Benzodiazepine or Opiate Overdose CLIFF Peer Review

1. *Strength of evidence presented in CLIFF in modeling the characteristics and mission impact of this medical condition within the spaceflight environment?*

   Score: 1

   Grading Scale:

   4 - Confident

   3 - Somewhat confident

   2 – Neutral

   1 – Somewhat unconfident

   0 – Not confident

2. How confident are you that these data accurately represent the spaceflight environment?	*Tables 1, 2* *Composite Incidence and Level of Confidence*	*Table 3, 4 BC/WC* *Loss of Crew and probability*	*Table 4 - Clinical Phase 1, 2 durations* *Table 5 – CP 2 Loss of Crew*	*Table 4 – RTDC %* *Table 6 – RTDC Loss of Crew*	*Table 4 – Loss of Crew Life %* *Table 7 – Loss of Crew Life, Loss of Crew*	*Table 8 – TI*
Score	*1*	*2*	*3*	*1*	*2*	*3*

Comments and limitations:

1. **General comments.** Benzodiazepines (BZD) are sedatives that are frequently prescribed for insomnia and anxiety. Tolerance to the drug can develop with chronic use. In drug-naïve individuals the risk of side effects with initial dosing can be high. Side effects of overdoses of BZD's can lead to CNS depression, including symptoms such as altered mental status, slurred speech, and ataxia. BDZ or BDZ-like agents have been widely used in spaceflight, particularly as sleeping aids. Post-sleep drowsiness and mild cognitive delay were witnessed by this reviewer during spaceflights and more severe complications such as amnesia have been reported. Intentional overdose or respiratory depression has not been documented. Opioids include pain-relieving prescription medications such as morphine, oxycodone, hydrocodone, fentanyl, hydromorphone and methadone. Opioid overdose similarly leads to altered mental status due to CNS depression, but compared to BZD, respiratory suppression is more pronounced and can be fatal without treatment. Unlike BDZ, opiates have seldom, if ever, been used during spaceflight. Review papers reporting the use of analgesics did not mention a case where opiates have been used. It is expected that opiates would seldom be used except in the case of severe injury such as a fracture. In addition, the use of these drugs would be closely monitored and behavior or symptoms consistent with opiate overdose would be quickly

appreciated by other crewmembers. The best case is considered to be a benzodiazepine or opioid medication overdose that resolves within 8 hours and does not require treatment while the worst case is a benzodiazepine or opioid medication overdose that requires more than 8 hours to resolve and/or requires treatment.

2. **Incidence.** The calculation of composite incidence was very difficult due to a paucity of spaceflight data and the low level of confidence that the terrestrial studies are applicable to the spaceflight environment. The definition of the condition is also problematic in that it is unclear how to differentiate between "overdose" and "side effects." Side effects can be a result of over-dosing or they could occur even when the drug is appropriately dosed, but distinguishing between the two situations can be difficult. There are two anecdotal cases of BDZ's causing undesirable symptoms. However, these cases are only mentioned in presentations and not in a peer-reviewed journal. On the other hand, an analog terrestrial study in a military population looks at ER visits resulting from opiate and BDZ overdoses. Using this study to compute spaceflight incidence most certainly results in a significant overestimation of opiate overdoses during spaceflight. Military personnel are free to use BDZ and opiates recreationally during their off-duty hours, something that would not occur during spaceflight. As mentioned above, opiates are rarely, if ever, used during spaceflight. In fact, the risk of opiate overdose is probably close to zero in astronauts while in space. However, in the analog study opiate overdoses were more common than BDZ overdose. In spaceflight BDZ are much more commonly used and side effects may be under-reported. In summary, the choice was to use either a non-representative analog study or to use poorly documented spaceflight data that has never been published to inform the incidence. It was decided to use the analog data. While the terrestrial study most likely over-estimates spaceflight opiate incidence, it probably under-estimates the side effects of BDZ's used during spaceflight. Since the number of subjects in the analog study is so large, the standard deviation is extremely small. This means that that there is an unwarranted confidence in the incidence calculation. The best case/worst case probabilities used data from two terrestrial studies quoting a worst case of 44% and 52%. This is certainly an overestimation of the worst case during spaceflight given that most BDZ side effects are minor and self-resolving. The clinical phase durations, return to definitive care (RTDC) and loss of crew life probabilities are supported by terrestrial evidence, and I am in agreement with their calculation. There is very little data to support the untreated worst case values for loss of crew life and RTDC. The probability density curve that was derived appears to be a reasonable representation of the data presented.

3. **Clinical phase data**. I am in agreement with the clinical phase 1 duration entered in this CLIFF. This data was compiled by a team of expert clinicians, and I was involved in the discussions leading to the calculation of the clinical phase duration. CP2 was supported by terrestrial evidence.

4. **Task impairment**. The analysis was performed and reviewed by a separate team of expert clinicians. I am aware of the methods that were used but did not directly participate in the discussions.

5. **Dependence on mission phase or duration of mission**. This medical condition is not dependent on mission phase as a prior dose of opiates or BDZ could affect any phase of the mission.

6. **Limitations**

- Under-reporting for this condition could have occurred during past space missions due to subtle side effects from BDZ's that were not of clinical consequence. This may result in underestimation of the incidence.

- There is no published data on overdoses of BDZ or opiates during spaceflight. Thus, an analog study was used. While the population (military personnel) fit the astronaut demographics fairly well, the emphasis on opiate overdoses in this study does not transfer well to the spaceflight environment. The risk of opiate overdose during a spaceflight is thought to be near zero.
- Opioid overdose by the best case definition is not truly an overdose if it is self-limiting and does not require treatment.
- Consideration should be given to re-defining the "best case scenario" definition in future iterations to be "respiratory perturbation that results in reduction in oxygen saturation no lower than 95%."
- In future versions, it is recommended that the worst case scenario be defined as "respiratory perturbation that results in reduction in oxygen saturation below 88%" to reflect the increased danger of reductions in oxygen saturation below that important inflection point of the hemoglobin-oxygen dissociation curve.
- The current worst case definition of an episode lasting greater than 8 hours or requiring treatment is similarly difficult to distinguish from the treatment state of the patient. Therefore, it complicates the computations for this CLiFF as the need for treatment is found in the definition, which creates a paradox with UBC and TBC and UWC and TWC.

Reviewed by:

David C. Hilmers