Cabergoline versus bromocriptine in the treatment of hyperprolactinemia: a systematic review of randomized controlled trials and meta-analysis

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CRD summary
The review found cabergoline was significantly more effective than bromocriptine in normalising prolactin level, reducing persistent amenorrhoea, menses normalisation and returning normal ovulatory cycles in treatment of prolactinomas and idiopathic hyperprolactinaemia. Cabergoline also had significantly fewer adverse events. Substantial differences between studies for the main outcome and relatively low patient numbers make the reliability of the authors’ conclusions unclear.

Authors’ objectives
To compare the efficacy and safety of cabergoline versus bromocriptine in the treatment of hyperprolactinaemia.

Searching
EMBASE (from 1980), PubMed (from 1966), LILACS (from 1982) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to March 2009 with no language restrictions; search terms were reported.

Study selection
Randomised (RCTs) and quasi-randomised (quasi-RCTs) controlled trials of cabergoline versus bromocriptine in the treatment of adult patients with idiopathic hyperprolactinaemia and prolactinomas were eligible for inclusion. Hyperprolactinaemia had to be diagnosed by elevated serum prolactin and other causes of hyperprolactinaemia had to be excluded. The primary outcome was normalisation of prolactin secretion. Secondary outcomes included restoration of gonadal function, reduction of tumour volume, quality of life and adverse drug effects.

Half of the studies were multicentre. Regimens were 5mg or 10mg/day bromocriptine or 0.5mg to 2mg/week cabergoline. Length of treatment ranged from eight to 24 weeks. Patient ages ranged from 16 to 48 years. Base level prolactin levels ranged from greater than the reference value to less than three times the reference value. Where reported, amenorrhoea was for more than three months. All studies excluded patients with thyroid, renal, adrenal or hepatic disease or polycystic ovary syndrome. Individual studies had additional exclusion criteria. «GN15

Two independent reviewers performed study selection.

Assessment of study quality
The Cochrane criterion of allocation concealment was assessed: A (adequate), B (unclear), C (inadequate, including quasi-RCTs) and D (score not assigned).

Two independent reviewers assessed study quality. Disagreements were resolved by discussion.

Data extraction
Relative risks (RR) and 95% confidence intervals (CI) were calculated for dichotomous outcomes. Mean differences and 95% CIs were calculated for continuous variables.

Two independent reviewers performed data extraction. Disagreements were resolved by discussion.

Methods of synthesis
Pooled relative risks and 95% confidence intervals were calculated for dichotomous data. Weighted mean differences (WMDs) and 95% confidence intervals were calculated for continuous data. A fixed-effect model was used unless there was significant heterogeneity. I² was used to determine between-study heterogeneity. Numbers needed to treat (NNT) were calculated. Subgroup analyses were performed for adverse events.

Results of the review
Four studies (all RCTs) were identified (743 patients, range 34 to 459). Three studies were B quality and one was A quality.

Normalisation of serum prolactin level was significantly improved for cabergoline versus bromocriptine (WMD 0.67, 95% CI 0.57 to 0.80; I²=54%, four RCTs). Cabergoline also significantly reduced persistent amenorrhoea compared to bromocriptine (RR 2.18, 95% CI 1.43 to 3.32; I²=0%, three studies) but there was no significant benefit for persistent galactorrhoea (I²=45%; three studies). There was a higher frequency of menses normalisation and return of normal ovulatory cycles for cabergoline versus bromocriptine (RR 0.74, 95% CI 0.67 to 0.83; I²=0%, three studies).

The number of adverse events was significantly higher for bromocriptine versus cabergoline (RR 1.43, 95% CI 1.03 to 1.98; I²=70%, four studies). Two studies provided suitable data for subgroup analyses for different adverse events and found both nausea (RR 1.66, 95% CI 1.33 to 2.06) and vomiting (RR 2.02, 95% CI 1.13 to 3.59) were significantly lower for cabergoline versus bromocriptine. There were no significant differences for any of the other specific adverse events evaluated.

Some additional individual study results were reported.

**Authors’ conclusions**
The meta-analysis showed new evidence that favoured use of cabergoline in comparison with bromocriptine for treatment of prolactinomas and idiopathic hyperprolactinaemia. Clinical and biochemical success rates were significantly higher and adverse events significantly lower in cabergoline users.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched with no language restrictions. Little effort to identify unpublished studies was reported and some relevant studies may have been missed. Study quality was assessed but only one criterion was used so it was difficult to assess overall study quality. Efforts were made to reduce error and bias during all stages of the review process. Relevant study details were reported.

Statistical heterogeneity was assessed. The statistical method used for the meta-analysis seemed appropriate. Suitable subgroup/sensitivity analyses were planned but not performed because data were too limited.

The review was performed well but the reliability of the authors’ conclusions is unclear as there were relatively few patients, there was substantial heterogeneity on the primary outcome and the risk of bias was unknown.

**Implications of the review for practice and research**
**Practice**: Cabergoline should be the first treatment option for patients with prolactinomas or other hyperprolactinaemic conditions for normalisation of prolactin levels, normalisation of menstruation and ovulation and reduction of adverse events.

**Research**: More clinical trials were needed to confirm these results, compare the effectiveness of the two drugs in reducing tumours and clarify the adverse events of both drugs.

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