Author's response to reviews

Title: Atypical depression is more common than melancholic in fibromyalgia

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Author's response to reviews: see over
Dear Ms. Cheong,

Please extend our gratitude to the reviewers for their insightful comments on our manuscript entitled “Atypical depression is more common than melancholic in fibromyalgia” (MS# 1522102872296509). We concur with all suggestions and have edited the text to incorporate the suggested data.

Specifically, in response to Items 1 through 11 from Reviewer #1, we edited the text as follows:

1. **Re: shared biological underpinnings. (P. 5)**
   Gold and Chrousos [15] postulated that atypical depression would be more prevalent in FM patients compared to melancholic depression due to the shared biological underpinnings of atypical depression and FM. Specifically, there is a blunting of hypothalamic-pituitary-adrenal (HPA) axis functioning as evidenced by low to normal levels of plasma cortisol following dexamethasone suppression testing. This blunting is secondary to glucocorticoid receptor desensitization as a result of chronic over secretion of cortisol. However, there are no studies to date that have evaluated the Gold and Chrousos assertions.

2. **Re: suggest that the hypothesis be rephrased. (P. 5)**
   Thus the first aim of this study was to test the hypotheses that atypical depressive episodes (ADE) and melancholic depressive episodes (MDE) occur in FM patients with ADE being the predominant subgroup. A secondary aim was to describe the demographic and clinical characteristics and diagnostic features of depression subgroups to determine if they exhibited the same symptom clusters as those in depressed, non-FM samples.

3. **Re: use of SIGH-SAD SR. (P. 7-8)**
   While there is an association between ADE and Seasonal Affective Disorder, this measure was used as it is the most commonly used questionnaire for ADE and contains the HAM-D. We concur that the title of the previous tool is misleading so we de-emphasized the reference to the SIGH-SAD-SR and we change the text as follows:
   The 2003 version of the *Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS)* was used to assess depression severity and subtype-specific diagnostic features. This interviewer-administered questionnaire is based on the 21-item Hamilton Depression Rating Scale (HAM-D) plus includes an 8-item addendum to assess ADE features [19]: social withdrawal, increased appetite, increased eating, weight gain, carbohydrate craving or eating, hypersomnia, fatigability and pattern of symptoms being worse in the afternoon. It also includes two un-scored questions regarding difficulty awakening and temperature discomfort that are indicative of ADE. The HAM-D also includes seven items that assess features of MDE as per the DSM-IV-TR [10]: loss of appetite, weight loss, terminal insomnia, guilt, agitation, psychomotor retardation and pattern of symptoms being worse in the morning. Scores range from 0 to 88 with lower scores reflective of lower depression severity. Reliability for scale items of the SIGH-ADS as measured by Cronbach’s alpha was established to be 0.87 in this sample.
   To insure instrumental validity of the SIGH-ADS, a patient self report version was used to verify the interviewer-obtained responses. The *Structured Interview Guide for the Hamilton Depression Rating Scale,*
Seasonal Affective Disorder - Self Report Version (SIGH-SAD-SR) [20] includes the same questions as the SIGH-ADS and has the same scoring matrix. After the SIGH-ADS was administered, the self-report questionnaire was reviewed by the PI. If responses differed by two or more points on any question, the PI clarified the question with the subject and rescored it accordingly. Reliability for scale items of the SIGH-SAD-SR as measured by Cronbach’s alpha was established to be 0.78 in this sample.

4. Re: clarification of how ADE/MDE diagnoses made and by whom.
To decrease inter-rater reliability issues, the principal investigator (PI) completed all examinations and interviewer-administered evaluations for all subjects. (P. 7)

The DSM-IV-TR diagnostic criteria for MDD with atypical features and MDD with melancholic features [10] were used to diagnose depressive subtypes. (P. 8)

5. Re: subject subgroups.
We added a recruitment flow diagram to clarify the composition of the subgroups and added the following text:
As only one depressed FM subject did not meet diagnostic criteria for either ADE or MDE (non-ADE/non-MDE, n=1), this data could not be used for group comparisons, thus was excluded from all statistical analyses. (P. 8)

See Figure 1 for full recruitment and enrollment details. (P.11)

6. Re: definition of what chi-square tested and sex differences between groups vs. whole sample in Table 1.
Title changed to Table 1. Comparison of demographic data by diagnostic group: count (%), mean (±SD) and χ² values. Shading was added to Table 1 in the Total Sample Column and BTW GROUPS was added to the final column of p values. In addition the text was changed as follows:

Chi-square (χ²) tests were used to determine if there were differences between groups on nominal and ordinal level variables and also to determine if diagnostic groups differed statistically on prevalence of subtype-specific diagnostic criteria. (P.10)

The total sample reflected the expected predominance of females (96%) versus males (4%) [27]. No significant differences existed between groups on demographic variables except on gender (p = 0.01). (P. 11)

7. Re: overlap in symptoms between ADE and MDE groups.
Major depressive disorder, with atypical and melancholic features, has been methodically investigated in depressed populations: yet there is still some debate as to the validity of the subtype-specific criteria, especially for atypical depression [13]. While several researchers have critiqued the current DSM-IV-TR criteria, a viable alternative has not been agreed upon [14]. Therefore, for the purpose of this study, the current prevailing criteria as per the DSM-IV-TR were used. (P.4-5)

Atypical Depressive Episode-specific criteria.
While groups exhibited predominant symptom patterns respective of their diagnostic classification (ADE vs. MDE), some individual symptoms overlapped between groups. In our sample, all subjects in the ADE group reported mood reactivity, a mandatory criterion for ADE, while 74.1% of the MDE and 44.4% of the non-MDD groups also experienced this symptom. (P. 12)

Conceptually, MDD subtype-specific criteria are exclusive to their respective diagnostic subgroup with no overlap between subgroups. In contrast, our data indicates the diagnostic features that differentiate ADE versus MDE do overlap and this finding has been substantiated by others [13,37]. A large trial of 579 depressed non-FM patients (ADE, n = 130; Non-ADE, n = 449) reported ADE symptoms in both groups, with the ADE group having the highest prevalence of mood reactivity (100% vs. 77.7%), hypersomnia (36.2% vs. 16.8%), hyperphagia (53.1% vs. 21.8%), leaden paralysis (60.8% vs. 28%), and interpersonal rejection sensitivity (75.4% vs. 40.9%)[13]. In line with Thase and colleagues [38], we found that mood...
reactivity, a mandatory criterion for ADE, was reported by the majority of the MDE group and almost half of the non-MDD group; this finding is congruent with the observations of Henkel and colleagues [39]. (P. 16)

8. Re: ADE and MDE should be spelled out in full the first time.
   This interviewer-administered questionnaire is based on the 21-item Hamilton Depression Rating Scale (HAM-D) plus includes an 8-item addendum to assess atypical depressive episode (ADE) features [19]: social withdrawal, increased appetite, increased eating, weight gain, carbohydrate craving or eating, hypersomnia, fatigability and pattern of symptoms being worse in the afternoon. It also includes two unscored questions regarding difficulty awakening and temperature discomfort that are indicative of ADE. The HAM-D also includes seven items that assess features of melancholic depressive episode (MDE) features as per the DSM-IV-TR [10]: loss of appetite, weight loss, terminal insomnia, guilt, agitation, psychomotor retardation and pattern of symptoms being worse in the morning. (P. 7)

9. Re: “outcome measures”.
   Deleted “outcome”, thus reads “Primary measures” and “Secondary measures”. (P. 7 & 9)

10. Re: replaced ‘symptomology with ‘symptomatology’. (Whole Ms.)

11. Re: menstrual females scheduled during luteal phase.
   To decrease the possibility of estrogen affecting symptom presentation, i.e.: hyperphagia and hypersomnia, menstruating females who continued to meet criteria were scheduled for a second visit during their next luteal phase, when estrogen levels are theoretically at their lowest. Males and non-menstruating females were scheduled within 30 days of their first visit. (P. 6)

In response to Items 1 through 10 from Reviewer #2, we edited the text as follows:

1. Re: Were antidepressant medications excluded?
   Subjects on medications that could potentially alter the HPA axis were excluded (e.g.: prednisone, opioids, corticosteroids, carbamazepine, etc.). Those on anti-depressants were not excluded, as research has shown the presence or absence of antidepressants while depressed, type of antidepressant or number of antidepressant trials previously used did not affect HPA axis perturbations or cortisol levels following the combined dexamethasone suppression/ corticotrophin-releasing hormone (DEX/CRH) test [18]. Thus depressed subject’s plasma cortisol levels, which are associated with subtype-specific symptom expression, would still be expected to reflect MDD subtype variations. (P. 6)

2. Re: scheduled during luteal phase. See response to 1st reviewer’s item #11. (P. 6)

3. Re: overlap of subtype-specific symptoms. See response to 1st reviewer’s item #7. (P. 4-5, 12)

4. Re: unexpected overlaps in symptoms. See response to 1st reviewer’s item #7. (P. 4-5, 12)

5. Re: the relationship between duration, subtype, and HPA axis functioning.
   We rewrote the Future Directions section to clarify our hypothesis regarding potential causes of temporality in FM with comorbid depression. (P. 17-18)
   A non-significant (p=0.09), yet potentially interesting finding was a trend toward differences among MDD subtypes in the number of years that FM symptoms were present. Similar to Wallace's findings [41], the ADE and non-MDD groups had symptoms of FM for approximately six years longer than the MDE group. (P. 16)

6. Re: hypothesis of increased prevalence of ADE in FM.
   Interestingly, the ADE prevalence rate of 52.6% is approximately twice that of the 30% reported in population studies of depressed people without FM. This finding is consistent with ADE being more prevalent in women and may be associated with the neuroendocrine underpinnings of the preponderance of women versus men (9:1) with FM [30]. (P. 15)
7. **Re: reference for second part of following sentence.**
   Combined, the atypical and melancholic subtypes represent approximately 60% of all MDD cases [11] and have been postulated to represent the two main subtypes of depression in FM [12], thus are the focus of this study. (P. 4)

8. **Re: exclusion criteria.**
   Males and females 18 years old or older who were diagnosed with FM as per the 1990 American College of Rheumatology criteria [17] for ≥ 2 years were eligible to participate in the study. Subjects also needed to speak and read English at a 6th grade level. Exclusion criteria, designed to decrease risk to subjects and potential confounding variables, excluded subjects who were acutely ill, pregnant, currently lactating or planning to conceive within 90 days. Additional exclusion criteria included a Beck Depression Scale score greater than 31 (extreme depression), any medical disorder that altered the HPA axis, suicidal ideation, abnormal thyroid stimulating hormone levels (less than 0.28uIU/ml or greater than 5.00uIU/ml), weight change greater than 15 pounds during the prior three months and subjects who did not meet diagnostic criteria for one of the three FM groups, i.e.: non-depressed, ADE or MDE (n = 1). Subjects on medications that could potentially alter the HPA axis were excluded (e.g.: prednisone, opioids, corticosteroids, carbamazepine, etc.). Those on anti-depressants were not excluded, as research has shown the presence or absence of antidepressants while depressed, type of antidepressant or number of antidepressant trials previously used did not affect HPA axis perturbations or cortisol levels following the combined dexamethasone suppression/ corticotrophin-releasing hormone (DEX/CRH) test [18]. Thus depressed subject’s plasma cortisol levels, which are associated with subtype-specific symptom expression, would still be expected to reflect MDD subtype variations. (P. 5-6)

9. **Re: number of participants excluded in groups.** See 2nd Reviewer’s item #7 above. (P. 16)

10. **Re: Quality of Life statistics appear twice in Table 2.** (P. 24)
   Second line deleted.

Thank you for your thoughtful review and attention to detail. We appreciate the opportunity to clarify the significant findings of our research. Please find attached the final revision of the manuscript and the separate files for the figure and tables. All co-authors have approved this final version and give their authorization to publish it as is.

Respectfully,

Rebecca Ross PhD, PMHNP