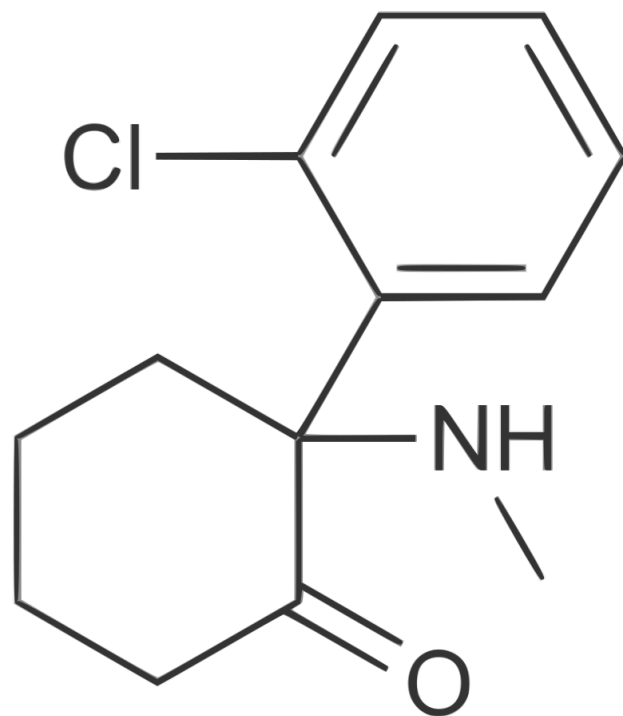
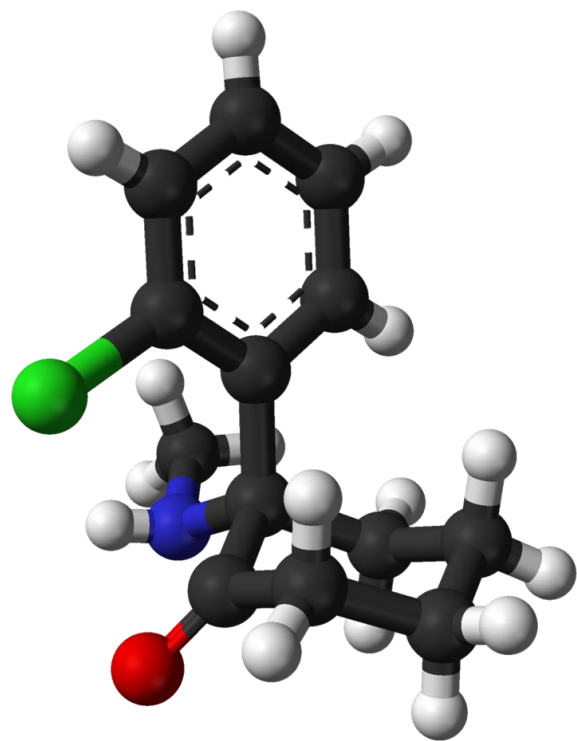


Ketamine for treatment of cancer pain

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Ketamine



Ketamine



Ketamine – “recreative use”

Background

Two stereoisomers:

S-ketamine (very active) and R-ketamine (less active)

Two formulations:

Esketamine pure S-ketamine

Ketalar contains both isomers

Pharmacology

- ▶ Very potent NMDA receptor antagonist
 - ▶ But also effect on opioid receptors, MAO-, and cholinergic transmitters
 - ▶ Inhibits catecholamine absorption, thus increasing adrenaline blood concentration
 - ▶ High first-pass metabolism -> oral bioavailability 10-20 %
 - ▶ Metabolized in the liver to norketamine, which is less potent but has a slower elimination

Routes of administration and bioavailability

- ▶ oral 10-20%
- ▶ sublingual 29%
- ▶ intranasal 50%
- ▶ intravenous 100%
- ▶ subcutaneous =IM?
- ▶ intramuscular 90%
- ▶ intrathecal 25%
- ▶ epidural =IT?



Clinical use

Anaesthesia: Good for acute surgery where circulation is compromised

In smaller doses for (peri-/postoperative) pain

Treatment resistant depression

In palliative care:

Mostly used for 'difficult pain'

Not generally used in hospices and palliative units in Denmark

Side effects

- ▶ Tachycardia
- ▶ Increased intracranial pressure
- ▶ Hallucinations, nightmares, unreality feeling
- ▶ Restlessness
- ▶ Salivation

Contraindications

- ▶ Increased intracranial pressure
- ▶ Heart failure
- ▶ Severe hypertension
- ▶ Delirium or psychosis
- ▶ Preeclampsia/eclampsia
- ▶ Glaucoma

Problem definition

Does the literature support
the routine use of ketamine
for difficult cancer pain?

Search strategy by August 2018

Pubmed search

Based on the first steps in the strategy of Bell's Cochrane study 2017

Synonyms for ketamine AND synonyms for malignancy

Palliativedrugs.com search for 'ketamine' and 'neuropathic pain'

Google search

Pubmed results August 2018: 1042 hits

- ▶ 321 without patients (animal studies, cell cultures)
- ▶ 192 covering only postoperative/perioperative pain treatment
- ▶ 130 written in other languages than English or Scandinavian
- ▶ 27 that were only about side effects of ketamine
- ▶ 29 about ketamine for other conditions than cancer pain (e.g. depression)
- ▶ 17 comments to other studies
- ▶ 18 using ketamine for patients with non-malignant pain
- ▶ 175 utterly irrelevant for other causes

150 abstracts and papers read

- ▶ **Selected**

- ▶ 25 case stories (1-3 patients)
- ▶ 26 papers with 8-396 pts., including one late-comer, 214 pts. late 2018
- ▶ 21 literature reviews

Google and palliativedrugs.com

Two Danish guidelines

A few protocols, guidelines and patient informations

Results

Administration route	Number of studies	Number of patients
Intravenous	26	1-396
Intramuscular	0	0
Subcutaneous	5	1-185
Spinal/epidural	6	1-48
Oral	9	1-214
Intranasal	2	1-20
Transmucosal (mouthwash)	2	1-30
Topical (skin/wounds)	1	16

Results

Type of study	Number of papers	Number of patients in each paper	Effect/some effect	No effect
Case stories	25	1-3	24	1
Retrospective/audit	10	9-396	10	0
Prospective	8	9-230	8	0
Randomised	8	10-214	4 (10-60 pts.)	4 (20-214 pts.)

Randomised studies

	Adm. route	# patients	Effect	Reservation
Lauretti 1999	Oral	60	Yes	Not placebo ctr.
Lauretti 1999	Epidural	48	Yes	Not placebo ctr.
Yang 1996	Intrathecal	20	Yes	
Mercadante 2000	IV	10	Yes	Few pts.
Ishizuka 2007	Oral	60	No	1 group < 10 pts.
Hardy 2012	SC	185	No	
Fallon 2018	Oral	214	No	
Salas 2012	IV	20	No	1 group < 10 pts.

Conclusion

Never a drug of first choice for cancer pain

Target subgroup is yet to be defined:

- Difficult cancer pain
- nociceptive and neuropathic pain
- Neuropathic pain where oral secondary analgesics cannot be given
- Central sensitization "Wind up"
- Opioid induced allodynia/hyperalgesia
- Pain despite opioid rotation

Can be tried in patients with a short expected survival, where everything else has failed

Recommendation in Danish to be made available on local/regional intranet