Spotlight on drugs

Advanced courses 2019

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Topics 2019

Developments in opioid analgesics
Matters arising
PCF6 snippets
- Hepatic impairment (FYI)
- Pancreatin
- Ketamine.

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Matters arising

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Better treatments for breathlessness in palliative care and end of life

- EU funded BETTER-B project
- seeking the views of *physicians* in respiratory/palliative medicine on the management of chronic breathlessness in COPD, ILD and lung cancer
- takes about 10−15 minutes
- closes end of July 2019.

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Better treatments for breathlessness in palliative care and end of life

https://www.smartsurvey.co.uk/s/F3J2M/

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Optimal Lung Cancer Pathway: Specialist Supportive/Palliative Care

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Optimal Lung Cancer Pathway: Specialist Supportive/Palliative Care

Specialist supportive/palliative care services, provided by specialist nurses and doctors, are often required and should be readily available to those patients with a high level of need.

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Optimal Lung Cancer Pathway: Specialist Supportive/Palliative Care

Further, a specialist supportive/palliative care review should be *routinely* offered to all patients:

- with stage IV disease, irrespective of any other treatment offered
- for whom the MDT treatment decision is 'Best supportive care'.

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Optimal Lung Cancer Pathway: Specialist Supportive/Palliative Care

Offering to see all patients with stage IV may previously have been achieved under the DH Enhanced Supportive Care initiative.

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Optimal Lung Cancer Pathway: Specialist Supportive/Palliative Care

Based on these experiences, WTE requirements for supportive/palliative care nurse specialists (1.5WTE) and physicians (0.2 WTE) are suggested in commissioning guidance, based on per 200 patients with stage IV disease per annum.

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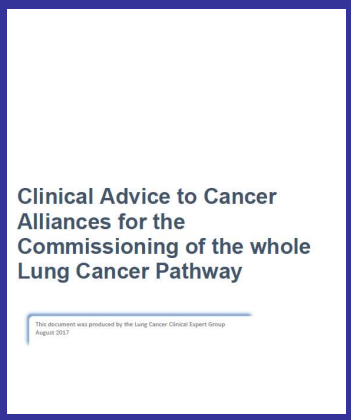

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Optimal Lung Cancer Pathway: Specialist Supportive/Palliative Care

- goal to achieve timely specialist supportive and palliative care assessment and input
- proposes maximum wait times to review.

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Optimal Lung Cancer Pathway: Specialist Supportive/Palliative Care

- specialist services may be based in a variety of settings…
- access may already be facilitated via attendance at the lung cancer MDT/joint clinics with respiratory and/or oncology colleagues
  - often allows review/assessment of the patient on the same day.

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Optimal Lung Cancer Pathway: Specialist Supportive/Palliative Care

- no nationally agreed maximum waiting times
- local standards likely to differ based on factors such as urgency of referral, service setting (e.g. community vs. hospital based) and resources/pattern of working (e.g. 5 vs. 7-day services)
- how an initial assessment is defined/carried out may also differ (e.g. face-to-face vs. via telephone).

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Optimal Lung Cancer Pathway: Specialist Supportive/Palliative Care

The following are proposed as reasonable standards :

- *urgent* referrals (e.g. uncontrolled symptoms/rapidly deteriorating health, distress and social crisis) should ideally be seen the same day, but should wait no longer than 48h
- *non-urgent/routine* referrals should wait no longer than 7 working days.

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Optimal Lung Cancer Pathway: Specialist Supportive/Palliative Care

What are your standards for:

- *urgent* referrals
  - 24h, 48h, other?
- *non-urgent/routine* referrals
  - 5, 7 days, other?

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Hepatic impairment

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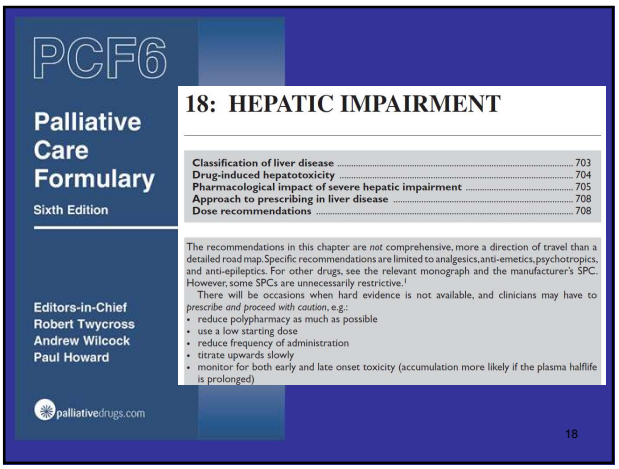

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Hepatic impairment chapter

- new for PCF6
- plan to review in same depth as renal chapter
- include dose recommendation tables, e.g.:
  - Non-opioids
  - Opioids
  - Anti-emetics
  - Benzodiazepines and Z-drugs
  - Antipsychotics
  - Antidepressants
  - Anti-epileptics

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Table 6 Anti-emetics in severe hepatic impairment. Before use, see introductory and class specific text above

Drug[a]	*PO bio-availability (%)*	*Protein-binding (%)*	*Halflife in normal liver function (h)*	*Significant hepatic metabolism*	*Significant biliary excretion of drug ± active metabolite(s)*	*Increase in halflife in severe hepatic impairment*	*Dose and comments*
Use cautiously							
Domperidone[b]	12–18	>90	7–9	Yes	No	50%	PO: start with 5mg b.d., maximum 10mg t.d.s.
Metoclopramide[b]	50–80	13–22	4–6	Yes	No	>100%	PO/SC: start with 5mg b.d., maximum 10mg b.d.– t.d.s.
Ondansetron	56–71	70–76	3–6	Yes	No data	>300%	PO/SC: maximum 8mg/24h
Avoid if possible							
Cyclizine[c]	50%	No data	20	Yes	No data	No data	If unavoidable, PO: start with 50mg b.d. SC: start with 25mg b.d.
Haloperidol[c]	45–75	92	12–38	Yes; active metabolite	Possible	No data	If unavoidable PO/SC: start with 500microgram.at bedtime and q4h p.r.n. *Also see Antipsychotics Table 8, p.000*
Levomepromazine[c]	20–40	No data	15–30	Yes; active metabolite	No data	No data	If unavoidable, PO/SC: start with 2.5–3.125mg at bedtime and q4h p.r.n.

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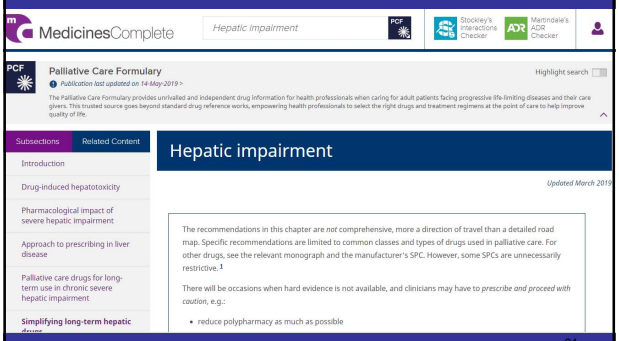
Already on website



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Vol. ■ No. ■ ■ 2019 Journal of Pain and Symptom Management 1

Therapeutic Reviews

Series Co-Editors: Andrew Wilcock, DM, FRCP, and Paul Howard, BMedSci MRCP

Therapeutic Reviews aim to provide essential independent information for health professionals about drugs used in palliative and hospice care. Additional content is available via www.palliativedrugs.com. The series editors welcome feedback on the articles.

Prescribing in chronic severe hepatic impairment

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Collaborators: Hepatic impairment

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Pancreatin

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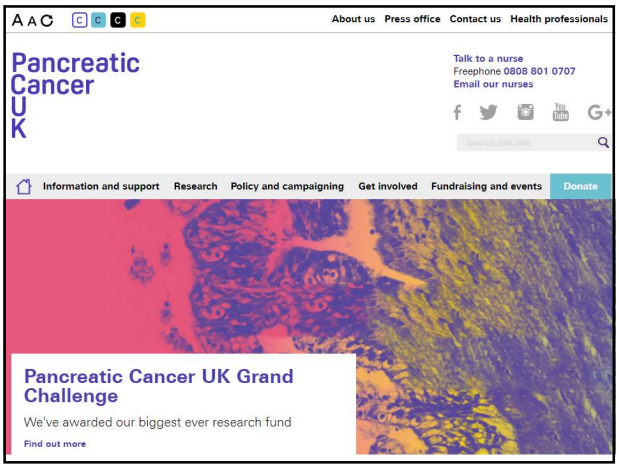

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Acknowledgments

Laura McGeeney
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Pancreatic Cancer UK

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Learning objectives: pancreatin

For PC clinicians to gain knowledge of:

- NICE recommendation for use in pancreatic cancer
- correct dose & use
  - not reflected in BNF
  - now reflected in *online* PCF.

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Pancreatin

- enzyme supplement
- indicated for pancreatic exocrine deficiency (PED)
  - insufficient production or delivery of pancreatic enzymes required for the digestion and absorption of food.

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Causes of PED

- cancer of the head/body of the pancreas
- chronic pancreatitis
- pancreatic resection
- cystic fibrosis
- duodenectomy
- gastrectomy
- untreated coeliac disease
  (via a reduction in cholecystokinin → post-prandial pancreatic stimulation)
- diabetes mellitus.

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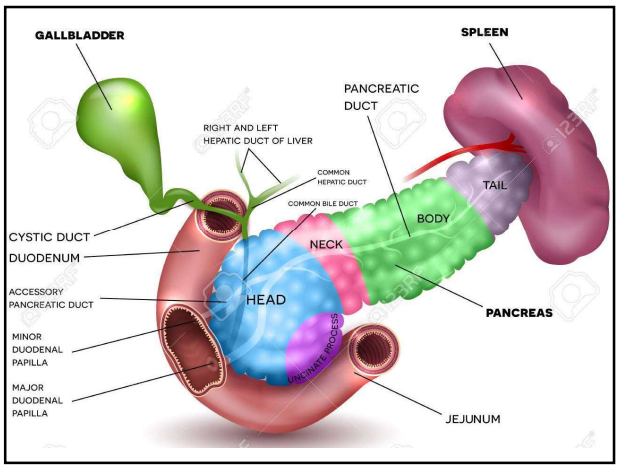

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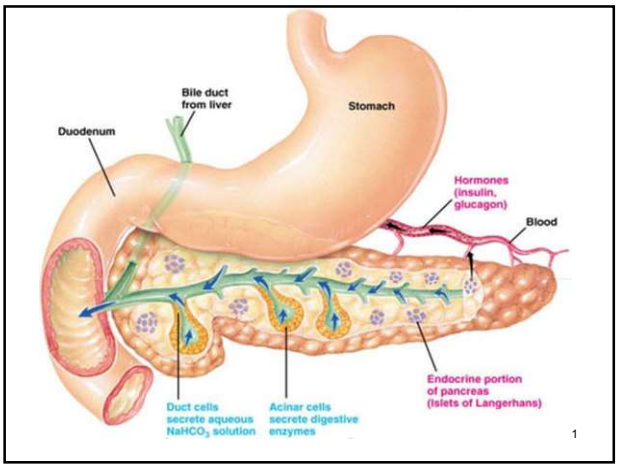

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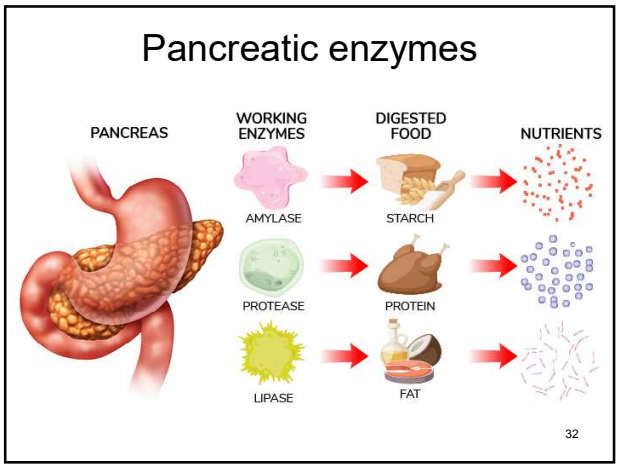

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PED

Results in undigested dietary carbohydrate, protein and fat → malabsorption, leading to:

- GI symptoms
- malnutrition
  - sarcopenia/osteoporosis
  - weight loss
- ↓ quality of life
- ↓ survival.

Dominguez-Munoz JE (2018) 33

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PED

Typical GI symptoms:

- abdominal pain and distension, ↑ flatus

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PED

Typical GI symptoms:

- abdominal pain and distension, ↑ flatus
- stools containing large amounts of fat (steatorrhoea)
  - pale, bulky, offensive, frothy, greasy and difficult to flush away.

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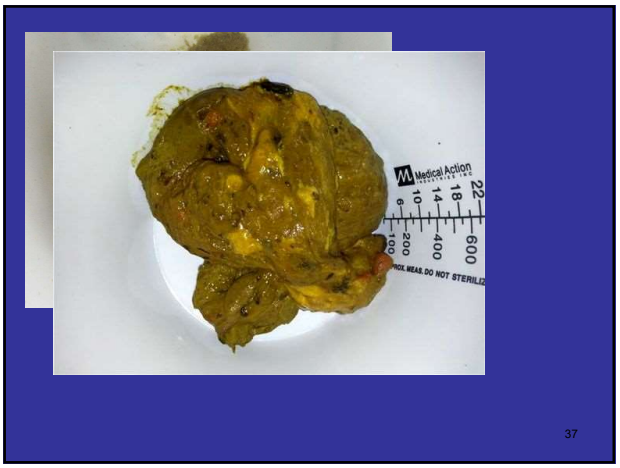

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PED

But:

- GI symptoms not always present / patients may avoid by adjusting diet
- malnutrition can be present even without weight loss, e.g.:
  - fat soluble vitamins A, D, E, K
  - micronutrients, Mg, Zn.

Dominguez-Munoz JE (2018) 40

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PED

Thus:

- malnutrition may not be immediately obvious and *malabsorption is common even in patients without overt steatorrhoea.*

Dominguez-Munoz JE and Iglesias-Garcia J (2010)
Imrie CW *et al.* (2010) 41

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Diagnosis of PED

When clinical uncertainty:

- a low faecal elastase (<200microgram/g) helps confirm the diagnosis
  - enzyme secreted by pancreas
  - eliminated unchanged in stool
  - level reduced in PED
- while awaiting the results of this, evaluate response to a therapeutic trial of pancreatin.

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Treatment of PED

Pancreatin:

- contains porcine enzymes
  - Jewish and Muslim faith leaders consider its use acceptable because of the lack of an alternative.

UKMI (2018); Pancreatic Cancer Action (2019) 43

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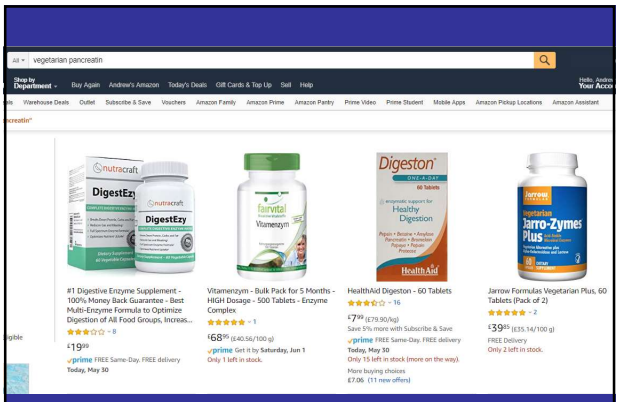

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Treatment of PED

Pancreatin:

- contains porcine lipase, proteases and amylase
  - hydrolyzes fats to glycerol & fatty acids
  - degrades protein into amino acids
  - converts starch into dextrins & sugars
- offer to all patients with PED to reduce malabsorption → improve nutrition ± steatorrhoea.

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Pancreatin in pancreatic cancer

- most patients with cancer of the pancreas have malabsorption at diagnosis
- *NICE consider pancreatin a routine supportive therapy*
- may improve survival in this group
  - data limited (e.g. small number, retrospective)
  - particularly in patients with >10% wt loss at diagnosis as ? greater levels of (correctable) PED.

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Pancreatin in pancreatic cancer

1.6 Nutritional management

1.6.1	Offer enteric-coated pancreatin for people with unresectable pancreatic cancer.
1.6.2	Consider enteric-coated pancreatin before and after pancreatic cancer resection.
1.6.3	Do not use fish oils as a nutritional intervention to manage weight loss in people with unresectable pancreatic cancer.
1.6.4	For people who have had pancreatoduodenectomy and who have a functioning gut, offer early enteral nutrition (including oral and tube feeding) rather than parenteral nutrition.
1.6.5	For more guidance on nutrition support, see the NICE guideline on nutrition support in adults.

NICE (2018) 47

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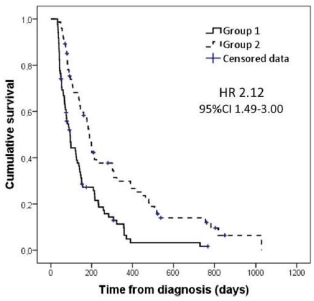
Pancreatin in unresectable ca pancreas



Standard treatment (Gp 1, n=86) vs. ST + assessed for PED (Gp 2, n=74)

0% in Gp 1 had pancreatin vs. 66% in Gp 2

Median survival ~doubled 100 vs. 200 days

Groups otherwise similar but more in Gp 2 had chemo: 72% vs. 47%

Dominguez-Munoz JE et al. (2018a) 48

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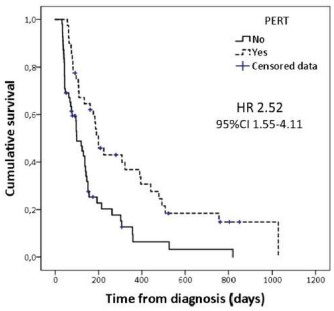
Pancreatin in unresectable ca pancreas with wt loss at diagnosis >10% (≤6 months)



No (n=55)
Yes (n=40)

Median survival ~doubled
100 vs. 200 days

Dominguez-Munoz JE et al. (2018a) 49

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Pancreatin

- capsules contain e/c or gastro-resistant granules; enzymes inactivated by gastric acid
  - (rarely other products may be required, e.g. EFT, seek specialist dietetic advice)
- an alkaline pH (>5.5) is required for optimal disintegration of e/c coating in the duodenum
- thus, acid suppression, e.g. with a PPI, improves efficacy.

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Pancreatin & acid suppression

But:

- guidelines generally recommend the addition of a PPI only when there are persistent symptoms despite reasonable doses of pancreatin, i.e.:
  - 75,000 units of lipase/meal
  - higher doses of pancreatin used only if this strategy fails.

Dominguez-Munoz JE (2018); Löhr JM *et al.* (2017) 51

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Pancreatin & acid suppression

However:

- some centres routinely prescribe a PPI when likely complete/significant loss of pancreatic bicarbonate excretion
  - important contribution to duodenal alkalinity
  - includes patients with pancreatic cancer
  - (survival data based on patients receiving routine acid suppression).

Thus, prescribe a PPI routinely in ca pancreas

Dominguez-Munoz JE (2018a) 52

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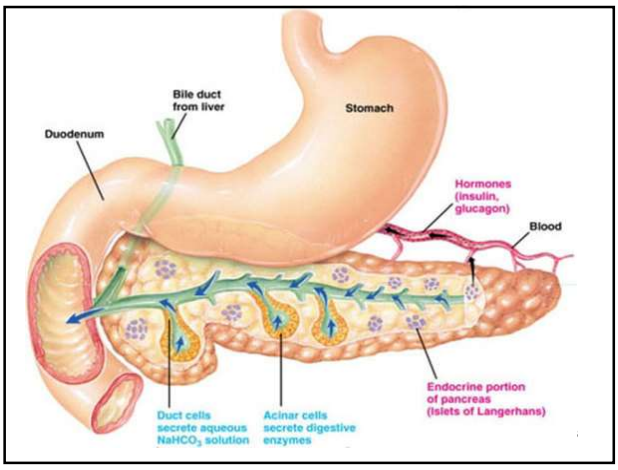

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Pancreatin

- various products, but Creon® cheapest & wide range of dose strengths
- dose expressed as lipase units, e.g.
  - Creon® 25,000, lipase 25,000 units, amylase 18,000 units, protease 1,000 units
  - ~~Creon® 40,000, lipase 40,000 units, amylase 25,000 units, protease 1,600 units~~ (from 1st July!)
- (i.e. don't forget the amylase & protease).

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Creon®

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Undesirable effects Creon®

- very common (>10%): abdominal pain
- common (<10%, >1%): nausea & vomiting, constipation or diarrhoea.

If abdominal symptoms worsen after starting Creon® anecdotally, tolerability improved by switching to another product, e.g. Nutrizym 22®.

Irritation of the anal canal can occur when active enzymes reach the rectum because of, e.g. excess dose, rapid GI transit.

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Undesirable effects Creon®

- very rarely, strictures of the ileo-caecum and proximal colon (fibrosing colonopathy) have been linked with very high doses of pancreatin (i.e. >10,000 units of lipase/*Kg*/24h)
- most reports involve children with cystic fibrosis, it has also occurred in adults with and without cystic fibrosis.

Hausler M *et al.* (1998); Bansi DS *et al.* (2000) 57

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Dose and use

- apart from enzyme replacement, other nutritional support may be required; seek advice from a dietitian
- start with Creon® 25,000 [*PCF6 book 10,000 – No!*]

Dietary intake	*Number of Creon® 25,000 capsules*
Snack/milky drink	1–2
Normal meal	2–3
Large meal/fatty foods/ 'takeaways'	3–4

- number of capsules varies with the size and the fat, carbohydrate or protein content of the snack/meal.

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Dose and use

- if necessary, increase dose every 3–4 days to normalize faecal size, consistency and frequency
- there is no maximum dose; however if lack of progressive improvement, consider other causes of malabsorption, e.g.:
  - bacterial overgrowth, bile salt malabsorption, coeliac disease
- ~~creon® 40,000 capsules can reduce the number of capsules required.~~

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Dose and use

If symptoms of steatorrhea not controlled despite doses of ~75,000 units of lipase/meal:

- consider adding a PPI before further increasing the dose of pancreatin
- *but* some add a PPI routinely in patients with unresectable pancreatic cancer.

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Dose and use

- a reduction in malabsorption should improve the patient's nutritional status and weight
- in some patients, only a slowing of the rate of weight loss is possible, e.g. those with pancreatic cancer.

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Newcastle question: Monitoring

How do you titrate dose/monitor when no symptoms/wt loss?

- in reality most will have lost wt / have GI symptoms
- if not, use recommended starting doses, monitor wt
- some guidelines mention measurement of fat soluble vitamins, minerals (Mg), markers of malnutrition, e.g. prealbumin, retinol-binding protein
- often part of supplements (seek dietetic advice).

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Dose and use: additional patient advice

- pancreatin is required for all meals, snacks, milky drinks and oral nutritional supplement drinks, *except* for:
  - small amounts of vegetables (except potatoes, beans, pulses)
  - small amounts of fruit (except avocado) or dried fruit
  - sugary sweets
  - drinks containing only a small amount of milk, fruit squashes or fizzy drinks
- to swallow the capsules whole with sips of a cold (≤ room temperature) drink, after the first few mouthfuls of food
- *not to crush/chew or hold the capsule in the mouth*; this can cause stomatitis.

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Dose and use: additional patient advice

- when taking more than one capsule, eating a large meal, or one that lasts >30min, spread out taking the capsules across the meal's duration
- to increase the dose to control symptoms rather than restrict diet (a low-fat diet is *not* indicated)
- if a dose is missed, don't make up by taking it later; resume correct dose with the next snack/milky drink/meal
- not to store capsules in hot places, e.g. direct sunlight, car glove box, trouser pocket
- to treat constipation with laxatives and not by reducing pancreatin.

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Dose and use: additional patient advice

- to report irritation of the anal passage
  - suggests active enzymes reaching lower bowel
  - prescribe barrier cream & add PPI (to enhance enzyme release in the duodenum) before making a dose reduction
- to report any symptoms suggestive of diabetes mellitus, e.g. thirst, polyuria:
  - by improving the absorption of carbohydrates, pancreatin may unmask an underlying diabetes.

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Patients with swallowing difficulties

- capsules relatively large
- smaller capsules available (e.g. Creon® 10,000), but the large number required likely impractical
- the capsules can be opened:
  - sprinkle granules on teaspoon of cold (≤ room temperature), *acidic* soft food
  - e.g. jam, yoghurt, apple sauce, tomato sauce
- must be taken immediately (the gastro-resistant coating dissolves on standing)
- must rinse the mouth with a cold drink to remove all granules, particularly between teeth/under dentures.

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Patients with swallowing difficulties

Important:

- the granules must not be crushed, chewed or added to *alkaline drinks or foods*, e.g. milk, as destroys the gastro-resistant coating.
- enzymes released in the mouth → loss of efficacy and stomatitis
- heat inactivates pancreatin and the granules must not be mixed with hot drinks or food, and the capsules stored appropriately (<25ºC).

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Summary

- quite a bit of thought and time needs to go into ensuring correct dose and use; patient counselling important
- knowledge gap about NICE recommendation and correct use.

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Summary

- offer pancreatin to all patients with PED to reduce malabsorption and thereby improve nutrition ± symptoms of steatorrhoea
- *includes those with no/minimal symptoms of steatorrhoea, because underlying malabsorption is common*
- recommended by NICE as a routine supportive treatment in ca pancreas; *add a PPI routinely*
- other nutritional support may be required; seek advice from a dietitian.

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Ketamine

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Ketamine

- use over last 5 years?
  - increasing
  - same
  - decreasing
- treatment of 'last resort' vs. other setting?
- short course vs. long-term?
- CSCI vs. PO?

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Ketamine: learning objectives

To update knowledge of:

- recent RCT - PO ketamine in neuropathic pain
- upper GI toxicity.

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PO ketamine for neuropathic pain

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Ketamine for cancer pain: evidence

Most recent Cochrane SR:

- found only three studies of sufficient quality
  - Yang CY *et al.* (1996) IT ketamine (n=20)
  - Mercadante S *et al.* (2000) IV ketamine (n=10)
  - Hardy J *et al.* (2012) CSCI 'burst' ketamine (n=185)
- concluded insufficient evidence to assess potential benefits and harms.

Bell RF *et al.* (2017)

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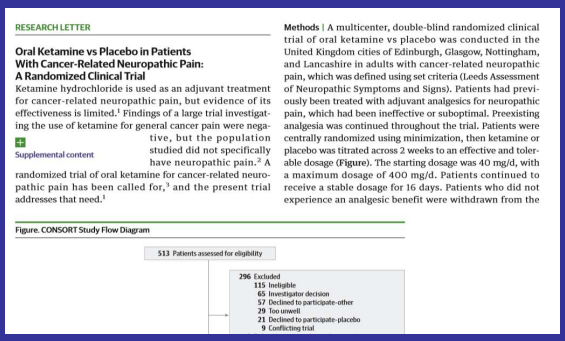
Recent large RCT: Fallon MT *et al.* (2018)



RESEARCH LETTER

Oral Ketamine vs Placebo in Patients With Cancer-Related Neuropathic Pain: A Randomized Clinical Trial

Ketamine hydrochloride is used as an adjuvant treatment for cancer-related neuropathic pain, but evidence of its effectiveness is limited.[1] Findings of a large trial investigating the use of ketamine for general cancer pain were negative, but the population studied did not specifically have neuropathic pain.[2] A randomized trial of oral ketamine for cancer-related neuropathic pain has been called for,[3] and the present trial addresses that need.[1]

Supplemental content

Methods | A multicenter, double-blind randomized clinical trial of oral ketamine vs placebo was conducted in the United Kingdom cities of Edinburgh, Glasgow, Nottingham, and Lancashire in adults with cancer-related neuropathic pain, which was defined using set criteria (Leeds Assessment of Neuropathic Symptoms and Signs). Patients had previously been treated with adjuvant analgesics for neuropathic pain, which had been ineffective or suboptimal. Preexisting analgesia was continued throughout the trial. Patients were centrally randomized using minimization, then ketamine or placebo was titrated across 2 weeks to an effective and tolerable dosage (**Figure**). The starting dosage was 40 mg/d, with a maximum dosage of 400 mg/d. Patients continued to receive a stable dosage for 16 days. Patients who did not experience an analgesic benefit were withdrawn from the

Figure. CONSORT Study Flow Diagram

513 Patients assessed for eligibility

296 Excluded
115 Ineligible
65 Investigator decision
57 Declined to participate-other
29 Too unwell
21 Declined to participate-placebo
9 Conflicting trial

(N=214) JAMA Oncology

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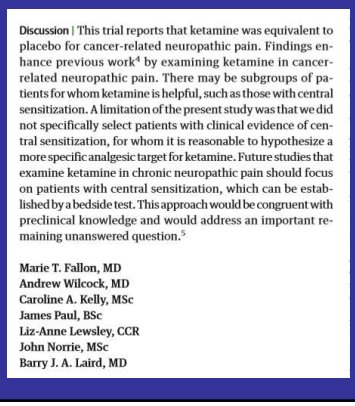
Recent large RCT: Fallon MT *et al.* (2018)



Discussion | This trial reports that ketamine was equivalent to placebo for cancer-related neuropathic pain. Findings enhance previous work[4] by examining ketamine in cancer-related neuropathic pain. There may be subgroups of patients for whom ketamine is helpful, such as those with central sensitization. A limitation of the present study was that we did not specifically select patients with clinical evidence of central sensitization, for whom it is reasonable to hypothesize a more specific analgesic target for ketamine. Future studies that examine ketamine in chronic neuropathic pain should focus on patients with central sensitization, which can be established by a bedside test. This approach would be congruent with preclinical knowledge and would address an important remaining unanswered question.[5]

Marie T. Fallon, MD
Andrew Wilcock, MD
Caroline A. Kelly, MSc
James Paul, BSc
Liz-Anne Lewsley, CCR
John Norrie, MSc
Barry J. A. Laird, MD

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Recent large RCT: Fallon MT *et al.* (2018)

Headlines:

- n=214
- PO racemic ketamine (encapsulated powder)
- cancer-related neuropathic pain
- no difference in duration of analgesic benefit between ketamine and placebo (median 0 days for both).

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Ketamine RCT: Fallon MT *et al.* (2018)

Inclusion criteria:

- diagnosis of cancer (previous or current)
- cancer-related neuropathic pain (>4 on NRS)
- neuropathic pain
  - positive Leeds Assessment of Neuropathic Symptoms and Signs score
- sensory score of McGill Pain Questionnaire >5
- trial of (≥1) adjuvant neuropathic agent.

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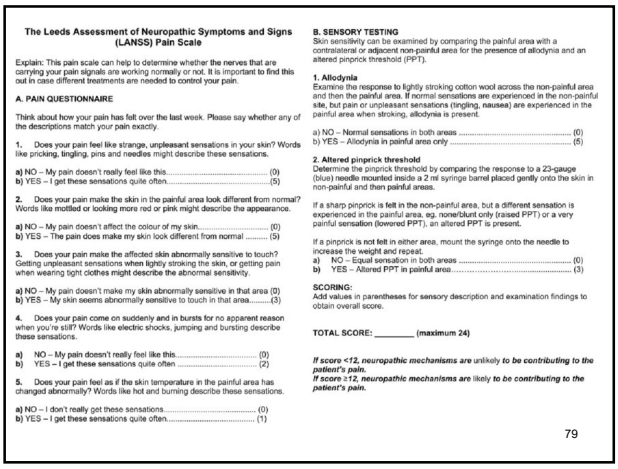

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale

Explain: This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find this out in case different treatments are needed to control your pain.

A. PAIN QUESTIONNAIRE

Think about how your pain has felt over the last week. Please say whether any of the descriptions match your pain exactly.

1. Does your pain feel like strange, unpleasant sensations in your skin? Words like pricking, tingling, pins and needles might describe these sensations.

a) NO – My pain doesn't really feel like this..... (0)
b) YES – I get these sensations quite often..... (5)

2. Does your pain make the skin in the painful area look different from normal? Words like mottled or looking more red or pink might describe the appearance.

a) NO – My pain doesn't affect the colour of my skin..... (0)
b) YES – The pain does make my skin look different from normal ..... (5)

3. Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.

a) NO – My pain doesn't make my skin abnormally sensitive in that area (0)
b) YES – My skin seems abnormally sensitive to touch in that area.....(3)

4. Does your pain come on suddenly and in bursts for no apparent reason when you're still? Words like electric shocks, jumping and bursting describe these sensations.

a) NO – My pain doesn't really feel like this..... (0)
b) YES – I get these sensations quite often ..... (2)

5. Does your pain feel as if the skin temperature in the painful area has changed abnormally? Words like hot and burning describe these sensations.

a) NO – I don't really get these sensations..... (0)
b) YES – I get these sensations quite often..... (1)

B. SENSORY TESTING

Skin sensitivity can be examined by comparing the painful area with a contralateral or adjacent non-painful area for the presence of allodynia and an altered pinprick threshold (PPT).

1. Allodynia

Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area. If normal sensations are experienced in the non-painful site, but pain or unpleasant sensations (tingling, nausea) are experienced in the painful area when stroking, allodynia is present.

a) NO – Normal sensations in both areas ..... (0)
b) YES – Allodynia in painful area only ..... (5)

2. Altered pinprick threshold

Determine the pinprick threshold by comparing the response to a 23-gauge (blue) needle mounted inside a 2 ml syringe barrel placed gently onto the skin in non-painful and then painful areas.

If a sharp pinprick is felt in the non-painful area, but a different sensation is experienced in the painful area, eg. none/blunt only (raised PPT) or a very painful sensation (lowered PPT), an altered PPT is present.

If a pinprick is not felt in either area, mount the syringe onto the needle to increase the weight and repeat.

a) NO – Equal sensation in both areas ..... (0)
b) YES – Altered PPT in painful area..... (3)

SCORING:

Add values in parentheses for sensory description and examination findings to obtain overall score.

TOTAL SCORE: _____ (maximum 24)

If score <12, neuropathic mechanisms are** unlikely **to be contributing to the patient's pain.
If score ≥12, neuropathic mechanisms are** likely **to be contributing to the patient's pain.

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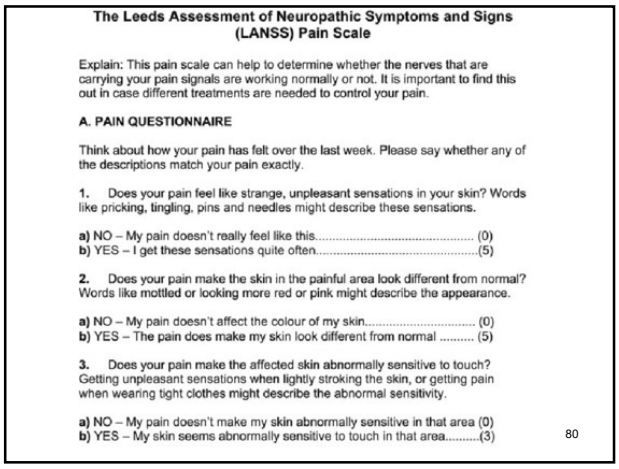

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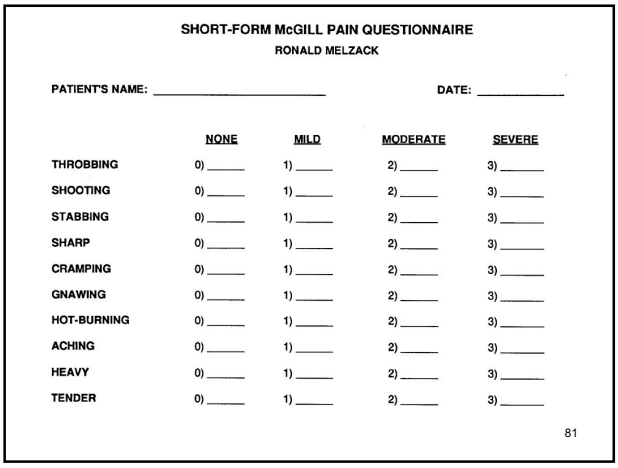

SHORT-FORM McGILL PAIN QUESTIONNAIRE

RONALD MELZACK

PATIENT'S NAME: _____ **DATE:** _____

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) _____	1) _____	2) _____	3) _____
SHOOTING	0) _____	1) _____	2) _____	3) _____
STABBING	0) _____	1) _____	2) _____	3) _____
SHARP	0) _____	1) _____	2) _____	3) _____
CRAMPING	0) _____	1) _____	2) _____	3) _____
GNAWING	0) _____	1) _____	2) _____	3) _____
HOT-BURNING	0) _____	1) _____	2) _____	3) _____
ACHING	0) _____	1) _____	2) _____	3) _____
HEAVY	0) _____	1) _____	2) _____	3) _____
TENDER	0) _____	1) _____	2) _____	3) _____

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Ketamine RCT: Fallon MT *et al*. (2018)

Three stages:

Run-in (2–10 days)

- to ensure existing analgesia and pain stable before patients proceeded in the trial.

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Ketamine RCT: Fallon MT *et al*. (2018)

Titration stage (0–14 days)

- randomised to ketamine/placebo. Contacted a minimum of every 2 days and titrated using pre-defined protocol
- 'optimal dose' = maximal analgesic effect + minimal undesirable effects
- patients failing to achieve sufficient improvement in pain (<5 drop in the SS-MPQ) did not proceed to the next stage.

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Ketamine RCT: Fallon MT *et al*. (2018)

Capsules (10mg, 20mg, 40mg strengths) taken q.d.s.

Day	Dose Level	Total Daily Dose (mg)
1	1	40
2	1	40
3	2	80
4	2	80
5	3	120
6	3	120
7	4	160
8	4	160
9	5	240
10	5	240
11	6	320
12	6	320
13	7	400
14	7	400

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Ketamine RCT: Fallon MT *et al*. (2018)

Assessment stage (for 16 days)

- patients continued same dose ketamine/placebo
- completed endpoint measures every 4 days.

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Ketamine RCT: Fallon MT *et al*. (2018)

Primary end-point = time to treatment 'failure':

- <5 point drop in the SS-MPQ during titration/assessment stage
- withdrawal during titration/assessment stage for any other reason (e.g. undesirable effects)
- patients requiring ≥30% change in opioid dose.

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Ketamine RCT: Fallon MT *et al*. (2018)

- took 6 years to recruit
- we (Nottingham) struggled
- almost all recruited in Glasgow/Edinburgh
  - special interest in chemo-related neuropathic pain

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Titration phase (0–14 days)

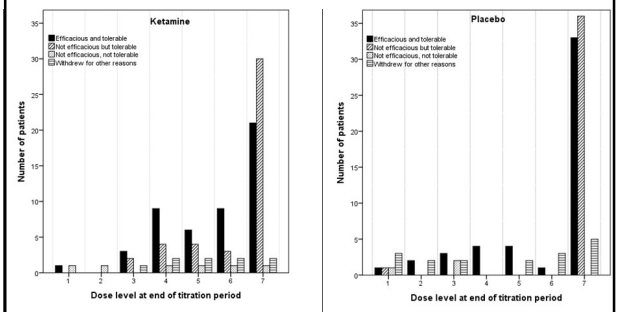

Figure 4a – The dose level at the end of the titration period and the reasons for the resulting level achieved – ketamine arm

Figure 4b – The dose level at the end of the titration period and the reasons for the resulting level achieved – placebo arm

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Titration phase (0–14 days)

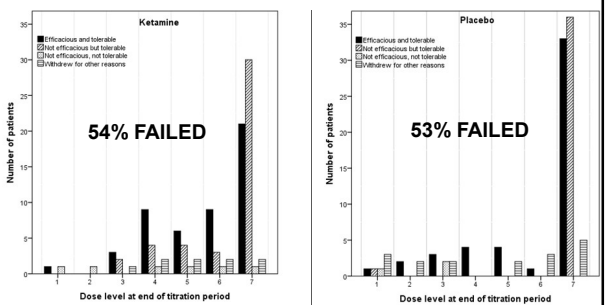

Figure 4a – The dose level at the end of the titration period and the reasons for the resulting level achieved – ketamine arm

Figure 4b – The dose level at the end of the titration period and the reasons for the resulting level achieved – placebo arm

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Ketamine RCT: Fallon MT *et al*. (2018)

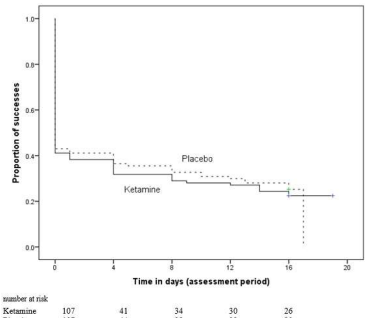

Figure 2 – Kaplan-Meier Curve's showing the proportion of successes (patient who remained on completed the trial with no significant change in opioid dose and had a 5-point drop in the sensory component of the SF-MPQ) per trial arm.

- no difference in the duration of analgesic benefit
- median duration 0 days for both ketamine and placebo

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Ketamine RCT: Fallon MT *et al*. (2018)

Table 3 – Adverse Events

	Ketamine		Placebo	
Serious Adverse Events	8		10	
	Titration (n=107)	Assessment (n=49)	Titration (n=107)	Assessment (n=50)
Adverse Events*				
Cognitive Disturbance	3	2	0	0
Dizziness	7	1	2	0
Fatigue	3	0	1	0
Nausea	3	0	3	1
Somnolence	4	0	1	0

***top five adverse events per trial arm.**

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Ketamine RCT: Fallon MT *et al*. (2018)

- another negative RCT

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Ketamine RCT: Fallon MT *et al*. (2018)

However, most patients:

- 80% had cancer treatment-related neuropathic pain (post-chemotherapy or surgery)
  - *only 13% had pain directly due to cancer*

Mechanism of pain from cancer damaging a nerve (ongoing inflammatory insult) likely to be different from nerve damage where the original insult is no longer present.

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Ketamine RCT: Fallon MT *et al*. (2018)

Further, most patients:

- were not taking opioids (median dose 0mg)
- overall not typical of patients
  - we see in our practice
  - we may have to consider ketamine for
  - you would want to expose to risks of ketamine, e.g. potentially cured/long prognosis.

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Ketamine RCT: Fallon MT *et al*. (2018)

Further, the ketamine product used (encapsulated powder):

- bio-availability unknown
- made by Pharmacy Production Unit, Western Infirmary, Glasgow
  - not commercially available.

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Ketamine RCT: Fallon MT *et al*. (2018)

sensitization. A limitation of the present study was that we did not specifically select patients with clinical evidence of central sensitization, for whom it is reasonable to hypothesize a more specific analgesic target for ketamine. Future studies that

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Brain Dynamics and Temporal Summation of Pain Predicts Neuropathic Pain Relief from Ketamine Infusion

Rachael L. Bosma, Ph.D., Joshua C. Cheng, Ph.D., Anton Rogachov, B.Sc., Junseok A. Kim, M.Sc., Kasey S. Hemington, Ph.D., Natalie R. Osborne, M.Sc., Lakshmikumar Venkat Raghavan, M.D., Anuj Bhatia, M.D., Karen D. Davis, Ph.D.

ABSTRACT

Background: Ketamine is an *N*-methyl-D-aspartate receptor antagonist that reduces temporal summation of pain and modulates antinociception. Ketamine infusions can produce significant relief of neuropathic pain, but the treatment is resource intensive and can be associated with adverse effects. Thus, it is crucial to select patients who might benefit from this treatment. The authors tested the hypothesis that patients with enhanced temporal summation of pain and the capacity to modulate pain *via* the descending antinociceptive brain pathway are predisposed to obtain pain relief from ketamine.

Methods: Patients with refractory neuropathic pain (n = 30) and healthy controls underwent quantitative sensory testing and resting-state functional magnetic resonance imaging and then completed validated questionnaires. Patients then received outpatient intravenous ketamine (0.5 to 2 mg · kg^{-1} · h^{-1}; mean dose 1.1 mg · kg^{-1} · h^{-1}) for 6 h/day for 5 consecutive days. Pain was assessed 1 month later. Treatment response was defined as greater than or equal to 30% pain relief (*i.e.*, reduction in pain scores). We determined the relationship between our primary outcome measure of pain relief with pretreatment temporal summation of pain and with brain imaging measures of dynamic functional connectivity between the default mode network and the descending antinociceptive brain pathway.

Results: Approximately 50% of patients achieved pain relief (mean ± SD; Responders, 61 ± 35%; Nonresponders, 7 ± 14%). Pretreatment temporal summation was associated with the effect of ketamine (ρ = −0.52, P = 0.003) and was significantly higher in Responders (median [25th, 75th] = 200 [100, 345]) compared with Nonresponders (44 [9, 92]; P = 0.001). Pretreatment dynamic connectivity was also associated with the clinical effect of ketamine (ρ = 0.51, P = 0.004) and was significantly higher in Responders (mean ± SD, 0.55 ± 0.05) compared with Nonresponders (0.51 ± 0.03; P = 0.006). Finally, the dynamic engagement of the descending antinociceptive system significantly mediated the relationship between pretreatment pain facilitation and pain relief (95% CI, 0.005 to 0.065).

Conclusions: These findings suggest that brain and behavioral measures have the potential to prognosticate and develop ketamine-based personalized pain therapy. (ANESTHESIOLOGY 2018; 129:1015-24)

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NMDA receptor

- upregulation associated with central sensitization and enhanced temporal summation:
  - increasing response to a repeated brief painful stimulus
  - presence in patients with refractory (non-cancer) neuropathic pain helps predict benefit from ketamine.

Bosma RL *et al.* (2018) 98

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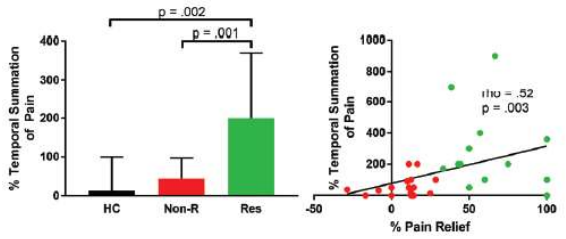
Temporal summation of pain and response to ketamine

Response = ≥30% reduction in pain after 1 month of ketamine



Bosma RL *et al.* (2018) 99

99

Quantitative sensory testing

But:

- this QST not widely available
- significant cost & training
- not a pragmatic clinical tool.

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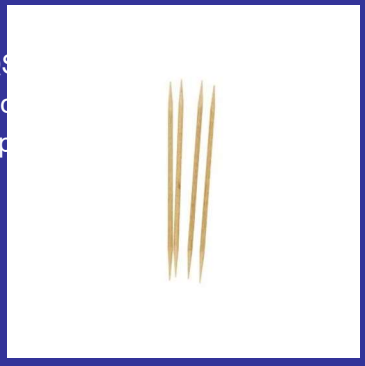
Quantitative sensory testing

But:

- this QS
- signific
- not a p



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Ketamine in cancer pain

- evidence of ketamine's efficacy mostly from case reports, retrospective surveys or uncontrolled studies
- nonetheless, it is considered a potentially useful treatment for cancer-pain failing to respond to usual treatments, i.e.:
  - opioids, non-opioids and adjuvant analgesics.

Bell RF and Kalso EA (2018) 102

102

Ketamine upper GI toxicity

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Ketamine toxicity

- already aware of hepatobiliary, urinary and possible neuropsychiatric toxicity
- need to add upper GI toxicity to the list.

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Ketamine toxicity

- most data concerns long-term frequent abusers of large doses of ketamine
  - generally by nasal insufflation
  - typically ~3.5g/24h for >3 years
- *but* toxicity has been reported in patients, sometimes after only days of use.

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Ketamine: upper GI toxicity

- mechanism of the toxicity is unknown; possible triggers include:
  - a direct irritant effect of ketamine/metabolite
  - disruption of the epithelial barrier (e.g. bladder, GI tract)
  - IgE-mediated hypersensitivity.

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Ketamine: upper GI toxicity

- c/o epigastric pain, vomiting
- common in ketamine abusers (K-cramps)

Liu SY et al. (2017) 107

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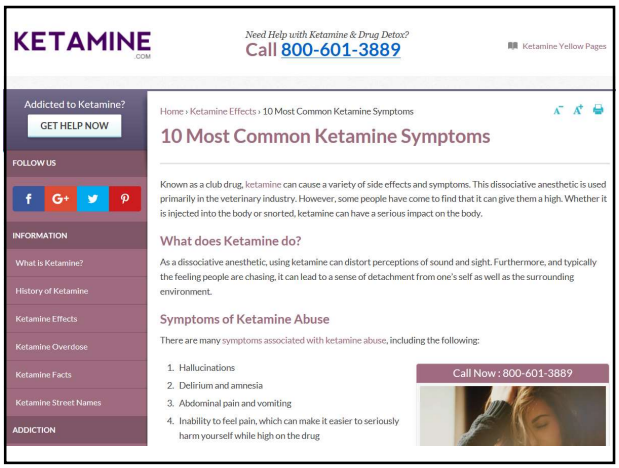

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Ketamine: upper GI toxicity

- often precedes urinary tract toxicity
- presentation may be acute and severe, e.g.:
  - hospital admission
  - upper GI bleeding
  - perforated peptic ulcer.

Liu SY et al. (2017) 109

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Ketamine: upper GI toxicity

Investigations may reveal:

- anaemia
- oesophagitis
- gastritis
- gastro-duodenal erosions/ulceration.

Liu SY et al. (2017) 110

110

Ketamine: upper GI toxicity

Management:

- treat any acute complication
- abstinence.

Liu SY et al. (2017) 111

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