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
Author’s response to reviews

Title: Atypical depression is more common than melancholic in fibromyalgia: an observational cohort study

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Author’s response to reviews: see over
Reviewer's report

Title: Atypical depression is more common than melancholic in fibromyalgia

Version: 3 Date: 22 February 2010

Reviewer: Kate Harkness

Reviewer's report:
The present paper is a resubmission of a study examining the prevalence of atypical and melancholic subtypes of depression in major depressive disorder in patients with fibromyalgia. The authors have responded adequately to all of the comments from my previous review. The paper is clearly written and should be of interest to researchers studying the comorbidity of depression with fibromyalgia. I have one final comment that is not major, but that may warrant some discussion by the authors:

Discretionary Revisions
- The authors now clarify that only one patient met criteria for MDD but did not evidence either the MDE or ADE subtype. This would be different from a non-FM MDD sample. Even though the authors did not include this one person in analyses, it might be useful to comment on the larger proportion of MDE and ADE in this FM sample. Why? Is it because MDD is more severe in an FM versus non-FM sample? More somatic symptoms?

In response to this comment, we edited the text in the 1st paragraph of the Discussion section on page 15 as follows:

Demarcation of MDD subtypes is a novel area of research in FM. Prior to completing this pilot study, it was not known if subtype prevalence in an FM sample would be consistent with the prevalence of MDD subtypes previously identified in the general population. We speculate the over-representation of ADE is likely due to the above and ADE being more prevalent in females in addition to the long-term effect of chronic stress blunting HPA axis function resulting in lower cortisol levels. It is unclear as to why only one subject out of 77 was identified with the non-ADE/non-MDE subtype. It is possible this finding was associated with self selection bias, differences in symptom presentation of MDD co-morbid with FM versus MDD alone, or the possibility the subject was transitioning from MDE to ADE. A larger study is needed to better characterize depression subtypes and their clinical features to determine if the above finding is reproducible. Our team plans to investigate this issue in future studies.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.
Reviewer's report

Title: Atypical depression is more common than melancholic in fibromyalgia

Version: 4 Date: 23 February 2010

Reviewer: Emily Bartley

Reviewer's report:
The authors have properly addressed most of my concerns and have improved the quality of the report; however, there are still a couple of issues to contend with.

Major Compulsory Revisions:

1. The authors have provided additional information regarding the overlap amongst the diagnostic classifications; however, I feel that this topic merits further discussion. An explanation is provided as to why there is substantial overlap among the "leaden paralysis" subtype; however, could the authors provide insight into the other overlapping symptoms that were found? Further, given that the authors suggest treatments could be altered depending on FM depression-specific subtype, and given there are overlaps amongst these classifications, could the authors provide further information as to what they speculate as to the clinical and research implications, as well as implications for future intervention?

We value your comments regarding the overlap amongst groups on diagnostic criteria and have incorporated the following text to provide a clearer explanation of the current state of knowledge from the depression literature and the paucity of data in the FM literature. The text and associated references can be found on page 15 in the discussion section under the “Overlap of diagnostic criteria between subtypes” heading in the 1st paragraph.

While conceptually, MDD subtype-specific criteria are exclusive to their respective diagnostic subtype with no overlap between subgroups, ours and other study data [13,37] indicate diagnostic features that differentiate ADE versus MDE do commonly overlap. Benazzi provides an in-depth discussion of the concept of depressive subtype symptom overlap in depressed non-FM populations and presents the hypothesis of mood disorders representing a continuum of overlapping disorders with common underlying biological pathways versus being absolute categorical definitions [38]. Consistent with our findings, Angst and colleagues [39] found in their 20 year prospective study that depressed non-FM subjects with pure melancholic and atypical depression exhibited many similar characteristics, as evidenced by no significant differences between groups on psychomotor retardation/agitation, weight gain or feelings of excessive or inappropriate guilt. In a large trial of 579 depressed non-FM patients (ADE, n = 130; Non-ADE, n = 449) ADE symptoms were reported 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%), leadin paralysis (60.8% vs. 28%), and interpersonal rejection sensitivity (75.4% vs. 40.9%) [13]. In line with Thase and colleagues [40], 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; which is also congruent with the observations of Henkel and colleagues [41]. We cautiously speculate the overlap in depressive subtype symptoms is likely due at least in part to dysfunction of the HPA axis as well as other neuroendocrine (e.g., serotonin and norepinephrine) and neuroimmune (e.g., pro-inflammatory cytokine response) systems. Although Juruena and Cleare [42] reviewed symptom overlap between ADE and other MDD subtypes in populations similar to FM including chronic fatigue syndrome, to our knowledge this study was the first to evaluate ADE and MDE specific diagnostic criterion in an FM population. Therefore, these findings need to be replicated in a larger sample before any conclusive assumption regarding the causes of the symptom overlap can occur.

The following text was also added to the Conclusion section on page 19:

Classic research provides evidence that the successful pharmacologic treatment of ADE differs from the treatment for MDE [51,52] and is proposed to be due to differing biological dysfunction of the HPA axis, locus ceruleus-noradrenergic system and the physiological stress systems. Thus, depression subtypes need to be addressed in future studies and clinical practice to eliminate the possibility of making erroneous conclusions from the data.

Minor Essential Revisions:

1. The authors indicate scheduling menstruating women for their second session during their luteal phase to decrease the probability of estrogen affecting symptom presentation since it is at its lowest during that phase. However, estrogen (i.e., estradiol) is not at its lowest during the luteal phase. In fact, there is significant hormonal variation across the menstrual cycle. Estradiol is at a low, steady level during the early-follicular phase and then gradually increases until it peaks prior to ovulation. There is also a small peak again during the mid-luteal phase, and then estradiol gradually decreases for the remainder of the cycle. Therefore, there are large differences in the concentration of estradiol during the luteal phase. There is also a significant amount of inter- and intra-individual variability in the phases of the menstrual cycle. Because of this, symptoms have been known to change depending on the timing of the menstrual cycle. Therefore, how was the second session (luteal-phase assessment) defined for pre-menopausal women? Did participants determine when their luteal phase occurred through calendar method, hormone assessment (i.e., hormonal assay, LH urine tests), basal body temperature, etc? Further, could the authors please provide data regarding the timing of this second assessment for all participants (i.e., what was the average length of time between the two sessions), as well as the average day of the menstrual cycle that pre-menopausal women had their session on.

Given the pilot nature of this minimally funded research study, we struggled with the most cost-efficient and consistent means to control for the potentially confounding effect of estrogen status. In regards to the question about how the menstrual phase was determined; it was from subjective reports of the number of days from the first day of the last menstrual period. This
subjective measure was clearly not sufficient on its own. In future studies we plan to also incorporate serial standardized estradiol assays to confirm that subjects are indeed in the luteal phase of their menstrual cycle. In the manuscript, we clarify our attempt was to test during the luteal phase. Furthermore, we concur with your comments as pertains to the levels of estrogen and luteal phase. The use of the phrase “during the luteal phase when estrogen is at its lowest” is incorrect and we have incorporated the following text to clarify.

Protocol (pg. 6, 1st paragraph)
In an attempt to decrease the possibility of estrogen fluctuations affecting symptom presentation, (e.g., fatigue, amotivation, hyperphagia and hypersomnia), menstruating females who continued to meet criteria were encouraged to schedule and attend the second visit during their next luteal phase (14 days after the first day of their last menstrual cycle), when estrogen levels would theoretically be at their highest. Menstrual phase was determined from subjective reports of the number of days from the first day of the last menstrual period. All other subjects were scheduled within 30 days of their first assessment.

Results (pg. 11, 1st paragraph)
All subjects (n= 63) were tested within an average of 17 (SD ± 20.43) days from the first assessment. Both premenopausal and post-menopausal females were seen an average of 14 days after their first assessment (SD: Premen ± 12.82; Postmen ± 14.53).

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.