Author’s response to reviews

Title: Sleep complaints in adolescent depression: One year naturalistic follow-up study

Authors:

Anna S Urrila (anna.urrila@helsinki.fi)
Linnea Karlsson (linnea.karlsson@utu.fi)
Olli Kiviruusu (olli.kiviruusu@thl.fi)
Maiju Pankakoski (maiju.pankakoski@thl.fi)
Mirjami Pelkonen (mirjami.pelkonen@thl.fi)
Thea Strandholm (thea.strandholm@thl.fi)
Mauri Marttunen (mauri.marttunen@thl.fi)

Version: 3
Date: 8 September 2014

Author’s response to reviews: see over
REVIEWER 1/Brandy Roane

The authors have satisfactorily revised the manuscript. No further revisions are recommended.

REVIEWER 2/Todd Arnedt

1. The rationale for the subgrouping of sleep complaints is not convincing and inadequate. Non-restorative sleep should not be categorized as "no/minor sleep complaints" since it could represent, for example, the presence of a medical sleep disorder, such as sleep disordered breathing, which is certainly not a minor sleep complaint. A preferred approach would be to devise a continuous measure of sleep complaints from the K-SADS sleep items scores, which would range from 6-18. This would avoid the need to categorize entirely and would allow the authors to still address the fundamental question of the relationship between baseline sleep complaints and clinical outcome.

We agree with the reviewer that complaints of non-restorative sleep often are present among adolescents with medical sleep disorders such as obstructive sleep apnea. However, complaints of non-restorative sleep are frequently present also in healthy adolescents, and they do not necessarily indicate objectively disrupted sleep. The prevalence of frequent complaints of non-restorative sleep among the general adolescent population in Finland is ~40% (Kronholm E et al, submitted data). None of the adolescents in our sample had on axis III a diagnosis of a medical disorder linked with sleep-disordered breathing (e.g. obstructive sleep apnea), other neurological sleep disorder, or obesity (which could increase the risk for sleep-disordered breathing). Thus, we find it highly unlikely that the presence of sleep-disordered breathing or other medical sleep disorder would have significantly influenced our results.

Despite this, since the division into categories was arbitrary in the previous version of the manuscript, we have now revised our manuscript according to the recommendation of the reviewer: instead of the categories used in the previous version of the manuscript, we have now used a continuous measure of sleep complaints ranging from 6-18, devised from the K-SADS sleep items (including also the complaint of non-restorative sleep). This continuous measure has now been used throughout the manuscript. Consequently,
many sections of the manuscript have been changed. In particular, modifications have been made to the following sections:

- Results: The association of baseline sleep complaints with one-year clinical course + Rate of depression symptom improvement
- Table 1
- Figure 2

The main results or conclusions did not change as compared to the previous version of the manuscript.

In figure 2, we decided to present categorized data. With this figure we wish to illustrate the observed findings in a clearer and simpler way for the interested clinician. The categories presented (only) in this figure are, however, now formed based on the sleep complaint severity score (scale 6-18; see Figure 2 legend for details).

2. The authors justified the use of the primary study measures well, but the GAF ratings should include an inter-rater reliability statistic if available. The authors indicate that there was good inter-rater reliability for the mood disorder diagnosis (lines 152-154), but this reliability may be different from the GAF reliability.

Unfortunately we have no data readily available to calculate inter-rater reliabilities for the GAF scores. However, the GAF scores (axis V assessment) along with the other DMS-IV diagnostic variables were subjected to a consensus meeting where the original investigator and one or two other research interviewers (of which at least one was a senior clinician) reached a consensus on all the measures included in the interview, including the GAF score. This consensus procedure and also the existing inter-rater reliability estimates on mood disorder diagnoses suggest that the interview-based measurements were used in a rather consistent manner between the interviewers.

We have now added the following mention in the text: “The diagnoses (axis I-V) were confirmed in a diagnostic meeting where the original investigator and at least one senior clinician reached consensus on all measures of the interview, and inter-rater reliability was assessed using 13 randomly selected videotaped interviews (good inter-rater reliability for mood disorder diagnoses; described in detail previously [24]).” (page 6, lines 151-155 in the clean version of the manuscript)

3. Lines 269-270: There remain concerns that no information is presented on any sleep-related treatment that may have been received by subjects. It appears that the authors only collected information on depression-related treatments, and thus it remains possible that the steeper trajectory of improvement among adolescents with sleep disturbances at baseline (pending the outcome following analyses with continuous sleep complaints outcome) could be related to joint treatment of the sleep disturbance and depression, which would be consistent with the adult literature. If information is explicitly available on sleep-related treatments, please include.
Unfortunately there is no explicit information available on the sleep-related treatments that the subjects have received during the naturalistic follow-up period. This is one of the weaknesses of the study, and it is now mentioned in the text. (p.15, lines 372-374)

Concerning **medication treatments** targeted to sleep problems, the picture is complicated. We have access to information on what medication (drug name + active ingredient) the adolescents were prescribed during the follow-up period. We have performed some additional analyses with this data, indicating that the use of nonbenzodiazepine sleep medication (z-drugs) was not associated with the baseline sleep complaint severity score (independent samples t-tests n.s.). (p. 11, lines 263-266) However, apart from the z-drugs (the only medication group clearly targeted to treat sleep problems in our sample), many other medications may have been used to ameliorate sleep. We have no information on e.g. if a benzodiazepine was prescribed for insomnia or for daytime anxiety. Similarly, many sedative neuroleptics, mirtazapine, hydroxyzine etc may have been used to ameliorate sleep (or to treat other symptoms). And, furthermore, all psychotropic medication can have positive/negative effects on sleep. This is now discussed in the discussion section (p.13-14, lines 326-336)

Concerning **non-medication treatments** specifically targeted to sleep problems, at the time of data collection (1998-2001), no systematic sleep-related psychological, behavioural, or chronotherapeutic treatments were used in the Finnish adolescent psychiatric treatment units. However, as the treatment choices were made individually, many adolescents may have been given advice on for example sleep hygiene measures during the appointments. This has not, however, been documented. The non-medication treatments for sleep problems are now mentioned in the discussion (p.14, lines 336-340)

4. The statement on lines 354-355 that "antidepressant drugs generally tend to ameliorate the sleep impairments in depression..." is not accurate. Antidepressants (mainly fluoxetine) have been shown repeatedly in laboratory sleep studies to objectively disrupt sleep, by reducing slow wave sleep, lengthening REM latency, increasing light stage 1 sleep, and fragmenting sleep overall. Please revise this sentence.

The reviewer is correct that antidepressants may disrupt sleep, and that e.g. fluoxetine has been shown to increase the lighter stages of sleep and increase awakenings during the night. The lengthening of the REM latency is, however, a potentially beneficial effect of SSRI medication, since depression in some patients is linked with shortened REM latency. The effects of different medications on sleep structure in depressed adolescents remain, however, understudied, and strong conclusions on the matter need to be avoided.

Based on the reviewer’s recommendation we have revised the sentence on the effects of antidepressant medication on sleep in depressed adolescents as follows:

Depressed patients with sleep disturbances may respond differently to both pharmacological and other treatment of depression compared to those without sleep problems [11,50-52]. The more detailed findings remain, however, mixed, and research evidence is lacking. **Antidepressant drugs may ameliorate the sleep impairments in depression by e.g. inhibiting REM sleep [53], and especially patients with reduced REM sleep latency may respond favourably to antidepressants [54]. In a preliminary study, however, fluoxetine had a negative impact on sleep in depressed children and adolescents 357 [55]. (...)** (p. 14, lines 341-346)