Author's response to reviews

Title: Hypersomnia and depressive symptoms: Methodological and clinical aspects

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Author's response to reviews:

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Dear Editor-in-Chief,

Please find enclosed the revised manuscript with title: Hypersomnia and depressive symptoms: Methodological and clinical aspects (Dauvilliers Yves, Lopez Régis, Ohayon Maurice & Bayard Sophie).

We are pleased that our work was found interesting and important, and we would like to thank our 2 reviewers for helpful comments. We would like to submit a revised version of the manuscript taking into account the comments of both reviewers. The responses were below and we have redrafted the manuscript taking into account the comments.

Reviewer(s)’ Comments to Author:

REVIEWER 1: KATHERINE KAPLAN

This manuscript is a welcome contribution to the literature on hypersomnia and depression, an underresearched and underrepresented area. The breadth of the review, which includes hypersomnias of central origin, integrates a wide literature. I recommend acceptance of the manuscript pending consideration of the following.

Major Compulsory Revisions

1. The parallels between hypersomnia in depressive disorders and insomnia in depressive disorders are considerable. PSG evidence for insomnia often does not match self-report, paralleling PSG studies of hypersomnia in mood disorders, and yet insomnia is considered an independent disorder meriting treatment. It is possible that, even if hypersomnia is only a “subjective sleep complaint,” it has the same societal burden (Jennum & Kjellberg, 2010) and merits the same clinical attention as it would if objective evidence were observed. This should be discussed somewhere in the manuscript.
Response: We thank the reviewer for this constructive remark. We do agree with the comment. We added this important point in the revised version of the manuscript as following:

One may question whether the diagnosis of hypersomnia requires objective evidence of daytime/nighttime sleepiness or hypersomnia may be resumed as a “subjective sleep complaint.” The complaint of EDS is rarely corroborated by the MSLT results and particularly in the context of associated mood disorders. Paralleling PSG-MSLT studies of hypersomnia in mood disorders PSG evidence for insomnia often does not match self-report, and yet insomnia is currently considered an independent disorder. We do believe that hypersomnia diagnosed by a structured clinical interview as in proposed DSM-5 criteria merits clinical attention. Thus, hypersomnia associated with mood disturbances may be a clinically-defined condition with significant socio-economical burden (Jennum Kjellberg 2010) that may justify a treatment. To date, no pharmacological drugs were approved to manage hypersomnia in depressive disorders. The management bias is a concern, with potential interactions between EDS, extended nocturnal sleep complaints, and drug intake. Some basic recommendations can be proposed such as avoiding psychotropic sedative drugs (i.e. benzodiazepine) and giving priority to noradrenergic antidepressant treatments for their action on the wake drive.

2. There are two separate “definitions” sections that describe hypersomnia, one on page 5 and another on page 9. It would help the flow of the paper to combine these definition sections.

Response: Accordingly, we decided to remove the definition from the Hypersomnia associated with mood disorders section to the Definition and assessment of hypersomnias section by adding a third paragraph: Hypersomnia associated with mood disorders.

Minor Essential Revisions

1. Page 4, parag 2: “major depression disorder” should be changed to “major depressive disorder.” Also, this term is again defined on page 5, parag 3.

2. Page 4, parag 2: add “the” before “result being unchanged.”

3. Page 10, parag 3: reference 43 may not be correctly placed.

Response: We apologize for these errors and omissions. As required, we modified the revised manuscript accordingly. We suppressed the reference # 43.

4. Page 13, parag 2: “Another case-control study found mood disorder symptoms in one-third of narcolepsy patients, but with similar frequency of formal mood disorder diagnoses.” – Was the frequency one-third, or the frequency was similar to mood disorder diagnoses in the general population? Also, add ‘an’ to the following: “and 35% had AN anxiety disorder”.

Response: We agreed that this sentence may lead to confusion. We specified
Another case-control study found mood disorder symptoms in one-third of narcolepsy patients. Nevertheless, no significant difference was found between patients and controls regarding the formal mood disorder diagnosis [70]. In contrast over half the patients had anxiety or panic attacks, and an 35% had anxiety disorder [70].

Discretionary Revisions

1. “of parag 1: The authors may wish to support their assertions on the inadequacy of self-report questionnaires with references. The authors may also wish to add references to page 14 parag 1 beginning with the term “Globally.”

Response: The subsequent references were cited:
- Page 8, bottom of § 1: We added the following reference “Buckley TC, Parker JD, Heggie J. A psychometric evaluation of the BDI-II in treatment-seeking substance abusers. J Subst Abuse Treat. 2001;20(3):197-204.

2. Page 16, parag 2: “Depressive symptoms were noted in 15 to 25%. “ how does this rate compare with the general population? 

Response: We do agree with this point that require clarification: See below the modifications performed in the revised version of the manuscript “ Depressive symptoms were noted in 15 to 25% using clinic-based samples of patients affected with IH, values being always higher than the general population”.

3. The authors discuss differentiating EDS from fatigue on page 9. I am also curious about the relationship between EDS and long sleep/excessive sleep quantity. Despite the fact that the diagnostic nomenclatures define EDS by “long sleep” (DSM-IV) or “sleep drunkenness” (ICD-10), it is unclear if EDS and excessive sleep co-occur. Indeed, in the Ohayon et al. 2012 paper cited, a weak relationship between EDS and sleep duration was observed. Although we include “excessive sleep” and “excessive daytime sleepiness” in our understanding of hypersomnia, is it possible they might be separate phenomena?

Response: We do agree with this important point. We decided to add some recent data in the revised manuscript accordingly (Article in press in Ann Neurol added in the references):

Based on a recent large cross-sectional telephone survey of adults representative of the adult general population of 15 U.S. states, we found that 6.3% of the sample reported a sleep duration of 9 hours or greater during the main sleep episode, and 8.4% reported sleeping at least 9 hours per 24-hour period (Ohayon et al 2013 Ann neurol). In addition, 25.1% of subjects sleeping #9 hours per night and 40.1% of subjects sleeping #9 hours per 24-hour period
Also experienced excessive sleepiness.

**REVIEWER 2: DAVID PLANTE**

This review is an overview of hypersomnia in depression, with the stated aims of 1) describing hypersomnia assessment methods, 2) defining hypersomnia in mood disorders, and 3) reviewing studies that have examined mood disorder symptoms in hypersomnias of central origin. The topic is a very important area for multiple fields. Attention to the following details would improve the overall quality of the manuscript:

**Major Compulsory Revisions**

None

**Minor Essential Revisions**

1. The review would be strengthened if the authors included a brief discussion about potential changes in nosology in the upcoming DSM-5, particularly proposals for Hypersomnia Disorder, given the scope of the review.

We do agree with this point. Accordingly we added a quite long paragraph in the revised manuscript

The proposed DSM-5 criteria for sleep-wake disorders nosology planned for publication this year included major changes regarding hypersomnia with elimination of the diagnosis of “primary hypersomnia” in favor of “hypersomnia disorder,” with concurrent specification of clinically comorbid conditions (Reynolds et al 2010). These modifications will also lead to elimination of “sleep disorder related to another mental disorder” and “sleep disorder due to a general medical condition,” in favor of “hypersomnia disorder” with concurrent specification of clinically comorbid medical and psychiatric conditions. Sleep disorders per se are frequently accompanied by depression, anxiety, and other cognitive mental status changes that warrant independent clinical attention and must be addressed in treatment management. As the primary users of DSM are mental health and general medical clinicians, not sleep disorder specialists, new DSM5 sleep-wake disorders criteria also included aggregation of hypersomnia disorder and narcolepsy without cataplexy, which will be distinguished from narcolepsy-cataplexy/hypocretin-1 deficiency disorder. Based on a recent cross-sectional telephone survey, a new definition of hypersomnia has been proposed in the proposed DSM-5 revision including a frequency of "excessive sleepiness" (defined by either recurrent periods of irrepessible need to sleep or to nap within the same day; recurrent naps within the same day; a nonrestorative (unrefreshing) prolonged main sleep episode of 9 hours or more per; and/or confusional arousals-sleep drunkenness) at least three times per week for at least 3 months, despite normal main sleep duration lasting 7 hours or longer, with significant daytime distress/impairment leading to a final prevalence of 1.5% (Ohayon et al 2012).

2. In the Definition and Assessment of Mood Disorders section (pg. 8); several questionnaires are enumerated to quantify mood symptom severity that are
described as “self-report”, however, the list includes both self-report and clinician-administered surveys. Please clarify for the reader which are self-report and which are clinician-administered for readers who may not be familiar with these instruments.

Response: As request, we brought some clarifications for this point.

Mood disorders are generally diagnostically assessed with the Structured Clinical Interview for DSM-IV Axis 1 Disorder [27]. This instrument is a semi-structured interview for making standardized, reliable, and accurate diagnoses of the DMS-IV Axis 1 disorders. Self- or hetero-report questionnaires are also commonly used to quantify mood symptom severity. Self-report questionnaires include the Beck Depression Inventory (BDI-II) [28], the Hamilton Depression Rating Scale [29], the Montgomery Åsberg Rating Scale [30], the Zung Rating Scale for Depression [31], the Hospital Anxiety and Depression Scale [32], and the Inventory of Depressive Symptomatology (self-rating, IDS-C30) [33]. These instruments are fulfilled by the patients themselves. Note that the IDS has also a clinician-rated version (IDS, C30) [33].

3. The methods described for Ref 54 (Vgontzas et al) in the Objective Assessment of Hypersomnia should be clarified, as in this manuscript the authors excluded patients on psychotropic medication in the final analysis.

Response: We do agree with this observation. As required, we clarified the methods of this study. The revised manuscript was modified accordingly.

Using the polysomnography and a non-conventional objective measure of EDS (i.e., two 60-minute naps at 9:00 and 12:30), Vgontzas and co-workers have compared the nighttime and the objective sleepiness of drug-free patients with diagnosis of primary (idiopathic) vs. psychiatric hypersomnia (i.e., mood, somatoform, anxiety, and personality disorders) and healthy controls. This group found that patients with psychiatry hypersomnia, although having complain of EDS, showed both during the day and during the night lower sleep propensity (i.e. higher sleep latency and total wake time) than patients with idiopathic hypersomnia and controls [54].

Discretionary Revisions

1. To be comprehensive, would consider including in the Objective Assessment of Hypersomnia section the manuscript by Sangal et al, Chest 1992;101;898-902, which also has MSLT/MWT data in depression.

2. To be comprehensive, would also consider including a recent manuscript by Plante et al Psychiatric Res 2012 that examines slow wave activity differences in depression and hypersomnia, given the scope of the review.

Response: As request, we considered this recent study. The revised manuscript was modified accordingly. However we do believe that the paper of Sangal et al was out of the scope of our review as it did not include patients with major depression. The latter study concerned consecutive patients whose clinical presentation required evaluation for excessive sleepiness.
The basis of hypersomnia in MDD is poorly understood; one may hypothesize that hypersomnia is related to abnormal sleep homeostasis in MDD. Interestingly, a recent high density electroencephalography study suggested that the presence of hypersomnia in MDD is associated with reduced parieto-occipital slow wave activity compared to those without hypersomnia (Plante 2012).

3. At the top of page 15 (Narcolepsy with Cataplexy Section), the authors mention animal data regarding the role of orexin in depression-like behavior. The authors could consider including a brief discussion regarding some of the human data regarding CSF orexin in depression, such as articles by Salomon et al Biol Psychiatry 2003, Schmidt et al Neuroscience Letters 2010, Schmidt et al Psychiatry Res 2011, and Brundin et al Eur Neuropsychopharmacol 2007. It could be emphasized that the role of orexin in depression segregated by differences in vigilance state/sleepiness has not been evaluated.

Response: As required by the Reviewer, we briefly presented the results of the suggested literature. We modified the Narcolepsy with cataplexy section as following:

Recent studies also support the role of specific hypocretin receptors in the modulation of depression-like behavior. A behavioral mice study after genetic or pharmacologic inhibition of hypocretin receptor signaling suggested that the hypocretin activity balance at either receptor 1 or receptor 2 produced an anti-depressant- or pro-depressant-like effect depending on the subtype activated [79]. Outside of the narcolepsy scope some human studies have compared the levels of CSF hypocretin-1 in patients with mood disorders with healthy controls leading to controversial results. A reduce amplitude in diurnal variations of hypocretin-1 has been found in patients with bipolar or unipolar depression (Salomon, 2003). Brundin and co-workers found that suicidal patients with major depressive disorder had significantly lower CFS-hypocretin levels than other suicidal patients (Brundin et al., 2007). In contrast other studies found similar CSF hypocretin-1 levels in patients with MDD and controls (Schmidt 2007, 2011. In addition, CSF hypocretin-1 levels did not correlate with the severity of depressive episode, the symptoms of depression or the number of episodes (Schmidt 2007, 2011). To our best knowledge, no studies have reported whether CSF hypocretin-1 levels are altered in depressive patients with hypersomnia or not. However, some of recent results hold promise for the use of non-selective hypocretin-1 and -2 agonists and antagonists to treat several neuropsychiatric disorders, including narcolepsy, insomnia, and drug addiction. Nevertheless, potential unwanted side effects must be carefully monitored.

Many thanks for your consideration of this paper.

Yours sincerely,

Professor Dauvilliers Yves