Opioid stewardship and identification of reversible causes: our approach to managing hyperactive delirium at the end of life ('terminal agitation')

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Terminal agitation is taught as a frequently encountered and expected condition at the end of life, possibly leading to a reversible cause of delirium not being identified with subsequent and unnecessary drug dose escalation. Opioids and sedative medications are recognised and potentially reversible causes of delirium. But what if we, in all the caring we do for our patients, often assume that the building distress is due to pain and continue to increase the opioid dose – could we possibly be contributing to end of life delirium?

Over the past ten years, there has been a significant change in prescribing practice within St Cuthbert's Hospice, Durham, as well as in the management of hyperactive delirium at the end of life. The clinical team at the Hospice performed retrospective data analysis, totalling all opioid, midazolam, levomepromazine and phenobarbital doses prescribed in the final 24 hours of life. Patient records were analysed for six-month periods at two yearly intervals from 2014 to 2022. All 24-hour syringe driver doses were included as well as all breakthrough medication and included all opioids, midazolam, levomepromazine and phenobarbital. To allow comparison, all opioid doses were converted to parenteral morphine equivalent and are referred to as opioid.

There were significant differences identified between the 2014 data and the subsequent data sets. In 2014, 64% of patients required a total of over 100mg of drugs (opioid, midazolam and levomepromazine) in their final 24 hours of life, reducing to 25% by 2022. The median dose of opioid more than halved from 72.5mg in 2014 to 32.5mg in 2022. The maximum dose of opioid was 920mg in 2014 compared to 480mg in 2022.

Our working hypothesis is that large and escalating opioid doses at the end of life lead to a higher risk of developing delirium at the end of life ('terminal agitation') which necessitates the use of larger doses of antipsychotics and benzodiazepines. Between 2014 and 2022, the median dose of midazolam fell from 30mg to 15mg, with a maximum recorded dose in 2014 of 225mg compared to 75mg in 2022. A similar trend was seen for levomepromazine, with a median dose of 50mg in 2014 to 6.25mg and 12.5mg in 2020 and 2022 respectively. The maximum dose of levomepromazine in 2014 was 200mg which dropped to only 30mg in 2022.

We also identified the patient who had received the most medication in their final 24 hours of life within each yearly data set. In 2014, that patient received a total of 2695mg which consisted of 920mg opioid, 225mg midazolam, 150mg of levomepromazine and 1400mg of phenobarbital. In 2022, the identified patient received a total of only 555mg (480mg opioid and 75mg of midazolam).

There have been no prescriptions for phenobarbital issued for any patients since 2014.

Our success in reducing end of life delirium and agitation is summarised below:

1. Avoiding opioid mixtures if possible.
2. Careful opioid titration at the end of life considering that deteriorating organ function could be leading to poor metabolism and impaired excretion.
3. Always consider and treat reversible causes of delirium.
4. Remember opioid tolerance and hyperalgesia/allodynia may require the use of NMDA receptor antagonists to maintain opioid effectiveness and prevent unnecessary and ineffective opioid dose escalation.

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