Potential Cardiac Valve Effects of Dopamine Agonists

Elena Valassi, M.D.

Dopamine agonists, specifically cabergoline and bromocriptine, represent first-line therapy for the treatment of prolactinomas. In particular, cabergoline is commonly used in hyperprolactinemic patients due to its high clinical efficacy, tolerability, and favorable pharmacokinetic profile. Cabergoline at doses as low as 0.5-1 mg weekly can normalize prolactin levels and restore gonadal function while promoting tumor shrinkage and regression of neurological symptoms in the majority of patients after an average of 6-24 months (1).

In recent years, several observational studies and case reports have been published showing a causal relationship between valvular heart disease and the use of dopamine agonist therapy (2-4). Two recent large scale studies have further strengthened the association between valvular heart disease and dopamine agonist use in patients primarily treated for Parkinson's disease (5-6). One of them, an echocardiographic prevalence study, showed that the incidence of moderate or severe valve regurgitation was 23.4% and 28.6% in patients treated with cabergoline or pergolide, respectively, and it was significantly higher than in patients either on therapy with non-ergot-derived dopamine agonists or healthy controls. Of note, patients with clinically significant regurgitation had been exposed to a higher cumulative dose (4015±3208 mg) of cabergoline compared with patients with less severe regurgitation (2341±2039 mg) (5). The other work, a population-based study of 11,417 subjects, observed an increased risk of newly diagnosed valve regurgitation in patients treated with pergolide or cabergoline, particularly at daily doses higher than 3 mg per day and administered for 6 or more months. No increased risk was observed for bromocriptine, lisuride, pramipexole, or ropinirole (6). The withdrawal of pergolide from the US market in 2007 was the direct consequence of these publications (7).

Following the studies on Parkinson's patients, concern has been raised among endocrinologists about the safety of long-term treatment with dopamine agonists, especially those with higher affinity to the 5HT2B receptor. As expected, over the

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past few months, a growing number of reports investigating potential valve effects of cabergoline in patients with prolactinomas have been brought to the attention of the scientific community. On the whole, results appear reassuring, but some comments are necessary (see Table 1).

Colao et al. studied 50 patients on cabergoline treatment and found a higher prevalence of moderate tricuspid regurgitation as compared with both age- and sex-matched controls and a control group with de novo hyperprolactinemia, and 72% of them had been treated with a cumulative dose of cabergoline above the median (11). However, these findings have not been confirmed by other reports (12-17). In particular, Bogazzi et al. evaluated 100 subjects and showed that in treated patients, prevalence of clinically relevant regurgitation at any valve was not different compared to controls. Moreover, subjects with moderate valvulopathy had been given lower cumulative doses of cabergoline and for shorter periods than those with the lowest grading of regurgitation (12).

Another report studying 78 patients (47 treated with cabergoline and 31 treated with other medications, including bromocriptine, or surgery) did not find any difference in the prevalence of moderate/severe valvular heart disease in patients on dopamine-agonists compared to healthy controls, but frequency of mild tricuspid regurgitation was significantly higher in patients who had been administered cabergoline than in healthy subjects (18). Similarly, Wakil et al. observed an increased prevalence of mild tricuspid and pulmonary regurgitation in a series of 44 patients treated with cabergoline compared to controls (17). Noteworthy, Kars et al. described some additional effects in the cabergoline group, including a significant appearance of mitral and aortic calcifications as well as leaflet thickening of the tricuspid valve (18). Similarly, a prospective study by Lancellotti et al. including 102 subjects receiving cabergoline, described an equal distribution of valvular disease between patients and controls, but found that mitral tenting area, an index of valvular restriction, was significantly more present in patients on cabergoline. Of note, mitral tenting area, which proportionally increased with the severity of the regurgitation, was greater in patients than in controls either at no or any of the lowest regurgitation grading and became significant in association with mild valvulopathy (19). Similarly, in Parkinson's patients on treatment with pergolide or cabergoline, a significantly greater mitral tenting area was documented compared to controls, even in those with no regurgitation (5). The clinical meaning of these findings is still to be elucidated, but it may be that cabergoline induces early, subclinical alterations of the valve architecture, predisposing to more severe and clinically evident changes as the treatment continues. Of note, there is a substantial overlap between the mean cumulative dose of cabergoline used for hyperprolactinemic patients in each report, and no association has emerged between the cumulative dose and pathological valvular characteristics in most reports, contrary to what has been observed in Parkinson's patients.

It should be highlighted that some important differences exist between the scheme of treatment with cabergoline for Parkinson's disease and hyperprolactinemia. Firstly, mean weekly doses of dopamine agonists are generally much higher in patients with Parkinson's disease (up to 25 mg) but the mean duration of the treatment is significantly lower (24.4±15.4 months) (5) than individuals treated for hyperprolactinemia. Additionally, patients treated for hyperprolactinemia usually begin treatment at a younger age and may require long-term treatment. Thus, particular attention should be paid to patients who have been exposed to high cabergoline doses for a prolonged period of time. Interestingly, in the paper by Kars, 8 out 9 patients with clinically significant valve regurgitation had received cabergoline for a mean period of 6.4 years (18). However, Bogazzi et al. did not find any significant difference in the valve score of the four patients receiving a dose higher than 3 mg/week for more than 6 years, though the low number of subjects analyzed makes it difficult to draw inferences from this finding (12).

No study has extensively evaluated the potential valvulopathic effects of bromocriptine in hyperprolactinemic patients, but some reports including experimental animals treated with bromocriptine, showed that previous treatment with bromocriptine was not associated with a higher prevalence of regurgitation compared with either patients who had been steadily on cabergoline or normal controls (12-13, 18-19). In particular, Kars et al. found that valvular heart disease was borderline significantly more prevalent in patients treated with cabergoline than in a small group of control subjects who had different therapies, including bromocriptine (18). Again, the low number of patients included in this study represents an important limitation that should be taken into consideration.

The data published to date substantiates the need for further investigation and offers in the interim some practical information for endocrinologists.

The ergot-derived dopamine agonists, including cabergoline and bromocriptine, may increase the risk of valvular heart disease. The affinity of each agonist at the 5HT2B receptor may dictate the risk of each drug, with respect to valvular disease potential. Insufficient evidence is available to make a consensus statement about the optimum treatment for each patient. While bromocriptine may have a lower risk of valvulopathy, it is associated with lower tolerability and therapeutic efficacy in terms of prolactin normalization and tumor shrinkage as compared with cabergoline; and due to its short half-life, requires more frequent dosing (1).

Patients taking these dopamine agonists, particularly cabergoline, should be warned about the potential risks associated with their use and the need for echocardiographic monitoring should be decided on an individual basis. Moreover, treatment with these drugs should be recommended at the lowest dose and for the shortest duration possible. In some selected individuals with prolactinomas, withdrawal of dopamine agonist therapy appears to be possible, without negative clinical consequences (20).

Even-derived dopamine agonists (not currently available in the US), such as quinagolide, pramipexole and ropinirole, may represent future therapeutic options.

In conclusion, although most of the reports investigating a possible relationship between the use of cabergoline or bromocriptine and valvular heart disease in patients with hyperprolactinemia do not show an increased occurrence of clinically relevant valvulopathy, caution must be exercised, especially in patients requiring long-term, high-dose medication regimens. Large, long-term, longitudinal studies, on the model of those published for Parkinson's patients, are necessary to conclusively assess the safety of dopamine agonists, at various doses and durations, in hyperprolactinemic patients.
Table 1

Recent studies of cabergoline use in patients with hyperprolactinemia and subsequent cardiac valvulopathy

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Mean cumulative cabergoline dose (mg)</th>
<th>Mean treatment duration (months)</th>
<th>Valvulopathy moderate/severe in patients (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lancellotti et al., 2008 (19)</td>
<td>204 (median)</td>
<td>79 (median)</td>
<td>1.9% (moderate)</td>
<td>Regurgitation grade at each valve not different from controls; significantly higher mitral tenting area in patients but no association with the cumulative dose.</td>
</tr>
<tr>
<td>Bogazzi et al., 2008 (12)</td>
<td>279 ± 301</td>
<td>67 ± 39</td>
<td>7% (moderate)</td>
<td>Regurgitation grade at each valve and mean total regurgitation score not different from controls. No association with the cumulative dose.</td>
</tr>
<tr>
<td>Kars et al., 2008 (18) Group A: 47 treated with cabergoline</td>
<td>363 ± 55</td>
<td>62.4 ± 4.8</td>
<td>15% (moderate) 2% (severe)</td>
<td>Mild tricuspid regurgitation more prevalent in group A than either group B or controls. Aortic calcifications more prevalent in groups A+B and A alone than controls; mitral calcifications and thickening of the tricuspid leaflets more prevalent in group A than controls. No association with the cumulative dose.</td>
</tr>
<tr>
<td>Vallette et al., 2008 (13)</td>
<td>282 ± 271</td>
<td>55 ± 22</td>
<td>5.7% (moderate)</td>
<td>Regurgitation grade at any valve not different from controls. No association with the cumulative dose.</td>
</tr>
<tr>
<td>Nachtigall et al., 2008 (14)</td>
<td>258 ± 58</td>
<td>48 ± 4</td>
<td>0%</td>
<td>Regurgitation grade at any valve not different from controls. No association with the cumulative dose.</td>
</tr>
<tr>
<td>Colao et al., 2008 (11)</td>
<td>280 (median) &gt;60 (68% of patients)</td>
<td>54% (moderate)</td>
<td>Higher prevalence of moderate tricuspid regurgitation in patients than in controls. Association with the cumulative dose.</td>
<td></td>
</tr>
<tr>
<td>Herring et al., 2008 (15)</td>
<td>492 ± 74</td>
<td>72 ± 6</td>
<td>0%</td>
<td>Regurgitation grade at any valve, valvular thickening and mitral valve tenting area not different from controls.</td>
</tr>
<tr>
<td>Devin et al., 2008 (16)</td>
<td>0.91 ± 0.96 mg/wk</td>
<td>39 ± 29</td>
<td>0%</td>
<td>Regurgitation grade at any valve, valvular thickening and mitral valve tenting area not different from controls. No association with the cumulative dose.</td>
</tr>
<tr>
<td>Wakil et al., 2008 (17)</td>
<td>311</td>
<td>36 – 48</td>
<td>0%</td>
<td>Higher prevalence of mild tricuspid and pulmonary regurgitation in patients than in controls. No association with the cumulative dose.</td>
</tr>
</tbody>
</table>

References

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Obesity and Antipsychotic Drug Use

Hideo Makimura, M.D., Ph.D.

Introduction
Schizophrenia affects approximately 1% of adults worldwide. The development of newer atypical antipsychotic medications over the years has resulted in an increase in available treatment options for these patients. However, many antipsychotic medications result in weight gain, development of insulin resistance and dyslipidemia. Not only is the development of these side effects associated with increased morbidity and mortality in and of itself, it also affects compliance rates and therefore effective treatment for the underlying psychiatric illness. The goal of this article is to review the literature on the metabolic complications associated with the use of antipsychotic medications.

Metabolic Effects of Antipsychotic Medications
Case reports may suggest that newer atypical antipsychotic agents are associated with weight gain, while the older typical antipsychotic agents are weight neutral. However, weight gain in association with treatment with typical antipsychotic agents such as chlorpromazine had been noted from its initial use in the 1950s (1). In addition, a meta-analysis including 81 published articles demonstrated treatment with most typical and atypical antipsychotic medications resulted in weight gain (Figure 1) (2). Of the evaluated medications, the atypical antipsychotics, clozapine and olanzapine, had the greatest weight gains, estimated at 4.45 kg and 4.15 kg, respectively, while haloperidol, a typical antipsychotic agent, was estimated to result in 1.08 kg weight gain at 10 weeks. As these estimates are based on available data at 10 weeks, it is possible that long term treatment would result in far greater weight gain over time. In the CATIE study (Clinical Antipsychotic Trials of Intervention Effectiveness), a multicenter randomized prospective study, 1493 patients with schizophrenia were randomized to receive a typical antipsychotic, perphenazine, or the atypical antipsychotics, olanzapine, quetiapine or risperidone, for 18 months or until discontinuation. In this study, olanzapine was associated with the greatest degree of weight gain, estimated at 0.9 kg/month (3). Interestingly, a few antipsychotic agents such as molindone, a typical antipsychotic agent of the dihydroindolone class (2) and aripiprazole, a newer atypical antipsychotic agent (4), appear to have a slight weight reducing effect in previous studies.

In addition to causing weight gain, antipsychotic agents, primarily clozapine and olanzapine, but not risperidone, were shown to increase insulin resistance and dyslipidemia even in the absence of obesity in patients with schizophrenia (5, 6). In fact, olanzapine worsened insulin resistance in 30 non-obese healthy volunteers after only 10 days, as measured by hyperinsulinemic-euglycemic clamp (7), potentially by impairing insulin-stimulated glucose transport at the level of the adipocyte (8). The previously mentioned CATIE study also demonstrated an effect of olanzapine to increase total cholesterol, triglycerides and glycosylated hemoglobin levels prospectively over 18 months (3). Although obesity, in association with worsening insulin resistance and dyslipidemia, would be predicted to increase the rate of cardiovascular mortality associated with antipsychotic drug use, this has yet to be established conclusively.

Pathophysiology
The exact mechanism underlying the development of obesity and its complications with antipsychotic medications is not yet clear. Interestingly, obesity itself is commonly associated with schizophrenia in the population (1). However, it is not clear if this is a true causal relationship as various contributing factors such as poor diet, lifestyle and genetic factors may also contribute to the increased obesity associated with this population.

Antipsychotic medications have a broad range of activity over central neurotransmitter systems including serotonin, dopamine, acetylcholine, and histamine systems. For example, olanzapine has direct or indirect activity at 19 different receptor sites (1) including antagonism of 5HT2C (9). The 5HT2C receptor is associated with appetite regulation and body weight in mice, such that knock out of this receptor in mice leads to hyperphagia and obesity (10). In humans, medications which activate 5HT2C receptors, such as dexfenfluramine, have been successfully used as appetite suppressants and weight loss medications. Furthermore, polymorphism of the promoter region of the 5HT2C receptor was found to be associated with decreased weight gain in response to clozapine (11), suggesting a central role for the serotonergic system in mediating the effect of antipsychotic drug-induced weight gain, even in humans. The role of other neurotransmitter systems in the regulation of appetite and metabolism is an active area of investigation.

Potential alteration in the growth hormone axis from antipsychotic medication use was also hypothesized recently. In a cross sectional study of 172 subjects, clozapine was found to decrease serum IGF-1 levels in Chinese patients with obesity secondary to clozapine use compared to obese...
subjects without known psychotic illness (12). Given the potential role of the growth hormone axis in mediating abdominal adiposity and its complications, this effect of antipsychotic medication use also bears further exploration.

Further studies are needed in both animal models and human research to advance our understanding of the metabolic effects of antipsychotic drug use.

Treatment
Weight gain associated with antipsychotic drug use may result in increased morbidity and mortality. The first step in management of this complication is preventing the development of this side effect with the choice of the most efficacious agent with the lowest weight gain liability. Communication between treating health care providers, including psychiatrists and endocrinologists, is essential to establish the best therapeutic plan.

Behavioral therapy or lifestyle modification can be effective in treating antipsychotic medication associated weight gain in the short term (13). However, no large scale study has been conducted to evaluate its long term effectiveness. Any behavior therapy would need to encompass nutrition and lifestyle education/counseling, as well as frequent monitoring and reinforcement to prevent recidivism.

Pharmacologic treatment modalities for weight loss at this time remain relatively sparse with only a few FDA approved medications, some of which stimulate central norepinephrine and serotonin systems (14). As the goal of antipsychotic agents generally involves decreasing the activity of central dopamine and serotonin systems, the use of these medications may potentially be at odds with the treatment goal. For example, case reports of patients developing psychotic episodes after initiation of phentermine, fenfluramine, or sibutramine have been documented (15-17). However, a recent randomized double-blind, placebo-controlled trial of sibutramine in 37 subjects with olanzapine-induced weight gain demonstrated successful loss of 6.8 kg in body weight, 3.4 kg/m² BMI units, and 6.1 cm in waist circumference over 12 weeks.

Alternatively, the use of these atypical antipsychotics has been proposed for the treatment of anorexia nervosa where the side effect of weight gain may be beneficial. Most recently a 10 week randomized, double-blind, placebo-controlled trial of olanzapine in patients with anorexia nervosa resulted in a more rapid weight gain compared to placebo (22).

Summary
Antipsychotic drug use can be associated with weight gain and development of insulin resistance and dyslipidemia.

Although the exact pathophysiological mechanism underlying this association is unknown, it likely leads to increased morbidity and mortality. Treatment of this condition requires coordination with the treating psychiatrist, close monitoring of their metabolic complications and the use of lifestyle intervention as well as adjuvant medical therapy as necessary. Each patient should be managed on a case by case basis with consideration of the degree of underlying psychiatric illness as well as previous responses to other antipsychotic agents and their individual risk factors for metabolic disease.

References:
The MGH Neuroendocrine Clinical Center hosted an Acromegaly Patient Education Day on May 30, 2008. The meeting was well attended by patients, families, and guests to gain a better understanding of the physiology and consequences of the disorder and current treatment approaches. The day was led by Anne Klibanski, M.D., Chief of the MGH Neuroendocrine Unit, and consisted of talks given by members of the Neuroendocrine Clinical Center. Topics included the following: pituitary physiology (Karen K. Miller, M.D.), clinical aspects of acromegaly and its diagnosis (Andrea Utz, M.D., Ph.D.), surgical and radiotherapy management of acromegaly with a video presentation of transsphenoidal surgery (Brooke Swearingen, M.D.), medical therapy of acromegaly (Lisa Nachtigall, M.D.), and practical issues in the testing and medical therapy for acromegaly (Karen Liebert, R.N., BSN and Michelle Gurel, R.N., BSN). This was followed by a panel discussion with Neuroendocrine Clinical Center physicians answering questions from patients and guests. As a finale, several patients participated in a panel to discuss their personal experience with acromegaly and to answer questions from the audience. We were treated to a touching and humorous poem from one of our participants about his acromegaly experience. This day provided a forum for patients to speak with each other to share their individual stories and to relate common experiences to others with this rare disorder.

The full content of the day can be seen on video at the following link: http://pituitary.mgh.harvard.edu/APED2008.htm

Selected patient questions and answers from Acromegaly Patient Education Day:

1. What are the beneficial effects of medical treatment for acromegaly?
The following are the available medical therapies for acromegaly: somatostatin analogs (octreotide, lanreotide), GH receptor antagonist (pegvisomant), dopamine agonists (cabergoline, bromocriptine). By lowering GH levels or blocking GH action, all three medication types can lead to a decline in IGF-1 level. The potential beneficial effect is to halt progression or improve the detrimental effects of acromegaly, including metabolic parameters (such as elevated blood glucose and hypertension), edema, cardiovascular abnormalities, arthralgias and bone growth, and increased mortality. Somatostatin analogs and in some cases dopamine agonists have the additional beneficial effect of potentially controlling tumor size.

2. What is the best test to determine if I still have acromegaly?
Normalization of the serum IGF-1 level is the primary measure of acromegaly control. Age appropriate IGF-1 reference ranges should be used. Additionally, oral glucose growth hormone suppression testing can also be used to confirm normal growth hormone suppressibility. Of note, glucose suppression testing is not useful in individuals taking pegvisomant.

3. What are the reasons to have a second surgery?
Repeat surgery is considered when individuals have tumor bulk compressing vital structures, such as the optic chiasm, causing mass effects. Additionally, tumor debulking can be employed in some cases to lower GH levels to make medical therapy more likely to normalize IGF-1 levels.

4. When is medical therapy used versus radiation therapy?
Medical therapy is frequently the second-line therapy following surgical resection. In cases of tumors with more potential to cause mass effects, radiation may be considered earlier in a patient’s course. Radiation is indicated when the biochemical measures of acromegaly cannot be controlled medically or surgically. Additionally, some patients choose to have radiotherapy earlier in their course to potentially limit the time that they will require medical therapy. The long term effects of radiotherapy, including potential hypopituitarism, should be discussed with patients.

5. What are the effects of acromegaly and its treatment on blood sugar?
Elevated GH levels worsen insulin resistance. It is also notable that somatostatin analogs may impair insulin release and subsequently increase blood glucose levels. Therefore, it is appropriate to monitor blood glucose in individuals on somatostatin therapy.

6. Does excess growth hormone prevent osteoporosis?
Although GH replacement, in the setting of GH deficiency, appears to improve bone density, the GH excess of acromegaly may not protect against osteoporotic fractures. In fact, some data suggest that fractures of the spine are increased in individuals with acromegaly.

7. What are the factors that contribute to headaches in acromegaly?
Headache in acromegaly may be due to compressive effects of large space-occupying pituitary lesions. Elevation in GH or IGF-1 levels may also contribute to headaches in some individuals.

8. Is acromegaly an inherited disorder?
Most cases of acromegaly are sporadic. There are rare known cases of inherited forms of acromegaly including: Multiple Endocrine Neoplasia-type 1 (MEN-1), Familial Acromegaly, McCune-Albright Syndrome, and Carney Complex.

The Acromegaly Patient Education Day was sponsored by an unrestricted grant from Tercica.
## RESEARCH STUDIES AVAILABLE

Patients may qualify for research studies in the Neuroendocrine Clinical Center. We are currently accepting the following categories of patients for screening to determine study eligibility. Depending on the study, subjects may receive free testing, medication and/or stipends.

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<td>Cushing’s Syndrome</td>
<td>• Evaluating a potential new medical therapy</td>
<td>Karen Pulaski-Liebert, R.N. Dr. Beverly M.K. Biller</td>
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<td>• Body composition and cardiovascular evaluation</td>
<td>Dr. Anne Klibanski</td>
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<tr>
<td>Patients with history of cured acromegaly with or without hypopituitarism</td>
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<td>Women with anorexia nervosa</td>
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<td>Adolescent athletes</td>
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<td>Dr. Elizabeth Lawson Dr. Karen K. Miller Dr. Anne Klibanski Dr. Madhu Misra</td>
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<tr>
<td>Healthy girls and women, ages 10 and up</td>
<td>• Investigating genetics of appetite-regulating and stress hormones</td>
<td>Dr. Elizabeth Lawson Dr. Karen K. Miller Dr. Anne Klibanski Dr. Madhu Misra</td>
</tr>
<tr>
<td>Healthy women, ages 18-45</td>
<td>• Investigating the link between cortisol regulation and bone density</td>
<td>Dr. Elizabeth Lawson Dr. Karen K. Miller Dr. Anne Klibanski</td>
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<tr>
<td>Women with irregular menstrual periods (hypothalamic amenorrhea), ages 18-45</td>
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<td>• Assessment of coronary artery atherosclerosis • Lifestyle modification strategies, including exercise and insulin sensitization</td>
<td>Dr. Steven Grinspoon Dr. Janet Lo Katie Fitch, ANP</td>
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<tr>
<td>HIV positive men and women with fat redistribution</td>
<td>• Use of GHRH, a growth hormone secretagogue, to increase endogenous GH levels, improve fat distribution and lipid profile • Among patients with reduced GH response to standard GH secretion testing, use of low dose GH as above</td>
<td>Dr. Steven Grinspoon Dr. Janet Lo Jim Liebau, ANP</td>
</tr>
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Scheduling
Outpatient clinical consultations can be arranged by calling the Neuroendocrine Center Office at (617) 726-7948.

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