



# Letter to the Editor Regarding: “Neurophysiological Assessments During Continuous Sedation Until Death Put Validity of Observational Assessments Into Question: A Prospective Observational Study”

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## Key Summary Points

The use of the ANI monitor is both possible and relevant for patients under CSD.

The interpretation of ANI measures must be done carefully, in particular in the context of global suffering in palliative care.

Collective acceptability of the ANI monitor has not been studied, and ANI assessment is complementary to clinical hetero-assessment by family and caregivers, neither being superior to the other.

The comfort of patients undergoing CSD will most likely remain, in part, mysterious.

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Dear editor,

Six et al. recently reported a prospective study of a small cohort of 12 patients under continuous sedation until death (CSD) in which they evaluated the correlation between clinical hetero-assessment, NeuroSENSE, which monitors for depth of sedation, and Analgesia/Nociception Index (ANI), which monitors for pain. [1]. In their study, clinical assessment and ANI were discordant in 9/108 evaluations (8.7%): ANI scores indicated discomfort while hetero-evaluation did not. They also found that 85.6% of ANI measurements were > 70, indicating possible opioid overdose [2, 3].

Six et al. computed sensibility and specificity of caregiver evaluations based on ANI and Neurosense values, which were considered to be more objective, and used gold standards for self-reported pain in CSD as surrogate. Their results show that subjective caregiver assessments have a positive predictive value for pain/discomfort of 0.0% compared with objective ANI monitoring and a negative predictive value of 91.9% (probability of correctly identifying the absence of pain/discomfort). The authors conclude that technically assisted comfort evaluation is more reliable than subjective caregiver assessment to avoid under-treating patients and potential discomfort or over-dosage, possibly hastening death [4, 5].

We will discuss these conclusions.

First, Six et al. highlight the difference between caregiver perception and technically assisted and presumably objective measures. In so doing, they raise the question of uncertainty in palliative care (PC): despite all the care to assess and prevent pain and discomfort in patients under CSD, there is a risk that caregivers may not detect discomfort. Comfort assessment using standardized scales or intuitive clinical experience is based on subjective interpretation [6, 7]. The authors present the ANI as a technique that does not interpret and that provides numeric results, though results still need to be interpreted by clinicians. ANI measures may give the impression that technology is superior to clinical assessment and makes no mistakes. However, ANI measures have pharmacological and biological limits and biases that are inherent to the technique: for example, ANI results are modified by anticholinergic medication. Since the use of ANI has not been extensive among PC patients, ANI results may be modified by other unknown elements [5]. We suggest that data on the use of ANI among the PC population are too limited to consider it entirely reliable, much less a new gold standard when self-reporting is impossible.

In particular, we question the interpretation of ANI measures as mainly indicating pain. Several studies have shown that heart rate variability measures the autonomic nervous system tone, which is strongly influenced by pain, stress and anxiety [8, 9]. The ANI index can therefore be considered as a vagal tone index and also be used to assess stress and anxiety. Among PC patients, levels of stress and anxiety can be elevated, and ANI measures may be biased regarding pain. We would also like to highlight the fact that pain may be neuropathic and not respond well to opioid treatment and that, to our knowledge, there are no data on how neuropathic or even chronic pain affects ANI measures. The authors' suggestion that ANI can be used as a basis to adjust opioid treatment requires some nuance, according to us. Ongoing studies are currently evaluating the use of ANI to assess stress or anxiety as well as pain in PC patients and should shed more light on these questions [10]. Therefore, when ANI is low, we

suggest that both pain relief and anxiolytic treatments should be adjusted [11].

These doubts about the scope of what ANI measures beg the question: what results can the ANI provide in a context of total pain, with physical, psychological, social and spiritual suffering? ANI interpretation calls for prudence in light of studies on total pain, as it requires pharmaceutical and non-pharmaceutical interdisciplinary responses [12]. These remarks also argue for the adapted use of technical assistance in PC to improve patient comfort. The "objective" quantitative results provided by ANI should by no means simplify the complex interactions with a suffering other, in particular in the context of end-of-life sedation. We therefore would like to highlight the complementarity of clinical hetero-assessment by family and caregivers and ANI assessment, neither being superior to the other [13].

Last, we suggest that the use of techniques such as the ANI monitor may create a breach in teamwork: the authors suggest that monitoring devices should be the preferred method guiding comfort assessment during CSD, and that feasibility and acceptability for caregivers and family members have already been demonstrated [14]. In this study based on face-to-face interviews, individual acceptability was explored, but collective acceptability was not. It might prove interesting to study the consequences of ANI use on the interactions within a PC team. Currently, the best-known way to approach objectivity is by intersubjective hetero-assessment. If the ANI becomes a guide for caregivers, what weight will their colleague's evaluation carry? We suggest that the ANI should be used as a complement to clinical hetero-evaluation, and not replace it, to reduce the risk of under-estimating patient discomfort while preserving teamwork and inter-subjectivity, which are core values in PC [15].

The comfort of patients undergoing CSD will most likely remain, in part, mysterious. We can but concur with Six et al. when they stress the need for further research to validate the use of ANI monitors among PC patients.

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## REFERENCES

1. Six S, Laureys S, Poelaert J, et al. Neurophysiological assessments during continuous sedation until death put validity of observational assessments into question: a prospective observational study. *Pain Ther.* 2021;10:377–90.
2. Logier R, Jeanne M, De Jonckheere J et al. Physiodoloris: a monitoring device for analgesia/nociception balance evaluation using heart rate variability analysis. In 2010 annual international conference of the IEEE engineering in medicine and biology, IEEE, pp.1194–1197 2010
3. Broucqsaault-Dédrie C, De Jonckheere J, Jeanne M, Nseir S. Measurement of heart rate variability to assess pain in sedated critically ill patients: a prospective observational study. *PLoS ONE.* 2016;11:e0147720.
4. Six S, Laureys S, Poelaert J, et al. Should we include monitors to improve assessment of awareness and pain in unconscious palliatively sedated patients? A case report. *Palliat Med.* 2019;33:712–6.
5. Dieudonné Rahm N, Morawska G, Pautex S, Elia N. Monitoring nociception and awareness during palliative sedation: a systematic review. *Palliat Med.* 2021;35(8):1407–20.
6. Belar A, Arantzamendi M, Payne S, et al. How to measure the effects and potential adverse events of palliative sedation? An integrative review. *Palliat Med.* 2021;35:295–314.
7. Deschepper R, Bilsen J, Laureys S. Assessment of patient comfort during palliative sedation: is it always reliable? In: Vincent J-L, editor. *Annual update in intensive care and emergency medicine* 2014. Berlin: Springer; 2014. p. 663–75.
8. De Jonckheere J, Rommel D, Nandrino J, Jeanne M, Logier R. Heart rate variability analysis as an index of emotion regulation processes: Interest of the Analgesia Nociception Index (ANI). In: 2012 Annual international conference of the IEEE engineering in medicine and biology society, IEEE, 2012; pp. 3432–3435
9. De jonckheere J, Logier R, Jounwaz R, Vidal R, Jeanne M. From pain to stress evaluation using heart rate variability analysis: development of an evaluation platform. In: 2010 Annual international

- conference of the IEEE engineering in medicine and biology, IEEE, 2010; pp. 3852–3855
10. Analgesia Nociception Index (ANI) for Pain and anxiety assessment in palliative care: a pilot study in University Hospital of Rennes. <https://clinicaltrials.gov/ct2/show/NCT03983590> (2019)
  11. Bauschert L, Prod'homme C, Pierrat M, Chevalier L, Lesaffre H, Touzet L. End-of-life comfort evaluation, is clinic enough? A retrospective cohort study of combined comfort evaluation with analgesia/nociception index and clinic in non-communicative patients. *J Palliat Care*. 2021. <https://doi.org/10.1177/08258597211063687>.
  12. Clark D. 'Total pain', disciplinary power and the body in the work of Cicely Saunders, 1958–1967. *Soc Sci Med*. 1999;49(6):727–36.
  13. Six S, Laureys S, Poelaert J, Bilsen J, Theuns P, Deschepper R. Comfort in palliative sedation (Compas): a transdisciplinary mixed method study protocol for linking objective assessments to subjective experiences. *BMC Palliat Care*. 2018;17:62.
  14. Six S, Van Overmeire R, Bilsen J, et al. Attitudes of professional caregivers and family members regarding the use of monitoring devices to improve assessments of pain and discomfort during continuous sedation until death. *J Pain Symp Manag*. 2020;60(2):390–9.
  15. Prodhomme C, Touzet L, Bauschert L, Le Berre R. Monitoring comfort during palliative sedation: ethical issues of innovations in palliative care. *J Int Bioeth* 2021