July 30, 2014

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Editors-in-Chief
World Journal of Gastroenterology
e-Submission

Dear Editors-in-Chief:

My co-authors and I received a revise and resubmit decision on the manuscript, titled "Neuroendocrine Tumors Treated with High Dose Octreotide-LAR: A Systematic Literature Review" (Manuscript # 10318), submitted for publication in *World Journal of Gastroenterology*. We have addressed each comment raised by the three reviewers and made clarifications in the manuscript as requested. Our specific responses to the reviewers' comments are attached below. In response to the reviewers' comments, we have specified the sections for our corresponding revisions in the manuscript and quoted text where reviewers' comments were addressed. In the body of the manuscript, we have used track-changes and highlighted the edited and new text.

My co-authors and I would like to sincerely thank the *World Journal of Gastroenterology* Editors-In-Chief and reviewers for their review of our manuscript.

Thank you for your time and consideration. We look forward to your decision.

Sincerely,

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RESPONSE TO REVIEWERS

Manuscript number: #10318

Title: Neuroendocrine Tumors Treated with High Dose Octreotide-LAR: A Systematic Literature Review

REVIEWER 02528717

1. **[Reviewer Comment] However there are many repetitions in the paper. These repetitions must be excluded and also unnecessary detail (such as bevacizumab using and comparison in these cases) must be excluded.**

[Authors' response] We have eliminated repetitious and extraneous text throughout the paper and some text replicated in the tables. All of our changes are marked in track-changes and highlighted throughout the manuscript. These changes are reflected by the decreased word count of the edited manuscript form 3,180 (prior version) to 2,983 (current version, excluding new section on Strengths and Limitations). We have also significantly edited the tables to improve readability, with these changes reflected by decreased number of tables (from 6 to 4) and total number of words/characters in these tables from 3,827/21,715 (prior version) to 2,230/12,605 (current version).

Per this comment, we have also excluded the detail regarding "bevacizumab" in the 3rd paragraph of the Results Efficacy section:

"Koumarianou[15] studied efficacy of ~~temozolamide and bevacizumab in combination therapy with~~ octreotide-LAR (30 mg/3 weeks) combination therapy in 13 subjects with NETs."

REVIEWER 02528832

2. **[Reviewer Comment] The results are of interest, but, in a certain way they can only transmit what the authors properly state in the last sentence of the conclusion, i.e., the need for further studies.**

[Authors' response] This is the first comprehensive review and synthesis of global literature for clinical studies and real world evidence, published in peer-reviewed journals and is presented at professional congresses, on above-label use of SLAR in patients with NETs. However, as this reviewer suggested, this study also has limitations and future research is warranted.

We have reinforced this message (in addition to other new statements on future research) at the end of Strengths and Limitations section in the Discussion:

"Future research efforts should focus on establishing efficacy and safety of prescribing octreotide-LAR at doses higher than the FDA-approved 30mg/month for management of neuroendocrine tumors using generalizable randomized controlled trial study designs. "

We have also reinforced the Conclusion section:

"This review suggests that increased doses of octreotide-LAR are being used frequently for the management of NETs in clinical practice and excess toxicity has not been observed in the reviewed studies. In most cases, the use of high dose octreotide-LAR appears to be prescribed in patients with disease progression or uncontrolled symptoms while on standard dose therapy. Expert clinical opinion, as reported in this review, supports escalation of SSAs for patients with refractory hormonal symptoms. However, the given limited published information on this topic, the safety and efficacy of above label dose and/or frequency of octreotide-LAR in treatment of NETs warrants further evaluation."

REVIEWER 02854566

3. **[Reviewer Comment] The tables should be shortened to improve readability. The results are now difficult to interpret.**

[Authors' response] We have dramatically shortened and clarified the tables to improve readability. Specifically, original Tables 1-3 were combined into a single Table 1. There are now only 4 tables instead of former 6 in total. These changes are reflected by decreased total number of words/characters in these tables from 3,827/21,715 (prior version) to 2,230/12,605 (current version).

4. **[Reviewer Comment] The conclusion of the manuscript is based on expert opinion. Although efficacy and safety data is heterogeneous, the authors should try to form their own expert opinion based on the efficacy and safety data retrieved from the individual studies. This would add value to the manuscript.**

[Authors' response] We have provided our expert interpretation of the data abstracted in this literature review in the Results and Discussion sections:

- End of the Results Efficacy section:
  "Considering these studies together, there is a trend supporting the use of octreotide-LAR at beyond the standard label doses to control symptoms and tumor progression."
- End of the Results Safety section:
  "Overall, our review shows that adverse events were not well described. This may be because octreotide-LAR has a favorable safety profile and that modest increases in the dose may not lead to significant increases in toxicity, or because the studies were too small to identify rare events."
- End of the Results Expert Clinical Opinion section:
  "Overall, our review indicated that clinical experts support dose escalation of octreotide-LAR."
- 1st paragraph of the Discussion section:
  "There is a general trend supporting the use of high dose octreotide-LAR for control of symptoms and limited data supporting the use of high-dose octreotide for control of tumor progression in patients with NETs. There were no published data identified suggesting increased toxicity of octreotide-LAR at above FDA-approved dosage and frequency of

administration. The lack of data may imply that there is no significant toxicity, which is consistent with reports of higher doses used in acromegaly without significant toxicity[22], or that the studies were too small to identify uncommon adverse events."

- 3rd paragraph of the Discussion section:

  "Our review of 4 articles and 4 abstracts, evaluating over 222 patients[11,12,14-17,19,22], found no evidence of increased toxicity associated with doses of octreotide-LAR >30 mg/month. None of the studies included in this review reported significant toxicity, although these studies did not report power analyses or a priori calculations of sample size."

- Conclusions section in the Discussion:

  "This review suggests that increased doses of octreotide-LAR are being used frequently for the management of NETs in clinical practice and excess toxicity has not been observed in the reviewed studies. In most cases, the use of high dose octreotide-LAR appears to be prescribed in patients with disease progression or uncontrolled symptoms while on standard dose therapy. Expert clinical opinion, as reported in this review, supports escalation of SSAs for patients with refractory hormonal symptoms. However, the given limited published information on this topic, the safety and efficacy of above label dose and/or frequency of octreotide-LAR in treatment of NETs warrants further evaluation."

5. **[Reviewer Comment] The manuscript would improve by adding literature on efficacy and safety of octreotide-LAR in patients treated with doses < 30 mg/months. This would provide more insight if a higher dose is indeed equally effective or safe. Furthermore, patients who receive dose-escalation due to refractory symptoms should be separated from patients who receive an initial dose of > 30 mg/month, because it is harder for these patients to achieve treatment success.**

[Authors' response] We agree that the manuscript would be more comprehensive if we had also included data on use of octreotide-LAR in patients treated with doses <30 mg/months. However, the aim of our study was specifically to review literature on efficacy and safety of octreotide-LAR used at doses higher than the FDA-approved 30mg/month for treatment of NETs, and so the before mentioned objective was not in the scope of the current study. In response to this comment, we have included the following statements in the Discussion section.

- At the end of the 2nd paragraph in the Discussion section:

  "In most studies, higher octreotide-LAR doses were used as rescue or salvage therapy, and it may be that response rates would be higher in treatment-naïve patients."
- At the end of the new Strengths and Limitations section in the Discussion:

  "Studies comparing the safety of octreotide-LAR in patients treated with doses <30 mg/months versus those treated with above-label regimens of octreotide-LAR are also warranted."

The FDA label prescribing information advises to initiate octreotide-LAR at 20 mg every 4 weeks and increase octreotide-LAR up to 30 mg every 4 weeks if symptoms in patients with carcinoid tumors or VIPomas are not adequately controlled (www.FDA.gov). Hence, our review focused on understanding the treatment of patients with uncontrolled symptoms of NETs receiving increased doses of octreotide-LAR above the FDA-approved doses/frequencies of administration. Thus, we did not intend to specifically review studies for patients who were initially started on doses >30 mg/4 weeks because of the prescribing instructions in the FDA label (noted above) and because cases that were initiated at above-FDA label doses/frequencies of octreotide-LAR would be very uncommon.

6. [Reviewer Comment] The authors should include a primary outcome for the study. Which efficacy outcome was most important?

[Authors' response] Considering the variability of study designs and data reported, as seen in the included studies, we abstracted multiple measures of the outcome of interest—efficacy—without selecting a primary outcome for the study. The multiple measures of efficacy, defined based on expert clinical opinion, are symptoms, disease markers, and tumor progression. The efficacy and safety measures abstracted in this review are described in the Outcome Measures section of Materials and Methods and in Tables 1-3:

> "The outcomes of interest included reports of efficacy/effectiveness and safety surrounding the use of octreotide-LAR at doses higher than 30 mg or administered at a frequency greater than 4 weeks. We also reviewed expert clinical opinion statements surrounding the use of above-label use of octreotide-LAR. Measures of efficacy included symptom burden, disease markers, tumor response, time to progression of disease, requirements for additional intervention, and survival. Measures of safety included frequency of various adverse effects."

7. **[Reviewer Comment] Because co-therapy can affect efficacy and safety results, the results of these studies should be reported separately from the studies that evaluated octreotide-LAR monotherapy.**

[Authors' response] We agree it would be very informative to assess efficacy and safety results separately among patients treated with co-therapy versus octreotide-LAR monotherapy. However, given our current review, available published data are limited, making it difficult to examine the research question proposed by this reviewer. In response to this comment, we have included the following statement at the end of the new Strengths and Limitations section in the Discussion:

> "Finally, in this study, we were unable to assess separately the effects of octreotide-LAR co-therapy versus monotherapy on safety and efficacy outcomes given the limited data for co-therapy in this review."

8. **[Reviewer Comment] Why did the authors exclude case reports, but included letters to the editor? There is a large chance of selection bias in both study types.**

[Authors' response] Although both case reports and letters-to-editor (which represent expert clinical opinion) have the lowest Oxford's Centre for Evidence-based Medicine Levels of Evidence (OCEBM)grades, we only excluded case reports from our review but retained letters to editors. This study design for our literature review was determined after careful consideration and discussion among the co-authors and consultation with experts.

This was determined because our aim was to summarize the data on efficacy and safety associated with above label octreotide-LAR use in a patient *population* with NETs. To assess a patient population, data should come from studies that report results in patient samples instead of case reports, which report data on ≤3 patients and present data that are not generalizable.

Conversely, expert clinical opinion statements, such as those published in letters-to-editor, are typically produced by treating physicians based on interpretation of published population-based data and on personal experience in their daily clinical practice. Hence, we determined it was crucial to represent expert clinical opinion in our review.

In response to this comment, we have included the following clarification in the Materials and Methods Screening and Selection Criteria section:

> "In phase three, an article was excluded if an outcome of interest (efficacy, safety, and/or expert clinical opinion) was not reported or if the article was a case report, since case reports present data on too few patients to be able to draw any generalizable conclusions."

9. **[Reviewer Comment] The discussion would improve by adding a limitation section. Parts of the results can be used for this (see minor comment 3)**

[Authors' response] We have included an extensive Strengths and Limitation section at the end of the Discussion. At the end of this section, we have also included a comprehensive discussion on future research by describing a need to fulfill specific objectives.

10. **[Reviewer Comment] Studies containing the same patients as other studies should be excluded (Woltering 2005 & 2006).**

[Authors' response] We have excluded Woltering 2005 and retained the more relevant (i.e., since it contains data on outcomes of interest) and recent: Woltering 2006. The manuscript has been updated accordingly in the text, references, figure, and tables. Changes to the manuscript include the addition of the following statement in the Results Search and Screening section:

> "During abstraction, it was determined that 2 of the 10 included articles reported data on the same patients, hence only the most relevant and recent of the two study (Woltering 2006), which reported data on outcomes of interest, was retained in this review."

Study deleted from this review:

> **Woltering EA**, Mamikunian PM, Zietz S, Krutzik SR, Go VL, Vinik AI, Vinik E, O'Dorisio TM, Mamikunian G. Effect of octreotide LAR dose and weight on octreotide blood levels in patients with neuroendocrine tumors. *Pancreas* 2005 Nov; **31**(4): 392-400 [PMID: 16258376]

Study retained in this review:

Woltering EA, Hilton RS, Zolfoghary CM, Thomson J, Zietz S, Go VL, Vinik AI, Vinik E, O'Dorisio TM, Mamikunian G. Validation of serum versus plasma measurements of chromogranin a levels in patients with carcinoid tumors: lack of correlation between absolute chromogranin a levels and symptom frequency. *Pancreas* 2006; **33**(3): 250-364. [PMID: 17003646 DOI: 10.1097/01.mpa.0000235302.73615.d4]

11. **[Reviewer Comment] Why did the authors limit their search to articles published after 1998? In addition, why did the authors have different search limits for publishing year in pubmed (1998) and conference abstracts (2000)**

[Authors' response] The search year limit of "1998" was imposed based on octreotide acetate long acting repeatable (Sandostatin® LAR; Novartis Pharmaceutical Company, East Hanover, NJ, USA) original approval date of November 25, 1998 (source: Sandostatin® LAR Depot [prescribing information]; www.accessdata.fda.gov/). We've clarified this in the Materials and Methods Data Sources and Search Strategy section:

"The search year limit of "1998" was imposed based on octreotide acetate LAR (Sandostatin LAR) original approval date (www.accessdata.fda.gov/)."

To streamline the search, screening, review, and abstraction processes in this review, we assumed that data are typically presented at conferences first and then published in full-length articles, with about a 2 year transition between the two. Hence, although we included abstracts starting in "2000," we should have captured all relevant studies that were presented earlier at conferences in our full-article search. There was no need to search conferences starting with "1998" since only unique studies (preferably as full-length articles) were included in this review. If a conference abstract was later published as a full-length article, we retained the article in this review and not the abstract.

12. **[Reviewer Comment] Methods (paragraph quality assurance): What is meant by "sufficiently high" interrater reliability? Did the authors use specific cut-off values for the weighted kappa?**

[Authors' response] We have assessed our kappa value of "0.94" as "sufficiently high" inter-rater reliability based on a standard interpretation of Kappa values as described in reference #6 (Viera & Garrett. *Fam Med*. 2005) in this manuscript:

"Kappa Agreement:

<0	Less than chance agreement
0.01–0.20	Slight agreement
0.21– 0.40	Fair agreement
0.41–0.60	Moderate agreement
0.61–0.80	Substantial agreement
0.81–0.99	Almost perfect agreement"

We have now made sure reference #6 (Anthony & Garrett. *Family Medicine*. 2005) is being cited in the manuscript text whenever kappa is being discussed. Specifically, we have also included the following statements:

- In Materials and Methods Quality Assurance section:

  "The weighted Kappa inter-rater reliability was calculated between the two reviewers at the screening phase using an independently-screened sample of articles, considering that a Kappa value ranging from 0.81 to 0.99 is interpreted to indicate "almost perfect agreement"[6]. After determining that the inter-rater reliability was high (i.e., >0.81)[6], the remaining articles were divided between the two reviewers."

13. **[Reviewer Comment] The efficacy paragraph in the results section should be divided in subheadings according to different efficacy outcomes to improve readability.**

[Authors' response] Per reviewer # 02528717 (comment #1 above), we have edited the manuscript, including the Results Efficacy section, to contain fewer repetitions to improve readability. The most efficient way to organize the discussion of included articles in each section was to fully present each relevant study at one time instead of repeating the study when certain outcomes are being presented. This way, the Efficacy Results section is at it shortest form, given there were only 10 articles that presented some data on efficacy outcomes (per Table 2) with 5 on symptoms, 3 on disease markers, and 8 on tumor response/disease progression. As described in the Strengths and Limitations sections:

"The studies included in this review varied in design, patient population, octreotide-LAR regimens, and definitions of outcomes, and the data were reported in several ways across the reviewed studies. Thus, the heterogeneity of these data made it difficult to compare directly between studies and prevented us from conducting a meta-analysis"

Considering comments of all three reviewers, we hope our changes have greatly improved the readability and flow of the manuscript.

14. **[Reviewer Comment] Large sections of the results can be moved to the discussion. For example, the last paragraph of the efficacy paragraph in the results, which describes the limitations of the included studies.**

[Authors' response] We moved this paragraph to the new Strengths and Limitations section in the Discussion.