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# Treatment of hyperprolactinemia: a systematic review and meta-analysis

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## Abstract

**Background:** Hyperprolactinemia is a common endocrine disorder that can be associated with significant morbidity. We conducted a systematic review and meta-analyses of outcomes of hyperprolactinemic patients, including microadenomas and macroadenomas, to provide evidence-based recommendations for practitioners. Through this review, we aimed to compare efficacy and adverse effects of medications, surgery and radiotherapy in the treatment of hyperprolactinemia.

**Methods:** We searched electronic databases, reviewed bibliographies of included articles, and contacted experts in the field. Eligible studies provided longitudinal follow-up of patients with hyperprolactinemia and evaluated outcomes of interest. We collected descriptive, quality and outcome data (tumor growth, visual field defects, infertility, sexual dysfunction, amenorrhea/oligomenorrhea and prolactin levels).

**Results:** After review, 8 randomized and 178 nonrandomized studies (over 3,000 patients) met inclusion criteria. Compared to no treatment, dopamine agonists significantly reduced prolactin level (weighted mean difference, -45; 95% confidence interval, -77 to -11) and the likelihood of persistent hyperprolactinemia (relative risk, 0.90; 95% confidence interval, 0.81 to 0.99). Cabergoline was more effective than bromocriptine in reducing persistent hyperprolactinemia, amenorrhea/oligomenorrhea, and galactorrhea. A large body of noncomparative literature showed dopamine agonists improved other patient-important outcomes. Low-to-moderate quality evidence supports improved outcomes with surgery and radiotherapy compared to no treatment in patients who were resistant to or intolerant of dopamine agonists.

**Conclusion:** Our results provide evidence to support the use of dopamine agonists in reducing prolactin levels and persistent hyperprolactinemia, with cabergoline proving more efficacious than bromocriptine. Radiotherapy and surgery are useful in patients with resistance or intolerance to dopamine agonists.

**Keywords:** Treatment, Hyperprolactinemia, Macroprolactinoma, Microprolactinoma

## Background

Hyperprolactinemia is the most common disorder of the hypothalamic-pituitary axis. Patients typically present with hypogonadism, infertility or, in the case of macroadenomas, symptoms related to mass effect (headache and visual field defects).

In general, treatment of hyperprolactinemia, secondary to pituitary macroadenoma, is accepted as necessary. Medications in the form of dopamine agonists are the first line of treatment, with surgery and radiotherapy reserved for refractory and medication-intolerant patients [1]. The primary aim of treatment in patients with pituitary macroadenoma is to control compressive effects of the tumor, including compression of optic chiasm, with a secondary goal to restore gonadal function. However, indications and modalities of treatment of hyperprolactinemia due to pituitary microadenomas are less well defined [1]. Commonly cited indications for

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treatment of microprolactinomas include infertility, hypogonadism, prevention of bone loss and bothersome galactorrhea [1,2]. Treatment with dopamine agonists can restore normal prolactin levels and gonadal function. Dopamine agonists have been associated with various adverse effects including nausea, vomiting, psychosis and dyskinesia. However, the choice of which dopamine agonist is most efficacious and produces the least adverse effects is unclear.

To provide evidence-based recommendations to practicing clinicians facing these common therapeutic dilemmas, we conducted a systematic review and meta-analyses of the literature to evaluate outcomes and adverse effects with medications, surgery and radiotherapy in hyperprolactinemic patients. Outcomes of interest include prolactin levels, tumor size, and persistent hyperprolactinemia and patient-important outcomes, including visual disturbances, fertility, sexual dysfunction and galactorrhea,

## Methods

The results are reported according to the PRISMA statement (Preferred reporting items for systematic reviews and meta-analyses) [3]. We used the relevant components of the Ottawa-Newcastle tool (whether cohorts represent clinical practice, blinding of outcome assessment, analysis adjustment for confounders, and adequacy of follow-up) [4] and the Cochrane risk of bias tool (extent of blinding, allocation concealment, and funding) to evaluate the quality of observational and randomized trials, respectively. Summary judgments about the quality of evidence for each outcome followed the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework (Additional file 1: Tables 2–4) [5].

## Study eligibility

Eligible studies provided longitudinal follow-up data of cohorts of patients with hyperprolactinemia, that is, observational cohort studies or randomized controlled trials (RCTs). The outcomes of interest were tumor size, visual field defects, prolactin levels, galactorrhea, infertility, hypogonadism (amenorrhea/oligomenorrhea and low libido for premenopausal women, low libido or erectile dysfunction for men), bone density loss and fragility fracture rates, quality of life, and treatment adverse effects. We assumed author reports of “irregular menses” to mean amenorrhea or oligomenorrhea unless otherwise specified. We included studies with follow-up duration of at least six months and studies of at least 10 subjects. We did not impose any language restrictions.

## Search strategy

We sought articles addressing hyperprolactinemia or prolactin-secreting tumors that were treated by dopamine agonists, surgery or radiotherapy, which focused on outcomes from those treatments. The search concepts of hyperprolactinemia, outcomes of interest (specific sequelae of amenorrhea/oligomenorrhea, sexual dysfunction, vision disorders, cranial nerve disorders and bone disorders), treatments and study design (observational longitudinal studies or RCTs) were represented in the search strategy using database-specific controlled vocabulary. We searched in Ovid MEDLINE, Ovid EMBASE and the Ovid Cochrane Library, ISI Web of Science and Scopus from inception through September 2009. The search was updated on 15 December 2011. The complete search strategy was done with the help of an experienced research librarian and is available in the Additional file 1: Appendix.

## Study selection

Study selection and data extraction procedures were conducted by pairs of reviewers working independently until adequate agreement ( $\kappa \geq 0.90$ ) was obtained; then the process was conducted by single reviewers. First, eligibility criteria were applied to titles and abstracts, and potentially eligible studies were retrieved in full text. Then, eligibility criteria were applied to the full report. Disagreements were noted and resolved by discussion and consensus, erring on inclusion. We extracted descriptive data about enrolled patients, any treatment provided, study quality measures and outcome data from each study. Both study selection and data extraction were conducted using web-based software (Distiller SR, Ottawa, ON, Canada).

## Statistical analysis

The effect size and the associated measures of precision were estimated from each study (relative risk (RR) for dichotomous outcomes, weighted mean difference (WMD) for continuous outcomes, and event rate for uncontrolled studies).

Effect sizes were pooled across studies using a random effects meta-analytical model [6]. Heterogeneity was assessed using the  $I^2$  statistic, which represents the proportion of between-study differences that are not attributable to chance or random error [7].  $I^2$  values of <25%, 25 to 50% and >50% indicate mild, moderate and substantial heterogeneity, respectively. When meta-analysis includes less than three studies, the  $I^2$  is not calculable and is not reported. *A priori* planned subgroup interactions were based on sex and size of tumor (macro- vs. microprolactinomas). Median and range of event rates were estimated from uncontrolled cohort studies or case series that did not

provide sufficient data for meta-analysis. All analyses were completed using *Comprehensive Meta Analysis Version 2.2*, Biostat, Englewood NJ (2005).

## Results

Literature search revealed 2,103 potentially relevant references, of which 189 were included (Figure 1). The description, quality assessment and bibliography of the studies are available in the Additional file 1: Appendix.

Twenty-nine studies were controlled (that is, two arms allowing for comparative analysis) (Additional file 1: Table 1), whereas 157 were uncontrolled (that is, the entire cohort received the same intervention allowing the estimation of event rates but no comparative analysis). We contacted the authors of the comparative studies via e-mail if possible and by postal mail if no e-mail was available; 20 authors replied, of which 15 confirmed or corrected study data.

### Study quality

The quality of the observational studies was limited, with no blinding of outcome assessment and poor reporting of adjustments for confounders or other prognostic variables (Additional file 1: Tables 2 and 3). The quality of the eight RCTs [8-14] was fair (allocation was concealed in five; patients were blinded to assignment in six RCTs, caregivers in five) (Additional file 1: Table 4).

### Patients treated with dopamine agonists

A large body of noncomparative cohort studies supported the use of dopamine agonists in patients with hyperprolactinemia. Those studies included: bromocriptine (n = 39); cabergoline (n = 26); and quinagolide (CV 205-502) (n = 15), which is not approved in the US. Bromocriptine studies had the longest follow-up (exceeding 10 years) and showed consistent benefits on several patient-important outcomes and surrogate outcomes (Additional file 1: Table 5A). Comparing across studies, 68% (median %) of patients treated with bromocriptine had normalization of prolactin levels and 62%

experienced a reduction in tumor size. Bromocriptine also successfully treated other major outcomes, including 86% of patients with galactorrhea, 78% with amenorrhea, 67% with sexual dysfunction, 67% with visual field defects and 53% of patients with infertility. Studies of cabergoline and quinagolide showed similar results (Additional file 1: Tables 5B, C). In three observational studies that followed patients from 7 to 12 months, long-acting forms of bromocriptine were found to be as efficacious as the short-acting forms (Additional file 1: Table 5D). Other dopamine agonists typically used for other conditions, such as Parkinson's disease, were also used in this setting; namely, pergolide, lisuride, and roxindol (Additional file 1: Table 5E), with comparable findings.

A smaller body of evidence offers comparative effectiveness data from observational studies and eight RCTs. Forest plots depicting the results of these meta-analyses are in Additional file 1: Figures 1A-5B. The results are presented by comparison.

- *Bromocriptine vs. Cabergoline* (Figures 2 and 3): Six observational studies and three randomized trials compared bromocriptine to cabergoline. Bromocriptine was less effective than cabergoline in reducing the risk of persistent hyperprolactinemia (RR, 2.88; 95% CI, 2.20 to 3.74;  $I^2 = 0\%$ ), amenorrhea/oligomenorrhea (RR, 1.85; 95% CI, 1.40 to 2.36), and galactorrhea (RR, 3.41; 95% CI, 1.9 to 5.84). There were no significant differences between the two drugs in terms of overall change in prolactin level or other patient-important outcomes.
- *Bromocriptine vs. Quinagolide*: Two observational studies and four RCTs compared quinagolide to bromocriptine. There were no significant differences between these agents across all outcomes reviewed (Additional file 1: Figures 1A and 1B).
- *Dopamine agonists compared to no treatment*: Three observational studies and one RCT compared

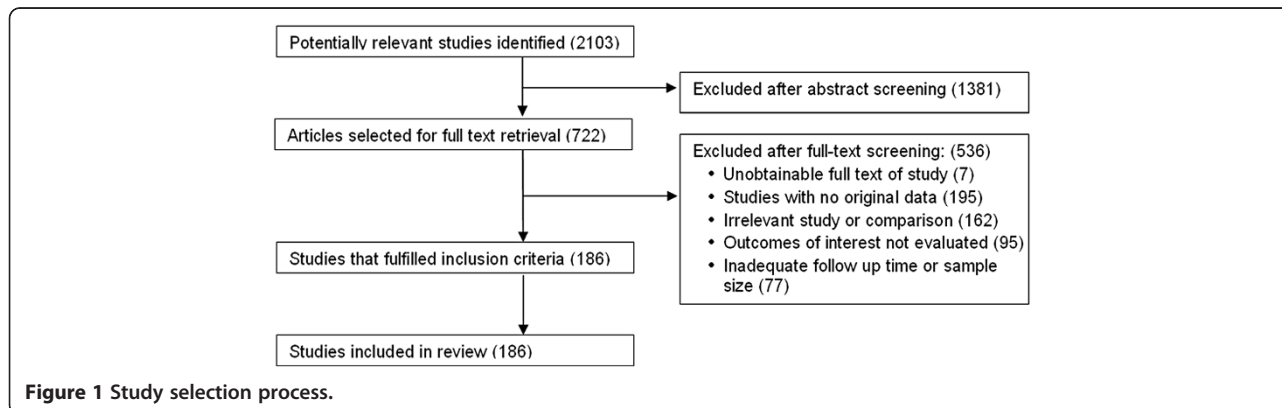


Figure 1 Study selection process.

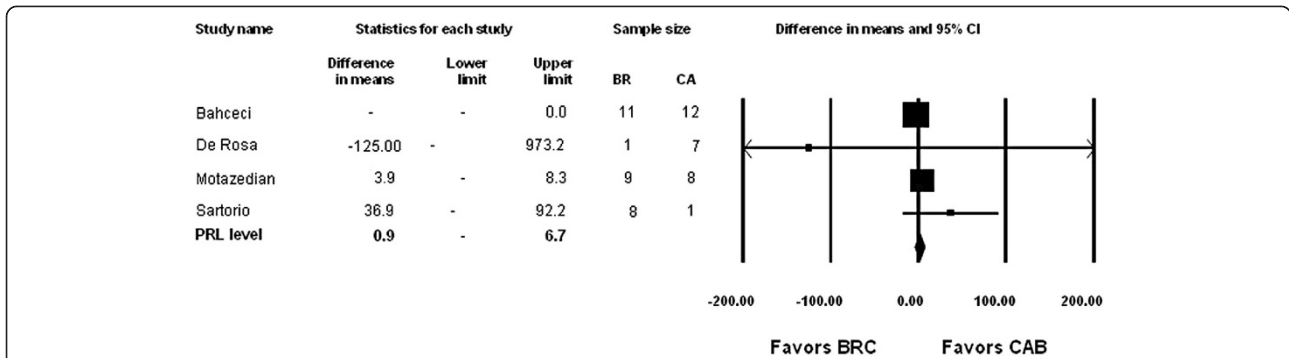


Figure 2 Bromocriptine vs. Cabergoline: prolactin levels.

dopamine agonists to no treatment. Dopamine agonists significantly reduced prolactin level (WMD, -45; 95% CI, -77 to -11) and the risk of persistent hyperprolactinemia (RR, 0.9; 95% CI, 0.81 to 0.99) but not other patient-important outcomes (Additional file 1: Figures 2A and 2B).

- Comparison of dopamine agonists vs. surgery and combinations thereof: Additional file 1: Figures 3-5B depict comparisons between surgery vs. dopamine agonists, dopamine agonists vs. dopamine agonists + surgery, and surgery vs. surgery + dopamine agonists. The only significant

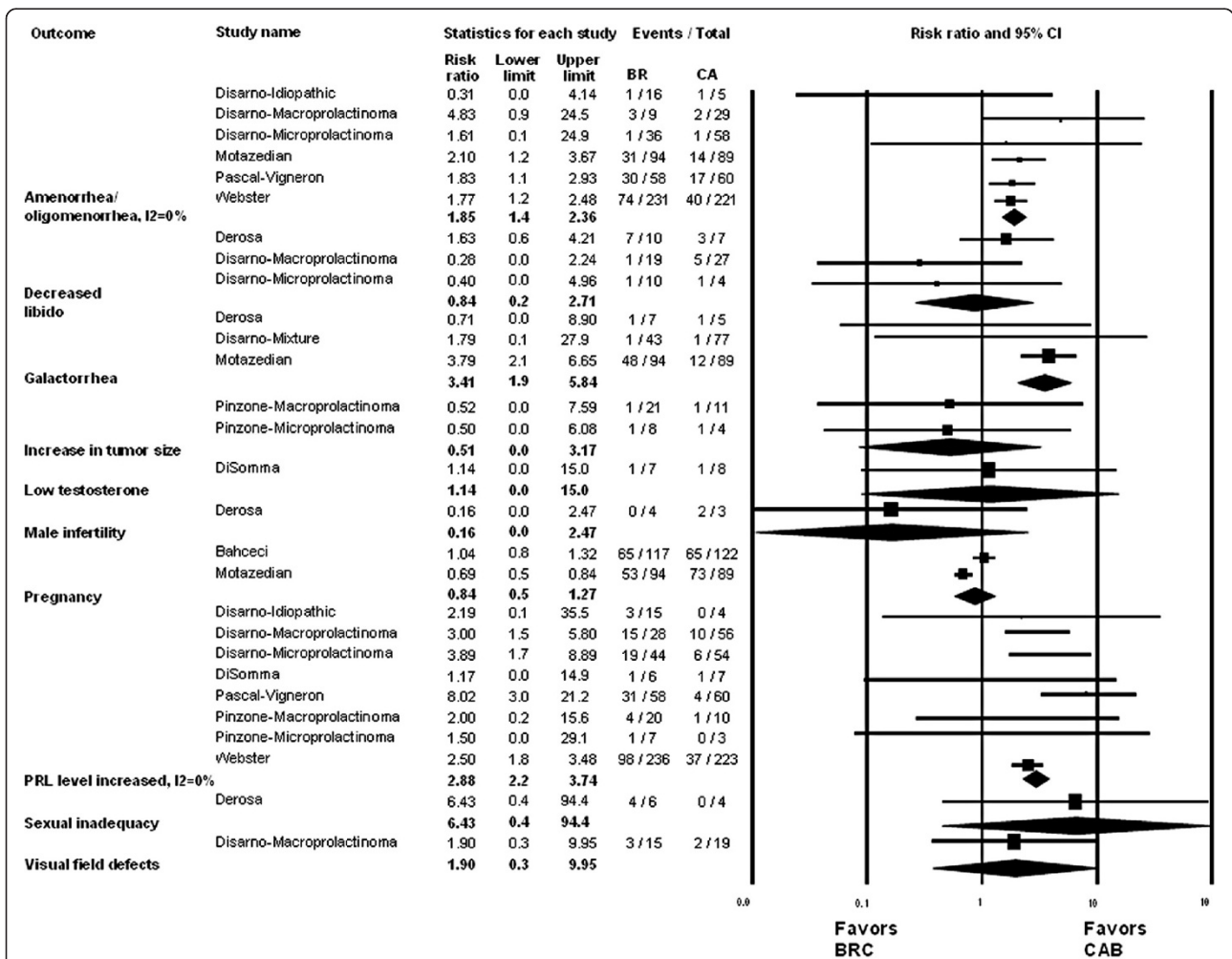


Figure 3 Bromocriptine vs. Cabergoline: clinical outcomes.

difference among these comparisons was dopamine agonists were more effective in reducing the risk of persistent hyperprolactinemia compared to surgery alone.

The quality of evidence in this comparison for all outcomes is very low due to methodological limitations of included studies and the serious imprecision of meta-analytic estimates that include both trivial and large effects. Subgroup analyses for these comparisons (Additional file 1: Table 6) did not reveal a significant interaction based on sex or tumor size (macro- vs. microprolactinoma).

#### **Patients treated with other modalities**

Other treatments, such as radiotherapy, surgery and combinations of treatments were evaluated in an uncontrolled series of patients. Meta-analysis was not conducted due to the significant clinical heterogeneity in terms of patient characteristics and symptomatology as well as the heterogeneity of study settings, design and follow-up duration.

Radiotherapy was evaluated in eight studies with follow-up of at least two years. In patients with medically and surgically refractory prolactinomas, radiotherapy produced a reduction in prolactin levels in nearly all patients and normalization in over a quarter of patients with low complication rates (Additional file 1: Table 7A). External and implanted radiotherapy methods were also used in conjunction with dopamine agonists and resulted in significant improvement in prolactin levels, visual symptoms and fertility (four studies with follow-up of between 12 and 140 months, Additional file 1: Table 7B).

Trans-sphenoidal surgery for pituitary adenomas was evaluated in 27 uncontrolled studies (Additional file 1: Table 7C) and was found to be effective in normalizing prolactin levels and resolving symptoms. Patients opting for this approach had often failed other management options and may have had a worse prognosis that was independent of the treatment; this selection bias may underestimate the effectiveness of surgery. In five studies, a combination of surgery and dopamine agonists achieved high rates of prolactin normalization and had relatively low rates of recurrence (Additional file 1: Table 7D). In two studies (Additional file 1: Table 7E), surgery combined with radiotherapy was also seen to be effective.

#### **Adverse effects**

Commonly reported side effects for all dopamine agonists included nausea, dizziness, postural hypotension and headache. In studies comparing cabergoline and bromocriptine, side effects were less frequent and milder

with cabergoline compared to bromocriptine. In one study, 18%, 18%, 9% and 3% of patients experienced nausea, hypotension, headache and vomiting, respectively, compared with 44%, 21%, 27% and 20% in patients receiving bromocriptine [Motazedian, 2010, #105]. Bahceci found an overall side effect rate of 2.5% for cabergoline versus 15.3% for bromocriptine [Bahceci, 2010, #103]. Another study found a 29% overall side effect rate for cabergoline vs. 70% with bromocriptine, and that cabergoline side effects were more mild, self-limited, and did not require intervention, compared to bromocriptine side effects which required dose reduction and intervention in 29% of cases [De Rosa, 1998, #104]. Non-comparative studies revealed similar findings with the most common side effects of dopamine agonists being nausea, vomiting, headache, hypotension, with rare side effects of rhinorrhea and hypotonia. Adverse effects reported with transsphenoidal surgery included cerebrospinal fluid leak, diabetes insipidus, rhinorrhea and hypopituitarism, while radiotherapy was associated with nausea, headache, visual disturbances and hearing loss.

#### **Pregnancy studies**

Twenty studies followed pregnant women and their offspring from 6 months up to 12 years (Additional file 1: Table 7F). A fairly consistent finding was that there was no significant increase in the risk of obstetric complications, miscarriages, fetal malformation or other pregnancy outcomes, even if they had been treated with dopamine agonists to induce ovulation. The quality of this evidence is low considering the lack of contemporary untreated control groups in most studies or the enrollment of nonconsecutive samples of patients.

#### **Discussion**

The two most commonly prescribed drugs in the treatment of hyperprolactinemia are bromocriptine and cabergoline. Both medications are dopamine receptor agonists and share many characteristics and adverse effects, such as headache, nausea and vomiting, among others, though frequency and severity of adverse effects appears to be less in cabergoline compared to bromocriptine. Previous concerns about valvular heart disease [15,16] with the use of these agents have largely been disproved by more recent reports [17-19]. Our review demonstrated that cabergoline was significantly better than bromocriptine in decreasing the risks of persistent hyperprolactinemia, amenorrhea/oligomenorrhea and galactorrhea. Frequency of dosing may also affect treatment decisions as cabergoline is dosed twice weekly, whereas bromocriptine is given daily. However, cabergoline costs at least twice as much as bromocriptine and was not found to be superior in other outcomes. Though both drugs have been found to be safe in pregnancy, the

number of reports studying bromocriptine in pregnancy far exceeds that of cabergoline in pregnancy.

A large body of moderate quality evidence from observational studies supports the use of dopamine agonists to normalize prolactin levels and resolve the symptoms related to mass effect and elevated prolactin levels. The large treatment effect of dopamine agonists, the potential dose response effect, biological plausibility, temporality between treatment and effect, consistency across studies, settings and methods, and coherence (consistency across agents within the same class), strongly support the effectiveness of these treatment agents in reducing prolactin levels and improving symptoms [20]. In addition, the recurrence of hyperprolactinemia after withdrawal of dopamine agonists strengthens the inference about causality (that is, challenge-rechallenge phenomenon). Clinicians using these medications are well aware of potential adverse effects that sometimes limit use, which include nausea, vomiting, psychosis and dyskinesia, among others.

Efficacy of surgery and radiotherapy in selected patients is also substantiated, although by low-to-moderate quality evidence at higher risk of bias. Radiotherapy and surgery appear to be efficacious in patients with resistance or intolerance to dopamine agonists. However, surgery as a primary therapy has also been described in a recent consecutive series of 212 patients with prolactinomas [21]. This study reports high short-term remission rates, particularly in patients with microadenomas and cystic tumors. Besides the usual surgical risks, hypopituitarism is a potential long-term effect of both radiotherapy and surgery and should be discussed with patients as part of the decision-making process.

### Comparison with previous reviews, strengths and limitations

Only a few previous systematic reviews have been published in this field, and to the best of our knowledge, this is the first to comprehensively address the efficacy questions outlined in our protocol. Our work is also referenced as unpublished data in the 2011 Endocrine Society Clinical Practice Guideline: Diagnosis and Treatment of Hyperprolactinemia [22]. Our results are similar to other reviews, including Dekkers' meta-analysis of the sustainability of normoprolactinemia after treatment withdrawal, which found recurrences in a substantial proportion of patients [23], and Dos Santos Nunes' systematic review and meta-analysis of four randomized controlled trials, which demonstrated that normalization of prolactin levels and menstruation favored cabergoline compared to bromocriptine [24].

The strengths of our review include the comprehensive nature of the literature search, the immediate relevancy of the questions at hand to decision making, and

the adoption of bias protection measures that included contacting the authors of the included studies. Limitations to the inferences presented in this report relate to the overall low quality of evidence due to the methodological limitations of the included studies, and by the imprecision and heterogeneity in the results. Also, this evidence is at high risk of publication and reporting biases, both of which are more likely when the evidence consists of mostly small RCTs and observational studies. Inferences should also be limited considering the frequent use of the surrogate outcome, prolactin level, as opposed to patient-important outcomes [25], such as loss of quality of life due to tumor-related and hypogonadal symptoms.

### Conclusion

This systematic review and meta-analyses affirm the use of dopamine agonists in treating hyperprolactinemia and reducing associated morbidity. Cabergoline was found to be more effective than bromocriptine in achieving normoprolactinemia and resolving amenorrhea/oligomenorrhea and galactorrhea. Radiotherapy and surgery are efficacious in patients with resistance or intolerance to dopamine agonists.

### Additional file

**Additional file 1: Appendix.** Treatment of hyperprolactinemia: a systematic review and meta-analysis. Description of data: Contents: Baseline characteristics of the included comparative studies (Supplemental Table 1), Quality of the included observational comparative studies (Supplemental Table 2), Quality of the included observational dopamine withdrawal studies (Supplemental Table 3), Quality of randomized trials (Supplemental Table 4), Summary of uncontrolled studies of dopamine agonists (Supplemental Tables 5A-E), Meta-analyses figures (Supplemental Figures 1A-5B), Subgroup analyses (Supplemental Tables 6A-D), Summary of uncontrolled studies of radiotherapy, surgery, combinations of treatment, and pregnancy (Supplemental Tables 7A-F), References, Search strategy [26-205].

### Abbreviations

PRISMA: Preferred reporting items for systematic reviews and meta-analyses; RCT: Randomized controlled trial; RR: Relative risk; WMD: Weighted mean difference.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

ATW, PJE, GYG, VMM and MHM were responsible for the study's conception and design. ATW, RJM, MAL, AH, CP, NWG, MMF, AB, FC, JC, TAE and, PJE acquired the data. ATW, RJM, MAL, TAE and MHM analyzed and interpreted the data. All the authors were responsible for drafting, critical revisions, and final approval of the manuscript.

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