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Investigation of impulsivity in patients on dopamine agonist therapy for hyperprolactinemia: a pilot study

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Abstract

The use of dopamine agonists (DAs) has been associated with increased impulsivity and impulse control disorders in several diseases, including Parkinson's disease. Such an effect of DAs on impulsivity has not been clearly characterized in hyperprolactinemic patients, where DAs are the mainstay of therapy. We studied the effects of DAs on impulsivity in hyperprolactinemic patients treated at a tertiary pituitary center, using validated psychometric tests. Cross-sectional study. Impulsivity was evaluated in 30 subjects, 10 hyperprolactinemic patients on DAs compared to two control groups; one comprising untreated hyperprolactinemic patients ($n = 10$) and a second group consisting of normoprolactinemic controls with pituitary lesions ($n = 10$). Measures of impulsivity included both self-report questionnaires as well as laboratory-based tasks. Hyperprolactinemic patients on DAs had a higher score (mean $\pm$ SD) in one self-report measure of impulsivity, the attention subscale of the Barratt Impulsiveness Scale (16.2 ± 2.7), as compared to the hyperprolactinemic control group (12.3 ± 2.5) and the normoprolactinemic group (14.7 ± 4.4) ($p = 0.04$). No statistically significant difference was found between groups with regards to the other impulsivity scales. In the DA-treated group, a correlation was observed between increased impulsivity (as assessed in the Experiential Discounting Task) and higher weekly cabergoline dose ($r^2 = 0.49$, $p = 0.04$). The use of DAs in hyperprolactinemic patients is associated with an increase in one aspect of impulsivity. This effect should be further characterized in larger, longitudinal studies.

Keywords

Cabergoline; Dopamine agonist; Hyperprolactinemia; Impulsivity; Pituitary adenoma

Introduction

Prolactinomas constitute approximately 40 % of all pituitary adenomas and are the most common type of secretory pituitary tumors [1]. All patients with macroadenomas and those with symptomatic or enlarging microadenomas typically require treatment. The mainstay of therapy involves the use of dopamine agonists (DAs), including bromocriptine and cabergoline. Both drugs are very effective in normalizing prolactin levels and reducing tumor volume and are usually well tolerated, the most common side effects being nausea and postural hypotension [2].

The use of DAs is not restricted to hyperprolactinemia. They are also widely used in other medical conditions, including Parkinson's disease (PD), multiple system atrophy, progressive supranuclear palsy, fibromyalgia and restless leg syndrome. In those conditions, therapy with dopaminergic drugs, usually at doses higher than those used to treat hyperprolactinemia, has been associated with increased impulsivity and the emergence of impulse control disorders (ICDs) [3–5]. The mechanism underlying this occurrence is presumed to be related to the role of dopamine as a neurotransmitter in the central pathways involved in reward and risk-taking behavior [3].

Impulsivity has been broadly defined as a predisposition toward unplanned and/or unduly risky behavioral responses to internal and external stimuli that demonstrates low regard for the negative consequences of these reactions to self or others [6]. ICDs are clinically significant conditions that include pathologic gambling, hypersexuality, compulsive eating or shopping. Their estimated prevalence in Parkinson's disease patients treated with DAs is as high as 17.1 % [5].

The occurrence of ICDs in patients with hyperprolactinemia receiving dopamine agonist therapy is not well characterized. The literature describing ICDs in this group of patients is very scarce, consisting of two case reports and one case series and is limited by the paucity of controlled studies and the lack of formal impulsivity evaluations [7–9].

Both the central role of DAs in the treatment of hyperprolactinemia and the published data on ICDs in patients on DAs underscore the clinical relevance of evaluating the effect of such therapy on impulsivity in this population. In this pilot study, we have investigated the impact of DAs on impulsivity in hyperprolactinemic patients using well-validated psychometric instruments. To our knowledge, this is the first study that formally evaluates the effect of dopaminergic therapy on impulsivity in this group of patients.

Subjects and methods

Study population

A total of 30 patients were enrolled at the time of their visit for clinical care at the Neuroendocrine Clinical Center at Massachusetts General Hospital (MGH). Eligible subjects were adults, aged 20–65 years. Ten patients with hyperprolactinemia (group 1), either idiopathic (defined as hyperprolactinemia in the absence of sellar mass or other clear cause) or secondary to a pituitary adenoma, and being treated with a DA were recruited. The other 20 patients formed two control groups: The first control group (n = 10, group 2) included patients with hyperprolactinemia who were managed expectantly (no dopamine agonist therapy for at least 6 months prior to the study visit). The second control group (n = 10, group 3) consisted of adult normoprolactinemic subjects with presumed Rathke's cleft cysts or non-functioning pituitary adenomas. Exclusion criteria for the three study groups were history of brain irradiation, acromegaly, hypercortisolism, known or suspected diagnosis of major depressive disorder, anxiety disorder, bipolar disorder, psychotic disorder, eating disorder or substance use disorder other than caffeine.

Screening tests and measures of impulsivity

The protocol was approved by the Partners Healthcare Research Committee. All study subjects signed an informed consent before enrollment. Eligible patients were first screened for psychiatric disorders and substance abuse or dependence using the short Structured Clinical Interview for DSM-IV (SCID) and the Consumptive Habits Questionnaire (CHQ), respectively. Subjects with a positive screening test were excluded from participation and referred for psychiatric evaluation as needed. Subjects in the three study groups were asked to complete two self-report questionnaires of impulsivity and two self-administered computerized performance-based tests of impulsivity.

Self-report questionnaires—Self-report measures included: (a) the Behavioral Inhibition/Activation System (BIS/BAS) [10, 11], a 24-item questionnaire measuring responses to reward (BAS) and punishment (BIS). BAS is further subdivided into three subscales: The drive subscale (measures pursuit of desired goals), the fun seeking subscale (reflects desire for and pursuit of new rewards) and the reward responsiveness subscale (focuses on positive response to anticipation of reward); (b) the Barratt Impulsiveness Scale (BIS-11) [12], a 30-item questionnaire that assesses the construct of impulsivity in three domains: attentional (inability to focus attention or concentrate), motor (acting without thinking) and nonplanning (lack of forethought). Both questionnaires consist of itemized statements to which subjects respond by entering a number from 1 to 4 on a Likert-type scale, ranging from strong agreement to strong disagreement.

Computer-based tests—In addition to the self-report questionnaires, patients completed two validated psychometric tests of impulsivity: (a) the Balloon Analog Risk Task (BART), a computerized instrument that involves actual risk-taking behavior [13]. Subjects pump a series of 30 virtual balloons that have the potential either to grow, in which case the player gains money, or explode, leading to no monetary gain for that balloon trial. The outcome measure of impulsivity is the adjusted mean number of pumps for each subject (mean number of pumps made on trials when the balloon did not explode); (b) the Experiential Discounting Task (EDT) is a real-time measure of delay discounting or preference for small but immediate rewards over possibly larger but delayed ones [14]. In this test, subjects are repeatedly asked in four consecutive session blocks to choose between two monetary reward options: one being fixed but delayed (by 0, 15, 30 or 60 s depending on the session block) and probabilistic (35 % likelihood of reward) and the other being variable in amount, but immediate and certain. The mean area under the curve (AUC) obtained at the completion of the test is used as a measure of impulsivity, a smaller AUC reflecting more discounting and thus greater impulsivity. To make the testing experience realistic, patients were paid the amount of money they made in both computerized tests at the end of the study session, as previously described [13].

Statistical analysis

Patient and disease characteristics in the three study groups were represented as mean $\pm$ SD for normally distributed variables and median with range in the absence of normal distribution. They were compared using Fisher's exact test for categorical variables, analysis of variance (ANOVA) followed by post hoc pairwise testing using the Tukey–Kramer test

for normally-distributed continuous variables, and Wilcoxon/Kruskal–Wallis test for continuous variables that were not normally distributed. Results of both self-report questionnaires and computer-based measures of impulsivity were represented as mean $\pm$ SD and compared between the groups using ANOVA. The association between demographic and treatment characteristics and different measures of impulsivity was assessed using univariate regression analysis and t tests as applicable. A p value < 0.05 was considered significant. Analyses were done using JMP PRO 9 (SAS Institute Inc, Cary, North Carolina, 2010).

Results

Patient characteristics

Baseline patient characteristics are reported in Table 1. There were no differences in age, gender, race, marital status, years of education and pituitary lesion size between the three study groups ($p = \text{NS}$). Group 1 patients, hyperprolactinemic patients on DA, had a slightly higher intake of alcohol (median of 2 drinks/week, $p = \text{NS}$) and caffeine (median of 14 cups/week, $p = 0.045$). As expected, group 2 patients, hyperprolactinemic controls, had higher serum levels of prolactin as compared to treated patients and to normoprolactinemic controls. None of the subjects reported use of any psychotropic medications. None of these patients had clinically evident ICDs.

In all hyperprolactinemic patients, the cause of hormone excess was considered to be either prolactin secretion from a pituitary adenoma or “stalk effect”; pregnancy, renal insufficiency, medications were excluded as possible causes. In group 1, 6/10 patients had a macroadenoma and 4/10 a microadenoma. In group 2, all patients had microadenomas. In group 3, only one patient had a macroadenoma while the others had a microadenoma or a Rathke’s cleft cyst. None of the patients had hydrocephalus or brain compression by a sellar mass.

All group 1 patients were treated with the dopamine agonist cabergoline, except for one patient who received bromocriptine. The mean weekly dose of cabergoline was 1.1 mg (± 0.5), with a range between 0.5 and 2 mg. The median duration of therapy was 33 months (range 7–192). In group 2, the majority of patients (7 out of 10) never received a DA in the past (no indication for treatment). Three patients were previously treated with cabergoline or bromocriptine, but treatment was stopped at least 2 years before the study visit. Only one patient, in group 2, had past transsphenoidal pituitary surgery. This patient had residual disease after surgery.

The prevalence of hypothyroidism in the three groups was 20, 10 and 10 % respectively ($p = \text{NS}$). Hypothyroidism was central in all patients, except for one in group 3 that had primary hypothyroidism. One patient had secondary adrenal insufficiency in group 3. Two patients had low IGF-1 levels (one in group 1 and one in group 2, who was maintained on an oral contraceptive). All patients with adrenal or thyroid hormone deficiencies were on adequate replacement at the time of the study. The prevalence of hypogonadism was 20 % in group 1 (both with central hypogonadism), 20 % in group 2 (1 primary and 1 postmenopausal), and 20 % in group 3 (both postmenopausal). Patients with hypogonadism were women, except

for two men in group 1 (one of whom was on transdermal testosterone replacement while the second was not replaced because of elevated serum prostate specific antigen levels). The prevalence of oral contraceptive use was 10 % in group 1 (endometriosis), 20 % in group 2 (1 woman with primary hypogonadism and 1 woman for contraception) and 10 % in group 3 (contraception). Postmenopausal women did not receive sex steroid replacement therapy.

Comparison of measures of impulsivity between the three study groups (Table 2)

Self-report questionnaires—Total as well as subscale scores in three domains of impulsivity were obtained from the BIS-11 questionnaire. Hyperprolactinemic patients treated with DAs, group 1, had a higher mean attentional impulsiveness subscale score (16.2 ± 2.7) than the hyperprolactinemic control group, group 2, (12.3 ± 2.5) and the normoprolactinemic group, group 3, (14.7 ± 4.4) ($p = 0.04$). The total BIS-11 score and the motor and nonplanning subscale scores were, however, similar between the three study groups ($p = \text{NS}$).

The three groups had similar mean scores on both the total scale results as well as on the subscale domains of drive, fun-seeking and reward responsiveness of the BIS/BAS questionnaire.

Computer-based tests—Subjects completed two computer-based measures of impulsivity, BART and EDT. On the EDT, hyperprolactinemic patients treated with DAs had a lower mean AUC (the outcome measure of interest being inversely related to impulsivity) (0.65 ± 0.11) than the untreated hyperprolactinemic group (0.74 ± 0.11) and the normoprolactinemic group (0.68 ± 0.14). This overall difference between the 3 groups did not reach statistical significance ($p = \text{NS}$). However, there was a trend towards lower AUC in the DA-treated group in comparison with hyperprolactinemic controls on pairwise testing ($p = 0.08$). The adjusted mean number of pumps obtained with the BART was similar between the three groups ($p = \text{NS}$).

Association between measures of impulsivity and treatment characteristics in hyperprolactinemic patients on DAs

After excluding the patient on bromocriptine, regression analysis was done to examine the association between the dose of cabergoline used and the different impulsivity scores of patients in the DA-treated group. A statistically significant negative correlation was found between the AUC on EDT and the DA dose; the higher the dose of cabergoline, the lower the AUC, indicating higher impulsivity ($r^2 = 0.49$, $p = 0.04$) (Fig. 1). No correlation was found between the other measures of impulsivity and the cabergoline dose (data not shown). On linear regression analysis, no relation was observed between the treatment duration (cabergoline or bromocriptine) and the impulsivity scores (data not shown).

Discussion

Impulsivity has long been viewed as a complex multidimensional trait with various manifestations, including impulsive choice, impulsive action or premature responding and rapid decisions [15]. In humans, impulsivity can be measured using both self-report

questionnaires (that reflect subjects' own attitudes) and laboratory-based tests (objective, quantifiable, performance-based psychometric measurements). The various measures of impulsivity currently available are thought to capture different domains of impulsivity. The multifactorial nature of this trait probably originates from separate brain circuits and neurotransmitter systems including dopamine [16]. Studies in both animals and humans have highlighted the role of dopamine in mediating reward and compulsive behavior [3]. In PD rodent models, the DA, pramipexole, was shown to increase probability discounting, a measurable aspect of risk taking [17]. Similarly, the use of DAs in patients with this disorder has been linked with increased impulsivity and higher ICD frequency [18].

The effect of DA therapy on impulsivity in hyperprolactinemic patients has not been well characterized. Two cases of ICDs in patients with pituitary adenomas on DAs are reported in the literature. In 2007, Davie et al. [9] first reported on a 38-year old woman with a prolactinoma who developed pathologic gambling after 1 year of cabergoline treatment. In 2009, a second case was reported of a 50-year old man who had both pathologic gambling and hypersexuality on cabergoline [8]. In 2011, a cross-sectional study using a structured interview of 20 consecutive patients with prolactinomas on DAs showed a 10 % prevalence of ICDs in this patient population [7]. Impulsivity was not formally evaluated in this study. It may also be noted that there has been one recent case report of a hyperprolactinemic patient presenting with mania after 8 months of cabergoline therapy [19].

In the current study, impulsivity was evaluated in a cross-sectional design in hyperprolactinemic patients on DAs and compared to two control groups using both self-report questionnaires as well as validated computer-based tasks. Hyperprolactinemic patients on DAs displayed a higher degree of impulsivity in the attention subscale of the BIS-11 questionnaire as compared to untreated hyperprolactinemic patients and to normoprolactinemic controls. The clinical significance of this higher score is a decreased ability to focus attention or concentrate and a tendency for quicker impulsive decisions or cognitive impulsiveness in the treated hyperprolactinemic group. Importantly, patients on DAs showed a correlation between greater impulsivity (as assessed in the EDT) and weekly cabergoline dose.

The results of this study suggest that dopaminergic therapy may have an effect on specific aspects of impulsivity in hyperprolactinemic patients. The effect of DAs on impulsivity in other disorders, including PD, appears to be more pronounced. Several explanations can be postulated to explain this observation. One possibility is that the current study is underestimating the true effect of DAs on impulsivity in hyperprolactinemia, as a result of subject selection bias. Patients who develop clinically relevant behaviors reflecting increased impulsivity may be more likely to have their DA treatment discontinued, and thus would be less likely to be included in this cross-sectional study. Patients included in the DA treatment group had a long duration of DA therapy (median of 33 months) and thus, most likely were tolerating the treatment relatively well. Another potential explanation is that the effect of DAs on impulsivity is limited to patients with certain predisposing factors that were not well represented in our patient population due to selection criteria or the relatively small sample size. Importantly, we specifically excluded patients with psychiatric disorders or history of substance use disorders, all of whom might be at greater risk for developing

increased impulsivity on DA therapy. Although this study design was chosen to omit potential confounders, we do not know whether patients with these disorders might be at greater risk for the development of impulsivity during dopamine agonist therapy.

The impact of the type and dose of the DA therapy on impulsivity is also of interest and might explain the possible differential effects of such therapy in various medical conditions. In PD, no association was found between the specific DA used and the occurrence of an ICD [5, 20]. In contrast to studied PD patients, who were most commonly receiving the D2/D3 receptor agonists pramipexole and ropinirole, the DA mostly used in the present study (as well as in hyperprolactinemic patients in general) is cabergoline, a selective D2 receptor agonist. Although ICDs have been reported in association with the use of cabergoline in restless leg syndrome, the data linking D2 agonists to impulsivity are scarcer [3]. Moreover, impulsivity is a multidimensional trait that may have a physiologic basis in diverse brain circuitry. The increase in certain aspects of impulsivity observed in this study might then be accounted for by the selective affinity of cabergoline to the D2 receptor as compared to the DAs used in Parkinson's. The effect of bromocriptine on impulsivity cannot be evaluated in the current study, as only one patient was treated with this drug.

In the hyperprolactinemic DA treated group of the present study, a higher cabergoline dose was associated with higher impulsive choices on the EDT test. Similarly, in PD, daily doses of DAs were higher in patients developing an ICD as compared to those who did not [20]. In the same disease population, the frequency of compulsive behaviors increased from 3 to 30 % by approximately doubling of the DA dose [21]. In contrast, increased impulsivity was reported with the lower doses of DA in patients with restless leg syndrome, where the prevalence of ICDs is 2.76 %, as compared to a prevalence of 13.6 % in PD [3, 20].

To our knowledge, this is the first controlled study formally investigating impulsivity in hyperprolactinemic patients on DAs in comparison with those hyperprolactinemic patients not on DAs and to normoprolactinemic controls with pituitary lesions, controlling in this way for any effect on impulsivity resulting from the pituitary disease process itself, whether the elevated prolactin or the pituitary mass. The similar patient demographic profile in the three study groups further minimizes potential confounding factors. Other strengths of the present study include the strict inclusion criteria: study patients were screened for the presence of psychiatric illnesses and substance abuse disorders which could have, if missed, increased impulsivity independently of DA treatment [15]. The absence of similar screening in the available literature in hyperprolactinemic patients on DAs might explain the higher prevalence of ICDs observed in those studies. Potential study limitations include the relatively small population size and the cross-sectional design of the study. In the absence of a longitudinal follow-up on patients, individual changes in impulsivity on DA therapy could have been missed. It is unknown whether patients who manifested symptoms suggesting impulsivity were discontinued from dopamine agonist therapy at an early time point.

Though this possible adverse effect of DA therapy in this patient population may seem rather limited in prevalence, it is essential for both patients and physicians to be aware of it. Providers should discuss it as a possible side effect of DA therapy. In many instances, as seen in the PD population and in case reports of hyperprolactinemic patients, DA-induced

impulsivity may result in pathological behaviors such as compulsive gambling and hypersexuality that could be detrimental to both personal and professional aspects of patients' lives. Such consequences may be avoidable if detected early on, and DA therapy is promptly discontinued. Understanding the predisposing factors to the development of increased impulsivity and ICDs will help caregivers to appropriately select and follow-up patients that require DA therapy.

In conclusion, the use of DA therapy (mostly cabergoline) in hyperprolactinemic patients in our study was associated with an increase in one aspect of impulsivity. In addition, higher doses of therapy were associated with greater impulsivity. Studies with larger sample size, wider DA dose range, and with longitudinal design are needed to help fully characterize the impact of such therapy on impulsivity in hyperprolactinemic patients.

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Fig. 1.

Regression analysis between the Experiential Discounting Task (EDT) area under the curve (AUC) and cabergoline dose (mg/week)

Table 1

Patients' demographic, clinical and laboratory characteristics

	HyperPRL on DA	HyperPRL controls	NormoPRL controls	<i>p</i> value
Number of Subjects	10	10	10	
Gender (% men)	40	10	40	NS
Age (years), mean $\pm$ SD	38.8 $\pm$ 12.6	38.9 $\pm$ 12.2	40.3 $\pm$ 13.1	NS
Race (% Caucasian)	100	60	80	NS
Education (years), mean $\pm$ SD	14.5 $\pm$ 1.6	15.3 $\pm$ 1.6	14.6 $\pm$ 1.8	NS
Married (%)	70	40	50	NS
Alcohol (drinks/week), median (range)	2 (0–6)	0.5 (0–3)	0 (0–3)	0.06
Caffeine (drinks/week), median (range)	14 (7–21)	5.5 (0–14)	12 (0–35)	0.04
Free T4 Level (fold ULN), mean $\pm$ SD	0.64 $\pm$ 0.13	0.63 $\pm$ 0.05	0.60 $\pm$ 0.09	NS
IGF-1 Level (fold ULN), median (range)	0.35 (0.1–0.8)	0.30 (0.2–1.1)	0.45 (0.3–0.7)	NS
Prolactin Level (fold ULN), median (range)	0.5 (0.07–7.9)	2.7 (1.6–26.8)	0.5 (0.2–0.5)	0.0003
Pituitary Lesion (largest diameter in mm), median (range)	6.5 (1.3–21)	4 (0–8)	5 (2–13)	0.08

HyperPRL Hyperprolactinemic patients, *NormoPRL* Normoprolactinemic patients, *ULN* Upper Limit of Normal

Table 2

Scores of self-report questionnaires and computerbased impulsivity tests in the study population (data expressed as mean $\pm$ SD)

	HyperPRL on DA	HyperPRL controls	NormoPRL controls	<i>p</i> value
BIS-11 questionnaire				
Total score	58.6 $\pm$ 5.4	51.1 $\pm$ 5.2	56.7 $\pm$ 12.8	<i>0.14</i>
Attentional score	16.2 $\pm$ 2.7	12.3 $\pm$ 2.5	14.7 $\pm$ 4.4	0.04
Motor score	20 $\pm$ 2.6	18.8 $\pm$ 2.1	19.8 $\pm$ 4.9	0.7
Nonplanning score	22.4 $\pm$ 4.6	20 $\pm$ 3.3	22.2 $\pm$ 5.0	0.41
BIS/BAS questionnaire				
BAS total score	38.8 $\pm$ 5.3	38.9 $\pm$ 6.6	39.3 $\pm$ 6.1	0.98
BAS drive score	10.6 $\pm$ 3.2	10.8 $\pm$ 3.3	10.9 $\pm$ 2.0	0.97
BAS fun seeking score	11 $\pm$ 1.9	10.5 $\pm$ 2.6	11.2 $\pm$ 3.2	0.83
BAS reward responsiveness score	17.2 $\pm$ 2.2	17.6 $\pm$ 2.0	17.2 $\pm$ 1.6	0.86
BIS score	21.4 $\pm$ 2.6	23.2 $\pm$ 3.3	20 $\pm$ 3.5	<i>0.09</i>
EDT (AUC)	0.65 $\pm$ 0.11	0.74 $\pm$ 0.11	0.68 $\pm$ 0.14	0.27
BART (pumps adjusted average)	26.6 $\pm$ 9.9	30.3 $\pm$ 8.9	33.8 $\pm$ 7.8	0.21

HyperPRL Hyperprolactinemic patients, *NormoPRL* Normoprolactinemic patients, *DA* Dopamine Agonist, *BIS-11* Barratt Impulsiveness Scale, *BIS/BAS* Behavioral Inhibition/Activation System, *EDT* Experiential Discounting Task, *AUC* Area Under the Curve, *BART* Balloon Analog Risk Task

Italicized *p* values correspond to non-significant values < 0.15