Evidence-based medicine in geriatrics

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Acetaminophen for self-reported sleep problems in an elderly population (ASLEEP): a randomized double-blind placebo-controlled trial


Abstract

Objectives: To investigate whether acetaminophen is effective in treating self-reported sleep problems in the elderly.

Design: Double-blind placebo-controlled randomized clinical trial (1:1)

Setting: Primary care

Participants: 61 individuals aged 65 years or older with self-reported sleep problems. Eligible participants should be able to give informed consent, should not be severely cognitively impaired (MMSE ≥ 20), should not have pain and should not use acetaminophen on a regular basis because of pain complaints.

Intervention: After a baseline week, acetaminophen 1000 mg or placebo at bedtime for a period of two weeks was randomly allocated by means of a computer-made randomization list. Participants, investigators and analysts were blinded to group assessment until the end of the study.

Measurements: The primary endpoint was the self-reported sleep at the end of the study, as measured by the Insomnia Severity Index (ISI).

Results: Between July 2011 and December 2012, 61 participants were enrolled and randomized. The median age was 73 years; 90% of the people lived at home and few had co-morbidities as reflected by the Charlson comorbidity index. There were no differences between the intervention (n=28) and control group (n=28) in the mean score on the ISI at the end of the study (14.3 vs. 15.3, p=0.38).

Conclusions: In this small sample, treatment with acetaminophen did not improve the severity of sleep problems. Thee participants were heterogeneous; consequently, we might have missed an effect. Although there is no evidence available that justifies the prescription of acetaminophen to people with sleep problems, older people who use acetaminophen as an over-the-counter drug and feel they benefit from its use can better continue acetaminophen than start benzodiazepines.
Acetaminophen for self-reported sleep problems

Introduction
The prevalence of sleep problems is high in older people. In the Established Populations for Epidemiologic Studies of the Elderly (EPESE), involving 9,282 community-dwelling persons aged 65 and older, 50% reported sleep complaints, of which 25% had insomnia (1). In a study among 1503 older patients in primary care practices, the most commonly reported sleep-related complaints were difficulty sleeping (45%), snoring (33.3%) and excessive daytime sleepiness (27.1%) (2). People with insomnia report a negative impact on quality of life (3).

There are various hypotheses why older people suffer from sleep problems. Medical conditions such as depression, cardiovascular diseases, and pulmonary problems can interfere with a good night’s rest. In addition, older people often use medication that causes sleep problems, such as beta blockers and psychopharmacological drugs (4). Furthermore, some older people suffer from changes in circadian rhythm, because of which they feel sleepy in the early evening and/or awake early (4).

The pharmacological approach of sleep problems is only advised if nonpharmacological measures had insufficient effect (4;5). Many older people are prescribed sedative benzodiazepine as a hypnotic, although they are at increased risk for harmful side effects because of the age-related pharmacodynamic and pharmokinetic changes (6). Adverse events, such as falls (7;8), cognitive impairment (9) and drug dependence (10) and even an risk of death are reported (11). Considering the major health impact, the complexity and the high prevalence in often vulnerable patients, sleep complaints are an important area of investigation and simple treatments with fewer side effects are urgently needed.

In geriatric clinical practice, we have noticed that older community dwelling patients use acetaminophen for chronic sleep problems without having specific underlying pain complaints. In a survey of 176 elderly people, 48% stated that they used non-prescription products for sleeping problems. Nineteen percent of the individuals who had used a non-prescription product used acetaminophen (12).

Although in the literature we did not find any trials or observational studies that report the effect of acetaminophen on sleep problems, there are some ideas as to why this medication might have a positive effect on sleep. Possibly, acetaminophen relieves unrecognized pain complaints during the night. Another hypothesis is that after metabolism in the brain, the breakdown product of acetaminophen reinforces the activity of the cannabinoid receptors, which in turn reinforce the activity of the serotonergic system (13;14). Acetaminophen lowers body temperature, also related to better sleep (15). Finally, its purported effect could be mainly placebo.

We performed a randomized controlled trial named ASLEEP - Acetaminophen for SLEEP Problems in Elderly Patients. The aim of this trial was to investigate whether acetaminophen has a beneficial effect on self-reported sleep problems in older people. In addition, in order to validate the subjective sleep parameters against objectively measured indices of the sleep-wake pattern, we aimed to study the effects of
acetaminophen on periods of wakefulness and sleep as measured by means of an actiwatch in a subgroup of our participants (16).

Methods and design

Trial design
This was a phase 3, investigator-initiated, multicenter, stratified (per center, with balanced randomization (1:1)) double-blind, placebo-controlled trial, conducted in the Netherlands, between July 2011 and December 2012 (three sites). Full details of the study protocol are described elsewhere(17). After trial commencement, an amendment was made to the protocol in order to enhance recruitment: both visitors to the outpatient clinic could be enrolled, as well as respondents to advertisements in local newspapers. The study was carried out in compliance with the Helsinki Declaration and Good Clinical Practice guidelines and approved by the Medical Ethics Committee of the Academic Medical Center. The executive boards of the other participating centers, the Slotervaart Hospital and Gelre Hospitals, provided local feasibility approval. Written informed consent was obtained from all participants. No data safety and monitoring board was installed, because acetaminophen was considered safe. This trial was registered at the Netherlands Trial Register (NTR2747).

Participants and setting
The study population comprised people aged 65 years and older who complained of disturbed sleep. Participants could be either patients that visited one of the participating hospitals’ outpatient clinics, or subjects recruited after advertising in local newspapers. The visitors of the outpatient clinic were enrolled during their visit; the respondents to the advertisements were invited to come to one of the participating hospitals for the intake. Sleep problems were defined as one or more of the following symptoms: difficulties with falling asleep, maintaining sleep and early awakenings without being able to fall asleep again, with a frequency of at least three nights a week, at least during three consecutive weeks (18). Eligible participants should have a score of five points or more on the Pittsburgh Sleep Quality Index (PSQI) (19). This is a validated instrument that assesses sleep quality and disturbances over a one-month time interval. A global PSQI score greater than five yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing good and poor sleepers (19). Further inclusion criteria were: a score of 20 points or more on the Minimal Mental State Examination (MMSE) (20) and participants had to be willing and medically able to receive therapy according to the protocol for the duration of the study. In addition, participants should be able to give informed consent themselves. Exclusion criteria were the inability to speak, understand or write Dutch, the inability to follow the study procedures as assessed by the researcher, alcohol abuse (≥ four units daily), pain complaints resulting in a pain score of six or higher at the visual analogue (VAS) scale, impaired liver function as reflected by increased ALAT or liver disease in the past,
suicidal tendencies and participation in other sleep trials. Use of acetaminophen and not being able to stop this medication during the study period was a reason for exclusion as well. In addition, participants with a life expectancy less than three months according to the physician or with a sleep problem due to a medical or somatic reason (such as obstructive sleep apnea syndrome, restless legs, delirium, or a depression needing the start of antidepressants) were excluded.

The inclusion took place at the outpatient clinics of one of the participating hospitals: the Academic Medical Center in Amsterdam (a major teaching hospital), and of two regional teaching hospitals, the Slotervaart Hospital in Amsterdam and Gelre Hospitals in Apeldoorn. During the study period, participants were at home.

**Interventions**

The study period per participant was three weeks. Use of study medication was limited to the last two weeks to enable baseline data collection in the first week. In the second and third week they took either acetaminophen, or placebo, once per day at bedtime. The medication comprised two tablets containing either 500 mg of acetaminophen (Pharmacy the Hague hospitals, The Netherlands) or a matched placebo. In the sleep diary, participants registered whether they had taken the study medication the night before. Participants who already used acetaminophen as a sleeping pill were asked to stop the medication for the complete study period of three weeks. Participants were allowed to continue their own chronic prescriptions, including their sleeping pills. Apart from the study medication, participants were asked not to start new sleeping pills or acetaminophen as a painkiller during the study period. Participants were excluded if they took sleeping pills of acetaminophen despite these restrictions. After exclusion, the study medication was stopped, but data collection was continued.

**Data collection**

At baseline, demographic data, medical history and present medication use were recorded. Functional status was assessed using the 15-item modified Katz Index of Activities of Daily Living (ADL) based on the situation two weeks prior to admission. Furthermore, sleep parameters registered in the sleep diary and the Insomnia Severity Index (ISI) after the first study week were registered. The severity and number of comorbidities was scored using the Charlson comorbidity index (21).

**Outcomes**

The primary outcome was the mean score on the Insomnia Severity Index (ISI) at 21 days (22;23). The ISI is a reliable and validated instrument for the evaluation of self-reported sleep-problems, and has also been investigated among seniors. It is a 0-28 point scale, the higher the score, the more sleep complaints a patient has (24-26). The following categories are used to classify sleep complaints: 0-7: not clinically significant, 8-14: sub threshold insomnia, 15-21: moderate insomnia and 22-28: severe insomnia. A minimal
important difference of 6 points on these scale has been reported (25); we assumed a
decrease or increase of three points compared to baseline on this scale as clinically
relevant because we were interested in a small effect as well.
We intended to measure objective sleep parameters as secondary outcome, registered by
means of an actiwatch (16;27). Detailed description of the actiwatch method can be found
in the protocol (17).
In addition to this, all participants recorded in a sleep diary the time they got into and out
of bed, the estimated time they fell asleep and woke up in the morning and the number of
awakenings during the night. These data were used to estimate the following sleep/wake
endpoints: total sleep time (minutes sleep between bedtime and wake time), sleep
efficiency (percentage of time asleep while in bed), sleep onset latency (minutes awake
between sleep onset and wake time) and number of wake episodes (16). Furthermore,
participants daily registered a pain score by means of a 10 cm visual analogue scale (VAS)
and rated their sleep quality with a score of 0-10. The registrations of the first week (mean
values), when participants used no medication, were compared with the mean values of
the second and third week taken together.

**Sample size**
The primary endpoint were subjective sleep problems, as reflected in the score on the ISI
at the end of the third week of the two groups. From the literature, a prevalence of sleep
problems of 30%-50% is reported (1). Group sample sizes of 75 per group were assumed
to achieve 80% power to detect a difference of three points on the Insomnia Severity
Index between the null hypothesis that both group mean differences are zero and the
alternative hypothesis that the mean difference of the intervention group is three with
assumed group standard deviations of 6.5. This calculation was based on data from a
study in which a group of participants with insomnia were treated with either eszopiclone
or placebo (28).

**Randomization and masking**
After baseline assessments, participants were randomized to acetaminophen or a
matched placebo treatment that looked, tasted and smelled the same. Randomization
was stratified by study center, with fixed blocks of 10 participants within the stratum.
Before the start of the study, the randomization schedule was generated with a computer
by an independent statistician; the randomization list was maintained by the trial-
pharmacist. The medication was provided in sequentially numbered containers according
to the randomization list. Study medication was manufactured and packaged in small
containers labeled according to Good Manufacturing Procedure (GMP) guidelines.
Investigators, other staff personnel and participants remained blinded until the last
participant had completed the study and the data analysis had been completed.
Statistical methods
Data were analyzed according to the intention-to-treat principle. The outcome measures were tested by using T-Tests and Mann-Whitney Tests for continuous variables and by using Chi-squared tests for categorical outcomes. We performed a pre-specified subgroup analysis for participants using sleeping pills at baseline and those who did not and for study center. The primary outcome, the score on the Insomnia Severity Index, was used as a continuous variable. Furthermore, we performed multivariate logistic regression for factors that might have an influence on the sleep quality, such as coffee and alcohol use and pain; as well as for baseline imbalance. Analyses were performed with the program Statistical Package for the Social Sciences (SPSS) version 20.0. P values <0.05 were considered statistically significant.

Results
Participants, recruitment and baseline data
Between July 2011 and December 2012 61 participants were eligible and gave their consent. After randomization, five participants were excluded or ended the study prematurely (Figure 1).

Figure 1: Flowchart of included patients

Unfortunately, no data were available for the participants who were lost to follow-up. Therefore, 56 participants were analyzed: 28 participants in the placebo-group and 28 in the acetaminophen group. Baseline characteristics were well matched among the two study groups (Table 1).
Table 1: Baseline characteristics of enrolled patients

<table>
<thead>
<tr>
<th></th>
<th>Acetaminophen (n=29)</th>
<th>Placebo (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ((year), median, range)</td>
<td>73.0 (65-89)</td>
<td>74.0 (65-88)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>48.3</td>
<td>34.4</td>
</tr>
<tr>
<td>Country of birth the Netherlands (%)</td>
<td>82.8</td>
<td>93.8</td>
</tr>
<tr>
<td>Living single (%)</td>
<td>51.7</td>
<td>43.8</td>
</tr>
<tr>
<td>Living independently (%)</td>
<td>89.7</td>
<td>90.0</td>
</tr>
<tr>
<td>Katz score (median, range)</td>
<td>0 (0-9)</td>
<td>0 (0-3)</td>
</tr>
<tr>
<td>Charlson comorbidity index (median, (range))</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
</tr>
<tr>
<td>No. of medications (median, (range))</td>
<td>5 (0-15)</td>
<td>3 (0-17)</td>
</tr>
<tr>
<td>Beta blockers n (%)</td>
<td>11 (37.9)</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>Sleeping pills n (%)</td>
<td>6 (20.7)</td>
<td>9 (28.1)</td>
</tr>
<tr>
<td>Pain killers n (%)</td>
<td>6 (20.7)</td>
<td>9 (28.1)</td>
</tr>
<tr>
<td>MMSE (median, range)</td>
<td>29.0 (21-30)</td>
<td>30 (26-30)</td>
</tr>
<tr>
<td>MMSE ≤ 24</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>BMI (mean (SD'))</td>
<td>27.8 (6.7)</td>
<td>25.6 (5.0)</td>
</tr>
<tr>
<td>Alcohol consumption yes n (%)</td>
<td>21 (72.4)</td>
<td>18 (56.3)</td>
</tr>
<tr>
<td>No. of alcoholic consumptions per day (SD)</td>
<td>1.5 (0.9)</td>
<td>1.5 (0.9)</td>
</tr>
<tr>
<td>Coffee consumption n (%)</td>
<td>24 (82.8)</td>
<td>28 (93.3)</td>
</tr>
<tr>
<td>No. of coffee consumptions per day (SD)</td>
<td>3.6 (2.0)</td>
<td>3.5 (1.8)</td>
</tr>
<tr>
<td>PSQI (mean (SD))</td>
<td>13.0 (3.1)</td>
<td>13.0 (3.2)</td>
</tr>
<tr>
<td>Mean VAS for pain during 1st week (median, range)</td>
<td>0.26 (0-5.2)</td>
<td>0.85 (0-5.9)</td>
</tr>
<tr>
<td>ISI at 7 days (mean (SD))</td>
<td>14.9 (4.6)</td>
<td>15.5 (3.7)</td>
</tr>
<tr>
<td>Mean total sleep time first week, hours (mean/SD)</td>
<td>6.0 (1.5)</td>
<td>5.6 (1.3)</td>
</tr>
<tr>
<td>No. of awakenings 1st week (mean (SD))</td>
<td>2.1 (1.0)</td>
<td>2.6 (1.2)</td>
</tr>
<tr>
<td>Sleep onset latency 1st week (minutes, median, (range))</td>
<td>49.3 (2.9-309.2)</td>
<td>58.9 (13.1-220.0)</td>
</tr>
<tr>
<td>Sleep efficiency, % (SD)</td>
<td>70.4 (16.7)</td>
<td>68.5 (16.5)</td>
</tr>
<tr>
<td>Mean mark for night’s rest 1st week (median, (range))</td>
<td>5.8 (1.0-7.3)</td>
<td>5.6 (3.1-6.9)</td>
</tr>
</tbody>
</table>

*Melatonin, benzodiazepines, zolpidem, zopiclon / 1Minimal mental state examination / Body Mass Index / Standard Deviation / Pittsburgh Sleep Quality Index / Visual Analogue Scale; the reported value is the mean of the seven VAS that patients scored daily / Insomnia Severity Index

Table 2: Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Acetaminophen (n=28)</th>
<th>Placebo (n=28)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISI at 21 days (mean (SD'))</td>
<td>14.3 (4.3)</td>
<td>15.3 (3.7)</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean difference ISI week 2/3 minus. week 1 (SD)</td>
<td>-0.24 (3.5)</td>
<td>0.00 (2.7)</td>
<td>0.78</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean total sleep time last two weeks, hours (mean (SD))</td>
<td>6.1 (1.3)</td>
<td>6.0 (1.2)</td>
<td>0.70</td>
</tr>
<tr>
<td>No. of awakenings 2nd and 3rd week (mean (SD))</td>
<td>1.9 (1.0)</td>
<td>2.4 (1.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Sleep onset latency 2nd and 3rd week (minutes, median)</td>
<td>50.4 (10.7-323.6)</td>
<td>61.3 (5.8-161.8)</td>
<td>0.68</td>
</tr>
<tr>
<td>Sleep efficiency, % (SD)</td>
<td>71.9 (15.2)</td>
<td>70.6 (13.4)</td>
<td>0.67</td>
</tr>
<tr>
<td>Mean mark for night’s rest (median, (range))</td>
<td>5.64 (3.1-7.0)</td>
<td>5.8 (1.0-7.9)</td>
<td>0.98</td>
</tr>
<tr>
<td>Mean VAS for pain 2nd and 3rd week (median, range)</td>
<td>0.21 (0-5.37)</td>
<td>0.34 (0-6.44)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*Insomnia Severity Index / Standard Deviation / Visual Analogue Scale

Median age was 73 years, 90% lived at home before admission and only one participant had an MMSE ≤ 24. Most participants were in good health, considering their low score on the Katz ADL index and the Charlson comorbidity-index.
Outcomes

No significant effect of acetaminophen on sleep problems could be demonstrated for the primary outcome: ISI at 21 days (Table 2). Pre-specifed subgroup analysis for participants who used sleeping pills at baseline (n=15) did not show differences (mean difference on Insomnia Severity Index 1.8 (95% confidence interval (CI) 1.6-5.0); neither did subgroup analysis for participants using pain killers ((n=15): the mean difference between the ISI at baseline and after the end of the study was 0.6 (95% CI 2.5-5.0).

Furthermore, in an exploratory analysis we investigated whether there was a difference between both groups in the number of participants whose score on the ISI increased or decreased. Again, there was no difference; in both the acetaminophen and placebo groups the distribution of participants whose score increased and whose score decreased was the same: in the placebo group 9 participants had a lower score on the ISI after three weeks, and in the intervention group 11 participants.

Logistic regression, adjusted for the stratification variable (treatment center) did not show a decrease on the ISI (Odds Ratio (OR) = 0.64, 95% CI 0.22-1.90). Furthermore, multivariate logistic regression (adjusted for factors that might influence sleep such as use of coffee and alcohol and for VAS, as there was a slight difference at baseline between the two groups) neither showed a treatment effect (OR = 0.92 (95% CI 0.29-2.93).

The secondary outcomes, the sleep parameters described in the sleep diary, were not statistically significant between groups (table 2). Unfortunately, the participants that were lost to follow-up (n=5) did not complete the protocol, usually for logistic reasons. Therefore, an intention-to-treat analysis was not possible. No harms were reported during the study period.

Unfortunately, the intended subgroup that used the actiwatch consisted of only five participants. This was mainly caused by logistic failure. In this small group, a non-significant increase of total sleep time (31 minutes) and a decrease of sleep onset latency (17 minutes) were shown in the treatment group (n=3).

Discussion

In this randomized double-blind placebo controlled clinical trial involving older participants with subjective sleep problems we found no effect of acetaminophen on the incidence and severity of sleep disorder. However, our sample was small and heterogeneous, therefore we might have missed an effect. Although there is no evidence available that justifies the prescription of acetaminophen to people with sleep problems, older people who use acetaminophen as an over-the-counter drug and feel they benefit from its use can safely continue acetaminophen. The effect for this group is probably mainly placebo.

It is known that performing research in older patients is difficult (29). The patients that visited the outpatient clinic of the participating hospitals often were not eligible because of cognitive impairment. Although many confirmed they had sleeping problems, they
usually gave priority to their other health problems and therefore considered the burden of participation in a trial as too big. Possibly, many potentially eligible patients considered their sleep problems as something that naturally occurs at older age and therefore did not want to participate. To enroll more participants, we had to expand our study population to people that responded to advertisements put in local newspapers. As a consequence, the participants in our study were generally younger and had fewer co-morbidities than the general population of geriatric outpatient clinics. Even though we designed the trial in such a way that the expected burden was as low as possible, we did not succeed in enrolling enough geriatric patients. Maybe enrolling patients visiting an outpatient clinic is not the most appropriate method, since they often are referred for more urgent other complaints. Possibly, performing this kind of trial in general practice and following up these patients by home visits would have resulted in a higher number of participants. Our study was underpowered to demonstrate a treatment effect. Therefore it is difficult to define the exact role of acetaminophen in the management of sleep problems. Appropriate treatment of sleep problems should start with nonpharmacologic interventions; pharmacologic treatment should only be started if indicated (30). Data suggest a slightly positive effect of cognitive behavioral interventions for insomnia in older people (31). Some authors recon that bright light therapy might help, because many poor sleepers have a disrupted cycle of their circadian rhythms; however there are no randomized trials available to base this conclusion on (32). Also, no trials were designed to test the effectiveness of physical exercise for the treatment of sleep problems in healthy older people (33). For patients with dementia, there is evidence that melatonin might be effective in circadian rhythm disturbances, thereby reducing sundowning (34). More studies are needed to establish the appropriate role and use of medications, and their safety and efficacy in the treatment of insomnia in older adults. Guidelines that direct the choice and use of pharmacologic and nonpharmacologic therapies are needed (35).
Acetaminophen for self-reported sleep problems

Reference list

Chapter 9


