REVIEW

Neuropsychiatric and metabolic aspects of dopaminergic therapy: perspectives from an endocrinologist and a psychiatrist

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Abstract

The dopaminergic treatment represents the primary treatment in prolactinomas, which are the most common pituitary adenomas and account for about 40% of all pituitary tumours with an annual incidence of six to ten cases per million population. The dopaminergic treatment includes ergot and non-ergot derivatives with high affinity for the dopamine receptors D1 or/and D2. Through the activation of the dopaminergic pathway on pituitary lactotrophs, the dopamine agonists inhibit the prolactin synthesis and secretion, therefore normalizing the prolactin levels and restoring eugonadism, but they also lead to tumour shrinkage. Treatment with dopamine agonists has been associated – apart from the common side effects such as gastrointestinal symptoms, dizziness and hypotension – with neuropsychiatric side effects such as impulse control disorders (e.g. pathological gambling, compulsive shopping, hypersexuality and binge eating) and also with behavioral changes from low mood, irritability and verbal aggressiveness up to psychotic and manic symptoms and paranoid delusions not only in patients with prolactinomas but also in patients with Parkinson's disease and restless leg syndrome. They usually have de novo onset after initiation of the dopaminergic treatment and have been mainly reported in patients with Parkinson's disease, who are being treated with higher doses of dopamine agonists. Moreover, dopamine and prolactin seem to play an essential role in the metabolic pathway. Patients with hyperprolactinemia tend to have increased body weight and an altered metabolic profile with hyperinsulinemia and increased prevalence of diabetes mellitus in comparison to healthy individuals and patients with non-functioning pituitary adenomas. Treatment with dopamine agonists in these patients in short-term studies seems to lead to weight loss and amelioration of the metabolic changes. Together these observations provide evidence that dopamine and prolactin have a crucial role both in the regard and metabolic system, findings that merit further investigation in long-term studies.

Key Words

- ▶ prolactinomas
- ▶ hyperprolactinemia
- ▶ dopaminergic treatment
- ▶ dopamine agonists

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Introduction

Case report

To emphasize the possible role of dopamine agonists in the development of impulse control disorders that could be potentially devastating for the patient's life, we report

a case of a giant-prolactinoma in a young male adult that developed severe pathological gambling under dopamine agonists. Informed consent for publication has been obtained from the patient after full explanation of the

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purpose and nature of all procedures used. The patient presented initially with tinnitus at the age of 19 years. The magnetic resonance imaging revealed a large, invasive pituitary tumor with a diameter of 60×60×65 mm with an intracranial frontal part and perifocal oedema of the white matter. The diagnosis of the prolactinoma was based on an enormous highly prolactin value of 10,000 ng/mL (normal range up to 25 ng/mL). The laboratory results at baseline revealed a pituitary insufficiency of the gonadotropic, thyrotropic and corticotropic axis, although stimulation tests were not performed at diagnosis due to the risk of bleeding or necrosis. Adequate hormonal substitution with testosterone, thyroid hormones and hydrocortisone was initiated. As first-line treatment, the patient received bromocriptine. The first psychiatric symptoms that were depressed mood and gambling tendencies were reported in February 1998, shortly after the diagnosis of prolactinoma and the beginning of bromocriptine treatment. Under 40 mg of bromocriptine neither imaging nor laboratory improvement could be documented so that quinagolide was initiated. Under quinagolide, the tumor shrank and prolactin fell. After at least two years of treatment with dopamine agonists (bromocriptine and quinagolide) and under ongoing quinagolide treatment, at the age of 21 years, the patient was admitted for the first time in a psychiatric clinic due to pathological gambling. He had started playing with gaming machines and in online casinos, gave up his studies and lost about 5000 Euro in one day. He used the credit cards of his father and used to play – even if he won – until all the money he had was gone. He was sentenced to a prison sentence of 1½ years and later on to another sentence of 5½ years due to fraud and other criminal acts in order to collect money. In that time, he accumulated private debts of about 200,000 Euro. Remarkably, there was no family history of impulsive or affective behavior or further psychiatric diseases. The patient did not abuse alcohol or other illegal drugs or medications. The psychiatric treatment at this time included behavior therapy initially in the outpatient unit and later on systemic psychotherapy in the psychiatric ward without medical treatment. Quinagolide was applied for a total of about two years (03.09.1998–01.03.1999; 24.06.1999–03.12.2001) with interruptions and in combination with cabergoline (02.10.1998–07.10.1999; 03.12.2001–ongoing). Interestingly, the psychiatric symptoms were similar under all dopamine agonists administered with the ICD codes including pathological gambling (F63), borderline personality disorder (F60.3) and major depressive disorder (F33.1) remaining stable over the years. Since 2010 and up to 2012, the patient

was under cabergoline and citalopram, and after 2012, the psychiatric medication was stopped. Today, sixteen years after the diagnosis of prolactinoma, the patient is biochemically well controlled under a weekly dose of 4 mg cabergoline and stable without psychiatric medication.

These findings and observations regarding our patient posed the following questions: what is the incidence of neuropsychiatric side effects to be seen under dopamine agonists and what are the predisposing factors for developing this kind of side effects?

Approval of the local ethical committee was not required for this study as clinical study in human subjects was not conducted.

The psychiatrist's perspective: neuropsychiatric aspects of the dopaminergic treatment

Apart from the common side effects of the dopaminergic treatment including gastrointestinal symptoms, hypotension and dizziness, an increased frequency of impulse control disorders (ICDs) has been widely reported, mainly in a subset of patients with Parkinson's disease (PD) and restless legs syndrome (RLS) that are being treated with dopamine agonists (DAs) in much higher doses (1). More specifically, these neuropsychiatric side effects include pathological gambling, hypersexuality, compulsive shopping and binge eating (2, 3, 4, 5). These symptoms are generally characterized by the maladaptive nature of the preoccupations and the inability of the subject to control these urges, and they mainly have a de novo onset after the initiation of the DA on the basis of a negative psychiatric history. Whereas the overall lifetime prevalence of pathological gambling under DAs has been reported to be from 3.4 up to 6.1% (6) in Parkinson's disease patients under DAs – significantly increased beyond that of the general population – the overall prevalence of at least one ICDs – including not only gambling but also compulsive buying, compulsive sexual behavior or binge eating – was as high as 17.1% under DAs in the study of Weintraub and coworkers with patients under DAs showing a 2- to 3.5-fold increased risk of developing an ICD (7). Furthermore, a retrospective analysis of 267 PD patients documented new-onset compulsive gambling or hypersexuality in nearly every fifth patient (18.4%) in the group of subjects taking therapeutic doses of dopamine agonists (defined as ≥2 mg of pramipexole or 6 mg of ropinirole daily) (8). Apart from the dosage, male gender, younger age and being unmarried have been identified as

risk factors for developing an ICD, both in the general population and in PD patients (7). All symptoms and signs abated with discontinuation of agonist therapy or dose reduction.

Similar side effects such as pathological gambling, compulsive shopping and hypersexuality have also been described in patients with restless leg syndrome treated with DAs, but the prevalence is less clearly established (9). In a prospective case-control study, the prevalence of ICDs in patients under modest doses of dopaminergic agents was as high as 17% (10).

In patients with prolactinomas, these rare central side effects have not been systematically investigated. Even if the doses of DAs used in these instances are considerably smaller (5–10 times) than those used to treat PD or RLS, distinct dopaminergic personality patterns have been already described. The largest study up to now by Bancos and coworkers was a case-control study (including a postal survey, review of medical electronic records and telephone interviews) comparing patients with prolactinomas with ongoing or past dopaminergic treatment and patients with non-functioning pituitary adenomas (NFPA) without history of dopaminergic treatment. The total prevalence of ICDs was significantly higher in patients with prolactinomas (24.6%-referring to the prevalence of one or more ICD) compared to the NFPA group (17.14%) or the general population of Sao Paulo, Brazil (8.4%) (11) with predominantly increased rate of hypersexuality. Males with prolactinomas treated with DAs showed a 9.9 higher risk than their counterparts with NFPA to develop an ICD, whereas female sex, age, type, dose and duration of treatment were no risk factors (12).

Apart from the aforementioned case-control study of Bancos and coworkers, there are six case reports and three case series that describe dopamine agonist-induced pathological gambling and hypersexuality in patients with prolactinomas, resulting in a number of 18 patients that developed hypersexuality and pathological gambling under DAs (13, 14, 15, 16, 17, 18, 19, 20). Interestingly, all patients had no psychiatric history and developed the symptoms after initiation of the dopamine agonist treatment. The dose of DAs was variable and symptoms were present regardless of the type of DAs as cabergoline, bromocriptine and quinagolide were implicated as treatment options.

De Sousa and coworkers suggested the term ‘dopa-testotoxicosis’ to refer to this distinct drug toxicity (18) as the phenomenon of a possible synergy between reward dopaminergic pathway stimulation by dopamine agonists and rapid restoration of the eugonadal state after prolonged

hypogonadism. The occurrences of these ICDs may possibly be due to overstimulation of mesolimbic dopamine receptors in the central dopaminergic reward system (1), but the factors that predispose for the development of these central side effects of a systematically administered drug are unknown. Gender seems to play a significant role with men being at a higher risk (18). Up to now, there are three female patients reported in the literature with hypersexuality under DAs (12). Another case of a female patient that developed hypersexuality under DAs was to be seen in terms of psychosis (21). The possible role of restoration of hypogonadism either pharmacological through testosterone substitution or physiological should be discussed, as patients with prolactinomas suffer from hypogonadism and its symptoms, including diminished libido and erectile dysfunction. The restoration of the hypogonadism, reflecting the state of relative testosterone excess, could potentially contribute to the development of hypersexuality.

However, as patients seem to react to DAs also with other ICDs such as gambling or binge eating that do not seem to be related with the sexual hormones, further possible pathophysiological mechanisms that contribute to this phenomenon should be discussed such as the ability of the medication to pass the blood-brain barrier, the physical barrier of the central nervous system, formed by endothelial cells and astrocytic expansions that restrict the penetration of specific molecules into the brain. This ability has been proven to be actively controlled by transporter molecules such as the P-glycoprotein (P-gp), encoded by the *ABCB1* gene (or alternatively multidrug resistance gene – *MDR1*), located on chromosome 7 (22), that transports substrates – among them cabergoline – back into the blood circulation, thus protecting the central nervous system from harmful substances. Specific genetic polymorphisms seem to correlate with different levels of the P-gp activity, leading to an increased or diminished function of this transporter molecule. At the moment, there is only one study conducted by our group, examining the hypothesis of the genetic predisposition for the development of central side effects, that revealed increased central common side effects such as fatigue, dizziness and sleep disorders under cabergoline in individuals with specific *ABCB1* polymorphisms, but no correlation with the rare neuropsychiatric side effects could be established (23). Whether the central side effects of cabergoline also depend from polymorphisms of the dopamine 2 receptor (*DRD2*) gene or the density or function of the D2 receptor is yet not known.

Furthermore, psychosis – not being included in the classical ICDs – seems to be a well-known side effect under DAs. Other psychotic symptoms such as hallucinations and illusions are also associated with the dopaminergic treatment. Several reports have described an induction of psychosis by most of the common dopamine agonists such as pergolide and bromocriptine in patients with PD, with dementia being a risk factor (24). In patients with prolactinomas, several case reports describing behavioral changes from low mood, irritability and verbal aggressiveness up to psychotic and manic symptoms and paranoid delusions have been published (25, 26, 27, 28). This phenomenon seems to be more frequent in patients with previous personal or familial history of mental illness with DAs triggering the development of the psychiatric illness. However, also previously healthy individuals seem to be affected (27). As psychosis is being treated with dopamine-receptor blockers (that in patients with prolactinomas may result in elevated serum prolactin, tumor growth or further uncontrolled hyperprolactinemia-related symptoms), clinicians are being confronted with the dilemma of treating patients while having to deal with severe possible side effects. According to the available literature, treatment options contain a discontinuation of the DA and/or adding clozapine for its low effect on prolactin and growth of the prolactinoma (26). Other approaches suggest administering aripiprazole, as it is a partial dopamine agonist especially at low doses and seems to reduce prolactin levels in patients with and without hyperprolactinemia (27, 29) whereas other studies propose quetiapine (30) or the combination of clozapine and quinagolide (31). The underlying mechanism of triggering psychosis or mania seems to be the stimulation of mesocortical and mesolimbic D2 and D3 receptors by the DAs (32, 33) whereas (ICDs) may also be mediated by D3 receptors.

As also in our case of the male patient, ICDs can have devastating consequences in these patients' and their families' lives, including relationship discord, financial consequences, job loss and illegal activities possibly leading to imprisonment. Taking into account these consequences, awareness of these rare but distinct ICDs from not only the treating physician but also the patient should lead to considerations of cessation of DA on time and alternative treatment options such as pituitary surgery. Due to the highly personal nature of the symptoms, patients may be reluctant to report them and therefore we consider these side effects as underreported, whereas De Sousa and coworkers suggested screening with at least one simple questionnaire within six months

of commencing DA therapy (18). The management and pathophysiological background of these side effects merits further investigation in longitudinal, prospective studies.

The endocrinologist's perspective: metabolic aspects

Hyperprolactinemia seems to be associated with a high prevalence of obesity, insulin resistance and low-grade inflammation (34) – independently of the body mass index (BMI) – (35) and patients with prolactinomas tend to have increased body weight in comparison to healthy individuals (36) but also to patients with non-functioning pituitary adenomas (NFPA) (37).

Dopaminergic treatment in prolactinomas seems to induce weight loss and lead to amelioration of other metabolic parameters such as lipid profile and insulin resistance in some patients (37, 38, 39) not only by normalizing prolactin or by mechanisms related to the pharmacological side effects (35, 40). As only data from few retrospective studies are available and as weight loss seems to take more than 6 and 12 months, improvement of metabolic parameters seems to occur in advance (35, 40, 41, 42).

The most recent study of Pala and coworkers (43) conducted in nineteen patients with prolactinomas showed that they presented with increased level of fasting plasma glucose, higher levels of leptin without a significant difference in adiponectin levels as compared to age-, gender- and BMI-matched healthy controls. There was a significant decrease of body weight and BMI after 3 months and a decrease of waist circumference, waist-to-hip ratio, total body fat, plasma glucose and leptin levels after 6 months of continuous treatment.

In a retrospective study conducted from our group in 44 prolactinoma patients, we examined whether the prevalence of *TAQ1A*, a polymorphism considered as a gene marker for the *DRD2* linked to altered brain dopaminergic activity due to reduced receptor binding and lower density of the dopamine 2 receptor, could be associated with a different metabolic profile and reduced weight loss response under DAs. In our cohort, we observed that continuous 2-year dopaminergic treatment leads to a significant mean weight loss regardless of the *Taq1a* status (44).

Delibasi and coworkers (45) attempted to investigate, whether this observed body weight gain and the consequent weight loss in patients with prolactinomas could be attributed to ghrelin. Both patients with

prolactinomas newly diagnosed and under ongoing cabergoline treatment but also healthy subjects were included. The study revealed no significant difference in terms of the ghrelin levels between these three groups suggesting that ghrelin levels have no significant effect on weight gain and could not explain increased obesity prevalence in prolactinoma.

Different studies not only in hyperprolactinemic patients but also in other patients' settings have addressed the metabolic impact of dopaminergic treatment. In diabetic patients, it could be shown that bromocriptine – as monotherapy or in conjunction with the available treatments for type 2 diabetes mellitus (metformin, sulfonylureas, thiazolidinediones and insulin) – can lower fasting glucose levels, postprandial glucose, HbA1c and potentially decrease cardiovascular events in this population so that in 2009 bromocriptine was approved by the Food and Drug Administration (FDA) as a treatment for type 2 diabetes mellitus (46). Cabergoline, a more specific central dopamine agonist, has been shown in one study to have significant effects in lowering HbA1c, fasting plasma glucose and postprandial glucose in diabetic patients; however, further studies in these patients are lacking (47).

Studies in obese normoprolactinemic individuals suggest that bromocriptine administration promotes significant weight and body fat loss (8), whereas cabergoline administration seems to improve glucose tolerance independent of weight loss or prolactin reduction (41, 48).

The exact mechanism of this phenomenon remains unclear. Dopamine in hibernating animals seems to be involved in changes seen in adipose tissue and insulin sensitivity, limiting resource utilization, a condition that seems to be similar to the obese state to survive hibernation (46). Animal models, including genetically obese ob/ob mice, have decreased hypothalamic dopamine and dopamine agonist administration decreases hepatic gluconeogenesis and lipid generation, promoting an insulin sensitivity state (49, 50). As the reduction of prolactin levels did not directly correlate with changes in serum leptin levels and BMI, changes in prolactin levels do not seem to be the predominant determinant of changes in body weight (51). The dose of DAs does not seem to play a significant role as in general, patients with prolactinomas are being treated with relatively low doses of DAs and weight loss has been documented even under a low dose of cabergoline (38). An alternative mechanism could be the increase of the central dopaminergic tone through

the dopaminergic stimulation leading to weight loss by mechanisms additionally to reducing hyperprolactinemia (51), a plausible hypothesis on the basis of the altered dopaminergic function experienced from these patients already documented (52, 53).

The role of the peripheral dopamine and its implications in weight loss should also be discussed. *In vitro* studies showed that human adipocytes express functional dopamine receptors, suggesting a regulatory function of peripheral dopamine in the adipose tissue (54). Furthermore, other receptors of the adipocytes such as the adrenergic receptor seem to interfere with dopamine agonists (55). Further prospective studies need to be conducted to address the important question of the metabolic impact of DAs.

Conclusion

The dopaminergic treatment in prolactinomas and also in Parkinson's disease and restless legs syndrome is associated with the development of neuropsychiatric side effects such as impulse control disorders (e.g. pathological gambling, compulsive shopping, hypersexuality and binge eating) with a varying prevalence in different studies and different patient groups up to 24.6%. Risk factors seem to be the dosage of dopamine agonist, male gender, younger age and being unmarried. Given the potentially devastating consequences of these side effects, further prospective studies are needed for a better understanding of the frequency of these behaviors and improvement of their medical management.

Moreover, dopamine and prolactin seem to play an essential role in the metabolic pathway. Patients with hyperprolactinemia tend to have an altered metabolic profile with hyperinsulinemia, increased body weight and increased prevalence of diabetes mellitus in comparison to healthy individuals and patients with non-functioning pituitary adenomas. Treatment with dopamine agonists in these patients in short-term studies seems to lead to weight loss and amelioration of the metabolic changes.

Together these observations provide evidence that dopamine and prolactin have a crucial role both in the regard and metabolic system, findings that merit further investigation in long-term studies.

Declaration of interest

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

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References

- Voon V, Fernagut PO, Wickens J, Baunez C, Rodriguez M, Pavon N, Juncos JL, Obeso JA & Bezaud E. Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. *Lancet Neurology* 2009 **8** 1140–1149. ([https://doi.org/10.1016/S1474-4422\(09\)70287-X](https://doi.org/10.1016/S1474-4422(09)70287-X))
- Voon V, Napier TC, Frank MJ, Sgambato-Faure V, Grace AA, Rodriguez-Oroz M, Obeso J, Bezaud E & Fernagut PO. Impulse control disorders and levodopa-induced dyskinesias in Parkinson's disease: an update. *Lancet Neurology* 2017 **16** 238–250. ([https://doi.org/10.1016/S1474-4422\(17\)30004-2](https://doi.org/10.1016/S1474-4422(17)30004-2))
- Driver-Duncley E, Samanta J & Stacy M. Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. *Neurology* 2003 **61** 422–423. (<https://doi.org/10.1212/01.WNL.0000076478.45005.EC>)
- Bostwick JM, Hecksel KA, Stevens SR, Bower JH & Ahlskog JE. Frequency of new-onset pathologic compulsive gambling or hypersexuality after drug treatment of idiopathic Parkinson disease. *Mayo Clinic Proceedings* 2009 **84** 310–316. ([https://doi.org/10.1016/S0025-6196\(11\)60538-7](https://doi.org/10.1016/S0025-6196(11)60538-7))
- Nirenberg MJ & Waters C. Compulsive eating and weight gain related to dopamine agonist use. *Movement Disorders* 2006 **21** 524–529. (<https://doi.org/10.1002/mds.20757>)
- Voon V, Hassan K, Zurowski M, Duff-Canning S, de Souza M, Fox S, Lang AE & Miyasaki J. Prospective prevalence of pathologic gambling and medication association in Parkinson disease. *Neurology* 2006 **66** 1750–1752. (<https://doi.org/10.1212/01.wnl.0000218206.20920.4d>)
- 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. *Archives of Neurology* 2010 **67** 589–595. (<https://doi.org/10.1001/archneurol.2010.65>)
- Cincotta AH & Meier AH. Bromocriptine (Ergoset) reduces body weight and improves glucose tolerance in obese subjects. *Diabetes Care* 1996 **19** 667–670. (<https://doi.org/10.2337/diacare.19.6.667>)
- Dang D, Cunningham D & Swieca J. The emergence of devastating impulse control disorders during dopamine agonist therapy of the restless legs syndrome. *Clinical Neuropharmacology* 2011 **34** 66–70. (<https://doi.org/10.1016/j.neuropharm.2010.07.007>)
- Cornelius JR, Tippmann-Peikert M, Slocumb NL, Frerichs CF & Silber MH. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. *Sleep* 2010 **33** 81–87. (<https://doi.org/10.1093/sleep/33.1.81>)
- Viana MC & Andrade LH. Lifetime prevalence, age and gender distribution and age-of-onset of psychiatric disorders in the Sao Paulo Metropolitan Area, Brazil: results from the Sao Paulo Megacity Mental Health Survey. *Revista Brasileira de Psiquiatria* 2012 **34** 249–260. (<https://doi.org/10.1016/j.rbp.2012.03.001>)
- 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. *Clinical Endocrinology* 2014 **80** 863–868. (<https://doi.org/10.1111/cen.12375>)
- Falhammar H & Yarker JY. Pathological gambling and hypersexuality in cabergoline-treated prolactinoma. *Medical Journal of Australia* 2009 **190** 97.
- Davie M. Pathological gambling associated with cabergoline therapy in a patient with a pituitary prolactinoma. *Journal of Neuropsychiatry and Clinical Neurosciences* 2007 **19** 473–474. (<https://doi.org/10.1176/jnp.2007.19.4.473>)
- Gahr M, Connemann BJ & Schonfeldt-Lecuona CJ. Pathological gambling induced by dopamine agonists. *Fortschritte der Neurologie-Psychiatrie* 2011 **79** 470–474. (<https://doi.org/10.1055/s-0031-1281580>)
- Martinkova J, Trejbalova L, Sasikova M, Benetin J & Valkovic P. Impulse control disorders associated with dopaminergic medication in patients with pituitary adenomas. *Clinical Neuropharmacology* 2011 **34** 179–181. (<https://doi.org/10.1097/WNF.0b013e3182281b2f>)
- Bulwer C, Conn R, Shankar A, Ferrau F, Kapur S, Ederies A, Korbonits M & Spodeas HA. Cabergoline-related impulse control disorder in an adolescent with a giant prolactinoma. *Clinical Endocrinology* 2017 **86** 862–864. (<https://doi.org/10.1111/cen.13339>)
- De Sousa SM, Chapman IM, Falhammar H & Torpy DJ. Dopamine testotoxicosis: disruptive hypersexuality in hypogonadal men with prolactinomas treated with dopamine agonists. *Endocrine* 2017 **55** 618–624. (<https://doi.org/10.1007/s12020-016-1088-1>)
- 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. *Clinical Neuropharmacology* 2013 **36** 170–172. (<https://doi.org/10.1097/WNF.0b013e31829fc165>)
- Almanzar S, Zapata-Vega MI & Raya JA. Dopamine agonist-induced impulse control disorders in a patient with prolactinoma. *Psychosomatics* 2013 **54** 387–391. (<https://doi.org/10.1016/j.psych.2012.10.002>)
- Sandyk R, Bergsneider M & Iacono RP. Acute psychosis in a woman with a prolactinoma. *International Journal of Neuroscience* 1987 **37** 187–190. (<https://doi.org/10.3109/00207458708987147>)
- Marzolini C, Paus E, Buclin T & Kim RB. Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance. *Clinical Pharmacology and Therapeutics* 2004 **75** 13–33. (<https://doi.org/10.1016/j.cpt.2003.09.012>)
- Athanasoulia AP, Sievers C, Ising M, Brockhaus AC, Yassouridis A, Stalla GK & Uhr M. Polymorphisms of the drug transporter gene ABCB1 predict side effects of treatment with cabergoline in patients with PRL adenomas. *European Journal of Endocrinology* 2012 **167** 327–335. (<https://doi.org/10.1530/EJE-12-0198>)
- Ecker D, Unrath A, Kassubek J & Sabolek M. Dopamine agonists and their risk to induce psychotic episodes in Parkinson's disease: a case-control study. *BMC Neurology* 2009 **9** 23. (<https://doi.org/10.1186/1471-2377-9-23>)
- Yuksel RN, Elyas Kaya Z, Dilbaz N & Cingi Yirun M. Cabergoline-induced manic episode: case report. *Therapeutic Advances in Psychopharmacology* 2016 **6** 229–231. (<https://doi.org/10.1177/2045125315626345>)
- Perez-Esparza R, Rojas-Guerrero CA, Andino-Rios GG, Arias-Garro P, Ramirez-Bermudez J & Portocarrero-Ortiz L. Clozapine treatment for cabergoline-induced psychosis in a patient with a giant prolactinoma. *Journal of Neuropsychiatry and Clinical Neurosciences* 2017 **29** 295–297. (<https://doi.org/10.1176/appi.neuropsych.16110313>)
- Burback L. Management of a microprolactinoma with aripiprazole in a woman with cabergoline-induced mania. *Endocrinology, Diabetes and Metabolism Case Reports* 2015 **2015** 150100. (<https://doi.org/10.1530/edm-15-0100>)
- Rovera C, Cremaschi L, Thanju A, Fiorentini A, Mauri MC, Serati M, Lindenmayer JP & Altamura AC. Cabergoline can induce mania with psychotic features in bipolar I disorder: a case report. *Asian Journal of Psychiatry* 2016 **22** 94–95. (<https://doi.org/10.1016/j.ajp.2016.05.010>)
- Bakker IC, Schubart CD & Zelissen PM. Successful treatment of a prolactinoma with the antipsychotic drug aripiprazole. *Endocrinology, Diabetes and Metabolism Case Reports* 2016 **2016** 160028. (<https://doi.org/10.1530/edm-16-0028>)
- Peuskens J, Pani L, Detraux J & De Hert M. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. *CNS Drugs* 2014 **28** 421–453. (<https://doi.org/10.1007/s40263-014-0157-3>)

- 31 Melkersson K & Hulting AL. Prolactin-secreting pituitary adenoma in neuroleptic treated patients with psychotic disorder. *European Archives of Psychiatry and Clinical Neuroscience* 2000 **250** 6–10. (<https://doi.org/10.1007/PL00007539>)
- 32 Noronha S, Stokes V, Karaviti N & Grossman A. Treating prolactinomas with dopamine agonists: always worth the gamble? *Endocrine* 2016 **51** 205–210. (<https://doi.org/10.1007/s12020-015-0727-2>)
- 33 Ali S, Miller KK & Freudenreich O. Management of psychosis associated with a prolactinoma: case report and review of the literature. *Psychosomatics* 2010 **51** 370–376. (<https://doi.org/10.1176/appi.psy.51.5.370>)
- 34 Schmid C & Brandle M. The influences of hyperprolactinaemia and obesity on cardiovascular risk markers: effects of cabergoline therapy. *Clinical Endocrinology* 2006 **65** 827–828. (<https://doi.org/10.1111/j.1365-2265.2006.02656.x>)
- 35 Serri O, Li L, Mamputu JC, Beauchamp MC, Maingrette F & Renier G. The influences of hyperprolactinemia and obesity on cardiovascular risk markers: effects of cabergoline therapy. *Clinical Endocrinology* 2006 **64** 366–370. (<https://doi.org/10.1111/j.1365-2265.2006.02656.x>)
- 36 Schmid C, Goede DL, Hauser RS & Brandle M. Increased prevalence of high Body Mass Index in patients presenting with pituitary tumours: severe obesity in patients with macroprolactinoma. *Swiss Medical Weekly* 2006 **136** 254–258. (<https://doi.org/10.4414/smw.2006.10955>)
- 37 Greenman Y, Tordjman K & Stern N. Increased body weight associated with prolactin secreting pituitary adenomas: weight loss with normalization of prolactin levels. *Clinical Endocrinology* 1998 **48** 547–553. (<https://doi.org/10.1046/j.1365-2265.1998.00403.x>)
- 38 Korner J, Lo J, Freda PU & Wardlaw SL. Treatment with cabergoline is associated with weight loss in patients with hyperprolactinemia. *Obesity Research* 2003 **11** 311–312. (<https://doi.org/10.1038/oby.2003.46>)
- 39 Berinder K, Nystrom T, Hoybye C, Hall K & Hulting AL. Insulin sensitivity and lipid profile in prolactinoma patients before and after normalization of prolactin by dopamine agonist therapy. *Pituitary* 2011 **14** 199–207. (<https://doi.org/10.1007/s11102-010-0277-9>)
- 40 dos Santos Silva CM, Barbosa FR, Lima GA, Warszawski L, Fontes R, Domingues RC & Gadelha MR. BMI and metabolic profile in patients with prolactinoma before and after treatment with dopamine agonists. *Obesity* 2011 **19** 800–805. (<https://doi.org/10.1038/oby.2010.150>)
- 41 Ciresi A, Amato MC, Guarnotta V, Lo Castro F & Giordano C. Higher doses of cabergoline further improve metabolic parameters in patients with prolactinoma regardless of the degree of reduction in prolactin levels. *Clinical Endocrinology* 2013 **79** 845–852. (<https://doi.org/10.1111/cen.12204>)
- 42 Yermus R & Ezzat S. Does normalization of prolactin levels result in weight loss in patients with prolactin secreting pituitary adenomas? *Clinical Endocrinology* 2002 **56** 562. (<https://doi.org/10.1046/j.1365-2265.2002.01510.x>)
- 43 Pala NA, Laway BA, Misgar RA, Shah ZA, Gojwari TA & Dar TA. Profile of leptin, adiponectin, and body fat in patients with hyperprolactinemia: response to treatment with cabergoline. *Indian Journal of Endocrinology and Metabolism* 2016 **20** 177–181. (<https://doi.org/10.4103/2230-8210.176346>)
- 44 Athanasoulia AP, Sievers C, Uhr M, Ising M, Stalla GK & Schneider HJ. The effect of the ANKK1/DRD2 Taq1A polymorphism on weight changes of dopaminergic treatment in prolactinomas. *Pituitary* 2014 **17** 240–245. (<https://doi.org/10.1007/s11102-013-0496-y>)
- 45 Delibasi T, Arslan MS, Cakal E, Sahin M, Topaloglu O, Tural E, Unsal IO, Karbek B, Ucan B, Gungunes A, et al. Hyperprolactinemia has no effect on plasma ghrelin levels in patients with prolactinoma. *Journal of the Turkish-German Gynecological Association* 2015 **16** 86–90. (<https://doi.org/10.5152/jtgga.2015.15015>)
- 46 Lamos EM, Levitt DL & Munir KM. A review of dopamine agonist therapy in type 2 diabetes and effects on cardio-metabolic parameters. *Primary Care Diabetes* 2016 **10** 60–65. (<https://doi.org/10.1016/j.pcd.2015.10.008>)
- 47 Taghavi SM, Fatemi SS & Rokni H. Cabergoline effect on blood sugar in type 2 diabetic patients with oral agent failure. *Medical Journal of Malaysia* 2012 **67** 390–392.
- 48 Gibson CD, Karmally W, McMahon DJ, Wardlaw SL & Korner J. Randomized pilot study of cabergoline, a dopamine receptor agonist: effects on body weight and glucose tolerance in obese adults. *Diabetes, Obesity and Metabolism* 2012 **14** 335–340. (<https://doi.org/10.1111/j.1463-1326.2011.01534.x>)
- 49 Cincotta AH, Schiller BC & Meier AH. Bromocriptine inhibits the seasonally occurring obesity, hyperinsulinemia, insulin resistance, and impaired glucose tolerance in the Syrian hamster, *Mesocricetus auratus*. *Metabolism: Clinical and Experimental* 1991 **40** 639–644. ([https://doi.org/10.1016/0026-0495\(91\)90057-4](https://doi.org/10.1016/0026-0495(91)90057-4))
- 50 Luo S, Meier AH & Cincotta AH. Bromocriptine reduces obesity, glucose intolerance and extracellular monoamine metabolite levels in the ventromedial hypothalamus of Syrian hamsters. *Neuroendocrinology* 1998 **68** 1–10. (<https://doi.org/10.1159/000054344>)
- 51 Doknic M, Pekic S, Zarkovic M, Medic-Stojanoska M, Dieguez C, Casanueva F & Popovic V. Dopaminergic tone and obesity: an insight from prolactinomas treated with bromocriptine. *European Journal of Endocrinology* 2002 **147** 77–84. (<https://doi.org/10.1530/eje.0.1470077>)
- 52 Naliato EC, Violante AH, Caldas D, Lamounier Filho A, Loureiro CR, Fontes R, Schrank Y, Souza RG, Costa PL & Colao A. Body fat in nonobese women with prolactinoma treated with dopamine agonists. *Clinical Endocrinology* 2007 **67** 845–852. (<https://doi.org/10.1111/j.1365-2265.2007.02973.x>)
- 53 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. (<https://doi.org/10.1159/000335996>)
- 54 Borcharding DC, Hugo ER, Idelman G, De Silva A, Richtand NW, Loftus J & Ben-Jonathan N. Dopamine receptors in human adipocytes: expression and functions. *PLoS ONE* 2011 **6** e25537. (<https://doi.org/10.1371/journal.pone.0025537>)
- 55 Mukherjee R & Yun JW. Bromocriptine inhibits adipogenesis and lipogenesis by agonistic action on alpha2-adrenergic receptor in 3T3-L1 adipocyte cells. *Molecular Biology Reports* 2013 **40** 3783–3792. (<https://doi.org/10.1007/s11033-012-2455-5>)

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