Author's response to reviews

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

Authors:

Amy T Wang (wang.amy@mayo.edu)
Rebecca J Mullan (mullan.rebecca@gmail.com)
Melanie A Lane (melanielane7@gmail.com)
Ahmad Hazem (adhazem@yahoo.com)
Chaithra Prasad (prasad.chaithra@mayo.edu)
Nicola W Gathaiya (gathaiya.nicola@mayo.edu)
M Merce Fernandez-Balsells (mercefernandez.girona.ics@gencat.cat)
Amy Bagatto (aimsjoy@gmail.com)
Fernando Coto-Yglesias (cotoyglesias@yahoo.com)
Jantey Carey (janteycarey@gmail.com)
Tarig A Elraiyah (elraiyah.tarig@mayo.edu)
Patricia J Erwin (erwin.patricia@mayo.edu)
Gunjan Y Gandhi (gandhi.gunjan@mayo.edu)
Victor M Montori (montori.victor@mayo.edu)
Mohammad H Murad (murad.mohammad@mayo.edu)

Version: 4 Date: 10 June 2012

Author's response to reviews: see over
Re: MS: 4948882576429296 - Treatment of hyperprolactinemia: a systematic review and meta-analysis

Dear Drs. Moher, Shekelle, and Stewart
Editors-in-Chief, Systematic Reviews

We appreciate receiving the comments from the review of our manuscript entitled “Treatment of hyperprolactinemia: a systematic review and meta-analysis.” We have responded to each of the items raised in the review, as presented below and in the revised manuscript. These comments have certainly improved the manuscript and we appreciate the opportunity to return it to you for consideration of publication.

Referee 1 Comments:

Wang et al. presented data on a systematic review and meta-analysis of different treatments of hyperprolactinemia. This was a huge work, rigorously performed. As expected, and in keeping with a large literature, dopamine agonists (DA) are affective, either on a clinical or biochemical ground, in the control of hyperprolactinemia. Even more, the Authors provided evidence that DA are the treatment of choice in hyperprolactinemic patients; on the other hand, pituitary adenomectomy and external radiotherapy may have a role in patients refractory to medical therapy.

I have only minor suggestions for this ms, which is well written in a logical sequence:

Referee 1 Request 1) Abstract: the conclusions are not fully supported by the data reported in the Results section of the Abstract;

Response: We agree that the conclusions stated in the abstract were not fully supported by the data reported in the abstract results. We have reworded this on page 2 to read: “in reducing prolactin levels and persistent hyperprolactinemia” from “in improving hyperprolactinemia and clinical outcomes of interest.”

Referee 1 Request 2) The aim of the study should be better stated; in the abstract the Authors stated that “we aimed to compare efficacy and adverse effects of medications, surgery, and radiotherapy in the treatment of hyperprolactinemia” whereas at the end of introduction the
Authors stated that they “evaluate the outcomes of treated hyperprolactinemia patients with regards to tumor growth and symptoms”.

Response: This point was also brought up in the Handling Editor’s 2nd comment which is copied below. We will respond to both of these comments together.

Handling Editor Request 2) There are several statements in the introduction and abstract that suggest various different objectives for this review. Please be clear and consistent in setting up and describing the review objectives. The third paragraph of the introduction refers to “this common therapeutic dilemma?”. This dilemma could refer to a couple different issues highlighted in the second paragraph: uncertainty about patient selection, and/or comparative effectiveness of the various treatment modalities. Please be more specific about these objectives. The patient selection issue, if this is indeed a focus of the paper, could be better synthesized in the results (see below).

Response: We changed the wording on page 3 from this common therapeutic dilemma to “these common therapeutic dilemmas” to reflect all the circumstances that the handling editor mentioned above.

??evaluate the outcomes of treated hyperprolactinemia patients with regards to tumor growth and symptoms? is quite a different objective than stated in the abstract (and, indeed, implied in the prior paragraph). Please reconcile these objectives.

Response: We agree that the objectives of the study need to be stated more clearly and consistently. We reworded the last paragraph of the Background on page 3 to reflect more detail and consistency with the objectives stated in the abstract. It now reads, “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.”

Handling Editor Requests:

1) Introduction, second paragraph, third sentence ? ??in these patients?? ? does this refer to refractory and intolerant patients, or all patients with macroadenoma? Please clarify.

Response: We agree that this is confusing. This was changed on page 3 from “these patients” to “patients with pituitary macroadenoma” for clarification.

2) Response: Answered above with Referee 1’s Request #2

3) Methods, end of first paragraph ? you refer to the GRADE framework, but I did not see a GRADE table, or, at the very least, a summary of evidence table. This may also help with consistency of terminology throughout the report ? at various points, evidence is described as “limited”, or “large body”, or “moderate quality”, but it is difficult to follow how you have arrived at these judgements.

Response: We opted to not present GRADE tables because it would require many tables for each comparison. The quality of the included observational comparative studies, the included observational dopamine withdrawal studies, and the included RCTs are included in the Appendix as Supplemental Figures 2, 3, and 4. We applied the GRADE criteria and found the evidence to be moderate to low. We describe the criteria in the discussion section on page 10, “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 (i.e.,
challenge-rechallenge phenomenon).”

4) **Methods, study selection, last sentence ? please clarify what you mean by ?sustainable
procedures? or delete this phrase.**

**Response:** This is meant to refer to paper-conserving environmentally friendly
procedures. This was deleted.

5) **Methods, statistical analysis ? some of these specifics re: RR and WMD could be
summarized in the figures themselves (and, indeed, this is already implied by the use of
?favors DA? vs ?favors no treatment?).**

**Response:** We agree. This paragraph was deleted from the manuscript text.

6) **Results ? the biggest gap in the manuscript as currently presented is the lack of adverse
effects information in the results section. Some of the tables do report a treatment was ?well-
tolerated?, but this is not enough. One of the seemingly key objectives of the review was to
compare efficacy and adverse effects of various treatments. Even if most studies did not report
adverse effects, it is important to highlight the lack of adverse event reporting. The second
paragraph of the discussion does discuss adverse effects, but none of this had been presented in
the results ? it would be important to present some summary data about the frequency of such
events. Please either add an ?adverse effects? paragraph to the results section, or include a
statement about adverse effects as pertinent to each of the treatment types.**

**Response:** We agree that adverse effects reporting is lacking. We added the following
paragraph to the results section on page 9.

**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 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 CSF leak,
diabetes insipidus, rhinorrhea, and hypopituitarism, while radiotherapy was associated
with nausea, headache, visual disturbances, and hearing loss.

7) **Discussion ? the first and third paragraphs cover much the same ground. Consider using the
third paragraph in place of the first. Also, as above, please clarify how the statements about
adverse effects specifically relate to the evidence base reviewed for this manuscript.**
Response: The first and third paragraphs of the discussion are now combined as represented on page 10. In addition, we clarified the discussion of the adverse events to relate to the evidence base for our review.

“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, and headache, 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 outnumbers 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 evidence about causality (i.e., 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.”

8) Please conduct an updated search and amend the manuscript accordingly.

Response: We recently updated the search in December 2011 upon the request of the editorial team of Systematic Reviews and only a few months have passed. We believe this review is quite current at the present time and we hope that you find this satisfactory without the need for a second update.

We sincerely hope that these revisions and responses will clarify and strengthen the manuscript to the satisfaction of the editorial team.

Respectfully,

Amy T. Wang, MD
Assistant Professor of Medicine
Mayo Clinic College of Medicine