# Ketamine for the treatment of pain in palliative care. NSCPM 8, 2019.

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**Background:** Ketamine has hypnotic as well as analgesic effect without the unfavorable effect of opioids on respiration and cardiovascular systems. Almost all routes of administration can be used, although caution is advised with neuraxial administration due to risk of neurotoxicity. In subanesthetic doses, the drug is believed to inhibit hyperalgesia and reverse opioid tolerance, thus having an opioid sparing effect. Also, ketamine could positively influence neuropathic pain. For cancer pain, ketamine is almost exclusively used in specialized palliative care. Not all palliative units and hospices in Denmark use ketamine.

**Aim:** Through a literature search to elucidate the relevance of ketamine in the treatment of cancer pain and thus also the usefulness in palliative care.

**Methods:** A Pubmed literature search was performed in the fall of 2018 including various synonyms for malignancy combined with synonyms for ketamine. Google and www.palliativedrugs.com were also searched for clinical guidelines on the use of ketamine.

**Results:** The Pubmed search revealed 1042 hits. Based on titles only, 892 hits were disregarded, describing non-human studies, post-/perioperative pain treatment or non-malignant pain, non- English or non-Scandinavian, on side effects only, other indications than cancer pain, and comments to other studies. Reading 150 abstracts, more were excluded, leaving 25 case stories (1-3 patients), 25 papers with 8-396 pts., and 21 literature reviews. Administration routes were neuraxial (7 studies), intranasal (1), intravenous (23), subcutaneous (7), transmucosal (2), oral (7), topical (1), and unknown (2). The Google search found two Danish guidelines about ketamine for cancer pain from 2005 and 2017, respectively. www.palliativedrugs.com revealed a few protocols and guidelines as well as patient informations. Ketamine is described in the most recent ESMO guideline, and in the upcoming 2019 update of EAPC pain treatment recommendations, ketamine treatment will be covered as well (Caraceni, personal communication).

**Discussion:** Almost all non-randomized studies reported positive effect of ketamine, response rates ranging 50-100%. These studies may be subject to publication bias. Randomized trials and the latest Cochrane analysis could not detect a significant effect of ketamine over placebo. However, this does not establish a lack of efficacy. In some of the randomized trials, one could speculate that the dosages and treatment regimens as well as the powering of the studies were insufficient. Still, the stunning effect of ketamine in some patients cannot be denied. There may be subgroups of patients for whom ketamine might be especially helpful, but such a subgroup is yet to be defined.

**Conclusion:** Ketamine in subanesthetic doses for pain is still not a treatment of first choice. A relatively short trial of ketamine should be considered as an adjuvant to opioids in a specialized palliative care setting in

1) patients with severe pain that is refractory to opioids and adjuvants
2) patients in whom opioid doses have to be rapidly increased, and where one would hope for an opioid sparing effect of ketamine
3) patients with neuropathic pain in whom oral administration of gabapentoids or TCAs is not possible and/or adding methadone is not sufficient

The trial period needs not be very long (hours to a few days). The drug should be discontinued in case of severe side effects or lack of effect. A revised recommendation in Danish for the use of ketamine in our palliative care department is being written, focusing on the subcutaneous route of administration. The recommendation will be made available on the local and regional intranet.