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

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Abstract Cabergoline and bromocriptine are the most used drugs in the treatment of hyperprolactinemia, they are able to normalize the prolactin levels, restore gonadal function and promote tumor reduction in the majority of patients. We undertake a systematic review and meta-analysis of randomized controlled trials to compare cabergoline versus bromocriptine in the treatment of patients with idiopathic hyperprolactinemia and prolactinomas. The data sources were: Embase, Pubmed, Lilacs and Cochrane Central. The outcome measures were: normalization of prolactin secretion, restoration of gonadal function, reduction of tumoral volume, quality of life and adverse drug effects. Were identified 418 references and after screening by title and abstract, we obtained complete copies of 34 articles potentially eligible for inclusion in the review. From this total, 19 were selected to be included, but fifteen of them were excluded due to the following reasons: one randomized study compared cabergoline versus placebo and other randomized study compared different doses of cabergoline; five references were cases series; four were only controlled studies; three were retrospectives series and; one was a cohort study. Therefore, four publications were included in the review and in the final analysis. The meta-analysis of normalization of serum prolactin levels and menstruation with return of ovulatory cycle showed a significant difference in favor of cabergoline group (RR 0.67 [CI 95% 0.57, 0.80]) e (RR 0.74 [CI 95% 0.67, 0.83]), respectively. The number of adverse effects was significantly higher in the bromocriptine number than in cabergoline group (RR 1.43 [CI 95% 1.03, 1.98]). The meta-analysis showed new evidence favoring the use of cabergoline in comparison with bromocriptine for the treatment of prolactinomas and idiopathic hyperprolactinemia.

Keywords Hyperprolactinemia · Prolactinoma · Systematic review · Meta-analysis · Dopaminergic agonists

Introduction

Hyperprolactinemia is a frequent condition in clinical practice, responsible for 20–25% of cases of secondary amenorrhea [1]. The causes of this abnormality are divided into three principle categories: physiological, pharmacological and pathological. Prolactinomas are an important cause of pathological hyperprolactinemia, and are generally classified according to their size as micro (less than 10 mm in diameter) or macroprolactinomas (more than 10 mm in diameter) [2].

The primary objective of treatment for microprolactinomas or idiopathic hyperprolactinemia is to restore gonadal and sexual function by normalizing prolactin (PRL) levels, whereas for macroprolactinomas is also fundamental to control the tumor growth [2].

Dopaminergic agonists are the first treatment option for prolactinoma. All dopamine agonists are efficacious, but cabergoline and bromocriptine are the most commonly used worldwide. These drugs are able to normalize the PRL

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levels, restore gonadal function and promote tumor reduction in the majority of patients [2]. For microprolactinomas bromocriptine normalizes PRL levels in 80–90% of patients, restoring gonadal function and shrinking tumor mass [3]. For macroprolactinomas normalization of PRL and tumor mass shrinkage occur in about 70% of patients, associated with improve of headache and visual field defects [4]. Regarding to cabergoline treatment, it also decreases significantly PRL levels; in a retrospective study of 455 patients [5], the treatment normalized PRL levels in 86% of 425 patients with available follow-up (92% of 244 patients with idiopathic hyperprolactinemia or microprolactinoma, and 77% of 181 patients with macroprolactinoma). A remarkable tumor-shrinking effect of cabergoline has been also observed in patients with macroprolactinomas; Colao and colleagues showed that cabergoline treatment induced further tumor shrinkage in 60% of patients previously treated with other dopamine-agonists compared with 82.3% of previously untreated patients [6].

We undertake a systematic review of randomized controlled trials to compare cabergoline versus bromocriptine in the treatment of patients with idiopathic hyperprolactinemia and prolactinomas.

Methods

Search strategy and selection

There was no language restriction. Trials were obtained from the following sources:

We searched the following electronic databases to identify studies involving bromocriptine and cabergoline in the treatment of hyperprolactinemia: Embase (1980–2009), Pubmed (1966–2009), Lilacs (1982–2009) and the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, issue 1 2009). The last search was performed in March 2009.

The Medical Subject Heading (MeSH) terms used included "Bromocriptine", "Cabergoline", "Hyperprolactinemia" and "Randomized Controlled Trial".

The inclusion factors were randomized and quasi-randomized clinical trials that evaluated adult participants with hyperprolactinemia, diagnosed by elevated serum levels of PRL, in whom other causes of hyperprolactinemia were excluded.

Two reviewers (VSN and RED) independently screened the titles and abstracts identified by the literature search, and the studies potentially eligible for inclusion in the review were selected for complete reading.

Data extraction and quality assessment

Both reviewers assessed study quality and extracted data using an extraction template. In case of disagreements, there was a debate between the reviewers before the final decision. For each trial, we assigned quality scores for allocation concealment, using the criteria described in the Cochrane Reviewers' Handbook [7]: (A) = adequate concealment of the allocation, (B) = unclear whether adequate concealment of the allocation, (C) = inadequate concealment of allocation (includes quasi-randomized studies), (D) = indicates the score was not assigned.

The primary outcome considered was normalization of PRL secretion, while the secondary outcomes included restoration of gonadal function, reduction of tumoral volume, quality of life and adverse drug effects.

Data synthesis and analysis

For the dichotomous outcomes, relative risk was calculated with a 95% confidence interval and we expressed continuous variables as weighted mean difference along with their 95% confidence intervals. The number needed to treat was also calculated.

Potential causes of heterogeneity among the studies were also analyzed. We used the I^2 statistic to measure the proportion of statistical heterogeneity for each outcome [8]. When the outcomes were homogeneous, we undertook a fixed effect meta-analysis (calculated in *Review Manager 5 software*).

The sensitivity analysis was also performed by excluding clinical trials of low methodological quality.

Results

Selection of studies

From the searches of databases, 418 references were identified (Fig. 1). After screening by title and abstract, we obtained complete copies of 34 articles potentially eligible for inclusion in the review. From this total, 19 were selected to be included and cited in this review. Fifteen of them were excluded due to the following reasons: one randomized study compared cabergoline versus placebo [9] and other randomized study compared different doses of cabergoline [10]; five references were cases series [11–15]; four were only controlled studies [16–19]; three were retrospectives series [5, 20, 21] and; one was a cohort study [22]. Therefore, four publications were included in the review and in the final analysis [23–26].

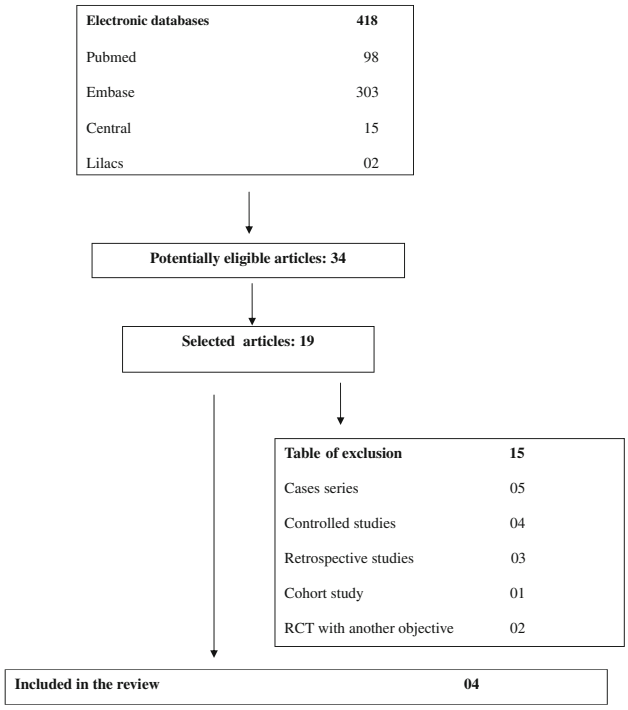

Fig. 1 Flowchart of Search Results. *RCT* randomized clinical trial

Included studies

The four studies included in the meta-analysis involved a total of 743 participants, and were all randomized clinical trials. Webster et al. [26] and Pascal-Vigneron et al. [25] conducted a multicenter double-blind studies, involving 67 centers of Gynecology and Endocrinology in Europe and Argentina and 21 French centers, respectively. The main characteristics of the studies are presented in Table 1.

Al-Husaynei et al. [23] analyzed 130 women between 20 and 39 years of age, treated for 8 weeks with 2.5 mg of bromocriptine twice a day and 0.5 mg of cabergoline weekly. Sabuncu et al. [24] evaluated 34 patients of both genders, mean age of 21 and 20 years in the bromocriptine and cabergoline groups, respectively. In this study, the dose of bromocriptine was 5 mg/day in microprolactinomas and 10 mg/day in macroprolactinomas, while the cabergoline dose was 1.0 mg/week, independent of the tumor size, and the patients were followed during 12 weeks. Pascal-Vigneron et al. [25] evaluated a total of 120 women aged between 16 and 45 years for 24 weeks, who received 5–10 mg/day of bromocriptine or 1–2 mg/week of cabergoline. Webster et al. [26] studied 459 women between 16 and 45 years, who were treated for 24 weeks with bromocriptine at 5–10 mg/day or cabergoline at 1.0–2.0 mg/week.

The outcomes analyzed in the study by Al-Husaynei et al. [23] were the occurrence of menstruation, absence of galactorrhea and normalization of serum prolactin levels.

Table 1 Characteristics of the included studies

Study	Method	Patients	Age	Intervention Br omo/Caberg	Criteria for inclusion	Criteria for exclusion	Outcomes	Quality
Sabuncu et al. [24]	RCT	34	18–48	5 mg–10 mg/day 1 mg/week	PRL > 3 times the RV	Thyroid, adrenal, renal and hepatic diseases; gestation; POS	Diminution of PRL; improvement of galactorrheia; of menstrual cycles; libido and potency, adverse events	B
Al-Husaynei et al. [23]	RCT	130	20–39	5 mg/day 0.5 mg/week	Amenorrhea >3 months, PRL > 2 times the RV	MAC, POS, thyroid, adrenal, renal and hepatic diseases, allergy to ergot, using medications that cause hyperprolactinemia	Occurrence of menstruation, absence of galactorrhea and normalization of PRL levels	A
Webster et al. [26]	RCT	459	16–45	5–10 mg/day 1–2 mg/week	Amenorrhea >3 months, PRL > 2 times the RV	MAC, POS, thyroid, adrenal, renal and hepatic diseases, allergy to ergot, previous use of one of the DAs without response	Occurrence of menstruation and ovulation, serum PRL concentration	B
Pascal-Vigneron et al. [25]	RCT	120	16–45	5–10 mg/day 1–2 mg/week	Amenorrhea >3 months and PRL > the RV	Resistance or intolerance to one of 2 DA, allergy to ergot, MAC, POS, thyroid, suprarenal, renal or liver disease	Levels of PRL, menstruation, ovulation, pregnancy, adverse effects	B

RCT randomized clinical trial, *RV* reference value, *PRL* prolactin, *MAC* macroadenoma, *DA* dopamine agonists, *POS* polycystic ovary syndrome, *A* adequate concealment of allocation, *B* concealment of allocation not described

Sabuncu et al. [24] analyzed clinical symptoms, adverse effects and serum prolactin levels. Pascal-Vigneron et al. [25] evaluated the total or partial normalization of prolactin levels, clinical and biochemical parameters (menstruation, ovulatory cycle and pregnancy) and adverse effects. Webster et al. [26] considered occurrence of menstruation and ovulation, and prolactin levels.

Meta-analysis of the outcomes analyzed: bromocriptine versus cabergoline

Normalization of PRL

The meta-analysis of the normalization of serum PRL levels showed a significant difference in favor of the cabergoline group (RR 0.67 [CI 95% 0.57, 0.80]) (Fig. 2). With regards to representations of meta-analyses with only one study [24], there was no statistically significant difference in any of the subcategories evaluated: idiopathic and microadenoma (RR 0.73 [CI 95% 0.45, 1.19]) or macroadenoma (RR 0.67 [CI 95% 0.22, 2.07]).

Persistent galactorrhea and amenorrhea

The meta-analysis demonstrated a significant difference in favor of participants receiving cabergoline (RR 2.18 [CI 95% 1.43, 3.32]) regarding to persistent amenorrhea (Fig. 3). The persistence of galactorrhea did not differ between the groups (RR 3.07 [CI 95% 0.68, 13.84]).

Adverse effects

The number of adverse effects was significantly higher in the bromocriptine than in the cabergoline group (RR 1.43 [CI 95% 1.03, 1.98]), (Fig. 4).

Adverse effects categorized into subgroups

Utilizing the studies of Webster et al. [26] and of Al-Husaynie et al. [23], adverse events such as nausea and vomiting were significantly less frequent in the cabergoline-treated patients, (RR 1.66 [CI 95% 1.33, 2.06]) and (RR 2.02 [CI 95% 1.13, 3.59], respectively). There were no differences in relation to the frequency of constipation, headache, dizziness, vertigo, abdominal pain, dyspepsia, gastritis, fatigue, mastalgia, depression, hot flashes, somnolence or postural hypotension, between the groups.

Normalization of menstruation and ovulation

There was a higher frequency of menses normalization and return of ovulatory cycles in patients treated with cabergoline (RR 0.74 [CI 95% 0.67, 0.83]; Fig. 5). The meta-analysis of the study Webster et al. [26] with the same expected clinical outcome also showed a statistically

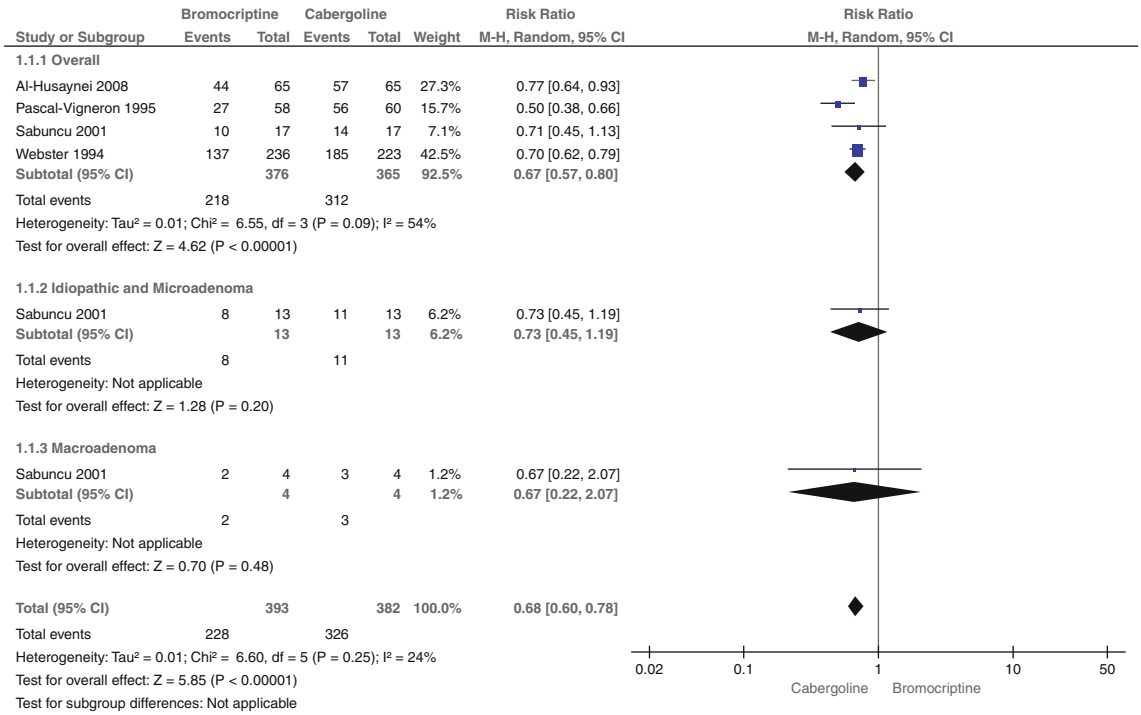

Fig. 2 Meta-analysis [23–26] comparing bromocriptine versus cabergoline, evaluating normalization of prolactin levels

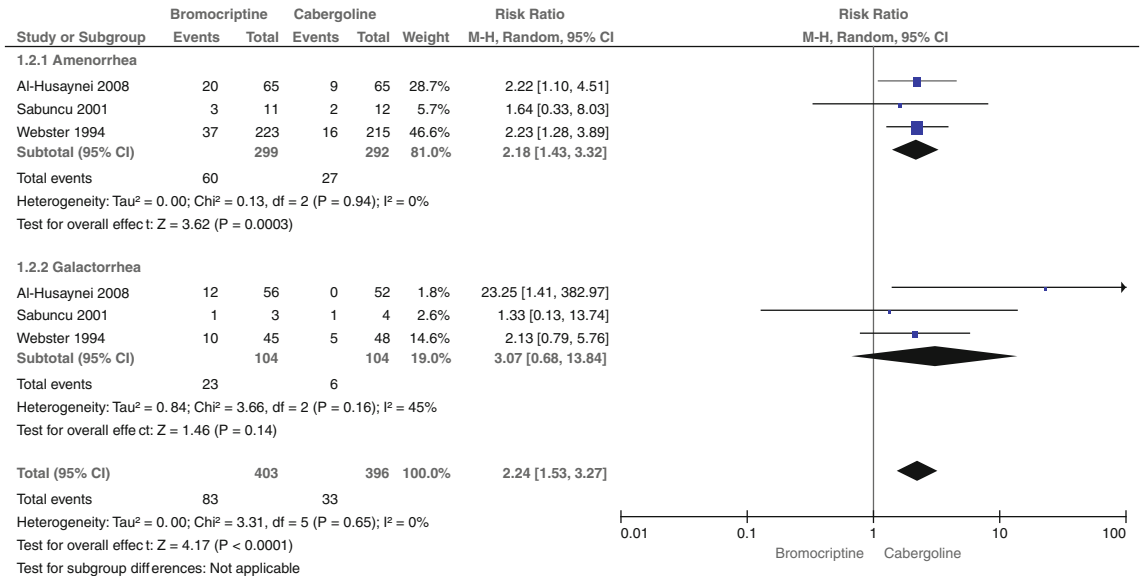

Fig. 3 Meta-analysis [23, 24, 26], comparing bromocriptine versus cabergoline evaluating galactorrhea and amenorrhea

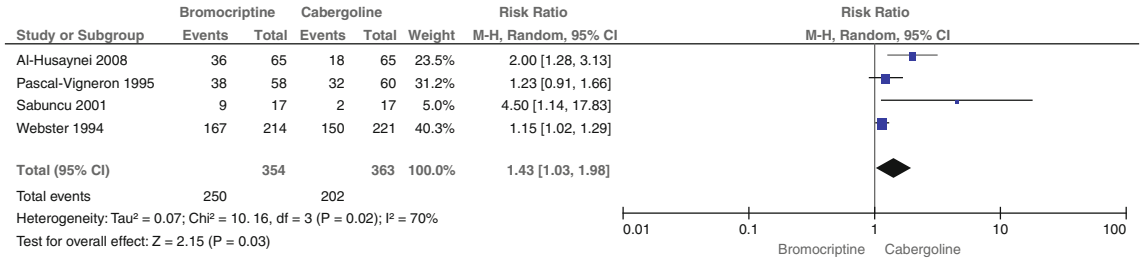

Fig. 4 Meta-analysis [23–26] comparing bromocriptine versus cabergoline -evaluating adverse effects (overall)

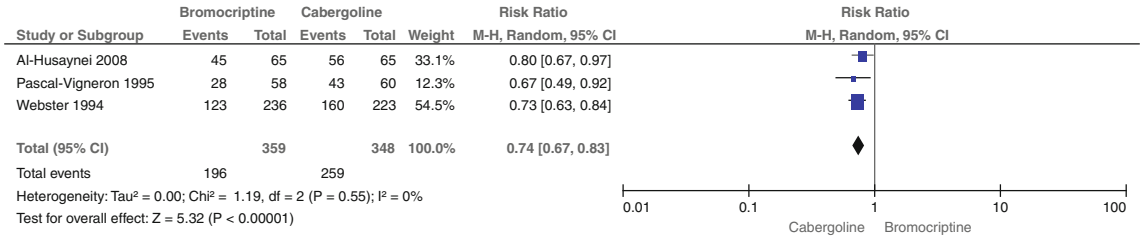

Fig. 5 Meta-analysis [23, 25, 26] comparing bromocriptine versus cabergoline evaluating normalization of menstruation and ovulation

significant difference favoring women that previously received cabergoline (RR 0.68 [CI 95% 0.57, 0.82]).

At least two consecutive menstruations and one ovulatory cycle or pregnancy, in addition to normalization of PRL levels

The study by Pascal-Vigneron et al. [25] assessed at least two consecutive menstruations and one ovulatory cycle or pregnancy, in addition to normalization of PRL levels, and found a significant difference in favor of cabergoline (RR 0.58 [CI 95% 0.41, 0.82]).

Discussion

Several studies comparing bromocriptine versus cabergoline have demonstrated superiority of cabergoline in relation to tolerability, reduction of PRL secretion, restoration of gonadal function and decrease in tumour volume [5, 26, 27]. On the other hand, bromocriptine has been satisfactorily used for years, with success rates for normalization of PRL in 80–90% of microadenomas and up to 70% of macroadenomas, associated with restoration of gonadal function and tumor reduction in most cases [4],

Cabergoline is an agonist specific to the D2 dopamine receptor and possesses a long half-life, allowing its weekly administration. Based on these characteristics and on several comparative studies, cabergoline has been considered superior to bromocriptine for the treatment of hyperprolactinemia and effective in many patients resistant to bromocriptine [16]. To prove this hypothesis, we have designed a systematic review and meta-analysis of only randomized clinical trials that evaluated bromocriptine versus carbegoline in the treatment of hyperprolactinemia.

Our preliminary research yielded four randomized studies with a total of 743 patients available for analysis.

It was verified that the allocation was adequate in one of the studies (Al-Husaynie and colleagues) [23]; in the others the generation of allocation and allocation concealment were not described. All the studies included in the meta-analysis allowed us to evaluate reduction or normalization of PRL levels, menses regularization and ovulation. Our results confirmed that cabergoline was superior in normalizing PRL, in restoring gonadal function, (lower rate of persistent amenorrhea, more frequent return of menses and ovulatory cycles), and, in general, was better tolerated, with fewer cases of adverse events, especially nausea and vomiting. Persistent galactorrheia and other adverse events were similarly reported in bromocriptine and cabergoline groups.

Our analysis did not allow a final conclusion in relation to the superiority of cabergoline to bromocriptine in reducing the size of prolactinomas. Despite many retrospective studies have suggested that cabergoline would be more efficacious in reducing prolactinomas, no randomized study has been published comparing the two drugs to assess this therapeutic outcome. For similar reason, quality of life could not be analyzed in the present review.

Implications for clinical practice

This systematic review offers updated evidence that favors the use of cabergoline compared with bromocriptine in the normalization of PRL levels, normalization of menstruation and ovulation, and diminution of the incidence of adverse effects.

Implications for research

More clinical trials must be performed, given the outcomes presented in the protocol of this systematic review, with the aim of confirming the data presented herein, to compare the effectiveness of these two drugs in reducing tumors, and in clarifying the adverse effects of both cabergoline and bromocriptine.

Conclusion

The meta-analysis showed new evidence favoring the use of cabergoline in comparison with bromocriptine for the treatment of prolactinomas and idiopathic hyperprolactinemia. Clinical and biochemical success rates were significantly higher and adverse events were significantly lower in cabergoline users. Therefore, except in particular situations, cabergoline should be the first treatment option for patients with prolactinomas or other hyperprolactinemic conditions.

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Conflict interests Nothing to declare.

References

1. Brue T, Delemer B (2007) Diagnosis and management of hyperprolactinemia: expert consensus—French society of endocrinology. Ann Endocrinol (Paris) 68:58–64
2. Casanueva FF et al (2006) Guidelines of the pituitary society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf) 65:265–273
3. Colao A, di Sarno A, Pivonello R, di Somma C, Lombardi G (2002) Dopamine receptor agonists for treating prolactinomas. Expert Opin Investig Drugs 11:787–800
4. Colao A, Pivonello R, Di Somma C, Savastano S, Grasso LF, Lombardi G (2009) Medical therapy of pituitary adenomas: effects on tumor shrinkage. Rev Endocr Metab Disord 10: 111–123
5. Verhelst J, Abs R, Maiter D, van den Bruel A, Vandeweghe M, Velkeniers B, Mockel J, Lamberigts G, Petrossians P, Coremans P, Mahler C, Stevenaert A, Verlooy J, Raftopoulos C, Beckers A (1999) Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. J Clin Endocrinol Metab 8:2518–2522
6. Colao A, Di Sarno A, Landi ML, Scavuzzo F, Cappabianca P, Pivonello R, Volpe R, Di Salle F, Cirillo S, Annunziato L, Lombardi G (2000) Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. J Clin Endocrinol Metab 85:2247–2252
7. Alderson P, Green S, Higgins JPT (eds) (2004) Cochrane reviewers' handbook 4.2.2 the Cochrane library [updated December 2003]. Wiley, Chichester
8. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
9. Webster J, Piscitelli G, Polli A, D'Alberton A, Falsetti L, Ferrari C, Fioretti P, Giordano G, L'Hermite M, Ciccarelli E et al (1992) Dose-dependent suppression of serum prolactin by cabergoline in hyperprolactinaemia: a placebo controlled, double blind, multicentre study. European multicentre cabergoline dose-finding study group. Clin Endocrinol (Oxf) 37:534–541
10. Mattei AM, Ferrari C, Baroldi P, Cavioni V, Paracchi A, Galparoli C, Romano C, Spellecchia D, Gerevini G, Crosignani PG (1988) Prolactin-lowering effect of acute and once weekly repetitive oral administration of cabergoline at two dose levels in hyperprolactinemic patients. J Clin Endocrinol Metab 66: 193–198

11. Bricaire C (2004) Interruption d'un traitement de longue durée par la cabergoline des hyperprolactinémies tumorales et non tumorales. La Revue du Praticien Gynécologie et Obstétrique 15:9–10
12. Freda PU, Reyes CM, Nuruzzaman AT, Sundeen RE, Khandji AG, Post KD (2004) Cabergoline therapy of growth hormone & growth hormone/prolactin secreting pituitary tumors. Pituitary 7:21–30
13. Di Somma C, Colao A, Di Sarno A, Klain M, Landi ML, Facciolli G, Pivonello R, Panza N, Salvatore M, Lombardi G (1998) Bone marker and bone density responses to dopamine agonist therapy in hyperprolactinemic males. J Clin Endocrinol Metab 83:807–813
14. Bolko P, Jaskula M, Wasko R, Wolun M, Sowinski J (2003) The assessment of cabergoline efficacy and tolerability in patients with pituitary prolactinoma type. Pol Arch Med Wewn 109: 489–495
15. Ferrari C, Barbieri C, Caldara R, Mucci M, Codecasa F, Paracchi A, Romano C, Boghen M, Dubini A (1986) Long-lasting prolactin-lowering effect of cabergoline, a new dopamine agonist, in hyperprolactinemic patients. J Clin Endocrinol Metab 63: 941–945
16. Di Sarno A, Landi ML, Cappabianca P, Di Salle F, Rossi FW, Pivonello R, Di Somma C, Faggiano A, Lombardi G, Colao A (2001) Resistance to cabergoline as compared with bromocriptine in hyperprolactinemia: prevalence, clinical definition, and therapeutic strategy. J Clin Endocrinol Metab 86:5256–5261
17. De Rosa M, Colao A, Di Sarno A, Ferone D, Landi ML, Zarrilli S, Paesano L, Merola B, Lombardi G (1998) Cabergoline treatment rapidly improves gonadal function in hyperprolactinemic males: a comparison with bromocriptine. Eur J Endocrinol 138: 286–293
18. Fideleff HL, Holland M, Chervin A, Gurucharri C, Sinai I (1997) Tratamiento de amenorreas hiperprolactinemicas con cabergolina. Medicina (B Aires) 57:657–661
19. Sartorio A, Conti A, Ambrosi B, Muratori M, Morabito F, Faglia G (1990) Osteocalcin levels in patients with microprolactinoma before and during medical treatment. J Endocrinol Invest 13:419–422
20. Vilar L et al (2008) Diagnosis and management of hyperprolactinemia: results of a Brazilian multicenter study with 1234 patients. J Endocrinol Invest 31:436–444
21. Berinder K, Stackenas I, Akre O, Hirschberg AL, Hulting AL (2005) Hyperprolactinaemia in 271 women: up to three decades of clinical follow-up. Clin Endocrinol (Oxf) 63:450–455
22. Cesar de Oliveira Naliato E, Dutra Violante AH, Caldas D, Lamounier Filho A, Rezende Loureiro C, Fontes R, Schrank Y, Gomes de Souza R, Vaisman M, Guerra E, Sebastian A, Colao A (2008) Quality of life in women with microprolactinoma treated with dopamine agonists. Pituitary 11:247–254
23. Al -Husaynei A, Mahmood I, Al -Jubori ZS (2008) Comparison of the effects of cabergoline and bromocriptine in women with hyperprolactinemic amenorrhea. Middle East Fertil Soc J 13: 33–38
24. Sabuncu T, Arikan E, Tasan E, Hatemi H (2001) Comparison of the effects of cabergoline and bromocriptine on prolactin levels in hyperprolactinemic patients. Intern Med 40:857–861
25. Pascal-Vigneron V, Weryha G, Bosc M, Leclere J (1995) Aménorrhée hyperprolactinémique: traitement par cabergoline versus bromocriptine. Résultats de l'étude nationale, multicentrique, randomisée en double insu. La Presse Médicale 20:753–757
26. Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF (1994) A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline comparative study group. N Engl J Med 331:904–909
27. Ferrari CI, Abs R, Bevan JS, Brabant G, Ciccarelli E, Motta T, Mucci M, Muratori M, Musatti L, Verbessem G, Scanlon MF (1997) Treatment of macroprolactinoma with cabergoline: a study of 85 patients. Clin Endocrinol (Oxf) 46:409–413