013	9.2±4.8 *vs* 5.5±3.8, *P*=0.000	9.1±4.3 *vs* 5.4±3.8, *P*=0.000

HBI score	ns	42.6±18.5 *vs* 22.2±5.1, *P*=0.000	N/A	ns	ns
HBCS score	28.2±12.8 *vs* 22.3±1.1, *P*=0.000	37.0±17.8 *vs* 22.7±2.4, *P*=0.001	56.8±14.1 *vs* 23.2±3.3, *P*=0.000	ns	ns

Abbreviations: A, anxiety score by DASS21; Ax, assessment; D, depression score by DASS21; Dx, diagnosis; GH, growth hormone; HBCS, Hypersexual Behavior Consequences Scale; HBI, Hypersexual Behavior Inventory; ICD, impulse control disorder; N/A, not applicable; ns, non-significant; QUIP-S, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Shortened Version; S, stress score by DASS21; SD, standard drinks; ^ n given if subset analysis performed due to missing data or if parameter not applicable in some cases e.g. testosterone levels only obtained in men, otherwise n=113.

Table 3. Questionnaire excerpts of negative effects of DA treatment in hyperprolactinemic patients.

Regarding hypersexuality
- *"I am fighting a constant internal battle between being the nice guy all love and respect, and an inner 'captain caveman' that keeps trying to come out. This is very much dependent on medication levels… One of the biggest issues for me is since treatment began I have not taken sexual rejection well. It considerably causes me to question my self-worth."* - *"I have separated from my wife of (decades) after being on Dostinex. This has been helpful in helping me to understand it a little better, even though obviously choices I made were mine."* - *"I feel I am sex obsessed and this potentially makes me vulnerable to female sexual predators. I have found it difficult to extricate myself from situations where I am the target of such an individual due to my own obsession which was not present prior to treatment."*
Regarding other ICDs
- *"I have become addicted to buying tools and cars to a point of almost financial ruin. I get a high when buying and then become very low when reality kicks in to then find the money to pay for purchases. Previously I never had this behavior but it's very consistent these days."*
Regarding non-ICD side effects
- *"I do feel my moods are very low. I found it hard to be happy or get excited about something. I don't feel I know what is happiness. Before I got this I used to be a very happy-go-lucky person."* - *"Self-harm side effects have included punching my head; bashing my head on ground, benchtops and walls; biting myself very hard on forearms; very frustrated; as often as 4 times every 7 days during the taking of medication."*

Table 4. Studies of DA-induced ICDs in hyperprolactinemic patients.

			ICD prevalence									
Study	n	Tool	Any	G	HS	B	E	H	P	W	M	Predictive factors
Martinkova 2011 (17)	20 pts	MIDI	10%	5%	5%	0%	5%	-	-	-	-	-
Bancos 2014 (18)	77 pts, 70 NFPA ctrls	MIDI, South Oaks Gambling Screen, modified HS & P questionnaires	25%	6%	13%	5%	-	-	9%	-	-	Male sex
Celik 2018(19)	25 pts, 31 NFPA ctrls, 32 HC	MIDI-R, BIS-11, SCL-90-R, BDI, BAI	8%	0%	8%	0%	-	0%	0%	-	-	Nil independent (age, sex, cumulative DA dose, smoking & alcohol predictive in combination)
Dogansen 2019 (20)	308 pts	Modified QUIP, BIS-11	17%	3%	10%	5%	6%	-	-	-	-	Male sex, alcohol, smoking, nadir PRL, others (incl T rise) only on univariate analysis
Present study	113 pts, 99 HC	QUIP-S, HBI, HBCS, DASS21, SDRS5	61%	6%	22%	16%	27%	22%	19%	8%	5%	Male sex, eugonadism, lower Hardy's tumor score, mental illness, younger age, others (incl T) only on univariate analysis

Abbreviations: B, compulsive buying; BART, Balloon Analog Risk Task; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BIS, Barratt Impulsiveness Scale; DA, dopamine agonist; DASS21, Depression, Anxiety and Stress Scale; E, compulsive eating; EDT, Experiential Discounting Task; G, pathological gambling; GH, growth hormone; H, hobbyism; HBCS, Hypersexual Behavior Consequences Scale; HBI, Hypersexual Behavior Inventory; HC, healthy controls; HS, hypersexuality; ICD, impulse control disorder; incl, including; M, compulsive medication use; MIDI, Minnesota Impulse Disorders Interview; NFPA, non-functioning pituitary adenoma; P, punding; pts, patients; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease; SDRS5, Socially Desirable Response Set Five-Item Survey; SCL-90-R, Symptom Checklist-90-R; T, testosterone; W, walkabout; - not tested.