Zolpidem as a Sleep Aid for Military Aviators

Guan Sen Kew; Brian See

INTRODUCTION: Zolpidem is a short-acting nonbenzodiazepine hypnotic that has been approved by the Republic of Singapore Air Force (RSAF) for aircrew sleep management since 2005. Prior to consuming zolpidem for operational reasons, each RSAF aircrew member is required to undergo a ground test to exclude operationally relevant adverse drug effects. This study describes the RSAF's zolpidem ground testing outcomes over a 12.5-yr period.

METHODS: This is a retrospective case series of 578 RSAF aircrew members who underwent zolpidem test dosing from 1 January 2005 to 30 June 2017.

RESULTS: The median age was 29 yr (range, 19–54 yr) and the mean age was 30.1 yr ± 6.3 yr. Of the aircrew members, 568 (98.3%) were men and all were of Asian origin; 558 (96.5%) were medically cleared for the operational use of zolpidem. Among the 20 (3.5%) who failed zolpidem ground testing, next-day drowsiness (cumulative incidence, 1.04%), headache (cumulative incidence, 0.87%), and dizziness (cumulative incidence, 0.35%) were the most common causes of failure. None of the aircrew members reported abnormal sleep behaviors or major adverse drug events from zolpidem ingestion.

DISCUSSION: Our results suggest a low occurrence of adverse effects among military aircrew members who undergo zolpidem test dosing prior to using the drug operationally. To our knowledge, this is the single largest published case series of zolpidem ground testing outcomes among Asian military aviators.

KEYWORDS: Asian, hypnotic, side effects, adverse drug events, fatigue, pilots.

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Zolpidem is a short-acting nonbenzodiazepine compound of the imdazopyridine class that has proved useful in the aviation context. Specifically, it promotes moderate-length sleep durations (4 to 7 h) when these sleep opportunities occur at times or in environments that are not conducive to sleep; aids in sleep initiation following eastward travel across 3 to 9 times zones; and has the advantage of a relatively short half-life of 2.5 h, which minimizes the possibility of post-sleep hangover effects.[5]

Zolpidem has been approved by the Republic of Singapore Air Force (RSAF) for aircrew sleep management since 2005. Originally, the drug was dosed at 10 mg immediately before sleep for aircrew members of both genders; however, following the issuance of a drug safety communication by the U.S. Food and Drug Administration in 2013 regarding new data that showed an increased risk of next-day impairment when performing morning tasks among women due to their slower elimination of zolpidem,[6] the dosage prescribed to female aircrew members was reduced to 5 mg. As a policy, the use of zolpidem by aircrew members as a fatigue countermeasure is strictly voluntary.

Prior to consuming zolpidem for operational reasons, each RSAF aircrew member is required to undergo a ground test to exclude operationally relevant adverse drug effects. This involves the self-administration of an appropriate oral zolpidem dosage just prior to usual bedtime, followed by the completion of a standardized questionnaire the next day. Completed questionnaires are then reviewed by a flight surgeon to determine the individual's suitability for zolpidem use, and all questionnaire results are subsequently entered into an electronic database at the RSAF Aeromedical Center. To our knowledge, this represents the single largest published database of zolpidem ground testing outcomes among Asian military aviators.

METHODS

This is a retrospective case series of 578 RSAF aircrew who underwent zolpidem ground testing from 1 January 2005 to

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30 June 2017. The aircrew members were identified using the RSAF Aeromedical Center's electronic database of zolpidem ground testing outcomes. The database records of aircrew members who were not medically cleared for the operational use of zolpidem were scrutinized to identify the reasons for failing ground testing. For those with missing data fields in the electronic database, their paper-based questionnaires were retrieved to obtain the requisite information. The study was approved by the Singapore Armed Forces Joint Medical Committee (Research).

RESULTS

The median age of the aircrew members was 29 yr (range, 19–54 yr) and their mean age was 30.1 yr ± 6.3 yr. Out of the 578 aircrew members, 568 (98.3%) were men and 10 (1.7%) were women. Based on medical records, all aircrew members were of Asian origin. None of the aircrew members declared a history of depression or pre-existing cardiac, respiratory, renal or liver impairment.

A total of 558 (96.5%) aircrew members were medically cleared for the operational use of zolpidem. Among the 20 (3.5%) aircrew members who failed zolpidem ground testing, next-day drowsiness (cumulative incidence, 1.04%), headache (cumulative incidence, 0.87%), and dizziness (cumulative incidence, 0.35%) were the most common causes of failure. Three (cumulative incidence, 0.52%) aircrew members were not medically cleared as they reported one of the following negative cognitive effects: slowed reaction, difficulty in focusing, or poor judgment. **Table I** presents a breakdown of the reasons for aircrew members failing zolpidem ground testing. None of the aircrew members reported abnormal sleep behaviors or major adverse drug events from zolpidem ingestion.

DISCUSSION

Zolpidem was approved by the FDA in 1992 as a short-term treatment of insomnia characterized by difficulties in sleep initiation, and subsequent experimental studies found the drug to be militarily useful. One study conducted on U.S. Army aviators found that zolpidem use improved their alertness and performance during the final 20 h of a 38-h continuous wakefulness period without causing operationally significant side effects.[3] Other studies revealed that zolpidem was more effective than melatonin or placebo in relieving jet lag symptoms,[13] as well as improving the nighttime sleep quality and subsequent daytime performance of subjects.[11] It also has a lower potential for dependence and abuse, compared with benzodiazepines.[8] The U.S. Air Force and U.S. Army have approved the use of zolpidem to promote sleep under specific circumstances.[4] The Indian Air Force and the Royal Australian Air Force have also reported that they issue zolpidem to their aircrew members when operationally indicated.[9,14]

Singapore's military has long recognized the need for sleep management to optimize the performance of its combatants.[7] The introduction of zolpidem, a short-acting hypnotic that decreases sleep-onset latency, improves sleep quality and does not exhibit tolerance or rebound following short-term use at recommended dosage,[2] to the RSAF's aircrew fatigue management armamentarium was thus an important measure to enhance medical support for sustained flying operations. Notwithstanding the pharmacological evidence that zolpidem has a better side effect profile compared to benzodiazepines, the RSAF requires its aircrew members to experience a zolpidem test dose under medical supervision before any operational usage to ensure the absence of duty-relevant side effects. In addition, a mandatory 8-h grounding period following each immediate-release zolpidem dose is imposed as a further safeguard against the drug's known acute negative effects on the specific cognitive functions of attention, verbal memory, and processing speed.[12] These regulations are in keeping with the Aerospace Medical Association's position statement on the military use of sleep-inducing agents.[5]

This study of the RSAF Aeromedical Center's zolpidem ground testing outcomes found the cumulative incidence of failure over a 12.5 yr period to be 3.5%. This is comparable to the approximately 4% of patients in clinical trials who discontinue the drug due to an adverse reaction.[1] The slightly lower incidence of reported side effects in our study population could be attributed to the higher doses of zolpidem (up to 90 mg) administered in some of the premarketing clinical trials. Based on data from a total of 685 subjects across 11 placebo-controlled short-term U.S. efficacy trials involving zolpidem doses of up to 10 mg, the most frequent adverse events observed at an incidence of ≥1% were headache, drowsiness, dizziness, and diarrhea.[1] Our real-world experience is consistent with the data from these clinical studies, with next-day drowsiness, headache, and dizziness being the most common reasons for failing ground testing, albeit with all three side effects occurring at lower cumulative incidences. A small number (0.52%) of aircrew members also reported symptoms congruous with zolpidem's known negative cognitive effects.

Several case reports have documented complex sleep-related behaviors induced by zolpidem, such as sleepwalking, sleep driving, and eating.[10,15,16] These somnambulism events are exceedingly rare and mostly occurred among patients who were prescribed zolpidem for more than a month for insomnia.

Table I. Reasons for Failing Zolpidem Ground Testing.

REASON FOR FAILURE	NUMBER (N = 578)	CUMULATIVE INCIDENCE (%)
Drowsiness	6	1.04
Headache	5	0.87
Dizziness	2	0.35
Rashes	1	0.18
Difficulty in focusing	1	0.18
Slowed reaction	1	0.18
Diarrhea	1	0.18
Generalized weakness	1	0.18
Poor judgment	1	0.18
No reason stated	1	0.18

Unsurprisingly, none of the RSAF aircrew members who underwent zolpidem test dosing reported abnormal sleep behaviors. Extrapolating this, we do not reasonably anticipate the occurrence of complex sleep-related behaviors among RSAF aircrew members who consume zolpidem during operations, as their prescriptions would be for short durations not exceeding a week.

A U.S. Air Force study of 27 personnel tasked to support remotely piloted aircraft surge operations found that 4 subjects (14.8%) experienced next day drowsiness, while another 4 subjects (14.8%) reported frequent awakening during the sleep period.[17] Apart from this small case series, most other studies published on the safety profile of zolpidem were conducted in experimental or clinical settings. This case series of 578 aircrew members who underwent zolpidem test dosing adds to the evidence base in support of the real-world use of zolpidem for fatigue management among aviators.

A particular strength of our study is its applicability to young Asian aircrew populations, with the mean and median ages of the study population being 30.1 yr and 29 yr, respectively. However, it has a couple of limitations: first, the case series design renders it intrinsically prone to bias; and secondly, the use of past records as the data source is suboptimal as our analysis was limited by the available information. Nonetheless, the results of this study do suggest a low occurrence of adverse effects among military aircrew members who undergo zolpidem test dosing prior to using the drug operationally and support its continued employment for aircrew fatigue management.

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