Date: Aug 09, 2018
To: "Gayatri Devi" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1258

RE: Manuscript Number ONG-18-1258

Menopause Related Cognitive Impairment

Dear Dr. Devi:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 30, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

This is a well written article reviewing menopause related cognitive impairment while highlighting two examples. I learned a lot reading this submission and agree that the broader implications of misdiagnosis can be devastating. I actually think this submission would be better suited as a review article on menopause related cognitive impairment. Although most gynecologists are familiar with women's complaints of memory loss and cognitive decline, I would venture to say that they do not know the detail provided in this review and the specific nature of the decline reported in the literature. Case reports in general are very unusual or rare cases and cognitive decline related to the menopause is neither.

1. While I appreciate the quote by Tilt, you can shorten it and still convey the same meaning.

2. In Line 196, I don't understand this sentence "In women who are not selected for any cognitive complaints, treatment with HT has found no effect on cognition."

3. Both of the examples that you give are women with mental illness on medication, how does that affect menopausal cognitive decline and perhaps confound your conclusion?

REVIEWER #2:

This is a VERY important topic for women's health care providers to understand- both the changes at menopause and age that affect memory and concentration, what we know about role of hormone therapy at menopause compared to later initiation and when should providers be concerned about dementia or Alzheimers.

Introduction

1. Would expand the section on issues at midlife and menopause that might affect memory including family and work stressors, aging parents, depression, grief, sleep disorders

2. Would differentiate between increased risk of dementia with early menopause, particularly early surgical menopause, and role of hormone therapy and then discuss difference between hormone therapy given at menopause and later in menopause.

3. Case 1- Her family history was not contributory- suggest specifically mention no early dementia or Alzheimer's

Discussion

4. Consider suggesting administration of a brief test of episodic memory such as a list of words or a name and address for later recall. The Mini-mental State Examination is of modest value if mild impairments and no functional decline.

5. When should providers worry? Are cognitive problems interfering with job performance, financial affairs, or social activities? Is there a family member or other informant who can provide feedback?

6. What recommendations could be given to improve women's memory-physical activity, mental activity, and social engagement? Henderson VW. Menopause, cognitive ageing and dementia: practice implications.

7. Please update the North American Menopause Position as NAMS released updated position statement on hormone therapy in 2017 (see below for summary of executive statement)
A summary statement such as: In 2017 in their Position Statement on Hormone Therapy, the North American Menopause Society found that estrogen therapy may have positive cognitive benefits when initiated immediately after early surgical menopause, but HT in the early natural postmenopause period has neutral effects on current cognitive function. Only limited support (observational studies) is available for a critical window hypothesis of HT in Alzheimer disease prevention. In the absence of more definitive findings, HT cannot be recommended at any age to prevent or treat a decline in cognitive function or dementia.

NAMS would agree that hormone therapy improves hot flashes, night sweats, sleep disruption which may improve memory or concentration.

Society. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. Menopause. 2017 Jul;24(7):728-753.

8. Many more excellent references

Henderson VW, St John JA, Hodis HN, et al. Cognitive effects of estradiol after menopause: a randomized trial of the timing hypothesis. Neurology 2016;87:699-708.

Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology 1992;17:485-495.

Espeland MA, Shumaker SA, Leng I, et al; WHIMSY Study Group. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. JAMA Intern Med 2013:1429-1436.

Shao H, Breitner JC, Whitmer RA, et al; Cache County Investigators. Hormone therapy and Alzheimer disease dementia: new findings from the Cache County Study. Neurology 2012;79:1846-1852.

Imtiaz B, Tuppurainen M, Rikkonen T, et al. Postmenopausal hormone therapy and Alzheimer disease: a prospective cohort study [published online ahead of print February 15, 2017]. Neurology.

Coker LH, Espeland MA, Hogan PE, et al; WHIMS-MRI Study Group. Change in brain and lesion volumes after CEE therapies: the WHIMS-MRI studies. Neurology 2014;82:427-434.
Herrera AY, Hodis HN, Mack WJ, Mather M Estradiol Therapy After Menopause Mitigates Effects of Stress on Cortisol and Working Memory. J Clin Endocrinol Metab. 2017 Dec 1;102(12):4457-4466.

9. Table 1 - Please correct: Laboratory evidence of perimenopause and menopause, such as high LH or reduced estradiol, but is not necessary for diagnosis. - Actually it is elevated FSH that makes the diagnosis of menopause, not LH

Executive summary 2017 NAMS HT PS - section on mood and cognition

In the absence of more definitive findings, HT cannot be recommended at any age to prevent or treat a decline in cognitive function or dementia.

On the basis of the WHI Memory Study, caution should be taken in initiating continuous- combined daily CEE + MPA in women aged older than 65 years, given the relatively small or infrequent increase in risk for dementia of an extra 23 cases per 10,000 person-years seen in the WHI.

Estrogen therapy may have positive cognitive benefits when initiated immediately after early surgical menopause, but HT in the early natural postmenopause period has neutral effects on current cognitive function.

Only limited support (observational studies) is available for a critical window hypothesis of HT in Alzheimer disease prevention.

The effect of HT may be modified by baseline cognitive function, with more favorable effects in women with normal

cognitive function before HT initiation.

REVIEWER #3:

This case report highlights an important topic. Several limitations preclude publishing as is. The following should be considered.

1) Introduction. Paragraph 1: Memory impairment related to Lyme disease is incredibly rare as documented by IOM. See . Halperin J. Common Miscomceptions about Lyme Disease. The American Journal of Medicine Volume 126, Issue 3, March 2013. Consider a different example of a chronic infection resulting in cognition impairment.

2) Introduction Last paragraph. The acronym MeRCI is not well accepted. Either reference this or use the more accepted term, Menopause Cognitive Impairment (MCI).

3) Case 1 and Case 2, depression has been well-described as a risk factor for cognitive impairment with menopause (Reference WHI). This should be acknowledged in the discussion and referenced appropriately.

4) Vivelle dot does not come as a 0.25 mg dose. I presume the author meant 0.025 mg.

5) Case 2, the example of refusing to change soiled clothing has nothing to do with verbal memory, episodic memory, list learning or verbal fluency suggested to be associated with menopause. This should be removed along with any reference to impaired judgement..

6) Discussion, paragraph 2, last sentence please change the position of the references and add the words "may ALSO" as follows, "Estrogen may help maintain health of the cardiovascular system [30-32] which MAY ALSO indirectly promote brain health."

7) Ref 33 is old (2000) and predates WHI. Please replace with more recent reference that is evidence based.

8) Discussion, paragraph 5, second sentence, "That such an entity exists is indisputable, given the numerous studies to date in the area. Give references.

9) Discussion, paragraph 5, 3rd sentence, "HT should alleviate symptoms in at least some women" is not scientifically based. See Hendrickson V, Progesterone and Human Cognition, Climacteric, 2018 for a recent manuscript on the issue of progesterone or estradiol plus progesterone and the treatment of cognitive impairment. In general, the author should temper his enthusiasm for treatment of cognitive difficulties at menopause with HT and reference his statements.

10) Discussion, paragraph 6, 2nd sentence is an overstatement. Data is certainly not altogether consistent in the finding of objective changes in cognition at menopause. Ref 15 Weber and Maki provide a nice review that the author cites, with a more tempered interpretation of the data on cognition at menopause. Do not overstate the conclusions of those you have referenced.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
   1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
   2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

3. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com

/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Case Reports should not exceed 8 typed, double-spaced pages (2,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

5. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your signature on the journal's author agreement form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

6. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

7. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

8. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Case Reports, 125 words. Please provide a word count.

9. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com /ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

10. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

11. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

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If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors, that each author has given approval to the final form of the revision, and that the agreement form signed by each author and submitted with the initial version remains valid.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 30, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

If you would like your personal information to be removed from the database, please contact the publication office.

August 25, 2018

Nancy C. Chescheir, MD, Editor-in-Chief,

Journal of the American College of Obstetrics and Gynecology

RE: Manuscript Number ONG-18-1258 “Menopause Related Cognitive Impairment.”

Dear Dr. Chescheir,

Thank you for giving me the opportunity to revise and resubmit this article for consideration for publication in your journal. The feedback from the reviewers was excellent and I very much enjoyed addressing their suggestions, both in the body of the article wherever possible, and in the response to comments. Thanks to the comments, I believe the paper much improved and more informative.

I have tracked all changes to the article.

The following overall changes were made in accordance with guidelines from the editors’ desk:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.

2: A signed transparency page is now uploaded.

5. There was no financial support for this article. No part of this was presented elsewhere.

A single sentence précis of 25 words has been provided on the second page, for use in the Table of Contents.

The total word count, excluding abstract (118 words) and precis (25 words) and references (67 numbers in body of article), and including table (82 words), is 1992 words.

In addition, throughout the paper, words were clarified or condensed, to keep within word limit guidelines while incorporating changes suggested by the reviewers. In addition, all drug names were changed to generic.

Responses follow the individual reviewer comments below.

REVIEWER #1:

This is a well written article reviewing menopause related cognitive impairment while highlighting two examples. I learned a lot reading this submission and agree that the broader implications of misdiagnosis can be devastating. I actually think this submission would be better suited as a review article on menopause related cognitive impairment.

Although most gynecologists are familiar with women's complaints of memory loss and cognitive decline, I would venture to say that they do not know the detail provided in this review and the specific nature of the decline reported in the literature. Case reports in general are very unusual or rare cases and cognitive decline related to the menopause is neither.

Thank you, inquired into changing article type. Submitting a review would require a withdrawal of present article, and resubmission, so have opted to expand the discussion, while maintaining word limit within the case report guidelines.

1. While I appreciate the quote by Tilt, you can shorten it and still convey the same meaning.

Agree and shortened further, could probably shorten it even more, but found it impressive that 150 years ago, women's complaints were almost verbatim what they are today. In addition, Tilt's monograph is impressive and would like to increase awareness of his work.

2. In Line 196, I don't understand this sentence "In women who are not selected for any cognitive complaints, treatment with HT has found no effect on cognition."

This is clarified now to state, "There was no change in carefully chosen objective cognitive and mood measures after four years, although the women were not queried as to preexistence of subjective cognitive complaints."

3. Both of the examples that you give are women with mental illness on medication, how does that affect menopausal cognitive decline and perhaps confound your conclusion?

This is an excellent point, and is now addressed in the discussion, as follows: "While both women suffered from chronic depression, a known risk factor for cognitive loss in menopause [12], and were on medications that could affect their cognition, their psychiatric symptoms and medications were stable throughout this period. Ms. H's behavioral symptoms, involving executive dysfunction, with poor insight, irritability, and impaired judgment, could represent psychiatric illness. However, she had no exacerbation of her depression, and never exhibited behavioral symptoms in the past. Impairment of executive function may be seen with MeRCI [17] [2] [3]."

REVIEWER #2:

This is a VERY important topic for women's health care providers to understand- both the changes at menopause and age that affect memory and concentration, what we know about role of hormone therapy at menopause compared to later initiation and when should providers be concerned about dementia or Alzheimers.

Thank you so very much for this gracious feedback and particularly, the thoughtful inclusion of references, and numerous overarching suggestions.

Introduction

1. Would expand the section on issues at midlife and menopause that might affect memory including family and work stressors, aging parents, depression, grief, sleep disorders.

Because of the word limitations of this article type, unable to address some of these important points at length. Arguably, both men and women deal with family and work stressors and aging parents (the so-called sandwich generation), although, as with depression, women bear a disproportionate burden of the tasks of caregiving and resultant health effects. I have added sleep deprivation to the list.

"These cognitive disturbances persist despite controlling for concomitant symptoms such as hot flashes- with associated sleep deprivation, depression, and anxiety, and mimic the deficits seen early in Alzheimer's disease [10]."

2. Would differentiate between increased risk of dementia with early menopause, particularly early surgical menopause, and role of hormone therapy and then discuss difference between hormone therapy given at menopause and later in menopause.

The issues concerning the use of hormones for preventive and remote effects is not discussed in this article, and this now made clear in the discussion.

"This discussion focuses on the identification and treatment of cognitive changes during the menopausal transition, as illustrated by these cases, and not on the association between menopause, HT, and future risk for cognitive impairment and Alzheimer's and other dementia."

3. Case 1- Her family history was not contributory- suggest specifically mention no early dementia or Alzheimer's

Agreed and done, now reads "There was no family history of dementia."

Discussion

4. Consider suggesting administration of a brief test of episodic memory such as a list of words or a name and address for later recall. The Mini-mental State Examination is of modest value if mild impairments and no functional decline.

Agree that the mini-mental status examination is not sensitive in this population for cognitive impairment, but a good cognitive screen is as yet elusive. I have added some information of clinical utility to the article to address your concerns. In addition, added the following:

"Clinical questions include how best to screen and treat women with MeRCI, and when to refer for further evaluation. Cognitive screening instruments are not sensitive in this population, but complaints correlate well with objective cognitive loss [8] [6]."

5. When should providers worry? Are cognitive problems interfering with job performance, financial affairs, or social activities? Is there a family member or other informant who can provide feedback?

Again, great point, addressed as follows:

“When symptoms persist past the transition, or significantly interfere with function, referral to a specialist may be necessary.”

7. Please update the North American Menopause Position as NAMS released updated position statement on hormone therapy in 2017 (see below for summary of executive statement) A summary statement such as: In 2017 in their Position Statement on Hormone Therapy, the North American Menopause Society found that estrogen therapy may have positive cognitive benefits when initiated immediately after early surgical menopause, but HT in the early natural postmenopause period has neutral effects on current cognitive function. Only limited support (observational studies) is available for a critical window hypothesis of HT in Alzheimer disease prevention. In the absence of more definitive findings, HT cannot be recommended at any age to prevent or treat a decline in cognitive function or dementia.

Done, as below. Again, the focus here was on treating cognitive decline during the transition and not addressing future risk reduction of dementia:

“With regard to treatment of cognitive symptoms during the menopausal transition, the North American Menopause Society (NAMS) recommends HT for treating cognitive symptoms immediately after surgical menopause, but not after early natural menopause, given neutral benefits [33] [21]. Further, NAMS does not recommend HT ‘at any age to prevent or treat a decline in cognitive function or dementia [21].’ This latter statement is somewhat problematic when used alone, inadvertently conflating any decline in cognitive function- from surgical menopause, for instance, with dementia.”

NAMS would agree that hormone therapy improves hot flashes, night sweats, sleep disruption which may improve memory or concentration.

Added, thank you.

“NAMS finds evidence for HT for vasomotor symptoms and sleep disturbances [21], which relief may indirectly have a salubrious effect on memory and concentration.”

Society. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. Menopause. 2017 Jul;24(7):728-753.

8. Many more excellent references

Excellent references, agreed, thank you, and added ones that pertain to treatment within the transition rather than the ones regarding preventative, long-term effects.

Henderson VW, St John JA, Hodis HN, et al. Cognitive effects of estradiol after menopause: a randomized trial of the timing hypothesis. Neurology 2016;87:699-708.
Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology 1992;17:485-495.
Espeland MA, Shumaker SA, Leng I, et al; WHIMSY Study Group. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. JAMA Intern Med 2013:1429-1436.
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Herrera AY, Hodis HN, Mack WJ, Mather M Estradiol Therapy After Menopause Mitigates Effects of Stress on Cortisol and Working Memory. J Clin Endocrinol Metab. 2017 Dec 1;102(12):4457-4466.

9. Table 1 - Please correct: Laboratory evidence of perimenopause and menopause, such as high LH or reduced estradiol, but is not necessary for diagnosis. - Actually it is elevated FSH that makes the diagnosis of menopause, not LH

Have corrected this error.

Executive summary 2017 NAMS HT PS - section on mood and cognition
In the absence of more definitive findings, HT cannot be recommended at any age to prevent or treat a decline in cognitive function or dementia. On the basis of the WHI Memory Study, caution should be taken in initiating continuous- combined daily CEE + MPA in women aged older than 65 years, given the relatively small or infrequent increase in risk for dementia of an extra 23 cases per 10,000 person-years seen in the WHI. Estrogen therapy may have positive cognitive benefits when initiated immediately after early surgical menopause, but HT in the early natural postmenopause period has neutral effects on current cognitive function. Only limited support (observational studies) is available for a critical window hypothesis of HT in Alzheimer disease prevention.The effect of HT may be modified by baseline cognitive function, with more favorable effects in women with normal cognitive function before HT initiation.

I have made the following changes:

“Although NAMS does not recommend HT for non-surgical cases of MeRCI, the author has found that some women in natural menopause, like Ms.H, experience symptom alleviation with HT. The author therefore uses short-term HT as a first-line treatment for MeRCI.”

REVIEWER #3:

This case report highlights an important topic. Several limitations preclude publishing as is. The following should be considered.

The reviewer's comments were thoughtful and much appreciated.

1) Introduction. Paragraph 1: Memory impairment related to Lyme disease is incredibly rare as documented by IOM. See . Halperin J. Common Misconceptions about Lyme Disease. The American Journal of Medicine Volume 126, Issue 3, March 2013.

I have replaced with 'environmental stressors,' a less controversial cause. The sentence now reads "Men and women experience cognitive difficulties with aging, arising from myriad sources, including medication effects, endocrine changes, environmental stressors, non-pathological age associated memory impairment, or of a more portentous nature of varying clinical significance from mild cognitive impairment to dementia [1] [2] [3]."

2) Introduction Last paragraph. The acronym MeRCI is not well accepted. Either reference this or use the more accepted term, Menopause Cognitive Impairment (MCI).

MCI is defined as Mild Cognitive Impairment. I was unable to find a reference to "Menopause Cognitive Impairment," in the literature. The point is clarified as follows:

The following two cases illustrate this situation and the term menopause related cognitive impairment (MeRCI) is proposed here to differentiate this condition from mild cognitive impairment (MCI), which term is often used as a dementia prodrome [23].

3) Case 1 and Case 2, depression has been well-described as a risk factor for cognitive impairment with menopause (Reference WHI). This should be acknowledged in the discussion and referenced appropriately.

"While both women suffered from chronic depression, a known risk factor for cognitive loss in menopause [12], and were on medications that could affect their cognition, their psychiatric symptoms and medications were stable throughout this period. Ms. H's behavioral symptoms, involving executive dysfunction, with poor insight, irritability, and impaired judgment, could represent psychiatric illness. However, she had no exacerbation of her depression, and never exhibited behavioral symptoms in the past. Impairment of executive function may be seen with MeRCI [17] [2] [3]."

4) Vivelle dot does not come as a 0.25 mg dose. I presume the author meant 0.025 mg.
Typo corrected, thank you.

5) Case 2, the example of refusing to change soiled clothing has nothing to do with verbal memory, episodic memory, list learning or verbal fluency suggested to be

associated with menopause. This should be removed along with any reference to impaired judgement.

There is data to suggest reduced executive functioning, now added in the body of the article, given prefrontal involvement. The issue with removing the soiled clothing was atypical for her and felt strongly that it should be left in, another reason why the therapist felt she had fronto-temporal dementia. There is now the following section added to the discussion to help clarify.

6) Discussion, paragraph 2, last sentence please change the position of the references and add the words "may ALSO" as follows, "Estrogen may help maintain health of the cardiovascular system [30-32] which MAY ALSO indirectly promote brain health."

Yes, excellent, done.

7) Ref 33 is old (2000) and predates WHI. Please replace with more recent reference that is evidence based.

I thought important to retain along with another excellent metanalyses, noted as early, along with later data.

8) Discussion, paragraph 5, second sentence, "That such an entity exists is indisputable, given the numerous studies to date in the area. Give references.

This sentence was removed during the editing and the statement below to section 9 added.

9) Discussion, paragraph 5, 3rd sentence, "HT should alleviate symptoms in at least some women" is not scientifically based. See Hendrickson V, Progesterone and Human Cognition, Climacteric, 2018 for a recent manuscript on the issue of progesterone or estradiol plus progesterone and the treatment of cognitive impairment. In general, the author should temper his enthusiasm for treatment of cognitive difficulties at menopause with HT and reference his statements.

The author has restated the penultimate paragraph as follows, and added a sentence about HT based on her clinical experience.

Treatment can be nonspecific, including better sleep hygiene and aerobic exercise [11]. Although NAMS does not recommend HT for non-surgical cases of MeRCI, the author has found that some women in natural menopause, like Ms.H, experience symptom alleviation with HT. The author therefore uses short-term HT as a first-line treatment for MeRCI. Cognitive remediation to address areas of deficit may be helpful [38]. One study found no benefit using the cholinesterase inhibitor donepezil [15], while another

found benefit from the use of the stimulant, lisdexamfetamine [2], although with the rise in prescription amphetamine abuse, close monitoring and short-time use is advisable.

10) Discussion, paragraph 6, 2nd sentence is an overstatement. Data is certainly not altogether consistent in the finding of objective changes in cognition at menopause. Ref 15 Weber and Maki provide a nice review that the author cites, with a more tempered interpretation of the data on cognition at menopause. Do not overstate the conclusions of those you have referenced.

The concluding paragraph reads as follows:

“In conclusion, MeRCI needs to be considered in the differential diagnosis of women in their 40’s and 50’s with cognitive complaints to prevent misdiagnosis and deleterious consequences. As to what constitutes appropriate treatment, and whether there is a role for HT -or some other intervention, in at least some women with significant menopausal related cognitive impairment, is an area that needs further study.”

Thank you again for this opportunity to revise and resubmit the paper. I hope the revision meets with your approval.

Sincerely,

Gayatri Devi

Daniel Mosier

From: Gayatri Devi [redacted]
Sent: Thursday, August 30, 2018 10:20 AM
To: Daniel Mosier
Subject: Re: Manuscript Revisions: ONG-18-1258R1
Attachments: 18-1258R1 ms (8-29-18v2)_3.docx

RE: Manuscript Number ONG-18-1258 "Menopause Related Cognitive Impairment."

Dear Editor,

I appreciate the feedback and revisions.

I believe there was an error in the editing statement that the submission was 1500 words over the limit, as this included a word count on the references. In my responses and changes, I retained some of the deletions, which were noted to be removed because of count limitations, believing them to have been the result of this possible miscount.

The entire submission, is now 1592 ((including title, abstract and box) without counting references.

The responses to individual queries follow below:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes. *I have made further minor changes to reduce word count.*
2. LINE 2: The journal uses no more than two academic degrees per author, so "FAAN" was removed.

OK, also removed MS to reduce word count and shortened affiliations.

3. LINE 53 (Deleted text): It is a given that this is an interesting observation from 150 years ago, but case reports do not have luxury of unlimited wording.

Reduced significantly to leave in, hoping OK, this work is a masterpiece on clinical observation and recording and rarely referenced.

4. LINE 112 (Deleted text): This was added in response to reviewer, but is not critical and can be removed to shorten the text.

Reduced significantly to leave in, but if the editor feels strongly, okay to remove.

5. LINE 118 (Deleted text): While accurate, simplifying this paragraph is necessary.

OK.

6. LINE 130 (Deleted text): The author elected not to resubmit as a review, and these studies though having much merit make the Discussion too long.

Hoping OK, reduced significantly to leave in.

7. LINE 139 (Deleted text): No room for a summary statement like this.

Hoping OK, reduced significantly.

8. REFERENCES: The Journal's maximum number of references for case reports is 8 references. Your paper currently has 39. Given that your paper is significantly over the word limit for case reports (2,000), please remove as many references as possible

OK, reduced references to 12 and can reduce further, if required.

Thank you very much.

Sincerely,

Gayatri Devi

On August 29, 2018 at 2:32 PM Daniel Mosier <dmosier@greenjournal.org> wrote:

Dear Dr. Devi,

Thank you for submitting your revised manuscript. It has been reviewed by the editor, and there are a few issues that must be addressed before we can consider your manuscript further:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.

2. LINE 2: The journal uses no more than two academic degrees per author, so "FAAN" was removed.

3. LINE 53 (Deleted text): It is a given that this is an interesting observation from 150 years ago, but case reports do not have luxury of unlimited wording.

4. LINE 112 (Deleted text): This was added in response to reviewer, but is not critical and can be removed to shorten the text.

5. LINE 118 (Deleted text): While accurate, simplifying this paragraph is necessary.

6. LINE 130 (Deleted text): The author elected not to resubmit as a review, and these studies though having much merit make the Discussion too long.

7. LINE 139 (Deleted text): No room for a summary statement like this.

8. REFERENCES: The Journal's maximum number of references for case reports is 8 references. Your paper currently has 39. Given that your paper is significantly over the word limit for case reports (2,000), please remove as many references as possible

Each of these points are marked in the attached manuscript. Please respond point-by-point to these queries in a return email, and make the requested changes to the manuscript. When revising, please leave the track changes on, and do not use the "Accept all Changes" function in Microsoft Word.

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on **Friday, August 31st**.

Sincerely,

-Daniel Mosier

Daniel Mosier

Editorial Assistant

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