Spotlight on drugs

Advanced courses 2018

Dr Andrew Wilcock DM FRCP
andrew.wilcock@nottingham.ac.uk

The University of Nottingham

1

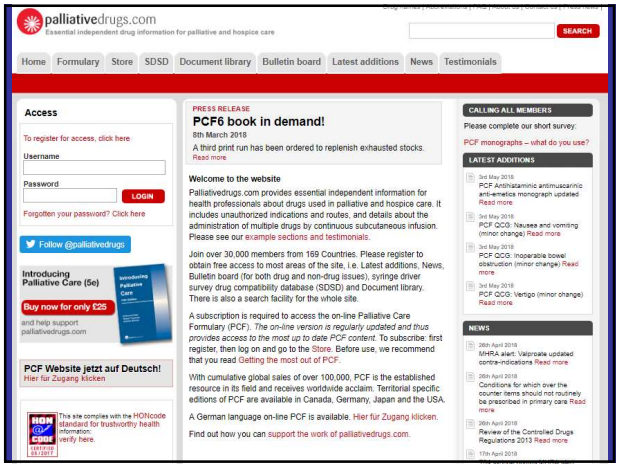
Spotlight on drugs

- highlight various topics relating to drugs
- biased selection, reflecting:
  - recent courses, topical interest, new drugs
  - broadest appeal (UK focus)
- your input required!
- 1h sessions x 2
- slides available on website at the end of the four courses.

2

Update

palliativedrugs.com



Website (May 2018)

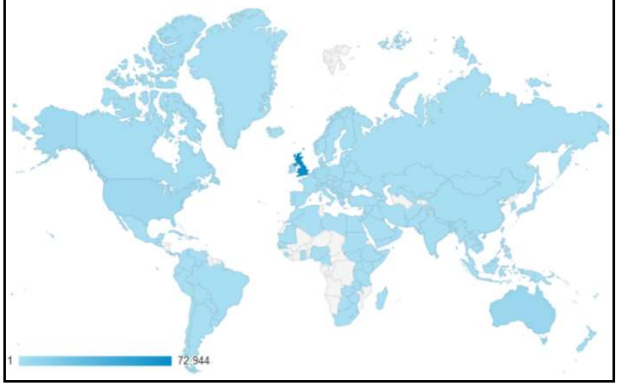
- 38,000 registered members
  - doctors (33%)
  - nurses (30%)
  - pharmacists (26%).

5

Website 2017–18

- 111,000 visits
- 69,000 unique visits
- 547,000 page impressions
- 190 unique visits/day
- 1,500 page impressions/day
- 153 countries.

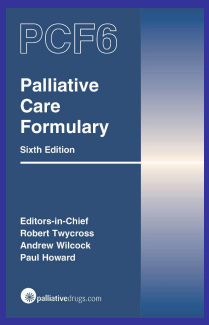
Global reach of pd.com 2018



On-line PCF

- continually updated
- £50 p.a.
- individual/small group subscription
- NHS Education for Scotland subscribe, so available free via NES ATHENS username/password.

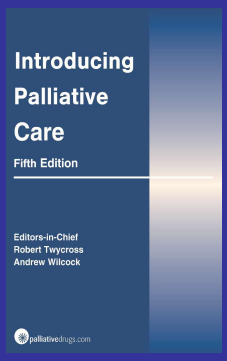
8



- Autumn 2017
- 890 pages
- reviewed/updated/new monographs
- £55 (inc p&p in UK)
- on 3rd print run.

From www.palliativedrugs.com

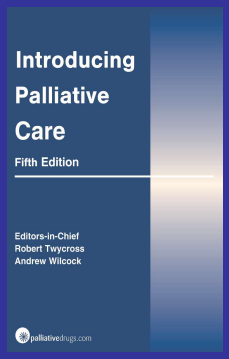
9



- collaborative project between palliativedrugs.com and 8 new contributors
- covers APM curriculum for medical undergraduates
- will also serve them well as junior hospital doctors and beyond
- useful to undergraduates and graduates of other disciplines

From www.palliativedrugs.com

10



- expanded sections on children, ethics, the law, symptom management
- contains the Essential Palliative Care Formulary
- £25 (inc. p&p in the UK)

From www.palliativedrugs.com

11

Summary

- formulary on website continually updated
  - PCF6+
- book version published every 3 years
  - PCF7 due 2020
- IPC5 available now.

12

Dr Robert Twycross MA DM Oxon FRCP FRCR
PCF Editor-in-Chief - retires after 20 years

- retired following the publication of PCF6
- with Andrew Wilcock, and latterly Paul Howard, has been a co-author/Editor-in-Chief for 20 years
- seen *PCF* change from 250 page first edition (1998) → 890 page sixth edition (2017)
- also production of American, Canadian, German, Italian and Japanese versions.

13

Dr Robert Twycross MA DM Oxon FRCP FRCR
PCF Editor-in-Chief - retires after 20 years

- with Andrew Wilcock, he founded palliativedrugs.com Ltd. in 2000 to provide on-line access to *PCF* (for many years as a free resource)
- continued to co-author other core text books: *Introducing Palliative Care* (5th edition 2016) and *Symptom Management in Advanced Cancer* (now out of print).

14

Dr Robert Twycross MA DM Oxon FRCP FRCR
PCF Editor-in-Chief - retires after 20 years

- throughout this time has taught in many countries, including Argentina, China, Hungary, India, Poland, and Russia
- we are honoured to have worked alongside such an inspirational and influential pioneer in the development of palliative care, and thank him wholeheartedly for his commitment, support and guidance.

15

With warmest wishes for your retirement, Robert

16

Editorial staff changes

Editor-in-chief:
- Sarah Charlesworth

Editors:
- Joanne Droney, London
- Stephen Oxberry, Huddersfield
- Anna Spathis, Cambridge

17

Topics 2018

PCF6 snippets
- Hepatic impairment (FYI)
- Denosumab
- Cyclizine
- Rifampicin
- Dexmedetomidine
- Mirtazapine
- Gabapentin

18

Hepatic impairment

18: HEPATIC IMPAIRMENT

The recommendations in this chapter are *not* comprehensive, more a direction of travel than a detailed road map. Specific recommendations are limited to analgesics, anti-emetics, psychotropics, and anti-epileptics. For other drugs, see the relevant monograph and the manufacturer's SPC. However, some SPCs are unnecessarily restrictive.[1]

There will be occasions when hard evidence is not available, and clinicians may have to *prescribe and proceed with caution*, e.g.:

- reduce polypharmacy as much as possible
- use a low starting dose
- reduce frequency of administration
- titrate upwards slowly
- monitor for both early and late onset toxicity (accumulation more likely if the plasma halflife is prolonged)

New : Hepatic impairment chapter

Dose recommendation tables:

- Non-opioids
- Opioids
- Anti-emetics
- Benzodiazepines and Z-drugs
- Antipsychotics
- Antidepressants
- Anti-epileptics

21

Table 4 Anti-emetics in cirrhosis or severe hepatic impairment. Before use, see introductory and class specific text above

Drug	*PO bio-availability (%)*	*Protein-binding (%)*	*Halflife in normal liver function (h)*	*Active metabolite(s)*	*Increase in halflife in severe hepatic impairment (h)*	*Dose and comments*
Use cautiously						
Domperidone	12–18	>90	7–9	No	50%	PO: start with 5mg b.d., maximum 10mg t.d.s.
Cyclizine	No data	No data	20	No	No data	Dose unchanged
Haloperidol	45–75	92	12–38	Yes	No data	Start with low dose, titrate slowly
Levomepromazine	20–40	No data	15–30	No	No data	Start with low dose, titrate slowly
Metoclopramide	50–80	13–22	4–6	No	>100%	PO/SC: start with 5mg b.d., maximum 10mg b.d.
Ondansetron	56–71	70–76	3–6	No	>300%	PO/SC: maximum 8mg/24h
Prochlorperazine	6	96	15–20	No	Probably ↑	Start with low dose, titrate slowly

Collaborators: Hepatic impairment

Similar process underway with help from:

- Stephen Oxberry, Palliative Medicine consultant
- Maria McKenna, Palliative Medicine consultant
- Wendy Prentice, Palliative Medcine consultant
- Paul Selby, Hepatology Pharmacist
- Sarah Cripps, Hepatology Pharmacist
- Aisling Considine, Hepatology Pharmacist
- Mary Mihalyo, Palliative Care Pharmacist
- Mark Wright, Hepatology consultant
- Sarah Tarff, Hepatology nurse

23

Hepatic impairment

- current chapter 'starting point'
- new chapter in development (→ www.palliativedrugs.com)
- will also publish as JPSM Therapeutic highlight
- please share any specific guidelines on 'end-of-life/last days' care in end-stage hepatic failure
  - andrew.wilcock@nottingham.ac.uk

24

Denosumab
New monograph / JPSM paper

25

Learning objectives: Denosumab

For PC clinicians to gain knowledge of:

- outline of pharmacology
- options for stopping / substituting
- role in 'refractory' tumour-induced hypercalcaemia.

26

Denosumab

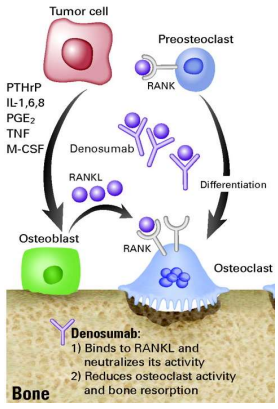
- PCF6 = a box in bisphosphonates
- ↑ use by oncologists as prophylaxis for skeletal-related events (SRE)
- ↑ numbers coming through to palliative care services.

27

Denosumab: Background

- human monoclonal antibody
- binds *Receptor Activator of Nuclear factor Kappa β Ligand* (RANKL), a cytokine and member of the tumour necrosis factor superfamily
- prevents interaction between RANKL and the RANK receptor on osteoclasts
- inhibits their maturation, function and survival, and thereby bone resorption.

28



29

Bisphosphonates: Background

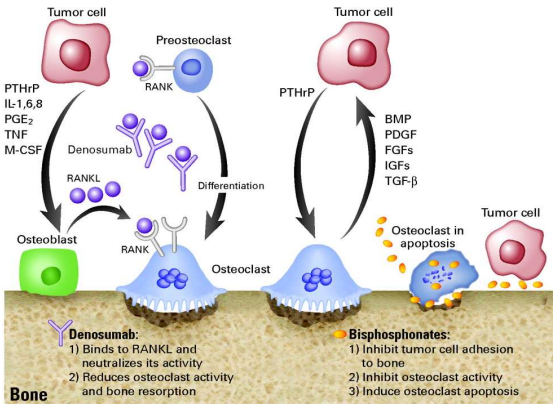
- stable analogues of pyrophosphate, a naturally occurring regulator of bone metabolism
- they have high affinity for ca^{2+} ions, and bind rapidly to hydroxyapatite crystals in mineralized bone [*forms a reservoir*]
- subsequently released and taken up by osteoclasts, interfering with their function and/or inducing their apoptosis (programmed cell death).

30

Bisphosphonates: Background

- **zoledronic acid** most potent nitrogen-containing bisphosphonate
- inhibits the mevalonate pathway vital for normal cellular function (e.g. vesicular trafficking, cell signalling, cytoskeleton function)
- these cellular effects also extend to macrophages, reducing the production of cytokines.

31



Denosumab vs. bisphosphonates (e.g. for prophylaxis of SRE)

	Denosumab	***Zoledronic acid***
Administration	SC injection	IVI (generally 15min)
Frequency (SRE)	Monthly (no 'reservoir' in body)	Monthly; every 3 months as effective (reservoir in bone)
Cost	120mg = £310 [£3,720 p.a.]	4mg = £10–£175 [£40–£700 p.a.]
Efficacy	+++ (cancer dependent)	++ (cancer dependent)
Tolerability	Greater risk: hypocalcaemia Similar risk: ONJ Lower risk: renal toxicity	

Prevention of skeletal-related events (SRE) in adults with advanced cancer involving bone

- include pathological fracture, spinal cord compression, pain and need for radiation or surgery to bone
- those used as outcomes vary between studies, as does their definition (e.g. radiological vs. clinical pathological fracture)
- this variation can limit direct comparison of study findings.

34

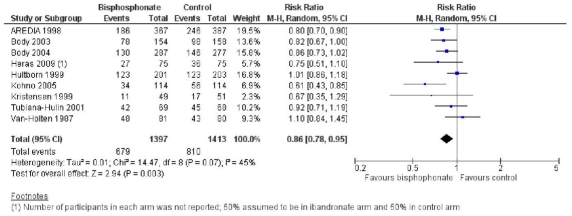
Prevention of skeletal-related events (SRE) in adults with advanced cancer involving bone

Bisphosphonates (vs. placebo), e.g. in metastatic breast cancer:

- reduce the risk of SRE by 14% (RR 0.86, 95% CI 0.78 to 0.95; P=0.003)
- delay median time to SRE with a median ratio of 1.43 (95% CI 1.29 to 1.58; P<0.00001) [median differences ranged by 4–6 months]
- reduce bone pain (modest effect).

O'Carrigan B *et al.* (2017); von Moos R *et al.* (2013) 35

Figure 9. Forest plot of comparison: 1 Breast cancer and Bone Metastases (BCBM), outcome: 1.2 Overall risk of SREs in BCBM: bisphosphonate versus control (excluding hypercalcaemia).



O'Carrigan B et al. (2017) 36

Prevention of skeletal-related events (SRE) in adults with advanced cancer involving bone

Denosumab is superior cf. zoledronic acid in breast cancer:

- reduces the risk of SRE by 22% (RR 0.78, 95% CI 0.72 to 0.85; P<0.001)
- delays time to SRE, HR 0.82 (95% CI 0.71 to 0.95; P=0.01).

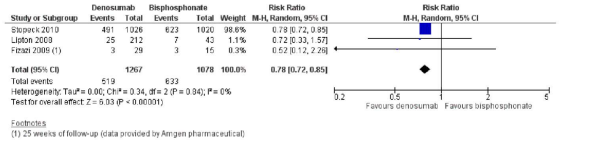
In other cancer types, less difference (myeloma = no difference).

O'Carrigan B *et al.* (2017); von Moos R *et al.* (2013)
Henry DH *et al.* (2011); Fizazi K et al. (2011); Raje N et al. (2018)

37

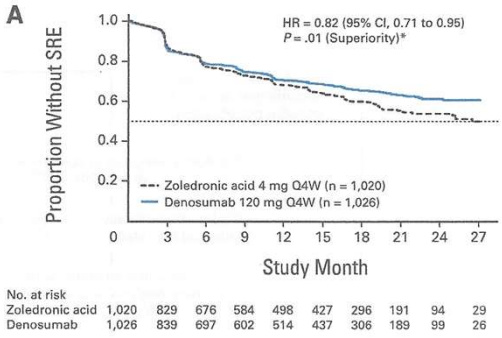
Denosumab vs. IV bisphosphonate in breast cancer

Figure 10. Forest plot of comparison: 1 Breast cancer with bone metastases (BCBM), outcome: 1.3 Overall risk of skeletal events in BCBM: denosumab versus bisphosphonate



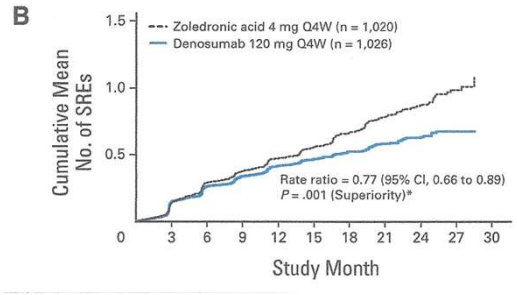
O'Carrigan B et al. (2017) 38

Denosumab vs. zoledronic acid in breast cancer: Time to first SRE



Stopeck AT *et al.* (2010)

Denosumab vs. zoledronic acid in breast cancer: Cummulative mean number of SRE



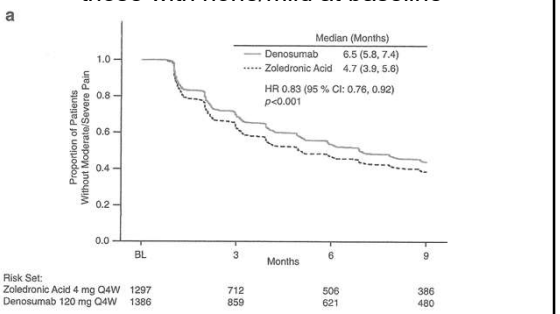
Stopeck AT *et al.* (2010)

Prevention of skeletal-related events (SRE) in adults with advanced cancer involving bone

- in a pooled analysis of mostly breast/prostate cancer, denosumab superior to zoledronic acid in delaying onset of moderate–severe pain.

von Moos R et al. (2013) 41

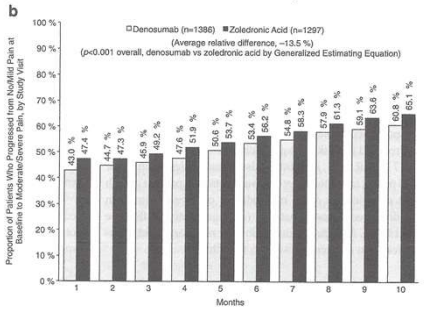
Denosumab vs. zoledronic acid: Time to first report of moderate/severe pain in those with none/mild at baseline



Pooled analysis, mostly breast and prostate cancer

Von Moos R *et al.* (2013)

Denosumab vs. zoledronic acid
Proportion of patients progressing none/mild → moderate/severe pain



Pooled analysis, mostly breast and prostate cancer

Von Moos R *et al.* (2013)

Prevention of skeletal-related events (SRE) in adults with advanced cancer involving bone

- overall no difference in survival
  - ➢trend for ↓ in myeloma; large study = no difference; *but efficacy same as cheaper bisphosphonates*
  - ➢trend for ↑ in NSCLC (by 6 weeks); recent study findings awaited.

44

Independent review (academic authors, no CoI)

PharmacoEconomics
https://doi.org/10.1007/s40273-017-0595-0

CrossMark

SYSTEMATIC REVIEW

Cost-Effectiveness of Treatments for the Management of Bone Metastases: A Systematic Literature Review

Lazaros Andronis[1,2] · Ilias Goranitis[1] · Sue Bayliss[3] · Rui Duarte[4]

45

Cost-effectiveness of denosumab

…Across types of cancer, evidence suggests that bisphosphonates result in lower morbidity and improved quality of life, for an additional cost, which is typically below conventional cost-effectiveness thresholds. *While denosumab leads to health gains compared with zoledronic acid, it also results in substantial additional costs and is unlikely to represent value for money…*

Andronis L *et al.* (2017) 46

Specialty guidelines

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): ii124–ii137, 2014
doi:10.1093/annonc/mdu103
Published online 29 April 2014

Bone health in cancer patients: ESMO Clinical Practice Guidelines†

R. Coleman[1], J. J. Body[2], M. Aapro[3], P. Hadji[4] & J. Herrstedt[5] on behalf of the ESMO Guidelines Working Group*

47

Specialty guidelines


VOLUME 36 · NUMBER 8 · MARCH 10, 2018
JOURNAL OF CLINICAL ONCOLOGY
ASCO SPECIAL ARTICLE

Role of Bone-Modifying Agents in Multiple Myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update

Kenneth Anderson, Nefyat Ismaila, Patrick J. Flynn, Susan Halabi, Sundar Jagannath, Mohammad S. Ogaily, Jen Orord, Noopur Raje, G. David Roodman, Gary C. Yee, and Robert A. Kyle

A B S T R A C T

Purpose
To update guideline recommendations on the role of bone-modifying agents in multiple myeloma.

Methods
An update panel conducted a targeted systematic literature review by searching PubMed and the Cochrane Library for randomized controlled trials, systematic reviews, meta-analyses, clinical practice guidelines, and observational studies.

Results
Thirty-five relevant studies were identified, and updated evidence supports the current recommendations.

Recommendations
For patients with active symptomatic multiple myeloma that requires systemic therapy with or without evidence of lytic destruction of bone or compression fracture of the spine from osteopenia on plain radiograph(s) or other imaging studies, intravenous administration of pamidronate 90 mg over at least 2 hours or zoledronic acid 4 mg over at least 15 minutes every 3 to 4 weeks is recommended. Denosumab has shown to be noninferior to zoledronic acid for the prevention of skeletal-related events and provides an alternative. Fewer adverse events related to renal toxicity have been noted with denosumab compared with zoledronic acid and may be preferred in this setting. The update panel recommends that clinicians consider reducing the initial pamidronate dose in patients with preexisting renal impairment. Zoledronic acid has not been studied in patients with severe renal impairment and is not recommended in this setting. The update panel suggests that bone-modifying treatment continue for up to 2 years. Less frequent dosing has been evaluated and should be considered in patients with responsive or stable disease. Continuous use is at the discretion of the treating physician and the risk of ongoing skeletal morbidity. Retreatment should be initiated at the time of disease relapse. The update panel discusses measures regarding osteonecrosis of the jaw. Additional information is available at www.asco.org/hematologic-malignancies-guidelines and www.asco.org/guidelines/wiki.

48

Specialty guidelines

VOLUME 35 · NUMBER 35 · DECEMBER 10, 2017

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology–Cancer Care Ontario Focused Guideline Update

ABSTRACT

49

Specialty guidelines: solid tumours

Generally recommend the preventative use of *either zoledronic acid or denosumab* for all patients with bone metastases arising from breast or hormone-relapsed prostate cancer, and for selected patients with other solid tumours, i.e. those considered at high risk of a SRE with a likely prognosis >3 months.

50

Specialty guidelines: myeloma

Note that denosumab is an option, particularly in those with renal impairment, but *generally favour an IV bisphosphonate*, based on lower cost and more flexible dosing interval, e.g. zoledronic acid can be reduced to every 3 months in those without active myeloma on maintenance treatment.

[Denosumab non-inferior to zoledronic acid in delaying the time to first SRE, but associated with a lower incidence of renal toxicity (12% vs. 17%)].

51

What does this mean for palliative care?

PCF view

PCF notes that:

- the cost-effectiveness of the additional benefit of denosumab over zoledronic acid for the prevention of SRE is questionable
- speciality guidelines generally recommend the use of either
- the risk of discontinuation fractures is greater with denosumab than zoledronic acid.

What does this mean for palliative care?

PCF view

Thus, for patients with cancer referred to a specialist palliative care service who have progressive metastatic bone disease despite monthly denosumab, unless there is severe renal impairment, *PCF* recommends considering substituting the denosumab for zoledronic acid.

What does this mean for palliative care?

PCF view (continued)

For patients with a limited prognosis, the zoledronic acid would need to be given only once, 4 weeks after the last dose of denosumab. However, if necessary, the zoledronic acid can be repeated every 3 months.

Do not just stop denosumab!

When stopped *in osteoporosis*:

- no body reservoir (unlike bisphosphonates)
- bone turnover ↑ within 3 months, bone mineral density falls to baseline levels within 12 months and there is an ↑ risk of multiple vertebral fractures
- ? rebound ↑ activity of osteoclasts.

Do not just stop denosumab!

- thus, when used for osteoporosis, denosumab should be administered regularly, and if discontinued, a bisphosphonate used instead
- by extrapolation, the same considerations apply to its use in the cancer setting; *potentially even more important, given osteoclast stimulating effect of cancer.*

Severe hypocalcaemia

- risk 10% denosumab vs. 5% zoldedronic acid
- can be life-threatening / fatal
- follow administration guidelines, e.g.:
  - prophylactic calcium and vitamin D
  - do not give if hypocalcaemic
- be prepared to replace IV
  - added new box into denosumab monograph.

57

Hypocalcaemia: IV calcium

Box A. Emergency treatment of hypocalcemia[26]

EKG monitoring is required because of the risk of cardiac arrhythmias.
Note: For patients with raised plasma phosphate levels, consult specialist renal and/or endocrinology guidance.

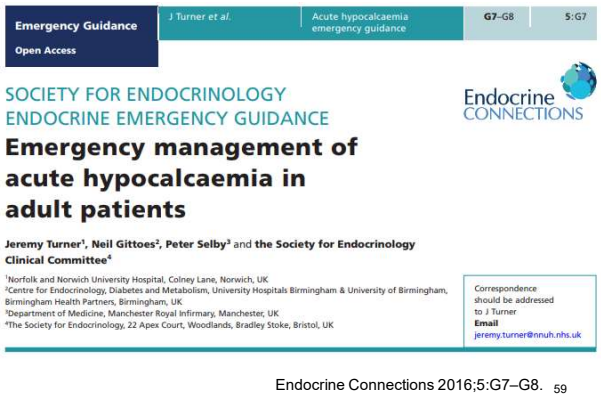
Initial treatment

- give 10–20mL calcium gluconate 10% (2.2–4.4mmol) IV diluted in 50–100mL sodium chloride 0.9% or glucose 5% over 10min
- use a central or large peripheral vein because of the risk of irritation
- repeat the dose until the patient is asymptomatic.

Follow up infusion

- give 100mL calcium gluconate 10% (22mmol) IVI diluted in 1L sodium chloride 0.9% or glucose 5% at a rate of 50–100mL/h; titrate to achieve normocalcemia
- check calcium levels 2h after the infusion.

58



Emergency Guidance
Open Access

J Turner *et al.* | Acute hypocalcaemia emergency guidance | G7–G8 | 5:G7

SOCIETY FOR ENDOCRINOLOGY
ENDOCRINE EMERGENCY GUIDANCE

Endocrine CONNECTIONS

Emergency management of acute hypocalcaemia in adult patients

Jeremy Turner[1], Neil Gittoes[2], Peter Selby[3] and the Society for Endocrinology Clinical Committee[4]

[1]Norfolk and Norwich University Hospital, Colney Lane, Norwich, UK
[2]Centre for Endocrinology, Diabetes and Metabolism, University Hospitals Birmingham & University of Birmingham, Birmingham Health Partners, Birmingham, UK
[3]Department of Medicine, Manchester Royal Infirmary, Manchester, UK
[4]The Society for Endocrinology, 22 Apex Court, Woodlands, Bradley Stoke, Bristol, UK

Correspondence should be addressed to J Turner
Email
jeremy.turner@nnuh.nhs.uk

Endocrine Connections 2016;5:G7–G8. 59

Severe hypocalcaemia

Severe hypocalcaemia: serum calcium <1.9 mmol/L and/or symptomatic at any level below reference range.

- **This is a medical emergency**
- Administer i.v. calcium gluconate
- Initially, give 10–20 mL 10% calcium gluconate in 50–100 mL of 5% dextrose i.v. over 10 min with ECG monitoring. This can be repeated until the patient is asymptomatic. It should be followed up with a calcium gluconate infusion as follows:
  - Dilute 100 mL of 10% calcium gluconate (10 vials) in 1 L of Normal saline or 5% dextrose and infuse at

60

Hazards of i.v. calcium administration

Uncommon, but include local thrombophlebitis, cardiotoxicity, hypotension, calcium taste, flushing, nausea, vomiting and sweating. Patients with cardiac arrhythmias or on digoxin therapy need continuous ECG monitoring during i.v. calcium replacement.

61

Hypocalcaemia: IV calcium

Reference source	*Date of ref source*	*Information*
Turner 2016		"Give calcium gluconate IV over 10min with ECG monitoring." Under hazards of IV administration: "Cardiotoxicity, hypotension…Patients with cardiac arrythmias or on digoxin therapy need continuous ECG monitoring during iv replacement." No additional references to these statements.
NUH hypocalcaemia guidelines	Jan 2018	Continuous cardiac monitoring should be performed during IV calcium administration in patients who have shown to have ECG changes, or those taking digoxin. Ideally cardiac monitoring should include continuous ECG monitoring. Stop/slow the infusion if the patient becomes bradycardic or hypotensive. ECG monitoring recommended especially in those at high risk of arrythmias or cardiac disease. Baseline observations should be carried out q4h (includes temp, BP, heart rate, resp rate, Oxygen sats and fluid balance)
BNF	Accessed 19/06/18	Severe acute hypocalcaemia: Initially 10–20 mL, calcium gluconate injection 10% (providing approximately 2.25–4.5 mmol of calcium) should be administered with plasma-calcium and ECG monitoring
SPC	3/01/18	*Section 4.2* The patient should be in the lying position and should be closely observed during injection. Monitoring should include heart rate or ECG. *Section 4.3* CI with cardiac glycosides *Section 4.5* The effects of digoxin and other cardiac glycosides may be potentiated by calcium, which may result in serious toxicity. Therefore, intravenous administration of calcium preparations to patients under therapy with cardiac glycosides is contraindicated.
MedUsa	12/07/17	ECG monitoring for Iv administration (references the BNF).
Injectable drugs guide	Accessed 19/06/18	Do not give to patients receiving cardiac glycosides. *Pre-treatment checks*: includes ECG but does state that not all are necessary in an emergency situation

62

Hypocalcaemia: IV calcium

Handbook on injectable drugs	Accessed 19/06/18	No information on ECG monitoring
Martindale	Accessed 06/06/18	No information on ECG monitoring
AHFS	Accessed 06/06/18	The only mention of ECG monitoring is for the treatment of hyperkalemia with secondary cardiac toxicity.
UKMI QA	June 2017	**How is acute hypocalcaemia treated in adults?** In severe acute hypocalcaemia or hypocalcaemic tetany, 2.2 to 4.5 mmol calcium (as gluconate) is administered as a slow intravenous injection over 5 to 10 minutes with ECG monitoring throughout the injection and afterwards (13-15). Note there is a risk of cardiac arrhythmias if the calcium is administered too quickly [Tohme 1996, BNF, MedUsa] Calcium salts are contraindicated in patients with ventricular fibrillation or hypercalcaemia and should be used with great caution in patients who are taking cardiac glycosides as calcium enhances the effects of digoxin on the heart and may precipitate digitalis intoxication. If administered too quickly, parenteral calcium solutions can cause cardiac arrhythmias and hypotension. [3, BNF, MedUsa] ECG monitoring should be performed during intravenous administration of calcium, especially in patients with a history of cardiac disease or those at risk of arrhythmias [Compston 1995, BNF, MedUsa]

63

Amended box

Hypocalcaemia increases the risk of cardiac arrhythmia. IV calcium administration can cause hypotension, cardiac arrhythmia and precipitate digoxin toxicity, and continuous heart rate monitoring is required in patients at higher risk of cardiotoxicity, e.g. those with ECG changes, cardiac disease or taking digoxin.[*NUH guidelines*] Recommendations on the need for continuous ECG monitoring vary, ranging from the ideal of its routine use to, as a minimum, in the high risk group above.[*ref Turner; UKMI; NUH guidelines*] Stop or slow the infusion if bradycardia or hypotension occur.

64

Denosumab for 'refractory' tumour-induced hypercalcaemia (TIH)

- bisphosphonates very effective
  - [remember forced diuresis/mithromycin/calcitonin?]
- generally, unresponsive hypercalcaemia part of terminal decline
- occasionally, main problem for a patient with a reasonable performance status.

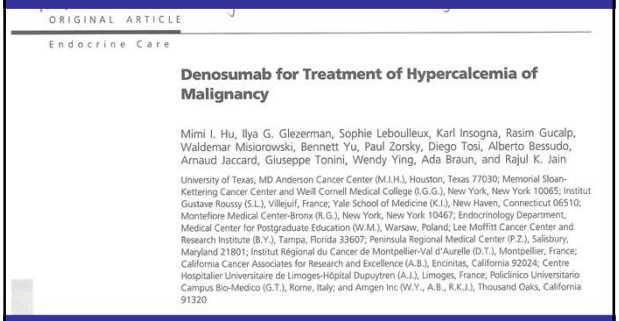
65

Denosumab for 'refractory' TIH

- in USA, Authorized use
- in UK = off label.

66

Denosumab for 'refractory' TIH



ORIGINAL ARTICLE

Endocrine Care

Denosumab for Treatment of Hypercalcemia of Malignancy

Mimi I. Hu, Ilya G. Glezerman, Sophie Leboulleux, Karl Insogna, Rasim Gucalp, Waldemar Misiorowski, Bennett Yu, Paul Zorsky, Diego Tosi, Alberto Bessudo, Arnaud Jaccard, Giuseppe Tonini, Wendy Ying, Ada Braun, and Rajul K. Jain

University of Texas, MD Anderson Cancer Center (M.I.H.), Houston, Texas 77030; Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College (I.G.G.), New York, New York 10065; Institut Gustave Roussy (S.L.), Villejuif, France; Yale School of Medicine (K.I.), New Haven, Connecticut 06510; Montefiore Medical Center-Bronx (R.G.), New York, New York 10467; Endocrinology Department, Medical Center for Postgraduate Education (W.M.), Warsaw, Poland; Lee Moffitt Cancer Center and Research Institute (B.Y.), Tampa, Florida 33607; Peninsula Regional Medical Center (P.Z.), Salisbury, Maryland 21801; Institut Régional du Cancer de Montpellier-Val d'Aurelle (D.T.), Montpellier, France; California Cancer Associates for Research and Excellence (A.B.), Encinitas, California 92024; Centre Hospitalier Universitaire de Limoges-Hôpital Dupuytren (A.J.), Limoges, France; Policlinico Universitario Campus Bio-Medico (G.T.), Rome, Italy; and Amgen Inc (W.Y., A.B., R.K.J.), Thousand Oaks, California 91320

Hu MI *et al.* (2014) 67

Denosumab for 'refractory' TIH

- small study, n=33
- mostly breast, myeloma, neuroendocrine, NSCLC, renal cancers
- hypercalcaemia = corr. calcium >3.1mmol/L; median 3.4mmol/L
- despite prior bisphosphonate use; median (range) 4 (1–41) months
- last dose within 8–30 days; median 17 days.

68

Denosumab for 'refractory' TIH

- concurrent IV fluids, corticosteroids and chemotherapy permitted (but not other calcium lowering treatments, e.g. calcitonin)

69

Denosumab for 'refractory' TIH

- give 120mg SC every 4 weeks; *give additional 120mg SC doses on days 8 and 15 of the first month of therapy*
- i.e. usual regimen with initial 'loading' to reach effective serum concentrations quicker (demonstrated in other setting)
- discontinued if calcium >3.1mmol/L after 4 doses.

70

Denosumab for 'refractory' TIH

Primary endpoint

- proportion of responders (calcium ≤2.9mmol/L) within 10 days of first dose

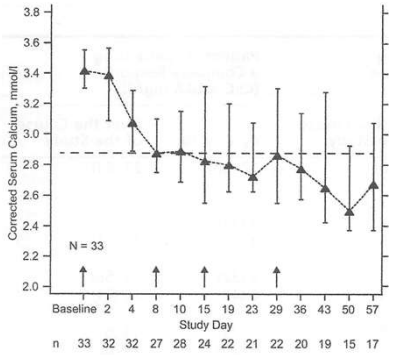
71

Denosumab for 'refractory' TIH

- high drop out (main reason death)
- received a median [IQR] of 4 [2–5] doses, maximum 25
- median [IQR] time on study 56 [18–79] days.

72

Denosumab for 'refractory' TIH



73

Denosumab for 'refractory' TIH

At day 10, Primary outcome:

- 21 (64%) responders (calcium ≤2.9mmol/L)

Secondary outcomes:

- 12 (36%) complete responders (calcium ≤2.7mmol/L)

Over the course of the study, overall:

- 23 (70%) responders
- 21 (64%) complete responders.

74

Denosumab for 'refractory' TIH

Estimated median times:

- to response: 9 days
  - ➢duration of response: 104 days
- to complete response: 23 days
  - ➢duration of complete response: 34 days.

75

Denosumab for 'refractory' TIH

- symptoms improved (~1/2) or resolved (~1/3)
- 2 patients had asymptomatic grade 2 hypocalcaemia (1.75–2mmol/L)
- [*PCF monograph includes Box on treatment*]
- 4 nausea (potentially treatment related)
- 1 cardiac arrest (possibly treatment related)
- 1 colitis (possibly treatment related).

76

What does this mean for palliative care?

- denosumab is a reasonable treatment option for TIH refractory to bisphosphonate therapy.

77

Denosumab 'breaking news'

- pooled analysis of four studies of patients with advanced cancer receiving treatment to reduce SRE (median duration ~1 year)
- incidence of a new primary cancer was double with denosumab 120mg (1.1%) vs. zoledronic acid 4mg (0.6%)
- full implications of this currently uncertain
  - – most relevant in early cancer/osteoporosis.

Amgen, Direct Healthcare Professional Communication, 2018

78

Cyclizine
Old drug, new tricks?

79

Learning objectives: cyclizine

For PC clinicians to gain knowledge of:

- implications of 'new' pharmacokinetic data
- rarer undesirable effects
- cost issues?

80

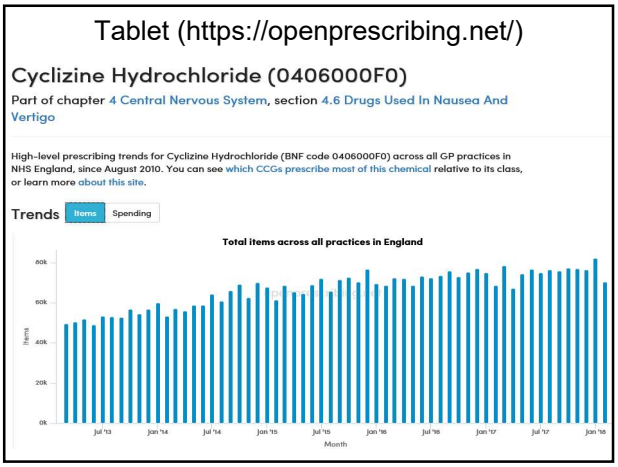
Cyclizine

Background:

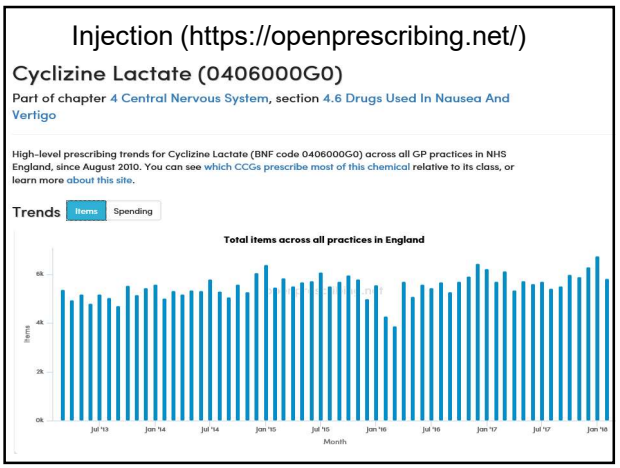
- helping prepare international RAPID pharmacovigilance project (Chair Richard McNeil, NZ)
- discussions around PK and undesirable effects → review of data and monograph
- recent cost increases in injection
  - *tablets* 50mg t.d.s. = £6/month
  - *injection* 150mg = £54/day (now £8/day).

81

Tablet (https://openprescribing.net/)



Injection (https://openprescribing.net/)



Cyclizine

- antihistaminic antimuscarinic anti-emetic
- ↓ excitability of the inner ear labyrinth and blocks conduction in the vestibular-cerebellar pathways, as well as acting directly on the vomiting centre
- effective in many causes of vomiting, including opioid-induced.

84

2018 palliativedrugs.com survey (n=60)

2) For which indication(s), where an anti-emetic is required, would you generally use cyclizine first-line? (many_of)

answer	votes	% of voters
Raised intracranial pressure	40	67
Vestibular symptoms	43	72
Chemical causes of vomiting, e.g. morphine, hypercalcaemia, renal failure	13	22
Gastritis, gastric stasis, functional bowel obstruction	9	15
Other (please state in comments section below)	9	15
Do not use cyclizine	4	7

85

2018 palliativedrugs.com survey (n=60)

Typical dosing: PO

3) What is your general PO starting dose for cyclizine in palliative care patients? (breakdown) (one_of)

answer	votes	% of vote
50mg PO b.d.	5	8%
50mg PO t.d.s	45	75%
Other (please state in comments section below)	5	8%
Do not use PO	4	7%

86

2018 palliativedrugs.com survey (n=60)

Typical dosing: CSCI

5) What is your general parenteral starting dose for cyclizine in palliative care patients if you use continuous subcutaneous infusion (CSCI)? (breakdown) (one_of)

answer	votes	% of vote
50mg/24h CSCI	4	7%
75mg/24h CSCI	1	2%
100mg/24h CSCI	12	20%
150mg/24h CSCI	34	57%
Other (please state in comments section below)	3	5%
Do not use CSCI	5	8%

87

2018 palliativedrugs.com survey (n=60)

Converting PO:SC

6) When converting a patient from PO to parenteral route, do you: (breakdown) (one_of)

answer	votes	% of vote
Use the same total daily dose	53	88%
Halve the daily dose, i.e. 50% less parenterally	2	3%

i.e. *mostly a PO:SC ratio of 1:1*

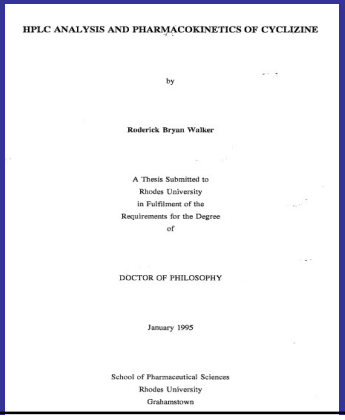
88

Cyclizine: 'new' old PK data

- for PCF1-6, PO bio-availability listed as 'no data'
- alerted to data from a 1995 PhD thesis
- unpublished in full (meeting abstract 1998)

89

Cyclizine: 'new' old PK data



HPLC ANALYSIS AND PHARMACOKINETICS OF CYCLIZINE

by

Roderick Bryan Walker

A Thesis Submitted to
Rhodes University
in Fulfilment of the
Requirements for the Degree
of

DOCTOR OF PHILOSOPHY

January 1995

School of Pharmaceutical Sciences
Rhodes University
Grahamstown

90

Cyclizine: 'new' old PK data

Table 5.4 Absorption Data for Cyclizine for Subjects 1 to 6 Following Oral Administration of a Single 50mg Dose of Cyclizine Hydrochloride.

SUB	C_{max} µg/ℓ	t_{max} hr	AUC* µg/ℓ.hr	AUMC* µg/ℓ.hr²	MRT hr	*MAT hr	*C_{max}/AUC* hr	¬k_a hr⁻¹	*F
1	14.06	2.5	230.31	6049.96	26.27	11.13	6.10	2.24	0.41
2	17.78	2.5	296.68	6579.52	22.18	6.55	5.99	1.31	0.49
3	13.41	2.0	292.06	7060.50	24.17	8.53	4.59	0.94	0.38
4	10.24	3.0	294.64	10667.22	36.20	23.63	3.48	0.96	0.49
5	22.42	1.5	359.68	8063.33	22.42	2.67	6.23	2.14	0.58
6	14.67	3.5	327.75	9234.84	28.18	14.15	4.48	1.63	0.46
Mean ± S.D.	15.43 3.83	2.0 0.82	300.19 39.35	7942.56 1598.24	26.57 4.79	11.11 6.64	5.15 1.03	1.54 0.52	0.47 0.06

* Calculated using equation 5.20
† Reported as (100 C_{max}/AUC*)
‡ Determined by "method of residuals"
¬ Calculated using equation 5.1 and data from phase 1

Healthy subjects, all male, 18–20 years.

91

What does this mean for palliative care?

- *the PO:SC conversion ratio is 2:1*
- i.e. 150mg/24h PO = 75mg/24h CSCI
- [think back to patients who may have undesirable effects with, e.g. 50mg IV, 150mg CSCI = relative overdosing cf. PO dose].

What does this mean for palliative care?

PCF6+ cyclizine dose recommendations:

- *PO*: start 50mg PO b.d.–t.d.s. & 50mg p.r.n.
- *SC/CSCI*: start 75mg/24h CSCI & 25mg SC p.r.n.; if necessary, increase to 150mg/24h CSCI & 50mg SC p.r.n.
- usual maximum daily dose 200mg PO and CSCI.

Cyclizine: 'new' old PK data

Confirmed long halflife 20h (PCF6 13h); and cummulation with t.d.s. dosing over 5 days

cyclizine determined in the present studies. Consequently, dosing eight hourly resulted in accumulation of cyclizine and steady state concentrations in excess of what was expected based on single dose studies. The recommended dosing regimen was more than likely based on limited pharmacokinetic information obtained using analytical methods lacking in sensitivity to accurately quantitate the low concentrations of cyclizine found in the blood. As a result, the dosing interval may have been based on the distribution kinetics and not the elimination kinetics. The use of this dosing frequency, for administration of cyclizine to both adults and children may result in unnecessary accumulation of the drug with associated untoward side-effects. Cyclizine could more than likely be administered less frequently with beneficial therapeutic effects. These recommendations are similar

94

What does this mean for palliative care?

- *a b.d. dosing regimen may suffice*
- supports existing *PCF* suggestion of b.d.–t.d.s. regimen.

Cyclizine

Rare undesirable effects:

- seizures
- movement disorders, e.g. tremor, dyskinesia, dystonia
- worsening of Parkinson's disease
- misuse/abuse of the injection
- transient paralysis (mostly after IV use).

96

Cyclizine: SPC

Lists

- *PO*: dystonia, dyskinesia, extrapyramidal motor disturbances, tremor, paraesthesia and generalised chorea, twitching, muscle spasms; seizures (particularly with overdose)
- *injection*: as above + paralysis (after IV use); some had an underlying neuromuscular disorder.

97

2018 palliativedrugs.com survey (n=60)

7) Have you seen a 50mg PO dose of cyclizine: (many_of)

answer	votes	% of voters	
Cause seizures	0	0	
Cause drug-induced movement disorders	4	7	
Worsen Parkinson's disease	2	3	
Misused/abused in a palliative care setting	0	0	

8) Have you seen a 50mg SC dose of cyclizine: (many_of)

answer	votes	% of voters	
Cause seizures	0	0	
Cause drug-induced movement disorders	4	7	
Worsen Parkinson's disease	1	2	
Misused/abused in a palliative care setting	3	5	

9) Have you seen a 50mg IV dose of cyclizine: (many_of)

answer	votes	% of voters	
Cause seizures	0	0	
Cause drug-induced movement disorders	2	3	
Worsen Parkinson's disease	0	0	
Misused/abused in a palliative care setting	5	8	

Cyclizine: seizures

MHRA reports, e.g.:

- 46 reports of seizure (no context given)

Case series, e.g.:

- with IV cyclizine misuse.

Ruben SM *et al*. (1989) 99

Cyclizine: movement disorders

Case reports, e.g.:

- acute dystonic reactions (IV, 34 y.o. F)
- chorea (PO/IV)

MHRA reports, e.g.:

- tremor, dyskinesia, parkinsonism

Thus, could exacerbate Parkinson's disease.

Likely mechanism is altered balance between DA:Ach; particularly relevant when existing movement disorder.

King H *et al*. (2003); Klawans H (1977); McDevitt L (2013); Lee P (2013) 100

Cyclizine: movement disorders

Case reports, e.g.:

- transient paralysis (IV, 21 y.o. F)
- locked-in syndrome:
  - ➢24 y.o. F, cyclizine 25mg SC t.d.s for 1 month
  - ➢immobile, uncommunicative, mouth care impossible as 'biting down'; but eyes open & following staff; 'alert but unresponsive'
  - ➢resolved 24h after stopping cyclizine
  - ➢(previously jaw dystonia with prochlorperazine).

King H *et al*. (2003); Klawans H (1977); McDevitt L (2013); Lee P (2013) 101

Cyclizine misuse

Long described, but not widely appreciated:

- mostly recreational drug misusers
- also in patients with chronic pain on long-term opioids
- case series in oncology / palliative care / nutritional unit.

102

Case series IV cyclizine misuse

Interviews with 20 cyclizine misusers:

- taken in large doses IV with methadone
- causes intense stimulation, often with hallucinations, sometimes with aggressive behaviour, and occasionally with seizures
- subsequent depressive mood often with a craving for cyclizine
- tolerance occurs but no clear withdrawal syndrome.

Ruben SM *et al.* (1989) 103

Case series IV cyclizine misuse

4 patients in cancer centre; features included:

- self-administering IV bolus via central line (exceeding usual dose), even though agreement was for SC use
- asking for IV bolus to be given rapidly
- drug-seeking behaviour, e.g.:
  - verbally aggressive when dose limited / challenged
  - involving relatives in providing IV bolus (instead of SC) when too unwell to self administer.

Bailey F & Davies A (2008) 104

Case series IV cyclizine misuse

4 patients in a nutritional unit; features included:

- reporting ↑ pain and nausea on attempts to stop cyclizine
- drug-seeking behaviour, e.g.:
  - stating only possible solution to nausea is cyclizine (alternatives don't work/can't be taken)
  - symptoms markedly deviating from objective clinical evidence
  - bizarre reasons for running out of cyclizine ± lost prescriptions
  - playing off one doctor against another.

Thursby-Pelham FW *et al.* (2009) 105

What does this mean for palliative care?

Rarely:

- movement disorders can occur with cyclizine
  - young (esp. dystonias) / those with existing neurological disorders at greater risk
- cyclizine can be misused (IV/SC)
  - seizures more likely in this context / with overdose.

Rifampicin for cholestatic pruritus

107

Learning objectives: rifampicin

For PC clinicians to gain knowledge of:

- use in cholestatic pruritus
- likely mechanism of action
- caution required particularly because of enzyme induction.

108

Case report

- Richard, 79 years old
- mesothelioma diagnosed 2016
- 5 cycles palliative chemotherapy with stable disease (April 2017)
- 28th March 2018 progressive disease:
  - 4/7 history of painless jaundice
  - intense *pruritus*, especially at night (upper abdominal mass obstructing biliary system)
  - *dysphagia* (oesophageal compression)
  - *fatigue* (rapid decline in general condition).

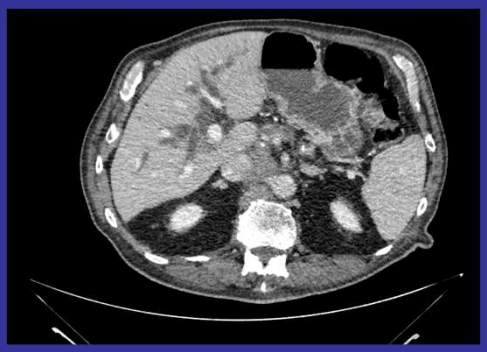
109

Case report

- Bilirubin 161 [10]
- Alk Phos 510 [106]
- AST 136 [27]
- ALT 228 [20]

110

Case report



111

Case report

- skin well hydrated, jaundiced, multiple scratch marks all over body
- dexamethasone (no benefit)
- SSRI (didn't tolerate/no benefit)
- 24th April failed ERCP (distorted anatomy around ampulla), plan for PTC (but ? well enough).

112

Case report

- 25th April; started rifampicin 150mg at night
- 28th April admitted to GI ward; rifampicin increased to 150mg b.d.
- 30th April PC review; pruritus had stopped within 24h
- 3rd May; RIP, pruritus controlled.

113

Rifampicin for cholestatic jaundice

- new monograph for PCF6: see for full details
- also paper in JPSM; Howard P et al (2015).

114

Treatment of cholestatic pruritus

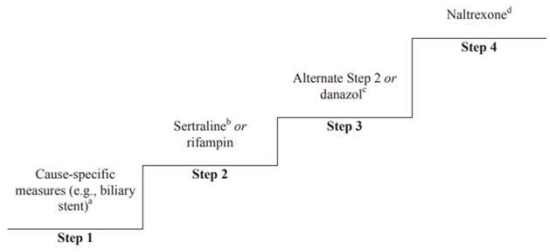
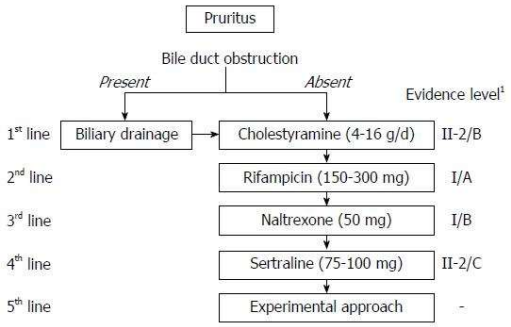


Fig. An approach to the treatment of cholestatic pruritus used in some centers
[a]specialist guidelines recommend cholestyramine for *incomplete* biliary obstruction, e.g., PBC.[18,19,21] Note. Because cholestyramine binds bile salts within the gut, it is ineffective in *complete* biliary obstruction. It is also unpalatable, and needs to be administered separately from other drugs.
[b]although experience with sertraline is limited (n=12 cross-over study in non-cancer cholestasis, mostly PBC),[22] its tolerability, familiarity and limited interactions compared with rifampin generally means that it is tried first.
[c]benefit reported with androgens remains anecdotal.[23,24]
[d]although benefit confirmed in two small RCTs (n=36, mostly PBC), naltrexone (an opioid antagonist) is contra-indicated in patients needing opioid analgesia.[25,26]

Management of cholestatic pruritus (AASLD)



116

Rifampicin for cholestatic jaundice

- pooled RCT data (n=61) supports efficacy (NNT = 1.8)
- non-cancer causes of cholestasis, mostly (80%) primary biliary cholangitis (PBC)
- RCTs were short-term (≤2 weeks), but long-term benefit (≤2 years) reported.

Khurana S and Singh P (2006); Bachs L *et al.* (1992) 117

Rifampicin for cholestatic jaundice

- rifampicin is a pregnane X receptor (PXR) agonist; involved in enzyme regulation
- activation of the PXR receptor inhibits the synthesis of the enzyme *autotaxin*
  - levels correlate with antipruritic effect of rifampicin
- autotaxin converts cell membrane phospholipids into the lipid signalling molecule *lysophosphatidic acid* (LPA)
  - levels correlate with the severity of pruritus and fall when benefit from rifampicin, bile acid sequestrants or biliary drainage.

118

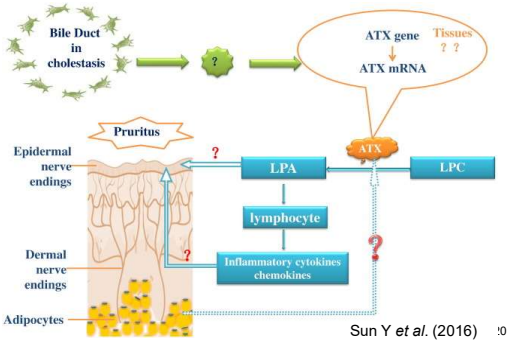
Rifampicin for cholestatic jaundice

How LPA causes pruritus in cholestasis is uncertain:

- ? immune: LPA affects histamine release from mast cells, eosinophil and lymphocyte trafficking
- ? neuro-modulation: affects synaptic transmission and plasticity; also activates transient receptor potential (TRP) receptors (e.g. TRPV1)
- ? co-factors: LPA can be increased in diseases not associated with pruritus.

119

Rifampicin (via PXR) inhibits autotaxin (ATX) and thereby lysophosphatidic acid (LPA)



Sun Y *et al.* (2016) 120

Rifampicin for cholestatic jaundice

Cautions (see PCF6):

- *induces* various enzymes including oxidation (CYP2B6, CYP2C19, CYP3A4), glucuronidation (UGT1A1) and glutathione conjugation (GSTA1)
- ↓ effect of a long list of drugs, including alfentanil, codeine, fentanyl, methadone, morphine, oxycodone
- close monitoring ± dose adjustment required
- onset/offset of induction is gradual; effects may not become fully evident for 2–3 weeks.

121

Rifampicin for cholestatic jaundice

Dose and use:

- start with rifampicin150mg PO at bedtime
- if necessary, increase to 150mg twice daily after 1 week (sooner if pruritus is severe and prognosis short)
- some patients need a higher dose (SPC advises a maximum dose of 8mg/kg/day in liver impairment).

122

What does this mean for palliative care?

- rifampicin is a useful approach when more definitive/simpler measures impossible or ineffective.

Horizon scanning: Dexmedetomidine

124

Dexmedetomidine

- alpha$_2$ adrenergic agonist; more selective & potent cf. clonidine
- used in ICU IVI; by some PCUs IVI/CSCI
- produces analgesia without respiratory depression; potentiates opioid analgesia; may prevent/treat delirium
- generally dying patients with intractable pain ± delirium
- occasionally to facilitate other Rx, e.g. RT.

Coyne PJ et al. (2010); Mo Y et al. (2013)
O'Hara C et al. (2015); Skrobik Y et al. (2018) 125

Dexmedetomidine

- provides 'arousable sedation'
- Richmond Agitation-Sedation Scale 0 to -2

TABLE 1. RICHMOND AGITATION–SEDATION SCALE

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitation	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
−2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

- potentially able to speak, eat, drink, etc.

126

Dexmedetomidine

- CSCI, compatible with metoclopramide, midazolam, morphine
- (midazolam added if deeper sedation becomes necessary)
- ? an alternative for patients with severe refractory symptoms (particularly pain + delirium) who wish to remain in lucid contact with those around them.

Hilliard N et al. (2015) 127

Dexmedetomidine
Do you use it?

128

Matters arising: Mirtazapine for gastroparesis

(follow up from 2014 course)

129

Learning objectives: mirtazapine

For PC clinicians to gain knowledge of:

- use in gastroparesis
- use in anorexia
- likely mechanism of action.

130

Mirtazapine: case report

- 52 year old male
- progressive dysphagia → 5 days projectile vomiting
- gastric volvulus + strangulation
- emergency gastroplexy
- NG tube for persistent nausea & vomiting

Johnstone M *et al*. (2009) 131

Mirtazapine: case report

- no improvement with erythromycin, metoclopramide, domperidone, ondansetron
- contrast failed to flow into small bowel
- TPN → feeding jejunostomy (4 weeks after surgery)
- further 4 weeks without improvement; high NG output continued.

Johnstone M *et al*. (2009) 132

Mirtazapine: case report

- mirtazapine 15mg SL for low mood
- within 12h tolerating fluids, ↓ NG output
- 48h tolerating soft diet – discharged
- reviewed 3 months later, tolerating full diet.

Johnstone M *et al.* (2009) 133

Mirtazapine

(NaSSA: noradrenergic and specific serotonergic antidepressant)

Blocks receptors inhibiting mono-amine release:

- α_2-adrenergic antagonism
  - – ↑ serotonin and noradrenaline release
- $5HT_{2A}$ and $5HT_{2C}$ antagonism
  - – ↑ noradrenaline and dopamine release

Also antagonizes H_1- and $5HT_3$-receptors

Anti-emetic and stimulates appetite/weight gain

134

Mirtazapine

- multiple other case reports in gastroparesis
  - ➢diabetic; post-infective; post-pancreatitis
- failure to respond to multiple anti-emetics
- mirtazapine → improvement in N&V
  - ➢often rapid 24–48h; <1 week.

Kim S-W et al. (2006); Kundu S *et al.* (2014); Song J *et al.* (2014) 135

Mirtazapine

Mechanism unclear, may include:

- anti-emetic (nausea → gastric stasis)
  - ➢5HT3 antagonist; effective in chemotherapy
- ↑ gastric emptying
- relaxation of gastric fundus
  - ➢via 5HT1A receptors
  - ➢↑ gastric accommodation
- central ↓ in gastric sensitivity/symptoms
- change in hormone levels, e.g. ↑ ghrelin.

Kumar N *et al.* (2017) 136

Mirtazapine

- open label study in gastroparesis (n=30); mostly idiopathic
  - ➢15mg at night
  - ➢60–80% improved nausea, vomiting, appetite, retching
  - ➢20% stopped; mostly drowsiness/lethargy
  - ➢[sedation should respond to increase in dose; for other UEs reduce starting dose to 7.5mg].

Malamood M *et al.* (2017) 137

Mirtazapine: anorexia

- stimulates appetite and weight gain
  - ➢5HT2A / H1 antagonist
  - ➢healthy vols. mean wt gain 1.3kg / 3 weeks (15mg)
- Phase II study in cancer 15–30mg
  - ➢ ~1/4 improved appetite and wt ≥1kg / 4 weeks
- Phase III study in cancer underway
  - ➢CI Catherine Naseef Hunter, Egypt.

Riechelmann RP *et al.* (2010) 138

What does this mean for palliative care?

- in gastroparesis when more usual anti-emetic approaches ineffective/unavailable may be a role for mirtazapine
- in above (and other settings), additional anti-emetic and appetite stimulating properties may be added advantages.

139

Gabapentin and respiratory depression

140

Learning objectives: gabapentin

For PC clinicians to gain knowledge of:

- risk of respiratory depression
- change in PIL.

141

MHRA October 2017

Drug safety update

- be aware of the risk of CNS depression, including severe respiratory depression, with gabapentin (± opioids)
- some groups may be at higher risk
- report suspected adverse reactions.

142

MHRA October 2017

Patients at increased risk may require dose adjustments, including those:

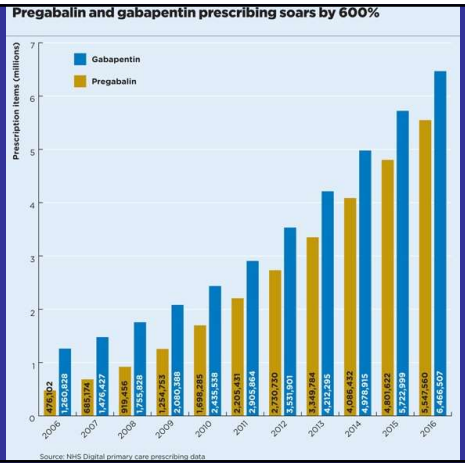
- with compromised respiratory function or respiratory disease
- with neurological disease
- with renal impairment
- using concomitant CNS depressants
- elderly people.

143

MHRA October 2017

- European review triggered by reports of respiratory depression *without* concomitant opioids (previously recognised *with* opioids)
- reviewed spontaneous reports/literature
- recommended SPC/PIL include warnings for severe respiratory depression
- frequency rare; up to 1:1,000 patients
- [England alone 6.5 million prescriptions 2016].

144



145

Example PIL: Other medicines & Neurontin

…If you are taking any medicines containing opioids (such as morphine), please tell your doctor or pharmacist as opioids may increase the effect of Neurontin. In addition, combination of Neurontin with opioids may cause symptoms like sleepiness and/or decrease in breathing.

146

Example PIL: Symptoms

Contact your doctor immediately if you experience any of the following symptoms after taking this medicine as they can be serious:

- breathing problems, which if severe you may need emergency and intensive care to continue breathing normally

147

Example PIL: Frequency of side effects

Rare: (may affect up to 1 in 1,000 people)

- trouble breathing, shallow breaths (respiratory depression)
- decrease in blood glucose levels (most often observed in patients with diabetes)
- loss of consciousness.

148

UK Yellow card reports

MHRA report states, over 20 years:

- 50 reports of respiratory depression or dyspnoea associated with gabapentin
- in 1/3 opioids used/co-suspected.

149

Gabapentin DAPS: Serious/fatal

Respiratory disorders NEC	***82***	***5***
Breathing abnormalities	*52*	*1*
Cheyne-Stokes respiration	1	0
Dyspnoea	39	0
Dyspnoea exertional	3	0
Hyperventilation	1	0
Hypoventilation	1	0
Respiratory arrest	2	0
Respiratory depression	2	1
Respiratory distress	1	0
Sleep apnoea syndrome	2	0
Conditions associated with abnormal gas exchange	*10*	*1*
Coughing and associated symptoms	*15*	*0*
Respiratory failures (excl neonatal)	*3*	*3*
Respiratory failure	3	3

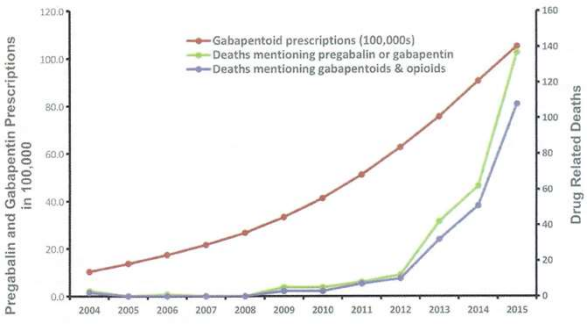
150

Pregabalin DAPS: Serious/fatal

Respiratory disorders NEC	147	7
Breathing abnormalities	116	2
Apnoea	2	1
Dyspnoea	94	0
Dyspnoea exertional	0	0
Dyspnoea paroxysmal nocturnal	1	0
Hypopnoea	1	0
Hypoventilation	2	0
Orthopnoea	1	0
Respiratory arrest	7	0
Respiratory depression	6	1
Respiratory distress	1	0
Sleep apnoea syndrome	1	0
Conditions associated with abnormal gas exchange	4	1
Coughing and associated symptoms	16	0
Respiratory failures (excl neonatal)	8	4
Acute respiratory failure	2	2
Respiratory failure	6	2
Respiratory tract disorders NEC	3	0

151

↑ use gabapentinoids in E&W = ↑ deaths



Lyndon A *et al.* (2017) 152

↑ use gabapentinoids in E&W = ↑ deaths

- 80% of deaths involved opioids, e.g. heroin, methadone
- most [known] deaths with opioids likely to represent problem drug users
- gabapentinoids (pregabalin > gabapentin) widely misused alongside opioids to enhance effects.

Lyndon A *et al.* (2017) 153

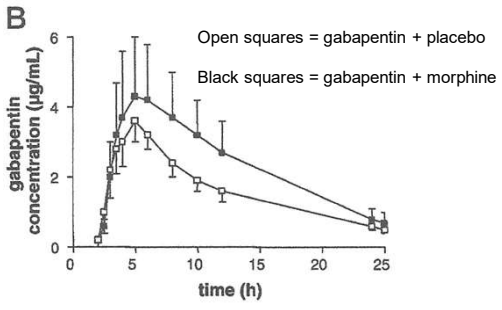
Mechanism?

Pharmacodynamic and pharmacokinetic:

- additive CNS depressant effects
- opioids slow intestinal transit
  - ↑ absorption of gabapentin
  - ↑ bio-availability; 44% ↑ in systemic exposure.

154

Morphine increases gabapentin exposure (AUC ↑ 44%)



Eckhardt K *et al.* 2000 155

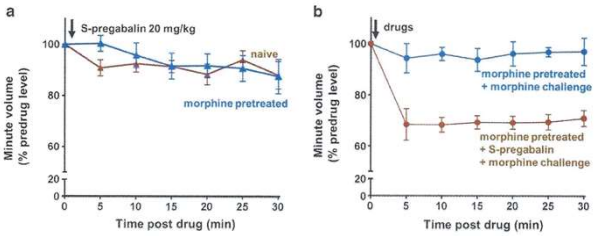
Mechanism??

In mice, given morphine:

- pregabalin (20mg/kg):
  - ➢did not depress respiration itself
  - ➢*reversed tolerance to morphine, depressing respiration*
- pregabalin (200mg/kg):
  - ➢depressed respiration
  - ➢summated effect with morphine.

Lyndon A *et al.* (2017) 156

Pregabalin + morphine reverses opioid tolerance in mice



Lyndon A *et al.* (2017) 157

Mechanism???

Gabapentin:

- ↑ brain GABA levels, an inhibitory neurotransmitter
- GABA has inhibitory effect on respiratory control centre.

158

Context: normal use or overuse?

Large retrospective USA cohort analysis, explored sustained overuse of:

- gabapentin alone (>3,600mg/day ≥9 months)
  - ➢typically 4,200–11,200mg/day
- opioids alone (>50mg/day OME ≥9 months)
  - ➢typically 50–190mg/day
- or both
  - ➢typically 8,500mg/day + 260mg/day OME.

Peckham AM *et al.* (2018) 159

Overuse & respiratory depression

Rates of respiratory depression with sustained overuse:

- gabapentin alone: 0.6% [vs. no overuse 0.6%]
  - ➢i.e. no significant increase with overuse
- opioids alone: 1.8% [vs. 0.5%] P<0.01
- *of both*: 3.2% [vs. 1.7%] P<0.01.

Peckham AM *et al.* (2018) 160

Overuse & respiratory depression

OR of respiratory depression with sustained overuse (adjusted for, e.g. known addiction, other CNS depressant use):

- gabapentin alone: 0.85 [vs. no overuse 1.0]
  - ➢i.e. no increase with overuse
- opioids alone: 1.8 [vs. 1.1] P<0.05
- *of both*: 4.1 [vs. 2.1] P<0.05.

Peckham AM *et al.* (2018) 161

Gabapentin & respiratory depression

Conclusions from this study:

- gabapentin overuse alone = no increased risk
- gabapentin + opioid = increased risk:
  - ➢when no misuse (risk ~ doubled)
  - ➢when both misused (risk ~ quadrupled).

Note. Sample 16–64 year olds, without cancer/chronic kidney disease.

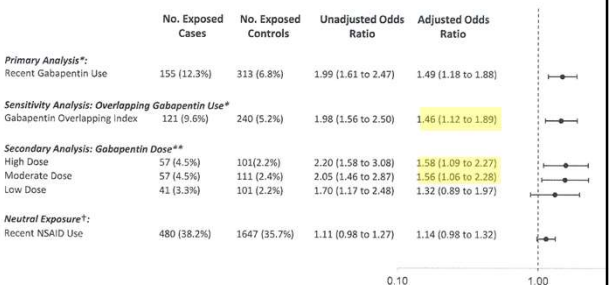
Peckham AM *et al.* (2018) 162

Gabapentin & opioid-related deaths

- Canadian, population-based, nested case-control study of patients 15–105 years
- prescribed ≥1 opioid for chronic non-cancer pain (excluded cancer, methadone)
- identified accidental opioid-related deaths (excluded suicide/murder)
- relationship to gabapentin exposure and dose.

Gomes T *et al.* (2017) 163

Gabapentin & opioid-related deaths



	No. Exposed Cases	No. Exposed Controls	Unadjusted Odds Ratio	Adjusted Odds Ratio
Primary Analysis*:				
Recent Gabapentin Use	155 (12.3%)	313 (6.8%)	1.99 (1.61 to 2.47)	1.49 (1.18 to 1.88)
Sensitivity Analysis: Overlapping Gabapentin Use*				
Gabapentin Overlapping Index	121 (9.6%)	240 (5.2%)	1.98 (1.56 to 2.50)	1.46 (1.12 to 1.89)
Secondary Analysis: Gabapentin Dose*†				
High Dose	57 (4.5%)	101(2.2%)	2.20 (1.58 to 3.08)	1.58 (1.09 to 2.27)
Moderate Dose	57 (4.5%)	111 (2.4%)	2.05 (1.46 to 2.87)	1.56 (1.06 to 2.28)
Low Dose	41 (3.3%)	101 (2.2%)	1.70 (1.17 to 2.48)	1.32 (0.89 to 1.97)
Neutral Exposure*‡:				
Recent NSAID Use	480 (38.2%)	1647 (35.7%)	1.11 (0.98 to 1.27)	1.14 (0.98 to 1.32)

Moderate dose 900–1799mg/day
High dose ≥1800mg/day

Gomes T *et al.* (2017) 164

Gabapentin & opioid-related deaths

Conclusion:

- in chronic pain patients receiving opioids, the co-prescription of moderate-large doses of gabapentin appears to increase the risk of opioid-related death by ~50%.

Note. 95% were <65 years old.

Gomes T *et al.* (2017) 165

Gabapentinoids & post-op respiratory depression

- *chronic use* of gabapentinoids → continued post-op, increased risk of requiring naloxone (compared to matched control group)
- OR 6.3 [2.4–16.7] P=0.001.

Deljou A *et al.* (2018) 166

What does this mean for palliative care?

- gabapentinoids *alone* do not generally cause respiratory depression, but there may be high risk groups where this is possible
- gabapentinoids are more likely to cause respiratory depression when combined with opioids

What does this mean for palliative care?

- ? in part due to a reversal in opioid tolerance
- be alert to the potential need to reduce the opioid dose when starting gabapentinoids:
  - ➢particularly with use of frequent p.r.n. opioids
  - ➢particularly when increased sedation
  - ➢always when respiratory depression.