



Society for Endocrinology position statement on the use of dopamine agonists in endocrine disorders

Dopamine agonists are important tools in the management of endocrine disorders. The potency and favourable side effect profile of cabergoline has made it the preferred dopamine agonist of many endocrinologists. Over the last decade evidence has emerged that the use of high doses of the ergot-derived dopamine agonists pergolide and cabergoline in the management of Parkinson's disease is associated with cardiac valve fibrosis. In January 2007, following the publication of two studies, the Food and Drug Administration (FDA) in the United States issued a bulletin announcing the voluntary withdrawal of pergolide by the manufacturer (<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01596.html>) and in the UK, the Medicines and Healthcare products Regulatory Authority (MHRA) imposed restrictions on the use of cabergoline for the treatment of Parkinson's disease but made no reference to patients with endocrine disease.

In October 2008, the MHRA published a Drug Safety Update (Appendix 1) specifically on ergot-derived dopamine agonists (cabergoline and bromocriptine) for endocrine disorders which stated: '*Chronic use of ergot-derived dopamine agonists is associated with a risk of fibrosis, particularly cardiac fibrosis. Cardiac valvulopathy should be excluded by echocardiography before treatment with cabergoline or bromocriptine.*' In patients being commenced on cabergoline the update suggests endocrinologists should:

- Monitor patients for signs of cardiac fibrosis during treatment
- Undertake echocardiography within 3–6 months of starting treatment and subsequently at 6–12-month intervals
- Stop treatment if echocardiography shows new or worsened valvular regurgitation, valvular restriction, or valve leaflet thickening
- Exclude pregnancy before administration of cabergoline
- Stop cabergoline in women who are planning a pregnancy one month before trying to conceive.

Subsequently, Pfizer, the manufacturer's of Dostinex (cabergoline) wrote to all endocrinologists stating that among the adverse events seen with cabergoline: '*Very common: cardiac valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion).*'

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The Society for Endocrinology has not had access to the evidence that underpins these statements and is in contact with the MHRA, European Medicines Agency (EMA) and Pfizer with the hope of seeing the data on which the Update is based. Until this is achieved it is the Society's position that:

- Dopamine agonists remain the first-line agents for the management of hyperprolactinaemia and a useful adjunct in the management of acromegaly.
- In keeping with good clinical practice, the lowest effective dose of dopamine agonist should be used to achieve the therapeutic goal.
- Patients who are established on a dopamine agonist should continue on their current therapy unless otherwise indicated.
- In keeping with good clinical practice, withdrawal of dopamine agonist should be considered when clinically appropriate.
- Members are encouraged to report any case of fibrotic reaction at any site associated with dopamine agonist therapy to the Committee on Safety of Medicines (CSM) using the established yellow card system.
- The Society continues to call for well controlled studies to determine the risk of cardiac valve disease associated with dopamine agonists, particularly cabergoline, in patients being treated for endocrine disorders.
- The Society would welcome detailed studies and analysis on the clinical and health-economic benefits of the intensive cardiac imaging recommended in the MHRA and EMA guidance.
- Pending the outcome of these studies and/or the emergence of other evidence, the Society recommends that endocrinologists should manage patients receiving cabergoline and bromocriptine in line with the guidance and warnings issued by the British National Formulary (Appendix 2) and MHRA Drug Safety Update (Appendix 1).
- An alternative agent to cabergoline and bromocriptine is quinagolide, a non-ergot derived dopamine agonist, although use of this agent may be associated with neuropsychiatric side effects. Long-term clinical experience with quinagolide is considerably less than with bromocriptine and cabergoline, which makes it difficult to comment on its relative safety over prolonged periods of treatment.

The Society will update its statement as and when new evidence becomes available. In the interim if you have any comments about this guidance or the issues addressed within please contact Dr Abhi Vora (abhi.vora@endocrinology.org) at the Society for Endocrinology

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*for and behalf of the Society for Endocrinology's Clinical Committee
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Appendix 1: MHRA Drug Safety Update

(reproduced with kind permission from the Medicines and Healthcare products Regulatory Agency).
<http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON028267>

Drug safety advice

Ergot-derived dopamine agonists: risk of fibrotic reactions in chronic endocrine uses

Keywords: ergot-derived dopamine agonists, cabergoline, bromocriptine, endocrine disorders, hyperprolactinaemia, fibrosis, cardiac valvulopathy

Chronic use of ergot-derived dopamine agonists is associated with a risk of fibrosis, particularly cardiac fibrosis. Cardiac valvulopathy should be excluded by echocardiography before treatment with cabergoline or bromocriptine. Patients should be monitored during treatment as outlined below

The European Medicines Agency has recommended new warnings and contraindications for ergot-derived dopamine agonists as a result of the risk of fibrosis, particularly cardiac fibrosis, associated with chronic use. The risk of cardiac fibrosis is higher with cabergoline and pergolide than with the other ergot-derived dopamine agonists.

Cabergoline, pergolide, and bromocriptine are indicated for the treatment of Parkinson's disease. Key advice on new warnings, contraindications, dose, and side-effects has previously been provided for this indication.

Cabergoline (brand leader Dostinex) is used in hyperprolactinaemia. The recommended initial Dostinex dose for this indication is 0.5 mg a week, given in one or two doses a week and titrated according to prolactin levels; therapeutic dose is usually 1 mg a week. Bromocriptine (brand leader Parlodel) is indicated for chronic endocrine disorders such as hyperprolactinaemia and acromegaly. For dosing information, refer to the Summaries of Product Characteristics. This new advice applies only to treatment of chronic endocrine disorders with these agents—it does not apply to the inhibition of lactation.

Advice for healthcare professionals:

Cabergoline and bromocriptine

- Exclude cardiac valvulopathy as determined by echocardiography before treatment
- Monitor patients for signs or symptoms of pleuropulmonary disease (eg, dyspnoea, shortness of breath, persistent cough, or chest pain) and retroperitoneal disorders during treatment. Renal insufficiency or ureteral or abdominal vascular obstruction might occur, with pain in the loin or flank and leg oedema. Abdominal masses or tenderness could suggest retroperitoneal fibrosis

Cabergoline

- Monitor patients for signs of cardiac fibrosis during treatment
- Echocardiography should be done within 3–6 months of starting treatment and subsequently at 6–12-month intervals
- Stop treatment if echocardiography shows new or worsened valvular regurgitation, valvular restriction, or valve leaflet thickening
- Pregnancy should be excluded before administration of cabergoline
- Women who are planning pregnancy should stop taking cabergoline 1 month before they try to conceive

See *Drug Safety Update* July 2008, p 9;
www.mhra.gov.uk/mhra/drugsafetyupdate

Access Summaries of Product
Characteristics at
<http://emc.medicines.org.uk/>

Further information is available at:
<http://www.emea.europa.eu/pdfs/human/press/pr/32239508en.pdf>



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Appendix 2: Current advice from BNF 56 (www.bnf.org/bnf/bnf/current/4458.htm#_200120)

Fibrotic reactions

The CSM has advised that ergot-derived dopamine receptor agonists, bromocriptine, cabergoline, lisuride [discontinued], and pergolide, have been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions.

Before starting treatment with these ergot derivatives it may be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful.