Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis

Dekkers OM, Lagro J, Burman P, Jorgensen JO, Romijn JA, Pereira AM

CRD summary
This review concluded that hyperprolactinaemia will recur after dopamine agonist withdrawal in a considerable proportion of patients and that the probability of treatment success was highest when cabergoline was used for at least two years. The authors’ conclusions should be treated with some caution given the high level of variation between studies and the lack of consideration of study quality.

Authors’ objectives
To assess the effect of dopamine agonist withdrawal in patients with idiopathic hyperprolactinaemia (increased levels of prolactin hormone) and prolactinomas (pituitary gland tumours).

Searching
PubMed, EMBASE, Web of Science and the Cochrane Library were searched from 1970 to July 2008. Search terms were reported. Reference lists were also searched for additional studies. There were no language restrictions.

Study selection
Clinical trials and observational studies of dopamine agonist treatment for patients with persisting normoprolactinaemia after treatment withdrawal were eligible for inclusion. In eligible studies, treatment had to last at least three months, with a follow-up period for patients of at least six months. During treatment normoprolactinaemia had to be achieved and the maximum allowable proportion of patients receiving pre-treatment with radiotherapy was 20%. Studies also had to report the proportion of patients with persisting normoprolactinaemia as an outcome, as well as details age, sex, type of dopamine agonist, treatment duration and normal reference values of prolactin.

The included studies assessed the following dopamine agonists: bromocriptine 3.58 to 20 mg/day; cabergoline 0.5 to 1.77mg/week; dihydroergocriptine 30mg/day; metergoline 12 to 24mg/day; and quinagolide 0.121 to 0.257mg/day. Mean treatment duration ranged from three to 63 months. Between 33.3 and 100% of patients were female and, where reported, their mean age ranged from 27 to 44 years.

Studies were selected by two reviewers independently with disagreements resolved by consensus.

Assessment of study quality
The authors did not state that they assessed study validity.

Data extraction
The proportion of patients with persisting normoprolactinaemia after dopamine agonist therapy withdrawal was extracted from each study. Hyperprolactinaemia and normoprolactinaemia were defined using the reference ranges reported in the studies. If a study reported outcomes at multiple times, only data for the final time point were extracted; only results from magnetic resonance imaging or computed tomography scans were used for tumour regression results. Results for pregnant patients were excluded where possible.

Data were extracted by two reviewers independently with disagreements resolved by consensus.

Methods of synthesis
Results were pooled using both fixed-effect and random-effects meta-analysis, weighted by the inverse variance. Heterogeneity was assessed with the I² statistic.

Analyses were stratified by the cause of hyperprolactinaemia (idiopathic or caused by microprolactinomas and...
Random-effects meta-regression was also used to look at the effect of treatment duration and dopamine agonist preparation on persisting normoprolactinaemia.

**Results of the review**

Nineteen studies (n=743 patients, range two to 221) were included.

The proportion of patients with persistent normoprolactinaemia after withdrawal of dopamine agonists ranged from zero to 74%. The pooled proportion, using a random-effects model, was 21% (95% CI 14 to 30; 19 studies), although heterogeneity was high ($I^2=81\%$).

A number of sensitivity analyses were performed. For the type of dopamine agonist, pooled proportions were 35% (95% CI 19 to 56; four studies; $I^2=85\%$) for cabergoline and 20% (95% CI 14 to 28; 12 studies; $I^2=20\%$) for bromocriptine. Studies of idiopathic hyperprolactinaemia had more treatment success (32%, 95% CI 5 to 80; three studies; $I^2=85\%$) compared with microprolactinomas (21%, 95% CI 10 to 37; 13 studies; $I^2=84\%$) and macroprolactinomas (16%, 95% CI 7 to 36; eight studies; $I^2=68\%$). Higher rates of persisting normoprolactinaemia were also seen in studies of more than 24 months duration (34%, 95% CI 19 to 52; seven studies; $I^2=91\%$) compared with shorter studies (16%, 95% CI 11 to 22; 12 studies; $I^2=0\%$).

Meta-regression showed that, after adjusting for the cause of hyperprolactinaemia, a longer treatment duration was associated with a higher proportion of persisting normoprolactinaemia ($p=0.015$).

**Authors' conclusions**

Hyperprolactinaemia will recur after dopamine agonist withdrawal in a considerable proportion of patients; the probability of treatment success was highest when cabergoline was used for at least two years.

**CRD commentary**

This review had clearly stated inclusion criteria for study design, intervention, participants and outcome. A number of databases were searched with no language restrictions. Study selection and data extraction were performed independently by two reviewers, which reduced the chance of error or bias during the review.

The authors did not assess the quality of the evidence, nor did they report the designs of the studies. As both clinical trials and observational studies were eligible for the review, some indication of study design would have been helpful to identify the more reliable studies. Results were pooled using both fixed-effect and random-effects meta-analyses. Statistical heterogeneity was assessed and explored. One study was found to have outlying results and the authors discussed the possible reasons for this.

The authors' conclusions should be treated with some caution given the high level of heterogeneity and lack of consideration of study quality. In addition, the authors' conclusion about cabergoline was not supported by the results presented, as only two studies used this treatment for longer than two years and did not form one of the subgroups reported in the review.

One author disclosed receipt of research grants and consultancy fees from Pfizer (manufacturers of cabergoline).

**Implications of the review for practice and research**

**Practice:** The authors stated that treatment with cabergoline for more than two years is associated with the best outcome.

**Research:** The authors stated that randomised controlled studies comparing different withdrawal strategies after successful treatment of hyperprolactinaemia are lacking. However, they did not make any explicit recommendations for research.