Psychological effects of dopamine agonist treatment in patients with hyperprolactinemia and prolactin-secreting adenomas

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Abstract

Background: Dopamine agonists (DAs) are the main treatment for patients with hyperprolactinemia and prolactinomas. Recently, an increasing number of reports emphasized DAs' psychological side effects, either *de novo* or as exacerbations of prior psychiatric disease.

Methods: Review of prospective and retrospective studies (PubMed 1976, September 2018) evaluating the psychological profile of DA-treated patients with hyperprolactinemia and prolactinomas. Case series and case reports of psychiatric complications were also reviewed.

Results: Most studies were cross-sectional and had a control group of healthy volunteers or patients with nonfunctioning pituitary adenomas. There were few prospective studies, with/without control group, that included small numbers of patients. Compared with controls, patients with hyperprolactinemia generally had worse quality of life, anxiety, depression and certain personality traits. Patients receiving DAs had higher impulsivity scores than normoprolactinemic controls. Impulse control disorders (ICDs) were reported in both genders, with hypersexuality mostly in men. Multiple ICDs were sometimes reported in the same patient, usually reversible after DA discontinuation. In case reports, DA therapy was temporally associated with severe depression, manic episodes or psychosis, which improved after discontinuation and administration of psychiatric medications. Gender type of DA, dose and duration of therapy did not correlate with occurrence of psychiatric pathology.

Conclusion: Patients with hyperprolactinemia receiving DAs may develop changes in mood and behavior regardless of prior psychiatric history. Increased awareness for ICDs, depression, mania and other types of psychosis is needed by all physicians who prescribe DAs. Larger prospective controlled clinical studies are needed to delineate prevalence, risk stratification and management.

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Introduction

Dopamine agonists (DAs) constitute the first-line treatment for prolactin-secreting adenomas (prolactinomas), the most common type of secretory pituitary adenoma.

Treatment is recommended to restore gonadal function, decrease galactorrhea, lower prolactin levels and decrease tumor size (1, 2). Treatment is long term in most patients (3).

Bromocriptine and cabergoline are currently approved for this indication in the United States; bromocriptine is also approved for treatment of type 2 diabetes. Quinagolide is another DA currently or previously used in some countries other than the United States.

The most frequent adverse effects of DAs are nausea, dizziness, orthostatic hypotension and headaches. In addition, a variety of psychological side effects have also been described, many as isolated case reports. Psychosis, mania, anxiety, depression, confusion, auditory hallucinations, hyperactivity, insomnia, nightmares, paranoia and impulse control disorders (ICDs) have been reported either *de novo* after starting DA therapy or as exacerbations of previously known psychiatric disease. Many endocrinologists are not aware of the association between DAs and psychiatric symptoms, and as a result, underreporting is likely. Moreover, there are no specific guidelines for the management of patients experiencing psychological problems as a result of DA therapy.

In this review, we examine the current knowledge regarding mechanisms, clinical presentation, course and management of psychological disturbances encountered in patients treated with DAs for hyperprolactinemia.

Methods

A US National Library of Medicine PubMed search through July 2018 was conducted using the search terms 'dopamine agonists' or 'bromocriptine' or 'cabergoline' and 'psychiatric disorders', 'impulse control disorders' or 'hypersexuality' 'depression' or 'mania'. All English language articles were read and reviewed by the authors for relevance and significance.

Mechanism of psychiatric disturbances in patients with prolactinomas treated with dopamine agonists

The endocrine system and mental health are closely entwined, especially when the hypothalamus and pituitary gland are involved. Dopamine is a neurotransmitter important for motor function, motivation, reinforcement learning and prolactin control. There are three main dopaminergic pathways: (1) nigrostriatal, involved in motor functions, (2) mesocorticolimbic, also known as the reward system, involved in the regulation of behavior, pleasure and addiction and (3) tuberoinfundibular, involved in the control of prolactin secretion (4).

DAs exert their endocrine effects by binding to dopamine type 2 (D2) receptors in the tuberoinfundibular system (5). Both D2 and D3 receptors are also expressed in the striatal pathway (6), and D3 receptors are present in high density in the mesolimbic cortex. DA binding is generally not specific to one receptor type from a certain neuronal pathway, which can explain some of the neuropsychiatric side effects of DAs (7). Bromocriptine, cabergoline and quinagolide bind with high affinity to D2 and with lower affinity to D1 and D3 receptors. Quinagolide and cabergoline have lower affinity for D1 than bromocriptine (8). Pramipexole and ropinirole, DAs approved for Parkinson's disease (PD) and restless leg syndrome (RLS), have a higher affinity for D3 compared with bromocriptine and cabergoline (9). Notably, selective D3 agonists were associated with more ICDs (10) in patients receiving DAs for PD and RLS.

Central nervous system (CNS) side effects depend on the drug's capacity to cross the blood-brain barrier, which is controlled by transporter molecules. P-glycoprotein 1 (P-gp) is a transport molecule encoded by the *ABCB1* gene that transports substrates released from the neuron back into the blood. Genetic polymorphisms of the *ABCB1* gene may influence or alter the function of the P-gp protein and could influence the predisposition to CNS side effects from DA therapy. This hypothesis is supported by an experimental *ABCB1*-knockout mouse model study and a case-control study of 79 patients with prolactinomas. In the latter, patients completed questionnaires to determine whether fatigue, dizziness, sleep disorders and headaches changed during cabergoline therapy. *ABCB1* SNPs rs1045642 were associated with fatigue and sleep disorders, while SNP rs2032582 associated with dizziness during DA therapy (11).

Whether patients with hyperprolactinemia are more susceptible to neuropsychiatric complications of DAs than individuals with normal prolactin levels remains to be determined. Several factors have been invoked, including central dopamine depletion (5), decreased gonadal sex steroid levels or hyperprolactinemia itself. It is difficult to tease them apart as they often occur simultaneously. Prolactin levels can increase during stress, and studies in normal subjects have reported surges in serum prolactin in induced situations that evoked feelings of rage and humiliation (12).

In summary, the mechanisms of psychologic and psychiatric disturbances in patients with prolactinomas treated with DAs are complex and incompletely understood. They entail specific affinities of the drugs on different classes of DA receptors in the brain, as well as the altered baseline tone of dopaminergic activity.

Psychological profile of patients with hyperprolactinemia

Early reports in the 1970–1990s included 3 to 14 patients and indicated increased levels of anxiety, distress and hostility (13, 14, 15, 16) and that treatment with bromocriptine was associated with amelioration of these symptoms (15, 16, 17). One study had a double-blind cross-over placebo-controlled design and included eight patients with hyperprolactinemia (16). However, a prospective study in nine patients treated with bromocriptine for 6–12 months (without a control group) did not reproduce these findings (18). In a cross-sectional study of ten women with hyperprolactinemia, patients were more likely to experience depression, anxiety and hostility than normoprolactinemic controls with amenorrhea (17).

A study in 39 patients with untreated prolactinoma had lower scores on the SF-36 questionnaire (36-Item Short Form Survey, a patient reported survey of health) compared with healthy controls. The domains affected were role physical, vitality, social functioning, role emotional, mental health and the mental summary. The physical functioning, bodily pain, general health and physical summary were similar to controls (19).

There are few controlled clinical studies that report systematic evaluation of neurocognitive and psychological functions in hyperprolactinemic patients at baseline and during DA treatment. In a single-center cross-sectional study of women treated with bromocriptine, cabergoline or quinagolide for microprolactinomas, 81 patients were invited to complete questionnaires (62 accepted) and were asked to provide a control person of comparable age and same sex (a relative, friend or neighbor). The control group consisted of 183 subjects. The health-related questionnaires (Nottingham Health Profile-NHP, SF-36, Multidimensional Fatigue Inventory-MFI-20 and Hospital Anxiety and Depression Scale-HADS) covered different dimensions of quality of life, including physical, emotional, mental and social aspects. The subscale for social functioning and role limitations due to physical problems on SF-36, the energy, emotional reaction and social isolation subscales on NHP, and general and physical, fatigue, activity and motivation subscales on MFI-20 were all impaired in the hyperprolactinemic patients when compared with controls. Furthermore, prolactinoma patients also had worse anxiety, depression and total scores for HADS compared with controls. Of note, the extent of psychological impairment did not correlate with either current DA use or duration of

therapy. In addition, neither the serum prolactin level, nor the presence of hypogonadism in premenopausal women correlated with the degree of quality of life and psychological impairments (20).

A study in 86 patients with prolactinomas described a distinct dopaminergic personality profile using the Eysenck Personality questionnaire and the Cloninger Temperament and Personality Questionnaire. Patients with prolactinoma were compared with 58 patients with nonfunctioning pituitary adenomas (NFA) and 172 controls. All patients with pituitary tumors had increased neuroticism, increased fear or uncertainty and increased fatigability and asthenia compared with controls. Patients with prolactinoma had higher neuroticism, reduced extraversion, increased shyness with strangers and lower scores on novelty seeking subscale impulsiveness compared with patients with NFA. A subgroup analysis in 55 patients receiving DAs showed that these patients were more dependent than 31 non-treated patients. In addition, treated patients who achieved normal serum prolactin levels had lower novelty seeking, exploratory excitability and extravagance tendencies compared with those with persistent hyperprolactinemia (21). This study supports the theory that patients with hyperprolactinemia have low dopaminergic activity, which has been associated with decreased novelty seeking and increased harm avoidance scores. Interestingly, these personality traits did not change after DA therapy in this study.

A recent study evaluated 25 patients with prolactinoma and 32 healthy controls with the revised Minnesota Impulsive Disorders Interview, Barratt Impulsiveness Scale, Symptom Check List questionnaire, Beck Depression Inventory and Beck Anxiety Inventory. At baseline, there were no differences between groups regarding somatization, anxiety, obsession, depression, interpersonal sensitivity, psychoticism, hostility, phobic anxiety or paranoid ideation. Similarly, there were no inter-group differences after 3 months of cabergoline treatment. More patients in the prolactinoma group screened positive for obsession, interpersonal sensitivity and paranoid ideation after 12 months of treatment (22).

In summary, based on available literature, patients with hyperprolactinemia appear to have decreased quality of life, and different personality profiles compared with control subjects. Some, but not all studies also indicate increased anxiety and depression. It is not clear whether DA therapy favorably influences the self-reported mental and physical health of patients with hyperprolactinemia. Further large controlled studies are needed to clarify this issue.

Dopamine agonist therapy and impulse control disorders

The ICDs are 'disruptive, impulse control and conduct disorders' defined as the failure to resist an impulse or the temptation to perform an act that is harmful to oneself or others. Manifestations include pathological gambling, hypersexuality, binge eating, compulsive shopping, compulsive medication use, obsessive hobbying and punding. Punding is defined as compulsive repetitive mechanical tasks (i.e. assembling and disassembling or sorting objects). ICDs can be serious with significant social and financial consequences.

The prevalence of ICD in the general population is estimated at 8% (7). A retrospective study based on FDA Adverse Event Reporting System between 2003 and 2012 identified 1580 ICD events. Of them, DA therapy accounted for 710 events (45%): pramipexole (410), ropirinoles (188), cabergoline (56) and bromocriptine (30). The study indicated affected patients had a median age of 55 and male gender preponderance (65.8%). There was a slightly higher reporting by patients than physicians. The FDA reporting increased progressively after 2006 and almost reached a plateau after 2009 (23). A recent review of DA-associated ICDs reported to the FDA indicated that 62% of the patients experiencing ICDs were treated for PD, 24% for RLS and 3.5% for hyperprolactinemia (24). The significantly higher number of reports in patients receiving DA therapy for PD and RLS support the involvement of mesolimbic D3 receptors; pramipexole and ropirinoles have higher D3 affinity than cabergoline and bromocriptine. In patients with PD who were treated with DAs, there is a reported prevalence of ICDs between 2.6 and 34.8% (4). Higher rates were noted in specific populations: 39.1% in patients treated for at least 3 consecutive months (25) and 58.3% in early-onset PD (26). In patients treated for RLS, ICDs prevalence was lower, at 7.1–11.4% (4).

The first case of pathological gambling in a patient treated with DAs for prolactinoma was reported in 2007 in a 47-year-old woman taking a low dose of cabergoline (27). She sought medical attention for major depression and paranoid delusions, having incurred a financial loss of \$700 000. Of note, the patient did not have these problems 25 years previously when she took bromocriptine. Table 1 summarizes the individual case reports of ICD during DA therapy administered for prolactinomas (24, 27, 28, 29, 30, 31).

Pathologic hypersexuality may include increased libido, sexual thoughts, sexual frequency and high-risk

sexual activities. Due to their personal nature, patients may not be forthcoming in reporting these manifestations, which can lead to relationship problems, financial loss, reduced work performance and illicit activities (e.g., engagement in prostitution, promiscuity and theft and use of recreational drugs). The mechanism entails reward pathway stimulation as do other ICDs; also, increasing levels of testosterone in men taking DA therapy may contribute to the hypersexuality. De Sousa *et al.* proposed the term 'dopa-testotoxicosis' in their report of eight men with prolactinoma and no prior history of psychiatric disease (32). Patients received cabergoline (0.5–1 mg weekly), bromocriptine (0.625–2.5 mg daily) and/or quinagolide (75 µg daily). Testosterone levels were low in six and in the lower half of the normal range in two patients, and increased during DA therapy, with all patients achieving normal testosterone levels. Six patients were bothered by hypersexuality and decreased the dose or stopped the DA, with resolution of symptoms, which did not recur after testosterone replacement or pituitary surgery. Additional case reports in men with prolactinomas who received cabergoline (0.5–2 mg weekly) or bromocriptine (7–15 mg daily) confirmed resolution of hypersexuality after the DA dose decreased or was stopped (29, 33, 34, 35). There are few case reports of hypersexuality in women: three with cabergoline or bromocriptine (33) and one with quinagolide (Table 1) (31). While there are more reports of disruptive hypersexuality in men undergoing DA therapy, testosterone levels were not supraphysiologic and the symptoms resolved after stopping the DA. Hence, the term 'dopa-testotoxicosis' does not seem appropriate.

There are few systematic studies of ICDs in patients treated with DAs for prolactinomas. A cross-sectional study evaluated 20 patients with the Minnesota Impulse Disorder Interview (MIDI). ICDs were identified in two male patients (10%), both treated with relatively low DA doses. Manifestations included pathological gambling, severe hypersexuality and compulsive eating (34). This study found that ICDs prevalence was comparable to that of the general population, but unfortunately did not include a control group.

Bancos *et al.* conducted the largest case control study aimed at ICD detection in 77 patients with DA-treated prolactinomas and 70 patients with NFA. Patients were selected through a postal survey sent to 200 patients in each group. The NFA group included more women than the prolactinoma group (64 vs 55%), with a similar mean age. The overall response rates were not different between men and women, but the responders were older than the nonresponders. Additional phone discussions

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Table 1 Individual case reports of patients with prolactinoma who developed dopamine agonist-associated impulse control disorders (ICDs).

Study	Age, sex (M/F), endocrine diagnosis	History of psychiatric disease (Y/N)	DA regimen	Length of exposure	Manifestations and social consequences	Outcomes
(27)	47 y, F, Micro	N	Cabergoline 0.25 mg/week	1 y	Gambling, major depression, paranoid delusions Loss of \$700 000	Resolved after stopping DA
(31)	44 y, F, Micro	N	Quinagolide 225 mg/day	5 y	Gambling, hypersexuality, mania Loss of 10 000 euro	Resolved after stopping DA
(29)	50 y, F, Micro	N	Cabergoline 0.25 mg/week	6 y	Gambling, hypersexuality Loss of \$100 000 Divorce proceedings	Resolved after stopping DA
(28)	Middle age, F, Micro	Y †	Bromocriptine 5 mg/day then Cabergoline 2.5 mg/week	2 y	Compulsive shopping, gambling and eating Worsened depression Separation from partner	Improved 3 weeks after stopping DA
(30)	16 y, F, Prolactinoma	N	Bromocriptine 20 mg/day	2 y	Gambling Financial debt	Resolved after stopping bromocriptine
(35)	19 yM, Giant prolactinoma	N	Cabergoline 1.5 mg/week	3 y	Hypersexuality	Improved during one-month trial off DA
(24)	19 y, M, Giant prolactinoma	N	Bromocriptine then quinagolide then cabergoline	Shortly after starting therapy	Gambling, depression Loss of 20 000 euro and prison sentence	Improved with psychotherapy and citalopram (cabergoline continued)

Micro, microadenoma. y, years; †, depression after marriage.

were undertaken to confirm the positive answers to the survey and to obtain details regarding symptoms. Patients with prolactinomas were diagnosed at least 12 months prior to participating in the study. DA treatment had a median duration of 94 months (range 5–455) and consisted of cabergoline (53% patients, 0.25–4 mg/week) and bromocriptine (29%, 8.75–70 mg/day), while 18% patients were not receiving DAs at the time of the interview. One or more ICDs were found in 24.68% of patients with prolactinomas. Duration of treatment, type of DA used, tumor diameter and post-treatment tumor shrinkage were not associated with the development of ICDs. Interestingly, patients with NFA also had a relatively high ICD prevalence (17.14%). Hypersexuality was the predominant ICD encountered in patients with DA-treated prolactinomas, which occurred less frequently in controls (12.99 vs 2.87%). While gender did not correlate with the risk of ICD per se, subgroup analysis showed that men with prolactinomas had almost 10 times higher risk of ICDs than men with NFAs (27.7 vs 3.7%) (33).

Barake *et al.* (36) evaluated impulsivity in 30 subjects in a cross-sectional design: 10 hyperprolactinemic patients on DA therapy, 10 untreated hyperprolactinemic patients

and 10 normoprolactinemic controls with other types of pituitary tumors. Patients with psychiatric disorders or a history of substance use disorders were excluded. Self-report measures included the Behavioral Inhibition/Activation System (BIS/BAS), a 24-item questionnaire measuring responses to reward (BAS) and punishment (BIS) and the Barratt Impulsiveness Scale (BIS-11), a 30-item questionnaire that measures the construct of impulsivity in three domains: attentional (inability to focus attention or concentrate), motor (acting without thinking) and non-planning (lack of forethought). Patients also completed two validated psychometric tests of impulsivity: the Balloon Analog Risk Task (BART), a computerized instrument that involves actual risk-taking behavior and the Experiential Discounting Task (EDT), a real-time measure of delay discounting or preference for small, but immediate rewards over possibly larger but delayed ones. Treatment with DAs consisted of cabergoline in all except one patient who received bromocriptine. The mean weekly cabergoline dose was 1.1 mg (range 0.5–2 mg), with a median therapy duration of 33 months (range 7–192). In this cross-sectional study, hyperprolactinemic patients on DAs displayed a higher degree of impulsivity

in the attention subscale of the BIS-11 questionnaire as compared to both untreated hyperprolactinemic patients and to normoprolactinemic controls. A higher cabergoline dose was associated with higher impulsive choices on the EDT test in hyperprolactinemic DA-treated group in this study (36).

Celik *et al.* (22) prospectively evaluated 25 patients with prolactinoma, 31 with NFA and 32 healthy controls for the presence of ICDs and other psychiatric disorders. Two cases of ICDs consisting of hypersexuality (8%) were associated with DAs use, which improved or resolved after discontinuation of the DA. When patients were exposed to smaller dose of the same DA, either no symptoms or less severe manifestations occurred (22).

The data are sparse regarding risk factors for ICDs in patients with prolactinoma treated with DA therapy. Young age and male gender were associated with ICDs in PD, especially with regard to pathological gambling and hypersexuality (4). However, a correlation between age and ICD development in prolactinoma patients could not be shown. More cases of hypersexuality were reported in men than in women with prolactinoma, but other types of ICDs did not have a gender predilection. Preexisting psychiatric disease, in particular anxiety and depression, may increase the risk of ICD; however, this was an exclusion criterion in some studies. It is unclear whether DA therapy association with ICDs is dose-dependent (suggested by one study that included nine patients taking cabergoline) (36) or related to the duration of DA treatment. Comparing the risk between different DAs is not possible because of different types of DAs that were available at the time of the report in different countries. Challenging patients who experienced ICDs while taking one DA with another DA has been attempted in a few cases and led to reoccurrence of ICD in some patients (24, 28). It is important to note that approximately 33% of reported patients developed multiple types of ICDs during DA therapy (32, 33). Finally, discontinuation of DAs or even reducing the dose along with adding psychotherapy or psychiatric medications were associated with improved or resolved ICDs (24, 27, 29, 31, 32, 33, 34, 35).

Based on the data accumulated, we suggest that physicians discuss the risk of ICDs at the time of DA therapy initiation and revisit this issue at follow-up visits. The ICD manifestations reported in the literature were mostly reversible after DA stopped or dose decreased; in some instances, ICDs only developed with one type of DA (24, 27). Therefore, in case of mild manifestations, a smaller dose of DA or another DA approved for use in hyperprolactinemia can be attempted, while the patient is carefully monitored

by both endocrinology and psychiatry. The antipsychotic aripiprazole has been approved for schizophrenia, bipolar disorder, major depressive disorder and autism spectrum disorder. Unlike most antipsychotics, aripiprazole has partial dopamine agonist D2 activity and has been shown to improve prolactin secretion in some patients with coexistence of a prolactin-secreting tumor and psychiatric disease (37, 38). Efficacy and safety studies in patients with prolactinomas are not available. The approach whereby aripiprazole replaces cabergoline or bromocriptine in patients with prolactinoma who developed ICDs requires further study. If the temporal association is demonstrated between pharmacologic treatment of hyperprolactinemia and *de novo* ICDs, surgical treatment of the pituitary tumor can be considered.

Psychiatric disorders other than ICDs during treatment with dopamine agonists for prolactinoma

There are reports of DA use associated with severe depression, manic episodes or psychosis, but the overall number is quite small. This is likely an under-reported association, as patients may not be forthcoming in the absence of direct questioning and because of publication bias (clinicians aware of this possibility may not consider it worth presenting). Table 2 summarizes these case reports, with the majority occurring in women taking cabergoline (37, 38, 39, 40, 41, 42, 43, 44, 45, 46). The severity of hyperprolactinemia ranged from 45 to 9400 ng/mL, some patients had prolactinomas and some had a NFA with stalk effect hyperprolactinemia. The psychiatric disturbances included severe depression, mania, psychosis and even catatonia. In most cases, the DA was stopped. In all but one case, an antipsychotic medication was initiated as well. One patient was treated with transsphenoidal resection of the prolactinoma (43). While some patients had a prior history of psychiatric disease, others did not. The duration of exposure to DAs ranged from 4 days to 6 years. In clinical practice, one should always be aware of the potential for the precipitation of psychiatric disease when using DAs, even in the absence of a prior history.

Clinical studies on this topic are sparse. In 1984, Turner *et al.* (47) performed a retrospective analysis of a 600 patients with acromegaly or hyperprolactinemia treated with DAs. Psychotic reactions were identified in eight patients, among them five women with prolactinoma ages 20–58 treated with bromocriptine (four patients, doses ranging from 7.5 to 60 mg) or lisuride (one patient, 1.2 mg daily). Psychiatric history prior to DA therapy was negative. Interestingly,

Table 2 Individual case reports of patients with hyperprolactinemia who developed depression, mania or psychosis while taking dopamine agonists.

Study	Age, sex (M/F), endocrine diagnosis	History of psychiatric disease (Y/N)	Prolactin level (ng/mL)	DA regimen	Length of exposure	Manifestations	Outcomes
(44)	Unknown	Unknown	Unknown	Bromocriptine	Unknown	Psychosis	Unknown
(43)	53 y, M, Macro	N	933	Bromocriptine 2.5 mg/day	4 days	Psychosis	Stop bromocriptine, pituitary surgery
(42)	25 y, F	N	300	Bromocriptine 10 mg/day	6 y, intermittent	Psychosis	Stop bromocriptine, initiate clozapine
(40)	23 y, F, Macro	Schizophrenia treated with ziprasidone	171	Cabergoline	4 y	Hallucinations, delusions, catatonia	Stop cabergoline, initiate aripiprazole; symptoms resolved after 2 weeks, prolactin normalized
(41)	39 y, F, Macro	N	9400	Bromocriptine 2.5 mg/ day, stopped 2 months prior to presentation	5 y	Depression, psychosis, delusions	Initiate aripiprazole, continue bromocriptine; symptoms resolved after 4 weeks
(45)	44 y, F, Unknown	Y	Unknown	Cabergoline	3 mo	Psychosis	Resolved immediately after stopping cabergoline
(39)	32 y, F, Micro	Depression N	48.1	Cabergoline 0.25 mg/ week	2 y	Worsening depression, delusions, hallucinations	Resolved after stopping cabergoline and initiating aripiprazole
(38)	30 y, F, Micro	Y	51.7	Bromocriptine 5/day*	'Short'	Worsening depression, insomnia, delusions, hallucinations	Resolved after stopping bromocriptine and initiating aripiprazole
(39)	34 y, F, Micro	Y	45	Cabergoline 0.5 mg/week	1 mo	Worsening depression, mania, disinhibition, spending	Stop cabergoline, initiate aripiprazole
(49)	26 y, F, PP galact	N	Unknown	Cabergoline 0.5 mg/day	'Short'	Mania with psychotic features (grandiose and paranoid delusions)	Improved 3 weeks after stopping cabergoline and initiating aripiprazole
(46)	25 y, F, Micro	N	60	Cabergoline 1 mg/week	6 mo	Mania	Resolved 4 weeks after stopping cabergoline and initiating lithium

*Patient was previously treated with cabergoline which caused emotional lability, insomnia and worsened depression.
Macro, macroadenoma; Micro, microadenoma; PP galact, postpartum galactorrhea; y, years; mo, months

all five patients developed paranoid psychosis. (47). Celic *et al.* (22) prospectively evaluated 25 patients with prolactinoma treated with cabergoline, 31 with NFA and 32 healthy controls. The study found more patients with prolactinoma screened positive for obsession, interpersonal sensitivity, paranoid ideation after 12 months of DA therapy. The cumulative DA dose was positively correlated to obsession, interpersonal sensitivity, paranoid ideation, hostility, phobic anxiety subscales and higher general severity index scores of SCL-90-R (Symptom Checklist-90-Revised) questionnaire (22).

Treatment of hyperprolactinemia in patients treated with antipsychotic medications

Particularly challenging is the treatment of hyperprolactinemia in the setting of known psychotic disorders, as the psychiatric medications of choice in this setting are often dopamine antagonists which may further raise prolactin (7). Risperidone and haloperidol are the most commonly reported psychotropic medications that cause hyperprolactinemia. The differential diagnosis of medication-induced hyperprolactinemia vs pituitary adenoma should be carefully considered. Current recommendations suggest withdrawal of any potentially offending drug for 3 days and repeating serum prolactin levels, which must be done in consultation with the patient's mental health specialist (1). If this approach does not seem safe with regard to the patient's psychiatric condition, an MRI of the pituitary gland should be considered. In patients with drug-induced hyperprolactinemia, evaluation for galactorrhea and hypogonadism is necessary. Whenever possible, alternative psychiatric medications that do not raise serum prolactin levels can be considered in collaboration with the patient's psychiatrist. In asymptomatic patients without hypogonadism (or taking gonadal replacement) the prolactin levels can be monitored. Similarly, small pituitary tumors can be closely observed. The antipsychotic aripiprazole may possess unique advantages in this specific setting (48). Unlike other antipsychotics, aripiprazole has partial dopamine agonist activity. Table 2 illustrates that aripiprazole was a satisfactory treatment in many of the reported cases (37, 38, 39, 40, 41, 49). Prolactin decreased on average by 74% in patients taking aripiprazole (50) and in many cases normalized. The combination of aripiprazole and bromocriptine or quinagolide was successful in patients who had both macroprolactinomas and schizophrenia (41, 51); while these results are encouraging, it is not known

whether the same degree of tumor involution would be expected. Finally, surgical therapy for prolactinoma was used in some cases in the setting of mass effect manifestations coexistent psychiatric disease (52, 53).

Advice for clinical practice

The prevalence of psychiatric complications from DAs used for hyperprolactinemia and the risk profile of affected patients are not well defined. Counseling all patients is worthwhile given the significant health and societal consequences that may occur during DA therapy. Before prescribing DA, it would be important to take a thorough history of psychiatric disease, and to initiate communication with psychiatry when necessary. Until further research identifies the standardized questionnaires best suited for patients with prolactinomas, the physicians may use direct questioning regarding prior or current history of ICDs, depression, anxiety or psychiatric medications. At follow-up visits, direct questions about changes in mood and behavioral changes are encouraged. If such alterations were identified, the patients would benefit from a multidisciplinary care that includes neuropsychology and psychiatry. Further prospective studies are necessary to make specific clinical recommendations regarding management of psychiatric complications of DA therapy.

Conclusions

Psychological changes in patients treated with DAs for hyperprolactinemia and prolactinomas vary in spectrum and severity and may have significant medical and social consequences. Physicians who prescribe DAs should be aware of the potential occurrence of ICDs, depression, mania and other types of psychosis. For patients with known psychiatric disease, a close collaboration with mental health specialists is required to assess individualized treatment for prolactinomas and the safety of adding DA therapy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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