Relationships Between Polypharmacy and the Sleep Cycle Among Active-Duty Service Members

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Context: Sleep disorders are frequent clinical presentations, especially among active-duty service members. Medications are one factor that can affect sleep in many ways.

Objective: To determine the effect of increasing numbers of medications on the sleep cycle of active-duty service members.

Methods: Medical records for active-duty service members who completed enhanced sleep assessments at the Psychiatry Continuity Service at Walter Reed National Military Medical Center from October 1, 2010, through November 30, 2013, were retrospectively reviewed. Data were collected on home sleep study findings, sleep-related self-report instrument scores, and active medications.

Results: A total of 135 medical records were reviewed. One hundred patients (74.07%) had an active prescription for a psychoactive drug. Among all patients, the mean (SD) number of active medications per participant was 2.52 (2.09), with 118 patients (82.96%) having an active medication for depression or insomnia. As the number of prescribed medications increased, the percentage of the sleep cycle in deep sleep decreased (P=.049), the percentage of light sleep increased (P=.016), the percentage of rapid eye movement sleep decreased (P=.083), and the first episode of deep sleep was delayed (P=.056). An increased number of medications had no significant impact on total sleep time (P>.05).

Conclusion: An increasing number of medications did not influence total sleep time but negatively affected the sleep cycle.

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Conservative estimates suggest that one-third of the US population has a sleep disorder, accounting for its frequent clinical presentation.[1] Insomnia has been reported as the most commonly cited problem among service members returning from a combat deployment.[2] In our experience, sleep problems are particularly prevalent among active-duty service members with combat-related posttraumatic stress disorder (PTSD). According to Ribeiro et al,[3] insomnia is a risk factor for suicidal tendencies among recent military veterans. Because roughly half of all individuals with chronic insomnia have a psychiatric disorder,[4] prescription medications are also common in this patient population.

Medications can affect sleep in many ways; even those that are prescribed for insomnia can produce unhelpful side effects. Commonly prescribed sedative hypnotics such as temazepam, triazolam, and zolpidem reduce total rapid eye movement (REM) sleep.[5] Among other psychotherapeutic medications, commonly prescribed selective serotonin uptake inhibitors reduce slow wave sleep, reduce total REM sleep, reduce total sleep time, and im-

pair sleep continuity.[6] Tricyclic antidepressants and trazodone increase slow wave sleep and total sleep time, with trazodone also promoting sleep continuity.[7] Antihistamines such as diphenhydramine increase slow wave sleep while also reducing total REM sleep.[5] Some of these same medications also cause nightmares or especially vivid dreams.[8,9] Multiple sedating medications may also affect respiration during sleep.[10]

For the current study, we investigated the effect of commonly prescribed medications, both alone and in combinations, on the sleep architecture of active-duty service members referred for psychiatric treatment. To our knowledge, we are the first to report findings of enhanced sleep assessments for this patient population. We hypothesized that medications would have a negative impact on a patient's sleep architecture.

Methods

Medical records were retrospectively reviewed for active-duty service members with sleep problems treated at the Psychiatry Continuity Service (PCS) at Walter Reed National Military Medical Center in Bethesda, Maryland, from October 1, 2010, through November 30, 2013. The study was reviewed by the Walter Reed National Military Medical Center's institutional review board and deemed exempt. Patients scoring above 20 on the Pittsburg Insomnia Rating Scale (PIRS) were included in the study.

The PIRS is a 20-item self-report instrument that assesses a person's sleep over the preceding 7-day period.[11] Scores on the PIRS range from 0 to 60, with scores above 20 suggesting insomnia. Typical questions on the PIRS include, "From the time you tried to go to sleep, how long did it take to fall asleep on most nights?" and "If you woke up during the night, how long did it take to fall back to sleep on most nights?"

In accordance with the PCS standard of care, patients who scored above 20 on the PIRS received an enhanced sleep assessment, which included a home sleep study and several standardized self-administered assessment instruments. For the present study, we examined patients' enhanced sleep assessment findings, as well as those patients' concurrent medications on the day the home sleep study was conducted.

PCS Enhanced Sleep Assessment Measures

Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) consists of 8 questions that ask patients to rate their chance of dozing during specific situations using a 4-point Likert-type scale ranging from 0 ("no chance of dozing") to 3 ("high chance of dozing").[12] Questions include situations such as "[s]itting and reading," "[w]atching TV," or "[s]itting inactive in a public space." Scores of 10 or greater suggest daytime sleepiness.

Pre-Sleep Arousal Scale

The Pre-Sleep Arousal Scale contains 16 questions with response options on a 5-point Likert scale ranging from 1 ("not at all") to 5 ("extremely").[13] The Pre-Sleep Arousal Scale has 2 subscales—somatic and cognitive. Somatic questions ask respondents about issues such as "a jittery, nervous feeling in your body," whereas the cognitive questions ask about issues such as "worry about falling asleep." Scores for each of the subscales range from 8 to 40. The Pre-Sleep Arousal scale does not have threshold scores, but higher scores indicate greater arousal before falling asleep. The clinician or researcher correlates higher scores with increasing somatic or cognitive factors that interfere with sleep initiation.

Zung Self-Rating Scales

The Zung Self-Rating Scales[15-17] are 20-item self-report instruments in which respondents answer questions regarding depression or anxiety. For both instruments, respondents can choose among 4 descriptions for each question—"a little of the time," "some of the time," "good part of the time," and "most of the time"—scored

as 1, 2, 3, and 4, respectively. Typical questions on the Zung Self-Rating Depression Scale include "I feel downhearted and blue" and "Morning is when I feel the best." The Zung Self-Rating Anxiety Scale includes questions such as, "I feel more nervous and anxious than usual" and "I fall asleep easily and get a good night's rest." Scores above 50 on the Zung Self-Rating Depression Scale suggest clinically significant depression, and scores above 45 on the Zung Self-Rating Anxiety Scale suggest clinically significant anxiety.

PCL-M

The PCL-M is a 17-item self-report instrument in which respondents choose among 5 descriptions (ie, "not at all," "a little bit," "moderately," "quite a bit," and "extremely," scored on a sliding scale of 1 through 5) in answering questions regarding stressful life experiences.[18] A typical question from the PCL-M asks the service member if they are "having physical reactions when something reminded you of a stressful military experience from the past." Scores above 49 suggest symptoms consistent with the clinical diagnosis of PTSD.

Home Sleep Studies

The WatchPAT 200 (Itamar Medical) was used to conduct the home sleep study portion of the enhanced sleep assessment.[19-21] This medical device, approved by the US Food and Drug Administration, calculates sleep apnea severity using 3 measurements: the apnea/hypopnea index (AHI), the oxygen desaturation index (ODI), and the respiratory disturbance index (RDI). The WatchPAT also reports values for body mass index and the sleep cycle in terms of percentage of the cycle in deep sleep, in light sleep, in REM sleep, and awake.

Statistical Analysis

SPSS statistical software (version 20; SPSS Inc) was used to analyze the data using descriptive, frequency, correlate, and comparison statistics. A *P* value less than .05 was considered statistically significant.

Results

A total of 135 medical records of active-duty service members were reviewed. Approximately two-thirds of patients were men (87 [64.4%]), with a median age range of 26 to 30 years.

Mean (SD) findings were as follows: PIRS score, 41.10 (10.52) (n=135); total sleep time, 6.12 (1.57) hours (n=134); percentage of the night in deep sleep, 20.8% (6.09%) (n=119); and percentage of the night awake, 21.25% (12.69%) (n=134). The clinical characteristics of the study patients were consistent with those of patients experiencing depression, PTSD, and anxiety (*Table 1*).

In terms of medications, approximately three-quarters of patients (100 of 135 [74.07%]) had an active prescription for a psychoactive drug, with a mean (SD) of 2.52 (2.09) active medications per patient. Of 135 active medications that comprised >5% of the identified drug, the majority (112 [82.96%]) were for depression, sleep problems, or both (*Table 2*).

Results showed that as the number of prescribed medications increased, the percentage of the sleep cycle in deep sleep significantly decreased (*P*=.049), the percentage of light sleep increased (*P*=.016), the percentage of REM sleep decreased (*P*=.083), and the first episode of deep sleep was delayed (*P*=.056). Increasing the number of medications did not significantly alter the amount of time awake, the number of arousals through the night, the total time slept, or sleep latency (*P*>.05) (*Table 3*). The number of active medications (ie, 1-6) did not have a statistically significant effect on total sleep time (*Table 4*).

Discussion

Chronic sleep problems can be a frustrating challenge for both the clinician and the patient, particularly when medications, either alone or in combination, do not produce an optimum outcome. Sedative-hypnotic medications may help a person fall asleep and may even promote an in-

Table 1.
Enhanced Sleep Assessment Findings Among Active-Duty Service Members (N=135)

Measure	Mean (SD)
PIRS	41.10 (10.52)
Epworth Sleepiness Scale[a]	8.96 (5.44)
Pre-Sleep Arousal Scale[a]	
Somatic	18 (6.57)
Cognitive	27.08 (7.56)
Total	45.01 (12.72)
Zung Self-Rating Scale[b]	
Anxiety	42.58 (13.76)
Depression	49.28 (11.76)
PCL-M[b]	51.36 (18.13)
BMI[c]	27.10 (4.28)
Sleep Time, %	
REM sleep[d]	20.63 (8.35)
Deep sleep[d]	20.81 (6.09)
Light sleep[d]	58.56 (11.14)
Awake[a]	21.25 (12.69)
Time to Sleep, min[e]	25.28 (15.60)
Total Sleep Time, min[a]	366.68 (93.61)
Sleep Apnea Severity[f]	
AHI	3.78 (4.60)
ODI	1.66 (2.69)
RDI	10.40 (6.49)

[a] n=134
[b] n=122
[c] n=133
[d] n=119
[e] n=118
[f] n=123

Abbreviations: AHI, apnea/hypopnea index; BMI, body mass index; ODI, oxygen desaturation index; PCL-M, Posttraumatic Stress Disorder Checklist – Military Version; PIRS, Pittsburg Insomnia Rating Scale; RDI, respiratory disturbance index; REM, rapid eye movement.

Table 2.
Current Medications of Active-Duty Service Members for Depression and Sleep Problems

Medication[a]	No. (%)[b]
Sertraline hydrochloride	24 (17.78)
Trazodone hydrochloride	23 (17.0)
Prazosin hydrochloride	18 (13.33)
Clonazepam	12 (8.89)
Zolpidem tartrate	10 (7.41)
Fluoxetine hydrochloride	10 (7.41)
Quetiapine fumarate	8 (5.93)
Eszopiclone	7 (5.19)

[a] Table lists only medications comprising >5% of the identified drug.
[b] A total of 135 medications met the >5% threshold. Most participants had more than 1 current medication.

crease in total sleep time. On awakening, however, the person may feel unrefreshed, tired, or groggy.

In addition to sleep problems, patients in the present study all had varying degrees of anxiety and depression, a common clinical finding.

The enhanced sleep assessments revealed that an increased number of psychoactive medications did not improve chronic insomnia and may have produced unintended, adverse effects. For example, the study showed that as the number of prescribed medications increased, the percentage of deep sleep decreased, the percentage of light sleep increased, the percentage of REM sleep decreased, and the first episode of deep sleep was delayed. Our study also found that increasing the number of medications did not significantly reduce the number of intrusive arousals through the night. In a similar finding, multiple medications did not improve the total time asleep.

It is important to note that the medications prescribed to the patients in this study are typical for patients with

Table 3.
Correlations Between Total Number of Current Medications and Sleep in Active-Duty Service Members (N=135)

Measure	Pearson Correlation	*P* Value[a]
Sleep Time, %		
Deep sleep[b]	−.181	.049
Light sleep[b]	.219	.016
REM sleep[b]	−.160	.083
Awake[c]	−.002	.981
Arousals, No.[d]	−.024	.801
Time to Sleep, min[e]	.105	.258
Onset of First Deep Sleep, min[e]	.176	.056
Total Sleep Time, min[c]	−.044	.611

[a] Statistical tests were 2-tailed.
[b] n=119
[c] n=134
[d] n=115
[e] n=118

Abbreviation: REM, rapid eye movement.

Table 4.
Number of Current Medications and Effect on Total Sleep Time in Active-Duty Service Members (N=135)

	Mean (SD)		
Medications, No.	Total Sleep Time, min	n[a]	*P* Value[b]
0	382 (63.65)	35	NA
1	385 (98.29)	9	.908
2	352 (114.63)	25	.212
3	351 (119.89)	27	.195
4	366 (57.80)	14	.415
5	364 (121.19)	10	.539
6	353 (75.18)	8	.269

[a] Seven participants had more than 6 current medications (data not shown).
[b] Statistical tests were 2-tailed.

Abbreviation: NA, not applicable.

anxiety, depression, and sleep problems. As individual drugs, they may each have pronounced effects on sleep architecture and—as the present study suggests—they may have a cumulative effect on the sleep cycle when used in combination.

Our study had some limitations. For example, patients may have been taking other unknown psychoactive drugs or not taking their prescribed medications as directed. In addition, alcohol use is always a wild card in the sense that its use may not be disclosed, but its pernicious effect on the sleep cycle would only augment the findings in the current study.[22] Mitigating these concerns are the large size of the study and the 3-year data collection time, but even so, replicating the study with a larger sample size would confirm our findings. Examining how specific combinations of medications affect sleep cycle would be an interesting area for future research.

In addition, although we did not exclude any types of medication in our study, the medications of our patient population likely differed from those of other populations. For example, because this study was conducted in a psychiatry unit, it was expected that the participants would be on more psychiatric-type medications. In addition, our population of active-duty service members is young and tends to be healthier than a similar age-matched sample. As such, the patients in our study likely had fewer types of medicine (eg, medication for diabetes mellitus is rare in our patients), which may have led to less confounding variables. Thus, additional research in other patient populations is warranted.

For individuals with chronic insomnia, nonpharmacologic treatment interventions, such as sleep restriction or cognitive behavior therapy, may be useful alternatives.[23] At the very least, the use of evidenced-based nonpharmacologic treatments for insomnia would not increase the potential risks associated with polypharmacy found in this study.

Conclusion

The findings of the present study suggest that medications alone may not resolve chronic sleep problems and, in some cases, may actually worsen the condition. On the basis of these findings, clinicians should reassess the risks and benefits of polypharmacy and consider nonpharmacologic treatment options for these patients.

Author Contributions

Both authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; both authors drafted the article or revised it critically for important intellectual content; both authors gave final approval of the version of the article to be published; and both authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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