PaCCSC

Palliative Care Clinical Studies Collaborative

Value adding to clinical care – randomised controlled trials (RCTs) in palliative care

David Currow
Professor, Discipline, Palliative and Supportive Services
Flinders University,
Adelaide,
Australia

Flinders University receives funding for PaCCSC from the Australian Government Department of Health and Ageing under the National Palliative Care Program.

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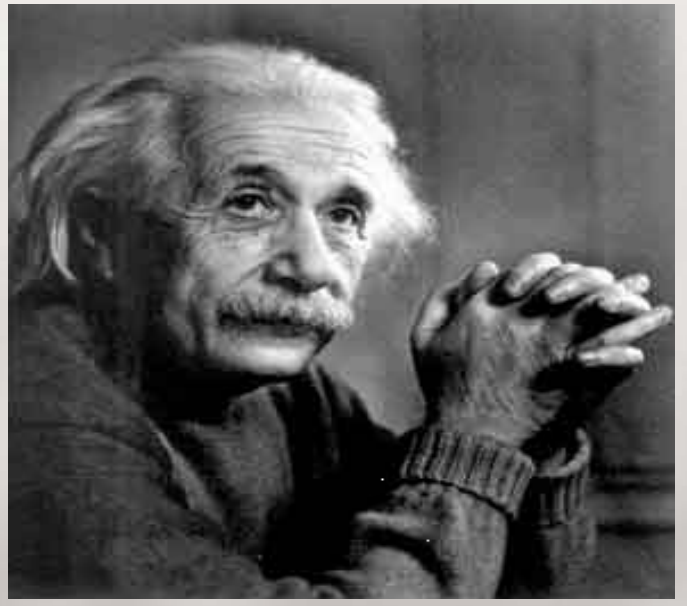
'If you always do what you've always done, you will always get what you always had'



Albert Einstein (1879-1955)

Evidence-based palliative care; Research questions and their ideal design

- Prevalence of a symptom:
  - *consecutive cohort study*
- understanding how people feel about taking on the caring role:
  - *qualitative study*
- testing a new intervention:
  - *randomised controlled trial*
- finding if there is a relationship between increasing doses and increasing toxicity with a medication:
  - *dose-ranging study*

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1. Why do we need to improve the care we offer?
2. What I have learnt from clinical trials
3. What patients and their caregivers say about clinical trials

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Why do we need to improve the care we offer?

- Palliative Care Outcomes Collaborative patient and caregiver survey
- Up to 50 consecutive patients per service per year (2008-2011)
- 49 services
- 35% community only, 33% combined community / inpatient
- 1800 respondents

Pidgeon T et al. BMJ Support Palliat Care 2015

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Why do we need to improve the care we offer?

- **Palliative Care Outcomes Collaborative patient and caregiver survey**

- **Palliative Outcomes Scale (version 2)**
  - **8 items – symptoms, psychological support and information**
  - **2 items – practical matters**

Pidgeon T et al. BMJ Support Palliat Care 2015; Hearn J et al Qual in Health Care 1999.

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Why do we need to improve the care we offer?

- **Pain – 83%**

(25% of respondents had overwhelming pain)

- **Other symptoms – 80%**

(17% had severe or overwhelming symptoms)

Pidgeon T et al. BMJ Support Palliat Care 2015

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Why do we need to improve the care we offer?

- Caregiver anxiety – 78%

(22% had severe or overwhelming anxiety)

- Family anxiety - 89%

(45% of respondents had overwhelming anxiety)

Pidgeon T et al. BMJ Support Palliat Care 2015

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Couple of great one liners from colleagues…

- When discussing the potential for broader availability of the medication if the study showed a positive outcome…
  - ‘I have no problems getting it from my pharmacy department’

Palliative care patients and their health care

- Rigorous, scientifically evidenced health care is an expectation of patients and their families and should be a reality across the entire life/health care journey.
- The reality is that medication prescribing in palliative care is often based on clinical opinion and anecdotal knowledge – until recently there has been limited real science to support clinical decision making in this area of health care.

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PaCCSC exists to:

- Give patients with life-threatening illnesses who are approaching the end of life, and their family and caregivers, a better experience that is based on quality use of medications to reduce or alleviate symptoms as safely and predictably as possible.

PaCCSC exists to:

- The palliative care population is the frailest population in clinical practice, and any iatrogenic harm is likely to have irreversible consequences.

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The hospice / palliative care population

- We serve a population that becomes increasingly frail as death approaches
- This is the population who is most at risk of iatrogenic harms
- We can, and do, cause morbidity and premature mortality

- If nothing else, a clinical trials program can help each of us to minimise any toxicities and harms, and maximise the benefits that people experience

PaCCSC aims to do improve evidence by:

- Conducting research across a range of symptoms commonly experienced with a life-limiting illness. Symptom nodes for phase II, III and IV studies include:
  - Pain
  - Breathlessness
  - Nausea
  - Appetite / anorexia / cachexia
  - Confusion / cognition
  - Gastrointestinal problems (bowel obstruction, constipation)
- Ultimately enabling the registration of a range medicines used in palliative care

PaCCSC is doing improving evidence by:

- Building a research culture and capacity to not only conduct research but to understand and adopt research findings into everyday clinical practice
- Disseminating the findings from the research to colleagues in palliative care and other disciplines
- Conducting critical appraisal workshops

PaCCSC is:

- a member based research collaborative
- made up of more than 20 palliative care / respiratory / oncology services across Australia that recruit participants to phase II and III studies; and, internationally, more than 50 sites in more than 10 countries who collect data for phase IV pharmacovigilance studies.

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So…

- Are such studies feasible?

PaCCSC undertakes public interest studies:

- The studies are being done for off-patent medications in palliative care will never be supported by the pharmaceutical industry.
- The Collaborative operates at ‘arms length’ from Government, but the need for the research is acknowledged by Government and they review the study design.
- Medications being studied are essential drugs in palliative care, and are particularly needed in the community setting where access is limited.

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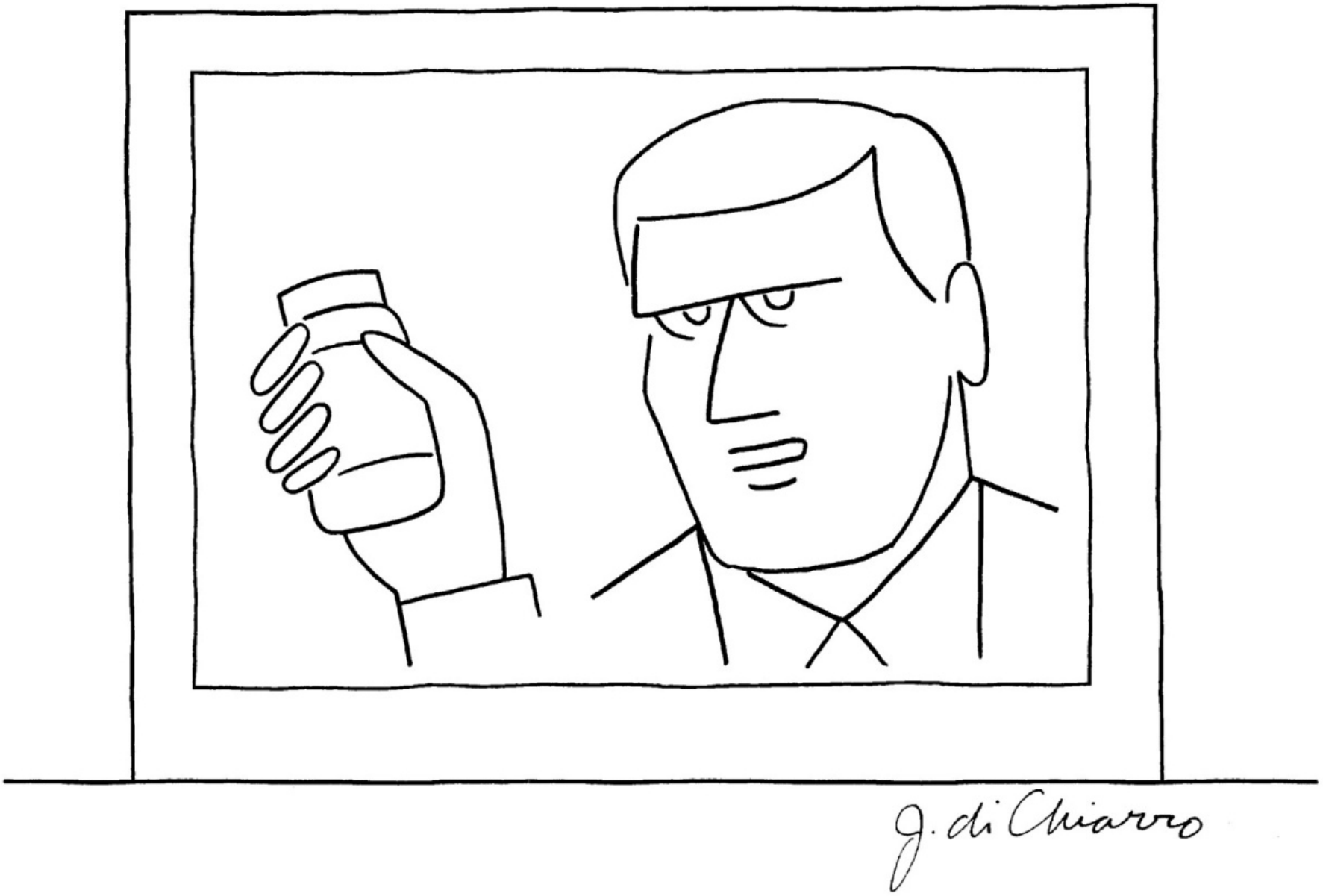
To date, PaCCSC has:

- Completed 6 phase III studies which have randomised more than 1700 participants
- Completed six phase IV studies (5 pharmacological studies, 1 non-pharmacological studies)
- Generated key studies in correlative science to better understand the underlying mechanisms of symptoms or their management (including healthy volunteer studies)



"If this medication should cause death, stop taking it immediately."

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1. Why do we need to improve the care we offer?
2. What I have learnt from clinical trials
3. What patients and their caregivers say about clinical trials

Research in Palliative Care

- How do we further build the evidence in each of the following areas?
  - Basic sciences
  - Phase I, II, III and IV studies
  - Population-based studies
  - Qualitative studies
  - Systematic reviews / meta-analyses

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What have I learnt?

In brief, I have learnt:

- We cannot be complacent about the quality of the symptom control that we achieve

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What have I learnt?

- In brief, I have learnt:
  - We can instantly make a symptom disappear NATIONALLY – simply open a clinical trial to study the symptom

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What have I learnt?

- In brief, I have learnt:
  - Despite doing large numbers of descriptive studies, we know little about the natural history of most of the symptoms we treat – and simple prospective work here can really make a difference

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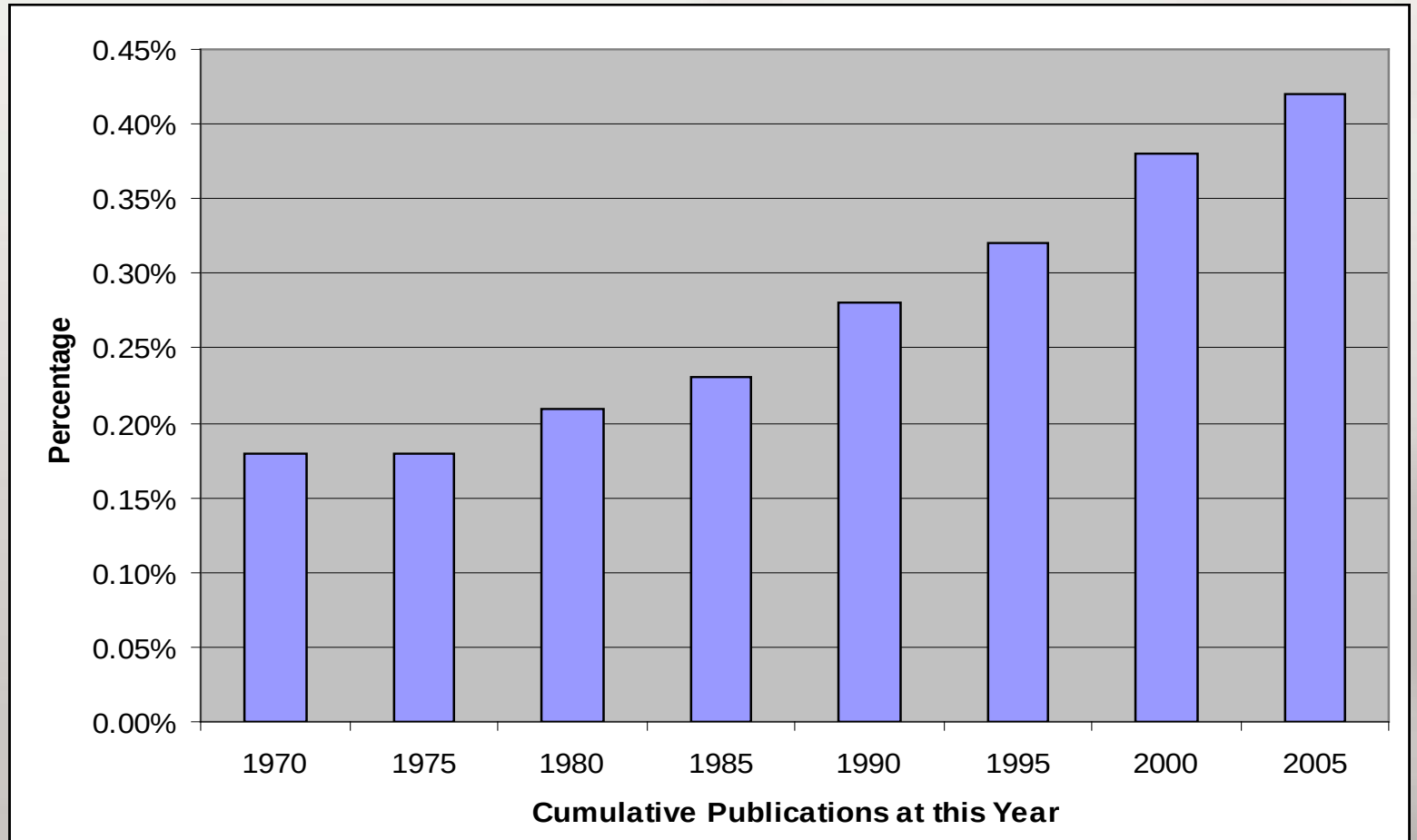
1/122 clinical trials *ever* published is in palliative care

Cumulative percentage growth in palliative care literature

(Palliative Care/Total Medline Citations)

Tieman et al. J Clin Oncol 2008



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What have I learnt?

www.caresearch.com.au

- Breadth of practice = breadth of evidence base
- (n=3171 clinical trials up to 2005)

- Top 0.125 3 journals
- Top 0.250 8 journals
- Top 0.500 43 journals
- Top 0.750 164 journals
- All 712 journals

Tieman et al. J Clin Oncol 2008

Vol. 43 No. 6 June 2012 Journal of Pain and Symptom Management 987

Original Article

Key Characteristics of Palliative Care Studies Reported in the Specialized Literature

Jane L. Wheeler, MSPH, Aine Greene, RN, FRCNA, Jennifer J. Tieman, BSc, MBA, Amy P. Abernethy, MD, and David C. Currow, BMed, MPH, FRACP

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Table 1

Study Type, Research Topic, and Funding of Palliative Care Studies ($n = 189$[a])

Topics of Research	All Studies, *n* (%)	Study Type: Prospective Studies,[b] *n* (%)	Study Type: Other Studies, *n* (%)	Funding: Pharmaceutical Company Funding, *n* (%)	Funding: Other Funding, *n* (%)	Funding: Unfunded, *n* (%)
Palliative care patient	106 (56)	26 (14)	80 (42)	8 (4)	44 (23)	55 (29)
Caregiver/family	17 (9)	2 (1)	15 (8)	0 (0)	11 (6)	6 (3)
Health professional	41 (21)	5 (3)	36 (19)	1 (1)	16 (8)	24 (13)
Service provision	16 (8)	0 (0)	16 (8)	2 (1)	11 (6)	3 (2)
Tool development	3 (2)	0 (0)	3 (2)	0 (0)	2 (1)	1 (1)
Healthy volunteer	2 (1)	1 (1)	1 (1)	1 (1)	0 (0)	1 (1)
Medication compatibility	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Community at large	3 (2)	0 (0)	3 (2)	0 (0)	2 (1)	1 (1)
Total	189 (100)	34 (18)	155 (82)	12 (6)	86 (46)	91 (48)

[a]Articles published in 2007, reporting new empirical data, retrieved from three journals: *Journal of Pain and Symptom Management*, 47% (51/113); *Palliative Medicine*, 58% (66/115); and *Journal of Palliative Medicine*, 40% (72/181).

[b]Only five of these studies were RCTs: four on patients and one about physician behavior. Three of the four patient RCTs were sponsored by the pharmaceutical industry. Three of the five were from the U.S., and one each was from Colombia and Australia.

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Why do we need to have a control arm in our studies?

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Non-randomised versus randomised controlled clinical trial exploring the same question

Differences may range from a 90% underestimate of effect to a 150% overestimate mostly with wider confidence intervals .

Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. BMJ. 1998 Oct 31;317(7167):1185-90.

…but I saw the medication work (and I trust my own judgment over any data in the literature)

- Placebo rates can be very high and often far higher than 1/3 of the population even in ‘refractory’ symptoms
- Nocebo rates can also be very high and shouldn’t be overlooked

Turner JA et al. JAMA 1994;271(20):1609-1614.
Sanderson C. JPSM 2013;46(5):722-730.

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What have I learnt?

- In brief, I have learnt:
  - We can use the phrase

    ‘it’s just the disease getting worse’

    too glibly

Let's characterise two of the RCTs done by PaCCSC

- Ketamine (while participant and clinician is still blinded)
- Response rate
  - Ketamine 29/93
  - Placebo 25/92
- Toxicity sufficient to cause withdrawal
  - Ketamine 17/93
  - Placebo 2/92
- No clinico-demographic predictors of responders

Let's characterise two of the RCTs done by PaCCSC

- Octreotide (while participant and clinician is still blinded)
- Response rate
  - octreotide 17/45
  - Placebo 14/42
- Toxicity sufficient to have additional medications
  - Octreotide twice as likely to have hyoscine butylbromide administered over the three days (more than three times as like 49-72/72 hours)
- No clinico-demographic predictors of responders

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‘When the facts change,
I change my mind.’

John Maynard Keynes
(1883-1946)

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What have I learnt?

In brief, I have learnt:

- Multi-site studies are the only way we can recruit to these studies in a timely way

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What have I learnt?

In brief, I have learnt:

- There are often simple collateral benefits from accurately measuring what we do as part of a clinical trial

What do we really know about bowel function at the end of life?

- Investigating bowel function

1. Prolonged transit time
2. Impaired function of the structures of defaecation
3. Both

Clark K et al. J Palliat Med 2013;16(5):1-4

What do we really know about bowel function at the end of life?

- **Investigating bowel function**

1. **Prolonged transit time – radio-opaque markers / plain abdominal x-ray on the 6th day. (normal <5/24 markers at that time)**
2. **Impaired function of the structures of defaecation – anal manometry (resting, squeeze, cough), balloon expulsion**

Clark K et al. J Palliat Med 2013;16(5):1-4

What do we really know about bowel function at the end of life?

- Investigating bowel function
- Anal manometry
- Resting pressure – internal anal sphincter tone
- Squeeze - external anal sphincter tone and puborectalis sling (pelvic floor)
- Cough – intact recto-anal contractile reflex?

Clark K et al. J Palliat Med 2013;16(5):1-4

What do we really know about bowel function at the end of life?

- Investigating bowel function
- Pilot study: n = 10

1. Prolonged transit time: med 11.5 (0-24) markers
2. Impaired function of the structures of defaecation

- Balloon expulsion – all participants failed this

- Clark K et al. J Palliat Med 2013;16(5):1-4

What do we really know about bowel function at the end of life?

- Investigating bowel function
- Pilot study: n = 10

1. Prolonged transit time 2 people
2. Impaired function of the structures of defaecation 2 people
3. Both 5 people
4. Neither 1 person

- Clark K et al. J Palliat Med 2013;16(5):1-4

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What have I learnt?

- In brief, I have learnt:
  - Shooting the messenger is still a time-honoured sport in our clinical community

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Couple of great one liners from colleagues…

The response I get most often from clinicians reflecting on studies' findings is that

'a medication is no longer available' and *not*

'look at the toxicity we have been causing with no symptomatic advantage'

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So…

- Are such studies useful?

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Changing Practice

- Critical appraisal skills
- Ketamine study presented May 2011; published Sept 2012
- Broad dissemination program undertaken
- Follow up survey of ANZSPM members conducted Sept 2013 – 123 members responded out of a possible 392, of which 92% had heard of the study; 91% had prescribed ketamine
- 65% of respondents had changed practice: 17% ceased to use the drug; 46% used less; 2% increased use

Hardy, J. R., O. Spruyt, et al. (2014). "Implementing practice change in chronic cancer pain management: clinician response to a phase III study of ketamine." Intern Med J 44(6): 586-591.

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Couple of great one liners from colleagues…

- When faced with a patient with a signed consent form who repeatedly said she wanted to be in the study…
  - ‘Don’t worry about the study. I know the medication works and I want you to have it’

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How patient-centred are we?

- Do we see evidence of ‘gate-keeping’?
- (This person wouldn’t want to participate in a clinical trial. I won’t even give them the option)

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How patient-centred are we?

- Yet, the evidence is that palliative care patients want to participate in clinical trials and value the experience having done so
- (Are patients tacitly telling us that the symptom control we offer is not as good as they hoped?)

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How patient-centred are we?

- Views of palliative health care professionals on referring to clinical trials
- 198/597 surveys
- More likely to refer to non-pharmacological studies
- Needed to minimise participant inconvenience
- Previous research experience improved likelihood

White C et al. Support Care Cancer 2008;16(12):1347-1405

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How patient-centred are we?

- General unwillingness to refer to randomised controlled trial in palliative care
- Gatekeeping …(blocks) recruitment and has the potential to introduce a selection bias.

White C et al. Support Care Cancer 2008;16(12):1347-1405

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So…

- Are such studies desirable?

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How patient-centred are we?

- Patients' (100) with advanced cancer and caregivers' (101) views on randomised trials
- 92% would participate in studies with simple interventions; 26% with complex interventions
- More than 75% of people wanted to help others
- Many prepared to complete short questionnaires, accept extra medications and investigations and undertake additional hospital visits
- Increasing age predicted lower willingness to participate

White C et al. Eur J Cancer 2008;44(13):1820-1828

How patient-centred are we?

- Patients' with advanced cancer and caregivers' views on randomised trials – a systematic review
- Key themes
  - Altruism
  - The wish to avoid complex studies
  - Desire to retain autonomy
- The views of palliative care patients towards research are similar to those of other patient populations

White C et al. Support Care Cancer 2010;18(8):905-911

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Design

- Practical questions that address day-to-day problems
- Clinically meaningful outcomes FOR PATIENTS
- Shortest possible duration to maximise participation and minimise withdrawal rates
- Minimal inconvenience to patients
- As close to normal clinical care pathways as possible
- Widest possible inclusion criteria

White C et al. Eur J Cancer 2008;44(13):1820-1828

PaCCSC – Symptom nodes & studies matrix (CURRENT program as at April 2016)

Symptom Node	Hypothesis generating idea (Pharmacovigilance & other)	Phase I/II; pilot; feasibility	Phase III (initiation or open to recruitment)	Dissemination & knowledge transfer (post close to recruitment)
Cognitive disorders	Midazolam for agitation Palliative sedation (audit)	Palliative sedation	Melatonin for delirium	Risperidone/ haloperidol for delirium dissemination
Nausea	Haloperidol Cyclizine	New nausea	Nausea 3	Nausea 1 & 2 analysis
Pain	Amitriptyline	Targin; CADET; Lignocaine	PAX-1	
Gastro intestinal	Macrogol (Movicol) for constipation	Pyridostigmine for constipation; PERT;	Ranitidine/dexamethasone for bowel obstruction	Octreotide survey
Breathlessness	Lorazepam	OPRA	Sertraline; Early intervention PC in Lung Cancer	MOP dissemination; Sertraline protocol publication & survey
Anorexia/appetite	Mirtazapine; Fn14 Cancer Induced Cachexia	Cannabis		Megestrol analysis
Collateral Studies	Missing data Hypodermoclysis Deprescribing	Renal Supportive Care;		Blood Transfusions dissemination

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‘The core of science is not controlled experiment or mathematical modelling; it is intellectual honesty

… one is either engaged in an honest appraisal of the evidence and logical arguments, or one isn’t’

Sam Harris (1967 -)
Letter to a Christian Nation p64-65