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Management of Psychosis Associated With a Prolactinoma: Case Report and Review of the Literature

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Abstract

Background—Prolactinomas are the most common pituitary tumors; they are treated with dopamine agonists, which may cause psychotic symptoms as a side effect. Psychosis is treated with dopamine-receptor blockers that may result in elevated serum prolactin and symptomatic hyperprolactinemia.

Objective—The authors will review a case of a patient with a prolactinoma as well as schizophrenia and illustrate the management of psychosis in this case.

Method—The review describes the management of prolactinoma, symptoms of hyperprolactinemia, and long-term effects of hyperprolactinemia.

Results—In the case presentation reviewed, the patient was finally discharged on risperidone long-acting injection and testosterone supplementation, with no growth of the adenoma after 3 years.

Discussion—This review provides recommendations and treatment strategy for management of prolactinoma in a patient with schizophrenia.

Prolactinomas are the most common pituitary tumors and are most often managed by use of dopamine-agonist medications, which lower serum prolactin and decrease the size of the tumors. Antipsychotic medications, the mechanism of which often involves dopamine antagonism, are used to treat schizophrenia, and may cause hyperprolactinemia as a side effect. In this article, we present a case of a patient, “Mr. A,” with a prolactinoma and hyperprolactinemia, as well as schizophrenia, and we review the management of these conditions when they coexist. Treating a patient comorbid for both of these illnesses can pose challenges because the standard treatment for one of the conditions may worsen the other. We will first describe a case that illustrates the complexity of treating these conditions when they co-occur.

CASE MANAGEMENT OF PSYCHOSIS AND PROLACTINOMA

A 25-year-old man, Mr. A, developed paranoid schizophrenia in 2003, with full positive-symptom remission on olanzapine 10 mg per day. As part of a work-up for first-episode psychosis, a magnetic resonance imaging (MRI) scan was obtained that revealed a 1.6-cm pituitary macroadenoma abutting the optic chiasm. Mr. A‘s initial serum prolactin level was

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1,986.5 ng/ml (15 ng/ml is the normal cutoff in men). Adrenal insufficiency was ruled out, and thyroid-function tests were normal, but his initial testosterone level was 157 ng/dl (normal range: 270 ng/dl–1,070 ng/dl for men). Visual-field testing showed intact visual fields and acuity. After discussions among the endocrinology, neurosurgery, and psychiatry departments, the treatment team recommended surgical treatment of the macroadenoma rather than dopamine-agonist treatment, which could potentially worsen his psychotic symptoms.

Mr. A had a trans-sphenoidal resection of the adenoma in January of 2004, and his postoperative prolactin level 2 months later was measured at 291.8 ng/ml. He was also treated with testosterone supplementation for his hypogonadism.

After a psychotic decompensation in the context of antipsychotic nonadherence, Mr. A had two successive psychiatric hospitalizations in June of 2006. During the second hospitalization, the inpatient team wished to use an injectable formulation of an antipsychotic (Risperdal Consta™), given his history of medication nonadherence, but they were concerned about the potential for risperidone to increase serum prolactin. In consultation with the patient's endocrinologist, the inpatient psychiatry team made the decision to use long-acting risperidone to treat the psychotic symptoms more effectively, despite its propensity to increase prolactin. Mr. A was discharged from the hospital on Risperdal Consta™ injections in June of 2006, and, 3 years later, has not been hospitalized again. The patient's most recent annual pituitary protocol brain MRI (5 years after the initial MRI) demonstrated no growth of the adenoma. His serum prolactin levels have been stable (most recently: 314.5 ng/ml) and are monitored twice yearly. He continues to do well on risperidone injections every other week, as well as testosterone injections, both administered by his primary-care physician.

Prolactinomas

Prolactinomas are prolactin-secreting pituitary tumors that account for 40% of pituitary adenomas. These tumors originate from the lactotroph cells of the anterior pituitary gland and are estimated to have an incidence of 100 per million adults.[1] Most of these tumors secrete only prolactin, with resultant hyperprolactinemia, which is defined as serum prolactin above the normal range (approximately 20 ng/ml–25 ng/ml in premenopausal women and 15 ng/ml in men and postmenopausal women).[2] Hyperprolactinemia also may occur, although less commonly, from pituitary adenoma co-secretion with other pituitary hormones, such as growth hormone (GH) and thyrotropin (TRH), or from compression of the pituitary stalk by nonfunctioning pituitary tumors or brain tumors in the area.[3]

Prolactinomas are classified by size and are managed differently according to their size (a description follows). Microprolactinomas are <1 cm in diameter and do not usually invade the parasellar region. The above report describes a patient with a macroprolactinoma, which is >1 cm in diameter and is more likely to locally invade and compress surrounding structures. In general, tumor size roughly correlates with serum prolactin levels. In our case, the initial serum level of prolactin was 1,986 ng/ml, which was consistent with the finding of a macroprolactinoma on initial MRI. A serum prolactin level >250 ng/ml is usually due to a macroadenoma, rather than a microadenoma.[2] Microadenomas are more commonly diagnosed in women, with a female-to-male ratio of 20-to-1, whereas macroadenomas are equally prevalent in men and women.

Symptoms and signs of prolactinoma may include the sequelae of symptomatic hyperprolactinemia: elevated serum prolactin, galactorrhea, amenorrhea, sexual dysfunction, and infertility, as well as symptoms due to tumor expansion, such as headache and visual changes.[3] Other symptoms of the mass effect from a prolactinoma, as described in a recent

case study, may include visual hallucinations, olfactory hallucinations, episodes of "losing time," and apathy.[4] In the case described, Mr. A continued to have psychotic symptoms after his prolactinoma was removed, suggesting that schizophrenia, rather than the prolactinoma, was a more likely cause of his symptoms.

Etiologically, antipsychotic medications have been associated with the development of prolactinomas, although this issue remains controversial. In a pharmaco-vigilance study, Szarfman et al.[5] examined reports of pituitary tumors, hyperprolactinemia, and galactorrhea to the Food and Drug Administration's Adverse Events Reporting System (AERS) in patients treated with olanzapine, risperidone, ziprasidone, aripiprazole, haloperidol, and quetiapine. There were a total of 77 reports of pituitary tumors associated with the seven antipsychotics, and 54 of the tumors were associated with risperidone. However, the conclusions that can be drawn from this data-set are limited. The voluntary nature of reporting captures a limited pool of data, and there is no healthy-control comparison for this study. Also, the AERS did not allow for coding pituitary tumor as an adverse event until 1997, so data on typical and atypical antipsychotics for the years before 1997 were not captured. Also, increased surveillance in those patients on antipsychotics, as compared with a healthy population, may have resulted in the discovery of tumors at a higher rate than in the general population.

Eight cases of neuroleptic treatment of psychotic patients who were diagnosed with prolactinomas have been reported.[6-10] However, a causal relationship cannot be inferred; all of these cases are from case reports and not from studies with control groups in the absence of anti-psychotic treatment. This is an area that needs further study because there are no prospective studies or randomized trials in this area.

Hyperprolactinemia

Hyperprolactinemia is defined as a serum prolactin above the normal range (as noted, approximately 20 ng/ml–25 ng/ml in premenopausal women and 15 ng/ml in men and postmenopausal women).[2] Serial measurements may be useful, as there is a circadian variation in the secretion of prolactin as well as other physiological factors that may affect its secretion. A patient may have asymptomatic elevation or symptomatic elevation, as, for unknown reasons, the degree of elevation does not necessarily predict the severity of effects.[3] Some patients with prolactin levels >100 ng/ml may be without the symptoms of hyperprolactinemia, whereas other patients may experience deleterious effects with minimal elevation of serum prolactin. However, generally, a higher prolactin level correlates with a higher risk of prolactin-related side effects.[2]

Hyperprolactinemia may be physiologic or pathophysiologic. Physiologic causes include pregnancy, sleep, exercise, and breastfeeding. Pathophysiologic causes include renal failure, cirrhosis of the liver, hypothyroidism, pituitary tumors, sellar brain tumors, and medication-induced hypersecretion of prolactin.[3] Classes of medication that have been associated with increased serum prolactin include antipsychotics, antiemetics, and antidepressants. These medications cause elevated serum prolactin because they disinhibit the tonic inhibition of prolactin by dopamine.[3,11,12]

Effect of Antipsychotics on Serum Prolactin

It is well established that both typical and atypical antipsychotics can elevate serum prolactin. One recent study examining chronically mentally ill patients on anti-psychotics found elevated serum prolactin levels in 71% of patients, with 37% of prolactin values more than twice the normal range. The prevalence of increased prolactin levels in patients treated with typical antipsychotics was 68%, and there was greater variability in patients treated

with atypical antipsychotics, depending on the specific medication. In the latter group, the prevalence was highest, at 91%, in risperidone-treated patients, and lowest, at 11%, in clozapine-treated patients.[13] This study did not include aripiprazole or other newer agents. However, this study did not include any baseline data on serum prolactin level in these patients before antipsychotic treatment. Another recent cross-sectional study, by Melkersson et al.,[14] included 75 patients with schizophrenia who received either clozapine, olanzapine, or risperidone, with subsequent measurement of prolactin levels and hyperprolactinemic symptoms. Elevated prolactin levels were found in 89% of the patients on risperidone, 24% of the patients on olanzapine, and none of the patients on clozapine. The prolactin level was higher in patients on risperidone than on olanzapine. Symptoms of hyperprolactinemia were found in 44% of patients treated with risperidone and only 3% of patients treated with olanzapine. These study results suggest that risperidone is most similar to the typical anti-psychotics in its likelihood of causing hyperprolactinemia. The study was limited in its generalizability by its small numbers (N=75) as well as the low doses of risperidone (median dose: 3 mg) and olanzapine (median daily dose: 10 mg), as compared with clozapine (median dose: 400 mg), which makes it more difficult to compare dose effect between groups.[14]

Another recent randomized, double-blind study compared the effect of risperidone and haloperidol on serum prolactin in schizophrenic patients after a 2-week washout period. Both drugs increased serum prolactin levels: 6 mg of risperidone induced the same level or prolactin elevation as 20 mg of haloperidol.[15] However, in this study, the dosages of the two medications were not equivalent in each experimental group, and the proportion of women was higher in the risperidone group, which may also have skewed the results, because women typically show a greater elevation in serum prolactin when receiving anti-psychotic medications.[15]

In the case presented at the beginning of this article, Mr. A was initially placed on olanzapine, a second-generation antipsychotic that is less likely to raise prolactin than others in its class. He was transitioned to risperidone to manage his refractory psychotic symptoms only after consultation with the endocrinology group. He has been psychiatrically and medically stable on risperidone, although risperidone has been associated with a greater propensity for raising serum prolactin.

Deleterious Effects of Hyperprolactinemia

The consequences of hyperprolactinemia can be subdivided into 1) the effects on tissues upon which prolactin directly acts; and 2) the effects due to the “downstream” hypogonadism caused by hyperprolactinemia. Direct tissue effects of hyperprolactinemia include galactorrhea and gynecomastia. Galactorrhea is more prevalent in women than men. Gynecomastia is a rare side effect in men with hyperprolactinemia.[2] Also, effects on mood and behavior, including depression, anxiety, and hostility have been attributed to hyperprolactinemia through unknown mechanisms, but causality has not been established.[16,17]

HPA-gonadal axis dysregulation is responsible for potentially serious long-term morbidity via the following mechanism: Increased prolactin inhibits gonadotropin-releasing hormone, which then inhibits luteinizing hormone and follicle-stimulating hormone production by the pituitary gland.[2] This, in turn, suppresses ovarian and testicular function and results in reduced production of the sex hormones testosterone in men and estrogen and progesterone in women. In women, this may lead to menstrual irregularities, including amenorrhea, and infertility. Hirsutism and acne are other possible consequences in women, caused by the stimulation of increased release of DHEA-S. In men, hypogonadism may manifest itself as decreased libido, sexual dysfunction, and infertility.[2] Low spinal bone-density in both men

and women has been associated with chronic hyperprolactinemia, due to decreased sex steroid levels, rather than hyperprolactinemia itself.[18,19]

Treatment of Prolactinomas in Non-Psychotic Patients

The goals of treatment of patients with prolactinomas with hyperprolactinemia are to control tumor expansion, if present, reduce tumor size, if mass effect is present, and restore gonadal function in hypogonadal patients.[1]

The primary treatment of prolactinomas is the use of the dopamine-agonist medications bromocriptine and cabergoline. Surgery and radiotherapy are other treatment options, which are discussed below.

It is important to note that many patients with prolactinomas can be monitored without intervention. This includes patients with microadenomas that do not have evidence of mass effect and those who have intact reproductive function; treatment is required for such patients only if serial MRIs demonstrate tumor growth. This also includes postmenopausal women with small tumors and no mass effect, in whom normalization of prolactin levels will not restore gonadal function. Again, such patients should be monitored for tumor growth, which would be an indication for treatment. Still other patients with microadenomas and hypogonadism can be treated symptomatically, for example, with gonadal steroids to prevent or treat bone loss. However, it is important to note that estrogen and testosterone can infrequently stimulate tumor growth, and, therefore, monitoring of tumor size with MRI scans is important in such patients. It is also important to note that prolactin is an imperfect tumor-marker. There have been reports of tumor growth in the absence of increasing prolactin levels. Therefore, the monitoring of prolactin levels alone is not adequate to exclude an expanding tumor mass.

Trans-sphenoidal resection of prolactinomas is not used as primary therapy because it does not typically result in long-term remission of the tumors or of hyperprolactinemia.[2] Resection of microprolactinomas results in normalization of prolactin levels initially in approximately 70% of patients.[3] Hyperprolactinemia recurs in approximately 50% of patients with macroadenomas who have undergone trans-sphenoidal resection.[3] Surgery is recommended for those in whom dopamine-agonist therapy is contraindicated, those who cannot tolerate dopamine-agonist therapy, and those with invasive macroadenomas that compromise their vision and do not respond to dopamine-agonist therapy.[3] If both dopamine agonists and surgery fail to stabilize the tumor mass, radiotherapy can be performed, but is reserved only for aggressive tumors because it can cause hypopituitarism and other complications, and it is not very effective at normalizing prolactin levels.

Bromocriptine is one of the oldest of the dopamine agonists, and it normalizes serum prolactin in approximately 70% of patients with microadenomas and macroadenomas; it decreases the size of these tumors, and restores menses and fertility in over 90% of patients of childbearing age.[2,3] Cabergoline is a newer agent, with greater selectivity for the D_2 receptor than bromocriptine. This medication treats successfully treats 70% of patients who do not respond to treatment with bromocriptine and may be more effective in reducing prolactin levels and decreasing tumor size than bromocriptine for both microadenomas and macroadenomas,[2,3] and with fewer side effects (Table 1).

After 3-to-5 years of normalization of serum prolactin and tumor shrinkage, the dopamine agonist may sometimes be slowly withdrawn. Serum levels of prolactin and MRI are then closely reassessed to evaluate whether the patient requires long-term dopamine-agonist therapy or may need surgery to resect the adenoma. Colao et al.[20] performed an observational study of withdrawal of cabergoline therapy in 200 patients with

microprolactinomas, macroprolactinomas, or non-tumoral hyperprolactinemia, who had greater than 50% tumor shrinkage, and had normalized prolactin levels. The patients were followed for up to 5 years to assess for regrowth of the tumor and elevated serum prolactin. Remission rates at 5 years after withdrawal of therapy were 67% and 57% in patients with microprolactinomas and macroprolactinomas, respectively. Patients who had no evidence of pituitary adenoma on MRI at the time of withdrawal of cabergoline therapy were less likely to have a recurrence of hyperprolactinemia.[20]

Common side effects of bromocriptine include nausea, vomiting, mild orthostatic hypotension, and headaches.[21] Uncommon CNS side effects of bromocriptine include nightmares, hallucinations, psychosis, and insomnia. As compared with bromocriptine, cabergoline is less likely to lead to nausea, vomiting, and hypotension. We identified in the literature two cases of psychosis exacerbation in schizophrenic patients treated with cabergoline for antipsychotic-induced hyperprolactinemia.[22] In patients with Parkinson's disease, use of cabergoline has been associated with an increased risk of valvular heart disease.[23] However, it is not known whether the dose of cabergoline used for treatment of prolactinomas is associated with this side effect; the recent smaller studies evaluating this question have been primarily, yet not uniformly, negative.[24–30]

MANAGEMENT OF PSYCHOSIS IN A PATIENT WITH A PROLACTINOMA: SURGERY VERSUS DOPAMINE AGONIST

In a patient with a history of psychosis, the psychiatrist and endocrinologist should decide together about management of the patient's prolactinoma, on the basis of location, mass effect, and endocrine side effects of the tumor. In such patients, it is safest to opt for initial surgical management of the prolactinoma if size and mass effect require intervention rather than monitoring. We do not recommend the use of dopamine agonists in patients with psychotic disorders because there are excellent alternative treatment options that do not pose the risk of psychiatric decompensation seen with dopamine agonists.[31] For example, in patients with tumors that are not exerting mass effect, an alternative option is gonadal steroid replacement and monitoring of tumor size without surgery or dopamine agonist, which is often done in patients with non-growing microadenomas.[24] In rare cases, a trial of dopamine-agonist therapy may be attempted, but only if the patient is concomitantly receiving an antipsychotic and only in a setting of close psychiatric monitoring. There are reports of patients who have experienced psychiatric decompensation soon after initiation of bromocriptine while still receiving an antipsychotic.[31] Also, there have been cases of psychiatric decompensation reported in patients with schizophrenia when treated with cabergoline.[22] Therefore, concomitant antipsychotic treatment does not always protect against psychiatric decompensation due to a dopamine agonist, although there have been no randomized, controlled trials in this area.

Choice of Antipsychotic

Arguably, the most important aspect in the choice of an antipsychotic for patients with prolactinomas is psychiatric stability. Any effects of hyperprolactinemia are either negligible clinically (lack of correlation between prolactin level and symptoms) or can be easily managed by the endocrinologist. Nevertheless, aripiprazole might be a rational choice as a first-line antipsychotic agent in a patient with both psychosis and a prolactinoma: it has been shown to lower prolactin, presumably through its mixed action of antagonism and agonism at the dopamine receptor.[32] However, there have been two cases published of galactorrhea in patients treated with aripiprazole, which may suggest some variability in the prolactin-level response to this antipsychotic.[33,34] In one of these cases, prolactin levels were measured at 30.1 ng/ml and 32.0 ng/ml after 2 days of administration of 15 mg of

aripiprazole.[34] In the other case, serum prolactin levels measured during administration of 5 mg to 15 mg of aripiprazole over 5 weeks were 27 ng/ml and 23.5 ng/ml.[33] In patients with symptoms attributable to increased prolactin levels from antipsychotics, aripiprazole has been used as an add-on strategy to reduce hyperprolactinemia from the antipsychotics.

We would not consider switching the patient to a prolactin-sparing antipsychotic such as olanzapine, ziprasidone, clozaril, or quetiapine[8,11,32] solely on the basis of its prolactin-sparing effects. Furthermore, from an endocrinologist's point of view, metabolic syndrome and diabetes mellitus are more serious potential complications from antipsychotic medications than hyperprolactinemia. The risk of particular antipsychotics, such as clozapine and olanzapine, of causing metabolic syndrome and diabetes must be weighed heavily in selecting an antipsychotic regimen. A long-acting, injectable antipsychotic might be indicated if nonadherence leads to psychiatric instability, as in the case of Mr. A, presented here, even at the risk of increasing prolactin levels.

Medical Monitoring

Growth of the prolactinoma should be monitored with neuroimaging (MRI) with and without gadolinium, using a pituitary protocol on a yearly basis. This is particularly important if the patient is receiving risperidone or a typical antipsychotic agent, as in the case of Mr. A, described here.[12] Serum prolactin levels should be measured regularly in collaboration with colleagues in endocrinology, the frequency depending on the specific case.

Treatment of a psychotic patient with a prolactinoma should also involve close monitoring not only of symptoms of hyperprolactinemia, but, particularly, the development of hypogonadism, which is the main cause of long-term medical morbidity related to hyperprolactinemia and symptoms of mass effect, including headache and visual symptoms. Hormonal treatments, such as oral contraceptives for women and testosterone replacement for men, are readily available to treat hypogonadism.[36] Both men and women, if hypogonadal, should have spinal bone-density testing. Hypogonadism, in women and men, may result in increased risk of osteopenia and osteoporosis.[18,19]

Symptomatic treatment for hypogonadism may result in increased adherence to the psychiatric medication regimen, as the effects of hypogonadism to patients can be particularly disconcerting and may lead to nonadherence.[11]

Consensus guidelines of the clinical monitoring for signs and symptoms of hyperprolactinemia in patients on antipsychotic treatments without prolactinomas have been published elsewhere and are not the focus of this review.[37] An excellent discussion is provided by Citrome.[38]

CONCLUSION

We have proposed an approach to caring for patients with comorbid schizophrenia and prolactinoma, one that weighs the risks and benefits of managing the patient's psychiatric stability on antipsychotics with the management of the prolactinoma and symptoms of hyperprolactinemia. The psychiatric arm of a collaborative treatment plan with endocrinology involves achieving long-term psychiatric remission; in some patients, a prolactin-sparing antipsychotic such as aripiprazole (which can lower prolactin levels) might be a good initial choice. However, if a patient's psychiatric condition cannot be stabilized with aripiprazole, in selecting an alternative or additional antipsychotic, the patient's psychiatric stability and the risk of causing diabetes should be prioritized over the risk of causing hyperprolactinemia and its effects, given that hyperprolactinemia can be easily

managed. We would recommend against the use of dopamine agonists in a patient with a history of psychosis, except in rare cases and with close psychiatric monitoring. For the patient with schizophrenia and a prolactinoma, the endocrinologist and psychiatrist should work in concert with one another and with the patient to monitor tumor size, serum prolactin levels, adherence to antipsychotic medication, and symptoms of hypogonadism, and to provide appropriate hormone supplementation.

References

1. Gilliam MP, Molitch ME, Lombard G, et al. Advances in treatment of prolactinomas. Endocr Rev. 2006; 27:485–534. [PubMed: 16705142]
2. Schlechte JA. Prolactinoma. N Engl J Med. 2003; 349:2035–2041. [PubMed: 14627789]
3. Melmed, S.; Jameson, JL. Disorders of the Anterior Pituitary and Hypothalamus, in Harrison's Principles of Internal Medicine. In: Fauci, AS.; Braunwald, E.; Kasper, DL., editors. 17. Vol. Chap. 333. The McGraw-Hill Companies, Inc., publisher; Accessed in http://www.accessmedicine.com.ezp-prod1.hul.harvard.edu/pqjcontent.aspx?aID=2876725
4. Zahajszky J, Quinn DK, Smith FA, et al. Cognitive and perceptual disturbances in a young man. Prim Care Companion J Clin Psychiatry. 2007; 9:59–63. [PubMed: 17599171]
5. Szarfman A, Tonning JM, Levine JG, et al. Atypical antipsychotics and pituitary tumors: a pharmacovigilance study. Pharmacotherapy. 2006; 26:748–758. [PubMed: 16716128]
6. Daradkeh TK, Ajlouni KM. The effect of neuroleptics on prolactinoma growth in a Jordanian schizophrenic girl. Acta Psychiatr Scand. 2008; 77:223–229.
7. Weingarten JC, Thompson TL. The effect of thioridazine on prolactinoma growth in a schizophrenic man: case report. Gen Hosp Psychiatry. 1985; 7:364–366. [PubMed: 4065553]
8. Melkersson K, Hulting AL. Prolactin-secreting pituitary adenoma in neuroleptic-treated patients with psychotic disorder. Eur Arch Psychiatry Clin Neurosci. 2000; 250:6–10. [PubMed: 10738858]
9. Pal JK, Sarino WA. Effect of risperidone on prolactinoma growth in a psychotic woman. Psychosom Med. 2000; 62:736–738. [PubMed: 11020104]
10. Konopelska S, Quinkler M, Strasburger CJ, et al. Difficulties in the medical treatment of prolactinoma in a patient with schizophrenia: a case report with review of the literature. J Clin Psychopharmacol. 2008; 28:120–121. [PubMed: 18204364]
11. Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinemia. Drugs. 2004; 64:2291–2314. [PubMed: 15456328]
12. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotics in patients with chronic schizophrenia. N Engl J Med. 2005; 353:1209–1223. [PubMed: 16172203]
13. Montgomery J, Winterbottom E, Jessani M, et al. Prevalence of hyperprolactinemia in schizophrenia: association with typical and atypical antipsychotic treatment. J Clin Psychiatry. 2004; 65:1491–1498. [PubMed: 15554761]
14. Melkersson K. Differences in prolactin elevation and related symptoms of atypical antipsychotics in schizophrenic patients. J Clin Psychiatry. 2004; 66:761–767. [PubMed: 15960571]
15. Zhang XY, Zhou DF, Cao LY, et al. Prolactin levels in male schizophrenic patients treated with risperidone and haloperidol: a double-blind and randomized study. Psychopharmacology. 2005; 178:35–40. [PubMed: 15289996]
16. Sonino N, Tomba E, Fava GA. Psychosocial approach to endocrine disease. Adv Psychosom Med. 2007; 28:21–33. [PubMed: 17684318]
17. Sobrinho LG. Emotional aspects of hyperprolactinemia. Psychother Psychosom. 1998; 67:133–139. [PubMed: 9667060]
18. Klibanski, Neer RM, Beitins IZ, et al. Decreased bone density in hyperprolactinemic women. N Engl J Med. 1980; 303:1511–1514. [PubMed: 7432421]
19. Greenspan SL, Neer RM, Ridgway EC, et al. Osteoporosis in men with hypoprolactinemic hypogonadism. Ann Intern Med. 1986; 104:777–782. [PubMed: 3706929]

20. Colao A, Disarno A, Cappabianca P, et al. Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. N Engl J Med. 2003; 349:2023–2033. [PubMed: 14627787]
21. Brunton, LB., editor. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 11. Vol. chap. 55. New York: McGraw-Hill, Inc; 2006. p. 1498-1501.
22. Chang S, Chen C, Lu M. Cabergoline-induced psychotic exacerbation in schizophrenic patients. Gen Hosp Psychiatry. 2008; 30:378–380. [PubMed: 18585544]
23. Zannettini R, Antonini A, Gatto G, et al. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. N Engl J Med. 2007; 356:39–46. [PubMed: 17202454]
24. Vallette S, Serri K, Rivera J, et al. Long term cabergoline therapy is not associated with valvular heart disease in patients with prolactinomas. Pituitary. 2008:1386–1341.
25. Colao A, Galderisi M, DiSarno A, et al. Increased prevalence of tricuspid regurgitation in patients chronically treated with cabergoline. J Clin Endocrinol Metab. 2008; 93:3777–3784. [PubMed: 18682513]
26. Devin JK, Lakhani VT, Byrd BF 3rd, et al. Prevalence of valvular heart disease in a cohort of patients taking cabergoline for management of hyperprolactinemia. Endocr Pract. 2008; 14:672–677. [PubMed: 18996784]
27. Lancellotti P, Livadariu E, Markov M, et al. Cabergoline and the risk of valvular lesions in endocrine disease. Eur J Endocrinol. 2008; 159:1–5. [PubMed: 18456868]
28. Bogazzi F, Buralli S, Manetti L, et al. Treatment with low doses of cabergoline is not associated with increased prevalence of cardiac valve regurgitation in patients with hyperprolactinemia. Int J Clin Pract. 2008; 62:1864–1869. [PubMed: 18462372]
29. Kars M, Pereira A, Bax J, et al. Cabergoline and cardiac valve disease in prolactinoma patients: additional studies during long-term treatment are required. Eur J Endocrinol. 2008; 159:363–367. [PubMed: 18703568]
30. Wakil A, Rigby A, Clark A, et al. Low-dose cabergoline for hyperprolactinemia is not associated with clinically significant valvular heart disease. Eur J Endocrinol. 2008; 159:R11–R14. [PubMed: 18625690]
31. Robbins RJ, Kern PA, Thompson TL. Interactions between thioridazine and bromocriptine in a patient with a prolactin-secreting pituitary adenoma. Am J Med. 1984; 76:921–923. [PubMed: 6720732]
32. Byerly M, Suppes T, Tran QV, et al. Clinical implications of antipsychotic-induced hyperprolactinemia in patients with schizophrenia spectrum or bipolar spectrum disorders: recent developments and current perspectives. J Clin Psychopharmacol. 2007; 27:639–661. [PubMed: 18004132]
33. Mendhekar DM, Andrade C. Galactorrhea with aripiprazole (letter). Can J Psychiatry. 2005; 50:243. [PubMed: 15898468]
34. Ruffatti A, Minervini L, Romano M, et al. Galactorrhea with aripiprazole. Psychother Psychosom. 2005; 74:391–392. [PubMed: 16244518]
35. Shim J, Shin J, Kelly D, et al. Adjunctive treatment with a dopamine partial agonist aripiprazole, for antipsychotic-induced hyperprolactinemia: a placebo-controlled trial. Am J Psychiatry. 2007; 164:1404–1410. [PubMed: 17728426]
36. Miller KK. Management of hyperprolactinemia in patients receiving antipsychotics. Neuroendocrine Clinical Center Bulletin. 2004 Spring-Summer;10
37. Marder SR, Essock SM, Miller AL, et al. Physical health monitoring of patients with schizophrenia. Am J Psychiatry. 2004; 161:1334–1349. [PubMed: 15285957]
38. Citrome L. Current guidelines and their recommendations for prolactin monitoring in psychosis. J Psychopharmacol. 2008; 22(2:suppl):90–97. [PubMed: 18477625]
39. Montastruc JL, Schmitt L, Bagheri H. Pathological gambling behavior in a patient with Parkinson's disease treated with levodopa and bromocriptine. Rev Neurol. 2003; 4:441–443. [PubMed: 12773874]
40. McGrath PJ, Quitkin FM, Klein DF. Bromocriptine treatment of relapses seen during selective serotonin re-uptake inhibitor treatment of depression. J Clin Psychopharmacol. 1995; 15:289–291. [PubMed: 7593717]

TABLE 1

Agents Used to Treat Prolactinomas and Associated Hyperprolactinemia in the United States[4,21,39,40]

Medication Name	Mechanism of Action	Medical Side Effects	Rare Psychiatric Side Effects	Comments
Bromocriptine	Dopamine (D_2) agonism	Nausea	Nightmares	Oldest agent: Daily to twice-daily dosing
		Vomiting	Hallucinations	
		Orthostatic hypotension	Psychosis	
		Headaches	Insomnia	
			Pathological gambling	
			Mood elevation	
Cabergoline	Dopamine (D_2 and weak D_1) agonism	Less likely to cause	Nightmares	Newer agent: Longer half-life
		Nausea	Hallucinations	Greater affinity for D_2 receptor
		Orthostatic hypotension	Psychosis	Once to twice-weekly dosing in most patients
		Headaches	Insomnia	
		Possible increased risk of cardiac valvular disease		