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Living FRIendly Summaries Of The Body Of Evidence Using Epistemonikos (FRISBEE)
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Cabergoline or bromocriptine for prolactinoma?

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Abstract

Cabergoline and bromocriptine are among the most commonly used drugs to treat prolactinoma. Cabergoline is a long-acting dopamine receptor agonist which might offer advantages over bromocriptine. However, it is not clear if this translates into clinical benefits. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified two systematic reviews including 12 studies addressing the question of this article, including five randomized controlled trials. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded cabergoline is more effective than bromocriptine in resolution of amenorrhea/oligomenorrhea and galactorrhea, it probably increases pregnancy rate, and it is associated to less adverse effects. It is not clear whether cabergoline is also more effective with respect to tumor growth because the certainty of the evidence is very low.

Problem

Prolactinoma produces symptoms by increased prolactin secretion and as consequence of tumor enlargement. Dopamine agonists inhibit prolactin pituitary secretion by stimulation of D2 receptors, and so they control hyperprolactinemia and tumor growth.
Bromocriptine has been effectively used for decades, but it is associated to adverse effects. Cabergoline, a long-acting dopamine agonist, may be associated with less adverse effects, but it is not clear whether its pharmacological advantages translate into better clinical outcomes.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- Cabergoline is more effective than bromocriptine in resolution of amenorrhea/oligomenorrhea and galactorrhea, and probably increases pregnancy rate.
- It is not clear whether cabergoline is more effective than bromocriptine in increasing libido, decreasing progression of visual defect or preventing tumor growth, because the certainty of the evidence is very low
- Cabergoline leads to less adverse effects than bromocriptine.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found two systematic reviews [1],[2] comprising 12 studies overall [3],[4],[5],[6],[7],[8],[9],[10],[11],[12], [13],[14], including five randomized controlled trials relevant for the question of this article [3],[9],[10],[12],[14]. This summary is based on data from the randomized trials except for outcomes that were only reported in non-randomized studies [5],[6],[11].
What types of patients were included	One trial included patients with prolactin blood level above normal [10], two studies used a 2-fold increase above normal [3],[14], and one a 3-fold increase [12]. We did not find data in any of the reviews regarding prolactin level used as inclusion criteria for one study[9]. Three studies included women with amenorrhea for more than 3 months [3],[10],[14], and one study included women with hyperprolactinemia undergoing intrauterine insemination [9]. The three non-randomized studies correspond to retrospective cohorts. Two included men with macroprolactinoma [5] and prolactinoma (micro and macroprolactinoma) [11]. One study included patients with hyperprolactinemia without other specification in the systematic reviews identified [6].
What types of interventions were included	All of the studies compared bromocriptine against cabergoline. Regarding bromocriptine: three trials administered doses of 5-10 mg per day [10],[12],[14]. Two studies used 5 mg per day [3],[9]. One non-randomized trial used 1.25 mg twice a day for one week, 2.5 mg twice a day for three weeks and then on according to prolactin levels [5]. Another trial used 2.5 mg pm for two weeks, then 5 mg at lunch and 2.5 mg pm, and subsequent doses were adjusted by prolactin level [6]. Regarding cabergoline: One trial administered a fixed dose of 0.25 mg twice a week [9], one trial used 0.5 mg per week [3], one study 1 mg per week [12] and two 1-2 mg per week [10],[14]. One non-randomized study used 0.5 mg once a week for 15 days, then 0.5 mg twice a week, and then according to prolactin levels [5]. Another trial used 0.25 mg once a week for one week and then 0.25 mg twice a week, then adjusted by prolactin level [6]. None of the reviews report information about cabergoline and bromocriptine doses used in one of the trials [11].
What types of outcomes were measured	The main outcomes meta-analysed in the different reviews were: Amenorrhea/oligomenorrhea and galactorrhea (pooled in both systematic reviews [1],[2]]. Decreased libido, increased tumor size, low testosterone, masculine infertility, pregnancy, sexual dysfunction, visual defect and prolactin level increase (pooled in only one systematic review [2]). Adverse effects (nausea, vomiting, hypotension, headache, among others) (pooled in only one systematic review [1]).

Summary of findings

The information on the effects of cabergoline versus bromocriptine is based on five randomized controlled trials involving 906 patients [3], [9], [10], [12], [14] and three non-randomized studies [5], [6, [11] which provided information about outcomes not reported in randomized trials. The five randomized trials (906 patients) measured oligomenorrhea/amenorrhea [3], [9], [10], [12], [14], four reported galactorrhea [3], [9], [12], [14], one provided information about pregnancy rates [9] and four trials reported adverse effects [3], [10], [12], [14]. Two non-randomized studies provided information on increase in libido [5], [6], one reported effects on tumor growth [11] and one addressed visual field defects [6].
The summary of findings is the following:

- Cabergoline is more effective than bromocriptine in resolving amenorrhea/oligomenorrhea. The certainty of the evidence is high.
- Cabergoline is more effective than bromocriptine in resolving galactorrhea. The certainty of the evidence is high.
- Cabergoline probably increases pregnancy rate in comparison to bromocriptine. The certainty of the evidence is moderate.
- It is not clear whether cabergoline is more effective than bromocriptine in increasing libido, because the certainty of the evidence is very low
- It is not clear whether cabergoline is more effective than bromocriptine in preventing tumor growth, because the certainty of the evidence is very low.
- It is not clear whether cabergoline is more effective than bromocriptine in diminishing visual defect, because the certainty of the evidence is very low.
- Cabergoline leads to less adverse effects than bromocriptine. The certainty of the evidence is high.

Cabergoline versus bromocriptine for prolactinoma

Patients Prolactinoma
Intervention Cabergoline
Comparisson Bromocriptine

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITH bromocriptine	**WITH cabergoline**		
	Difference: pacients per 1000			
Amenorrhea/ oligomenorrhea	344 per 1000	182 per 1000	RR 0.53 (0.42 to 0.67)	⨁⨁⨁⨁[1] High
	Difference: 162 patients less per 1000 (Margin of error: 114 to 200 less)			
Galactorrhea	359 per 1000	93 per 1000	RR 0.26 (0.17 a 0.42)	⨁⨁⨁⨁[2 3] High
	Difference: 266 patients less per 1000 (Margin of error: 208 to 298 less)			
Pregnancy rate	564 per 1000	818 per 1000	RR 1.45 (1.19 a 1.78)	⨁⨁⨁◯[2] Moderate
	Difference: 254 patients more per 1000 (Margin of error: 107 to 440 more)			
Decreased libido	231 per 1000	268 per 1000	RR 1.16 (0.27 a 5.07)	⨁◯◯◯[4 5] Very low
	Difference: 37 patients more per 1000 (Margin of error: 168 less to 939 more)			
Increased in tumor size	69 per 1000	133 per 1000	RR 1.93 (0.30 a 12.4)	⨁◯◯◯[4 5] Very low
	Difference: 64 patients more per 1000 (Margin of error: 48 less to 786 more)			
Visual field defects	200 per 1000	106 per 1000	RR 0.53 (0.10 a 2.76)	⨁◯◯◯[4 5] Very low
	Difference: 94 patients less per 1000 (Margin of error: 180 less to 352 more)			
Adverse effects	706 per 1000	501 per 1000	RR 0.71 (0.52 a 0.96)	⨁⨁⨁⨁[1 6] High
	Difference: 205 patients less per 1000 (Margin of error: 28 to 339 more)			

RR= Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITH bromocriptine** is based on the risk in the control group of the trials. The risk **WITH cabergoline** (and its margin of error) is calculated from relative effect (and its margin of error).

[1] Even though most studies have risk of bias, the study providing more data to meta-analysis has low risk. So, we did not downgrade the certainty of evidence for this aspect.
[2] Studies have serious risk of bias; therefore we downgraded the certainty of the evidence in one level.
[3] We upgraded the certainty of the evidence because of a large effect size.
[4] Studies providing data for this outcome are not randomized.
[5] We downgraded the certainty of the evidence in one level for imprecision.
[6] Even though there is inconsistency, it is explained by difference in the magnitude of the adverse effects reported, so clinical decision would not vary.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

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Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence provided in this summary applies to women who will initiate dopamine agonists for prolactinoma associated to oligo/amenorrhea, infertility or galactorrhea.

About the outcomes included in this summary

- Clinical results were privileged over biochemical effects (e.g. prolactin levels), based on the opinion of the authors of this summary, since these are the ones that motivate patients to seek treatment in the first place.
- They agree with the outcomes analyzed in the systematic reviews identified and the main guidelines.

Balance between benefits and risks, and certainty of the evidence

- Even though adverse effects are frequent, they are not specific or severe. The main difference is observed in the intensity and frequency of nausea and vomiting.
- Considering the observed clinical benefits, the high certainty of the evidence and the higher frequency of adverse effects, carbergoline is probably the best choice in terms of benefit/risk.

What would patients and their doctors think about this intervention

- Considering adverse effects profile and clinical benefit most patients and their doctors should prefer cabergoline, especially if there are no resource constraints.

Resource considerations

- Cabergoline is associated with higher direct cost than bromocriptine. However, considering it is more effective and safer, which determines less indirect costs, the cost/benefit might be in favor of cabergoline.
- Notwithstanding, it is important to mention bromocriptine leads to improvement in a substantial number of patients, making it a good choice in settings with resource constraints.

Differences between this summary and other sources

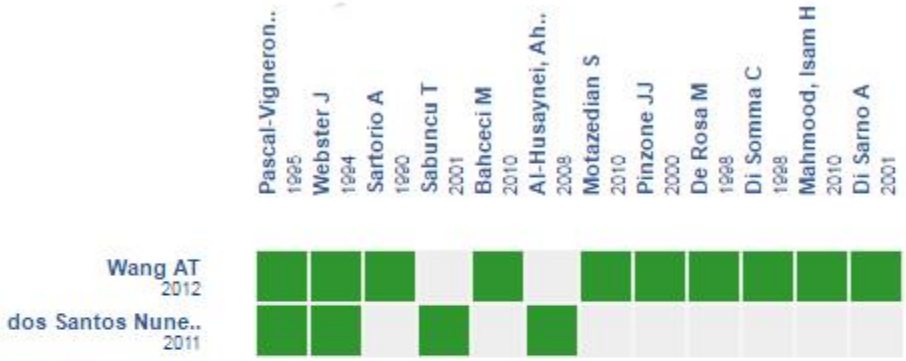
- The conclusions of this summary are consistent with the systematic reviews identified, which favor cabergoline over bromocriptine because of better outcomes and less adverse effects.
- The conclusions of this summary agree with the main guideline [15] which recommends cabergoline over bromocriptine because of better control of prolactin levels and tumor growth. It should be noticed this guideline is exclusively based on one of the systematic reviews included in this summary, which was commissioned by the scientific society producing the guideline. Therefore, part of the evidence included in this summary [2] was not considered.

Could this evidence change in the future?

- The probability of future evidence changing the conclusion of this summary regarding amenorrhea/oligomenorrhea, galactorrhea, pregnancy rate and adverse effects is low.
- Regarding decreased libido, tumor growth and visual defects, the certainty of the evidence is very low, therefore future evidence may change our conclusions.
- There are no ongoing trials regarding this question, at least according to the records of the World Health Organization International Clinical Trials Registry Platform.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Cabergoline versus bromocriptine for hyperprolactinemia or prolactinoma

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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