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Cabergoline Associated with First Episode Mania

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Dopamine agonists are commonly used in the treatment of hyperprolactinemia, Parkinson's disease, and restless leg syndrome. While generally well tolerated, these agents can cause psychiatric adverse side effects including depression, somnolence, anorexia, anxiety, insomnia, impaired concentration, nervousness, hallucinations, nightmares, psychosis, and mania. For bromocriptine, a non-selective ergot-derived D_2 agonist, the incidence of these side effects ranges from less than one percent to three percent.[1] Cabergoline, a long-acting and more selective ergot-derived D_2 receptor agonist has a similar incidence of many of these side effects.[1] However, cabergoline is not associated with the development of new onset delusions or hallucinations. Moreover, there has been no known published case of mania induced by cabergoline. Here we present a case of a cabergoline-associated manic episode.

Case Report

Ms. C, a 45-year-old woman, was evaluated 8 months prior to presentation for a 2-year history of amenorrhea. Ms. C was not sexually active, was not taking oral contraceptives, and had never been pregnant. She was not obese (BMI 24.5), had no acne, hirsutism, or acanthosis nigricans, and had no visual field defects or galactorrhea. Blood tests demonstrated an elevated prolactin level of 33.1 ng/mL (reference range 3–18.6 ng/mL), a FSH level of 5.1 IU/L, estradiol 61 pg/mL, normal TSH, and negative β-HCG. These results were suggestive of hyperprolactinemia in a pre-menopausal woman. A non-contrast MRI of the pituitary gland was unrevealing, and Ms. C was started on cabergoline 0.5 mg orally once a week. However, she remained amenorrheic despite cabergoline treatment.

Ms. C's medical history was significant only for uterine fibroids, and she took a daily multivitamin and no other medications. She reported no history of psychiatric illness and no

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prior psychiatric hospitalizations, and this information was corroborated by her family. Ms. C was single, lived alone, and worked as a college instructor, while also pursuing her Ph.D. She reported no alcohol, tobacco, or illicit substance use. At baseline, she was described by a cousin as a quiet, pleasant woman who was involved in her church. Her family history was notable medically for diabetes in her mother and maternal aunts and psychiatrically for schizophrenia in her father as well as in a paternal aunt, who committed suicide.

Three days prior to presentation, Ms. C was noted to have increased energy, decreased need for sleep, and to be planning overly-ambitious projects. On the day of presentation, she reported racing thoughts, stated that she was on a divine mission and began intruding into ongoing classes to recruit students to join her. Ms. C was evaluated at an emergency room where she was grandiose, loud, and thought-disordered. She was emergently treated with haloperidol 5 mg and lorazepam 2 mg intramuscularly and subsequently slept for the first time in days. A complete blood count, basic metabolic panel, alcohol level, and head CT without contrast were normal, and she was transferred to our hospital for psychiatric treatment.

Upon admission to the inpatient psychiatric unit, Ms. C's Young Mania Rating Scale (YMRS) score was remarkably high at 59. She was elated, irritable, and grandiose, informing the staff that she was on the unit conducting "research" for her Ph.D. and submitted a letter requesting discharge. Her speech was pressured, her thought process was circumstantial, and she reported that she could "connect the dots that others couldn't." Further workup in our hospital, including EKG, CBC, comprehensive metabolic panel, TSH, RPR, urinalysis, urine toxicology, was within normal limits. A normal prolactin level of 14.2 ng/mL (normal reference range: 2.8–29.2 ng/mL) and negative urine pregnancy test were obtained on admission. Ms. C had last taken her weekly dose of cabergoline 5 days prior to admission. Valproic acid was initiated and titrated to 750 mg daily for mood stabilization. Quetiapine 75 mg daily was chosen as adjunctive therapy targeting mood symptoms and insomnia, since it tends to have little impact on serum prolactin.[2] In consultation with her outpatient endocrinologist, cabergoline was not reinitiated and a prolactin level measured on day 6 remained normal (8.5 ng/mL). Ms. C tolerated these psychiatric medications without adverse side effects, valproic acid reached a therapeutic level of 100.7 μg/mL, and quetiapine was reduced to 25 mg at bedtime. On this regimen, Ms. C made a steady recovery, first with improved sleep, then euthymic mood, normalized thought process, content, speech, and improved insight, ultimately scoring a YMRS of 1 at the time of discharge, day 9. Ms. C was discharged with psychiatric aftercare and an appointment to see her endocrinologist during the week of discharge. Over the course of the following 10 months, quetiapine was discontinued and the valproic acid was tapered to 250 mg daily with the goal of ultimately discontinuing it. On this regimen, Ms. C has been euthymic and without evidence of psychosis and has returned to work. Two subsequent prolactin levels were within normal limits, although she remains amenorrheic.

Discussion

Ms. C's mania is unusual in a number of respects. Her first episode manifested at 45-years-old, much older than the typical age of onset in the 20s and early 30s.[3] She scored 59 on the

Young Mania Rating Scale (YMRS),[4] which evaluates patients for symptoms of mania on a scale of 0–60, indicating a severe episode. Finally, her episode resolved rapidly.[5] This unusual presentation raises the possibility that cabergoline may have precipitated her symptoms. Krauthammer and Klerman have coined the term “secondary” mania to describe mania with late age of onset, lack of personal or family history of mania, and an associated precipitating physiological cause, most commonly a drug.[6] To formally evaluate the probability that the manic episode represented an adverse reaction caused by cabergoline, we used the Naranjo algorithm, which assesses 10 characteristics of the reaction and classifies the relationship as doubtful, possible, probable, or definite on a scale from −5 to 13.[7] This case yields a score of 3, suggesting a possible adverse drug reaction. Although the circumstances of her case suggest that cabergoline may have contributed to the precipitation of her mania, Ms. C has not been re-challenged with cabergoline, so causality cannot be proven.

We believe this case represents the first report in the medical literature of a secondary mania associated with cabergoline use. A PubMed search did not yield any cases of mania in the context of cabergoline use. Nonetheless, among the adverse side effects reported for cabergoline, psychiatric symptoms include sedation, depression, and hallucinations.[1] In addition, closer inspection of the literature reveals cases of cabergoline-treated patients who developed depressed mood, reckless gambling, or hypersexuality,[8–10] symptoms often associated with bipolar disorder. Finally, on a website monitoring post-marketing surveillance data, mania was listed by 6 of 2,669 people reporting side effects from cabergoline.[11]

Dopamine agonists are classified as either ergot derivatives (e.g., bromocriptine, pergolide, cabergoline) or nonergolines (e.g., apomorphine, ropinirole, pramipexole, quinagolide). They are further divided based on their affinity for different dopamine receptor subtypes. The first dopamine agonist, apomorphine, was discovered in 1863, and came into clinical use as an emetic and sedative. In the 1970s, the ergot-derived class of dopamine agonists was developed, notably bromocriptine, which was used for both the suppression of prolactin and lactation as well as for Parkinson’s disease.[12] In 1996, cabergoline, a more potent and long-acting ergot-derived agonist was introduced for the treatment of hyperprolactinemia and Parkinson’s disease.[13] More recently, non-ergot-derived medications, such as pramipexole and ropinirole, have been introduced and used in Parkinson’s disease as well as restless leg syndrome. Another non-ergot dopamine agonist, quinagolide, has been introduced in Europe for the treatment of hyperprolactinemia. In psychiatry, dopamine agonists have a wide range of off-label uses, including the treatment of neuroleptic malignant syndrome, extrapyramidal symptoms, the negative symptoms of schizophrenia, treatment-resistant depression, bipolar depression, sleep disturbances, and fibromyalgia.[14–16] As noted above, the different agents have varying selectivity at dopamine receptor subtypes, with apomorphine and bromocriptine binding at both D_1 and D_2 receptors, cabergoline and quinagolide binding fairly selectively at D_2 receptors, and pramipexole and ropinirole having greater affinity for D_2 and D_3 receptors.[17,18]

Due to its long half-life (average elimination half-life is 63 to 69 hours[1]) and greater D_2 receptor selectivity, cabergoline is generally better tolerated than bromocriptine, which is

known to produce psychiatric side effects, including the precipitation of mania.[19] Other novel dopaminergic agents used in the treatment of Parkinson's disease, including quinagolide, pramipexole, and ropinirole have all been reported to cause manic symptoms infrequently. Table 1 reviews the characteristics of D_2 receptor agonist-associated mania. The characteristics of D_2/D_3 receptor agonist associated mania are listed in Supplemental Table 1. The majority of these cases occurred in patients with either a personal or family history of mental illness. In this respect, dopamine agonist-induced mania differs from the secondary mania described by Krauthammer and Klerman.[6] Consistent with these previous cases, Ms. C also had a family history of mental illness. The tables also illustrate that the duration of dopamine agonist therapy prior to onset of manic symptoms ranged from days to years, with some cases developing after months of therapy. This timing lends support to the association of cabergoline with the development of manic symptoms in Ms. C, which occurred after several months of therapy. The age and gender of patients developing manic symptoms while on dopamine agents seems to reflect the epidemiology of the underlying disorder under treatment (female predominance for post-partum lactation and prolactinomas, male predominance for Parkinson's disease).[20,21] It is interesting to note that many of the cases of bromocriptine-associated mania occurred during the postpartum period, a reflection of the historical use of bromocriptine for inhibiting lactation. The post-partum period is an especially vulnerable time for the development of mania[22] and thus, may have rendered these patients sensitive to the effects of bromocriptine.

In addition to cases of mania, dopamine agents, especially the D_2/D_3 receptor agonists pramipexole and ropinirole, are also associated with a marked propensity to develop impulse-control disorders (e.g., gambling, hypersexuality, compulsive shopping).[23] As noted above, these disorders share features with manic symptoms. This may reflect a shared pathophysiology between impulse-control disorders and bipolar disorder. Although there is limited data on the circuitry of mania, it is thought to involve decreased activity in the frontal cortex, including the ventromedial prefrontal/orbitofrontal cortex and increased activity in the basal ganglia-thalamocortical circuit.[24] Further changes also occur in the limbic and paralimbic areas.[25] Studies examining the circuitry of gambling and impulsivity have also implicated increases in the dopaminergic reward pathways in the basal ganglia as well as deficits in the ventromedial prefrontal/orbitofrontal cortex.[26,27]

Further evidence for the role of dopamine in impulse-control disorders comes from studies of impulsivity. Frustrative non-reward, an animal model of impulsivity that has been validated in humans, is abolished by the depletion of dopamine.[28] In clinical studies, impulsivity is associated with sensitization of dopamine release in the ventral striatum, dorsal caudate nucleus, and putamen.[29] Furthermore, different alleles of the genes encoding dopamine receptors have been linked with impulsivity-related personality traits, such as novelty seeking.[30]

The role of dopamine in the pathophysiology of mania is supported by a number of findings. First, the dopamine precursor L-Dopa and amphetamines (that promote dopamine release and inhibit its uptake) reliably precipitate mania in patients with bipolar disorder.[31,32] Furthermore, euthymic patients with bipolar disorder seem to be more sensitive to the behavioral effects of dopamine agonists.[33] Conversely, dopamine receptor antagonists

effectively treat mania (reviewed in[25]). Similarly, lithium, a first-line treatment for bipolar disorder, causes a dose-dependant reduction in dopamine formation (reviewed in[25]). Consistent with the circuitry of mania described above, Suhara et al. found reduced dopamine receptor (D_1) binding potential in the frontal cortex using PET imaging in patients with bipolar disorder who were medication-free.[34]

Impulsivity may form a stable characteristic of patients with bipolar disorder outside of mood episodes.[35] Not surprisingly, there is significant co-morbidity of impulse-control disorders and bipolar disorder.[36,37] Of interest, lithium has been used to successfully treat pathologic gambling in patients with bipolar spectrum disorders.[38] Collectively, these findings suggest that impulse-control disorders and bipolar disorder share a common dopamine-based pathophysiology.

Ms. C was started on cabergoline in the context of hyperprolactinemia. Hyperprolactinemia can be due to several causes, most commonly prolactin-secreting adenomas which tend to occur predominantly in women aged 20 to 50 years.[21] Other causes include compression of the pituitary stalk, hypothyroidism, renal insufficiency, and medications. Specific medications that increase prolactin levels include high-potency first- or second-generation antipsychotic agents (e.g., haloperidol or risperidone), tricyclic antidepressants (e.g., clomipramine) and antihypertensives, (e.g., verapamil).[2]

In cases of antipsychotic-induced hyperprolactinemia, the use of antipsychotic agents (such as quetiapine, aripiprazole, ziprasidone, and clozapine) might prove effective substitutes because of their low risk of increasing prolactin levels.[2] For patients with schizophrenia who develop prolactinomas, management can be challenging.[39] There is limited data suggesting that aripiprazole may help reduce prolactin levels while treating the psychotic symptoms,[40] although in some cases surgery or radiotherapy may be required.[41]

Given the potential of dopamine agonist agents to induce manic and psychotic symptoms, several studies have examined the use of dopamine agents to treat antipsychotic-induced hyperprolactinemia in patients with pre-existing schizophrenia and bipolar disorder. A pilot study of low dose cabergoline (0.125 to 0.25 mg weekly) in 19 schizophrenic patients with risperidone-induced hyperprolactinemia showed no change in psychopathology.[42] Another trial of low dose cabergoline in 10 patients with risperidone-induced hyperprolactinemia showed no worsening of psychotic symptoms.[43] A chart review of four patients treated with either cabergoline or bromocriptine also showed no worsening of psychosis.[44] Similarly, a chart review of four children treated with cabergoline for risperidone-induced hyperprolactinemia showed no adverse events.[45] In contrast, Chang et al. reported two cases of exacerbation of psychotic symptoms in patients treated with cabergoline for antipsychotic-induced hyperprolactinemia (0.5 mg) that rapidly resolved following cessation of cabergoline.[46] Similarly, case series examining the use of bromocriptine to treat antipsychotic-induced hyperprolactinemia report some instances of worsening psychotic symptoms (reviewed in [2]). In summary, the evidence at present for using dopamine agonists to treat antipsychotic-induced hyperprolactinemia is limited, consisting of small trials and case series, which have yielded mixed results.

Ms. C was started on cabergoline for mild hyperprolactinemia that was presumed to be causing amenorrhea. While she had no evidence of macroadenoma (>1 cm) on MRI, since the MRI was not done with contrast, a microprolactinoma could not be excluded. The Endocrine Society clinical practice guidelines recommend treating symptomatic microprolactinomas using dopamine agonists as first-line treatment.[47] Cabergoline is preferred over bromocriptine as it is more effective at decreasing prolactin levels and tumor size. Patients whose only symptom is amenorrhea may be treated either with dopamine agonists or with oral contraceptives. With symptom resolution, treatment may be tapered and discontinued after 2 years in patients with normal prolactin levels and no visible tumor on MRI.[47] However, as Ms. C's symptom of amenorrhea did not resolve with cabergoline treatment despite subsequent normal prolactin levels, and no macroadenoma was visible on MRI, it was reasonable to discontinue her cabergoline within a few months of treatment.

In conclusion, while cabergoline is generally a safe and effective method of reducing prolactin levels, it is associated with psychiatric side effects, including mania. Physicians should carefully screen patients for a personal as well as family history of psychiatric illness before initiating therapy. At risk patients may benefit from more frequent monitoring and cessation of therapy at the earliest safe juncture.

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TABLE 1

Dopamine Agonist-Induced Mania/Hypomania: D_2 Receptor Agonists

Dopamine Agonist	*n*	Age	Gender	Family History	Past Psychiatric History	Time to Symptom Onset	Clinical Context	Ref
Bromocriptine (D_2)	1	29	F	N/A	N/A	4 days	Post-partum	48
	1	33	F	N/A	Yes	1 week	Post-partum	49
	1	27	F	N/A	Yes	4 days	Post-partum	50
	1	19	F	Yes	Yes	3 days	Drug-induced hyperprolactinemia	51
	1	27	F	N/A	N/A	1 week	Post-partum	52
	1	30	F	No	No	15 days	Post-partum	53
	1	29	F	No	Yes	immediate	Post-partum	54
	2/5	49,63	M,F	N/A	Yes	>1 week	Bipolar depression	55
Quinagolide (selective D_2)	1	44	F	Yes	No	4 years	Micro-prolactinoma	56

N/A = not available; M = male; F = female.