A Potpourri of New Clinical Pearls in pain and symptom management

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I have no financial disclosures

Outline

- Review key palliative care articles of 2016 related to pain and symptom management
  - AAHPM
    - PC-FACS (monthly review of literature)
  - CAPC
    - “notes from the field”
    - “news bites”
  - Palliative Care Network of Wisconsin (PCNOW, home of “fast facts”)
  - Geripal (Geriatrics and palliative care blog)
  - Pallimed (Hospice and palliative care blog)
  - Up to date

A case…

- Gerry Powell is an 72 y.o. female with mild dementia, recent dx of breast cancer, found to be metastatic to bone upon diagnosis.
- In your office to establish care, and complains of pain in bilateral hips which correspond to osteoblastic lesions seen on recent imaging
- He pain is not responding to Tylenol, and you are reluctant to use NSAIDS due to her age and renal insufficiency

What do you start for her pain?

(A) Morphine 5mg PO q 4 hrs PRN

(B) Oxycodone 5mg PO q 4 hrs PRN

(C) Tramadol 50 mg PO q 4 hrs PRN

(D) Codeine 30mg PO q 4 hrs PRN

(E) I have not prescribed opioids since March 16th 2016, the day the new CDC guidelines came out

HAPPY ANNIVERSARY!

- Discovered in 1804
- First marketed to public in 1817

VOLUME 34 · NUMBER 5 · FEBRUARY 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Trial of Low-Dose Morphine Versus Weak Opioids in Moderate Cancer Pain

Elena Bandieri, Marilena Romero, Carla Ida Ripamonti, Fabrizio Artioli, Daniela Sichetti, Caterina Fanizza, Daniele Santini, Luigi Cavanna, Barbara Melotti, Pier Franco Conte, Fausto Roila, Stefano Cascinu, Eduardo Bruera, Gianni Tognoni, and Mario Luppi

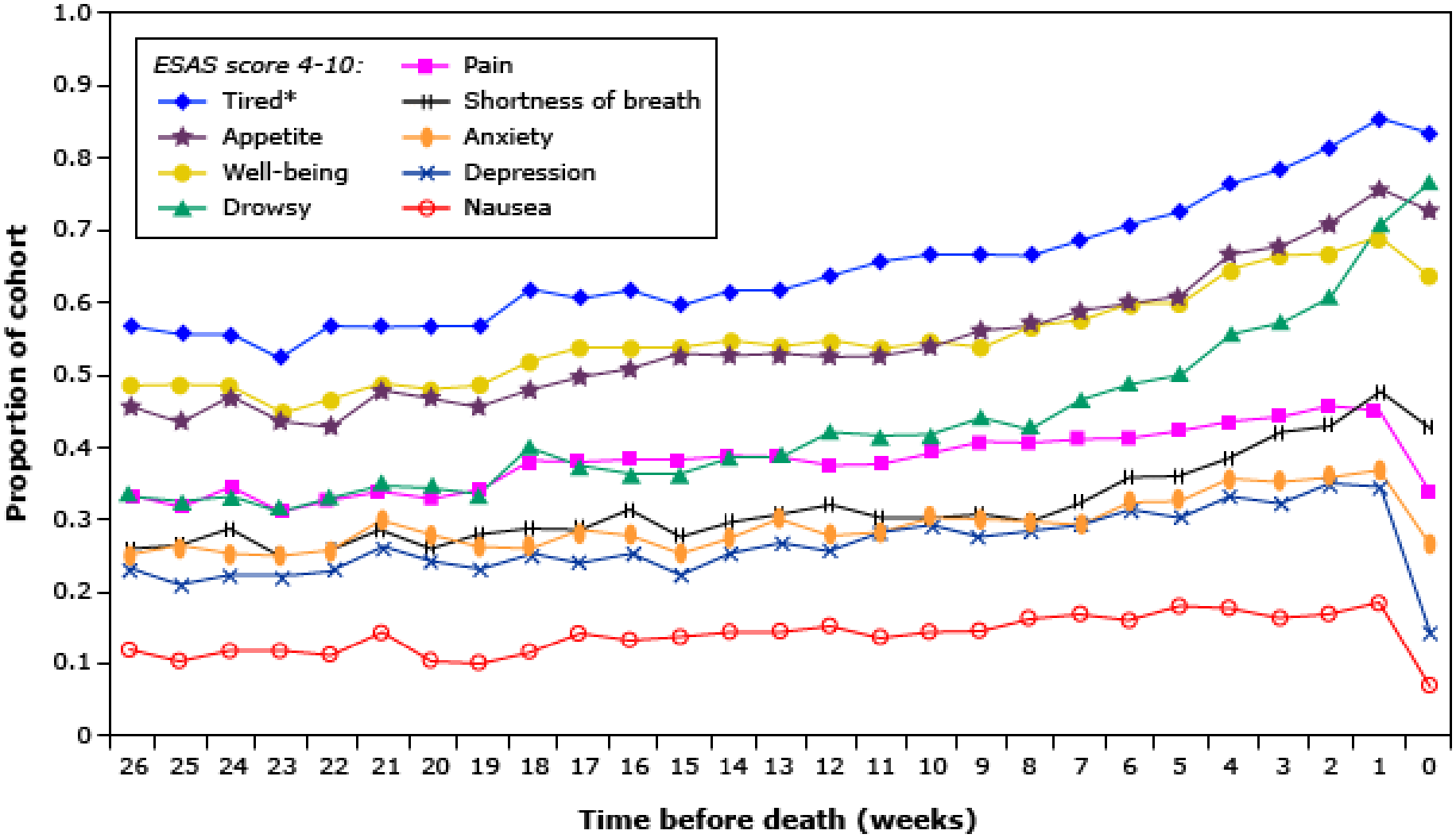
See accompanying editorial on page 399

*28 day open-label RCT done in 240 opioid naïve adults
*moderate cancer pain

Pts received either morphine or a weak opioid

- -Tramadol with paracetamol
- -Tramadol alone
- -Codeine with paracetamol
- -codeine alone

*Weekly symptom assessment with ESAS scores



J Clin Oncol 2011; 29:1151

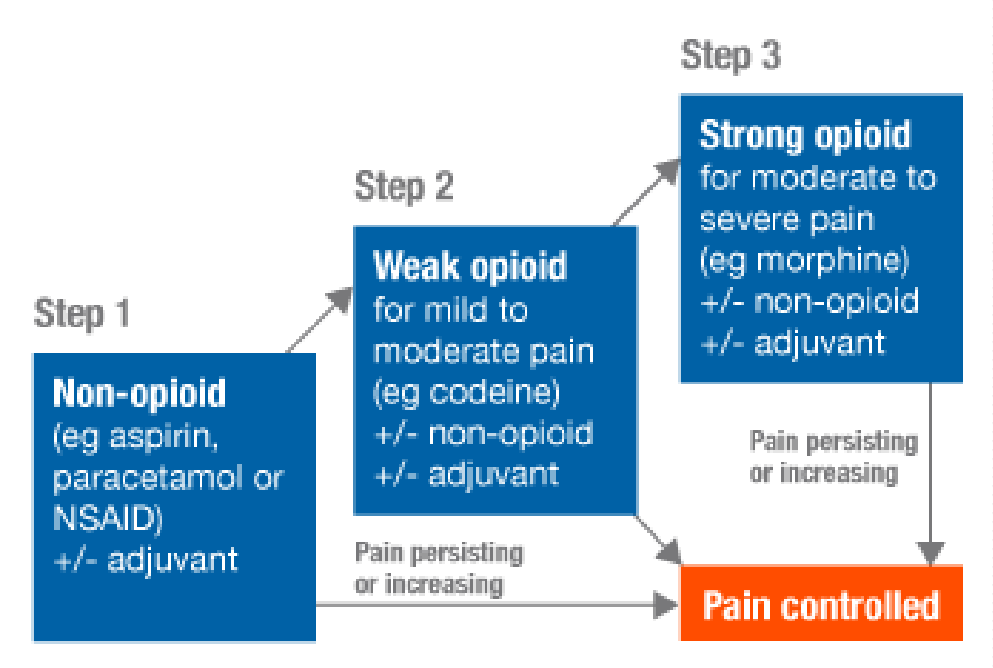
*Primary outcome was pain reduction of 20% or more,

*secondary outcomes were other ESAS scores

Results…for pain reduction

- 88% success in low dose morphine (M) group
- 58% success in the weak opioid (WO) group
  - Odds risk 6.18, 95% CI, 3.12 to 12.24; p =0.001)
- Benefits of M group over WO group evident as early as at the 1 wk observation point
- Change in assigned treatment more frequent in WO group due to inadequate analgesia
- Opioid escalation was lower in the M group (14% vs 28%)
- Adverse effects similar in both group

Move over WHO…



Morphine works better for moderate pain than weak opioids, with good tolerability and earlier effect…so, consider a 2 step latter, omitting step 2

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What about morphine vs. oxycodone?

Vol. 49 No. 2 February 2015 Journal of Pain and Symptom Management 161

Original Article

Morphine or Oxycodone for Cancer-Related Pain? A Randomized, Open-Label, Controlled Trial

Julia Riley, FRCP, MD, Ruth Branford, MRCP, PhD, Joanne Droney, MRCP, PhD, Sophy Gretton, MRCP, PhD, Hiroe Sato, MD, PhD, Alison Kennett, RGN, Christina Oyebode, BSc, Michael Thick, FRCS, Athol Wells, FRCP, MD, John Williams, FRCA, Ken Welsh, FRCP (Hons), PhD, and Joy Ross, FRCP, PhD
Royal Marsden NHS Foundation Trust (J.Ri., R.B., J.D., S.G., A.K., C.O., M.T., J.W., J.Ro.); National Heart & Lung Institute (J.Ri., R.B., J.D., S.G., H.S., A.W., K.W., J.Ro.), Imperial College London; and St. Joseph's Hospice (R.B.), London, United Kingdom

Compared morphine to oxycodone when used as a first-line or second line (after switching) treatment in patients with cancer related pain.

What they did

- Prospective, open-label Randomized controlled trial (n=198)
- Randomized to either morphine or oxycodone
- Doses titrated until the patient reported adequate pain control
- If they didn't respond to the first-line (inadequate analgesia, or excess side effects) they were switched to the other (median time was 7 days for patients who switched)

Who won?

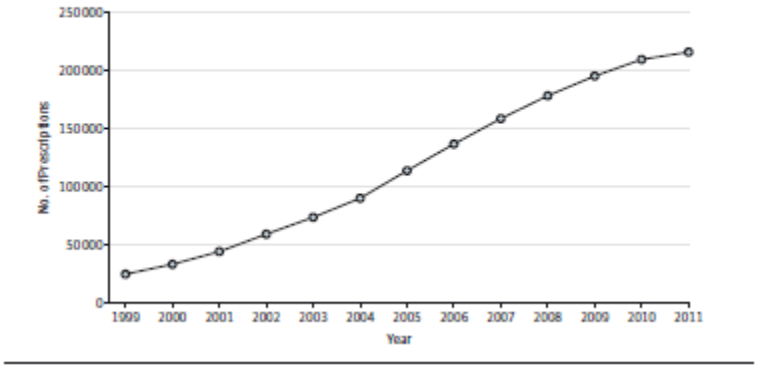
- No significant difference between the numbers of patients responding to morphine (62%) or oxycodone (67%) when used as first line or when used as 2nd line after switching due to inadequate response (67% vs. 52%)
- No difference in adverse reaction scores
- OVER HALF OF THOSE WHO DID NOT RESPOND TO THE FIRST LINE THERAPIES GOT RELIEF WITH 2ND LINE THERAPY (95% response rate to one or the other opioid)….So, this gives some evidence to our practice of rotating opioids when one is not working

Original Investigation

Tramadol Use and the Risk of Hospitalization for Hypoglycemia in Patients With Noncancer Pain

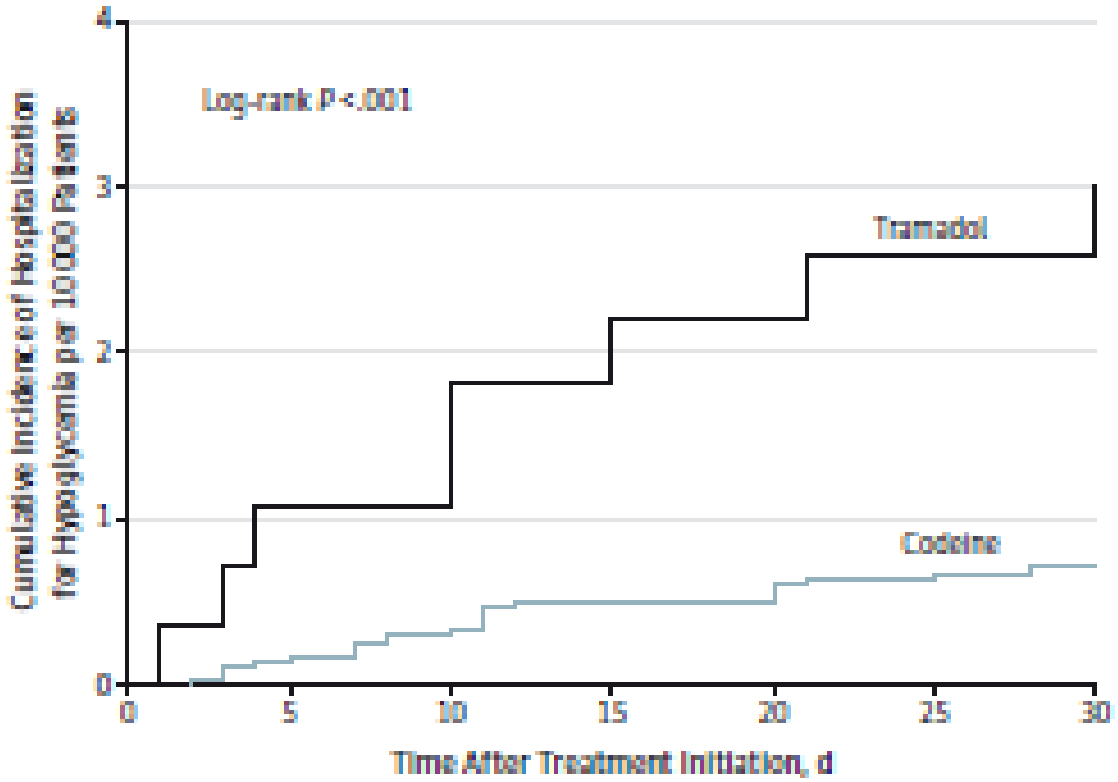
Jean-Pascal Fournier, MD, PhD; Laurent Azoulay, PhD; Hui Yin, MSc; Jean-Louis Montastruc, MD, PhD; Samy Suissa, PhD

Figure 1. Prescribing Trends of Tramadol Hydrochloride in the United Kingdom Clinical Practice Research Datalink Between 1999 and 2011



JAMA Intern Med. 2015;175(2):186-193. doi:10.1001/jamainternmed.2014.6512
Published online December 8, 2014.

Figure 2. Cumulative Incidence of Hospitalization for Hypoglycemia In Patients Newly Treated With Tramadol Hydrochloride and Codeine In the First 30 Days After Treatment Initiation



Hypoglycemia now joins the list of toxic side effects of tramadol:

-seizures

-serotonin syndrome

-excess drug/drug interactions

-Other opioid adverse effects (still risk of addiction, resp depression, and death)

Case continues

Remembering the old adage that “the same hand that writes the opioid, writes for the stool regimen…or disimpacts the patient”…you want to prescribe a bowel regimen. What do you start?

A) Docusate

B) Senna

C) Docusate + senna

D) Just tell her to eat lots of prunes

Original Article

Randomized, Double-Blind, Placebo-Controlled Trial of Oral Docusate in the Management of Constipation in Hospice Patients

Yoko Tarumi, MD, Mitchell P. Wilson, Olga Szafran, MHSA, and G. Richard Spooner, MD, CCFP, FCFP

Addition of DSS to senna (in hospice patients, 90% who were using opiates) resulted in no difference in stool frequency, volume, consistency, or ease of evacuation

THREE YEARS LATER…

LESS IS MORE

Pattern of Inpatient Laxative Use: Waste Not, Want Not

Todd C. Lee, MD, MPH
Emily G. McDonald, MD, MSc
Andre Bonnici, BPharm, MSc
Robyn Tamblyn, PhD

Author Affiliations: Clinical Practice Assessment Unit, Department of Medicine, McGill University Health Centre, Montréal, Canada (Lee, McDonald); Pharmacy Department, McGill University Health Centre, Montréal, Canada (Bonnici); Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montréal, Canada (Tamblyn).

JAMA Internal Medicine August 2016 Volume 176, Number 8

What did they do?

- Pharmacy data for fiscal year 2015 from the McGill University Health Centre in Canada
  - Compiled doses and drug costs for the medical and surgical units for oral laxatives
  - Estimated that it took 45 seconds of nursing time for each medication to be administered and assigned a cost to that based on Quebec nursing salaries

Table. Laxative Consumption on Inpatient Units for Fiscal Year 2015

	Medical (7828 Annualized Admissions)				Surgical (9236 Annualized Admissions)				Total		
Drug	Doses	Drug Cost, $[a]	Nursing Hours	Total Cost, $[a]	Doses	Drug Cost, $[a]	Nursing Hours	Total Cost, $[a]	Doses	Nursing Hours	Total Costs, $[a]
Docusate	70 079	5771.33	876	24 710.18	95 108	7324.46	1189	33 027.40	165 187	2065	57 737.58
Lactulose[b]	18 224	6003.20	228	10 928.24	7548	2486.40	94	4526.25	25 772	322	15 454.48
Sennosides	25 564	734.72	320	7643.39	19 854	1104.64	248	6470.18	45 418	568	14 113.57
Bisacodyl	8769	311.42	110	2681.24	4744	243.27	59	1525.34	13 513	169	4206.58
Psyllium	2907	769.04	36	1554.66	1558	443.44	19	864.49	4465	56	2419.15
Magnesium hydroxide[b]	1768	246.48	22	724.28	2482	346.02	31	1016.78	4250	53	1741.06
Total	127 311	13 836.19	1592	48 241.99	131 294	11 948.23	1640	47 430.44	258 605	3233	95 672.42
Per admission	NR	NR	NR	6.16	NR	NR	NR	5.14	15.2	0.2	5.61

*DSS was the most commonly prescribed laxative (>165,000)

*64% of all doses of laxatives

*Among those who were discharged, half got prescriptions for Docusate

*Total costs of all nursing time (2,065 hours annually) to just to administer Docusate was $57,000 Canadian dollars ($43,000 USD) which is nearly 2 full time RN positions

Conclusions

Inpatient laxative use is common and frequently persists following discharge. While seemingly trivial, the routine use of docusate products in a constrained health care system is wasteful. Perhaps it is time for a trial to address the efficacy and clinical benefit of inpatient laxative use so that we might avoid flushing good money down the toilet.

Commentary:

What Needs to Change? | Stopping the use of ineffective treatments such as docusate is an important issue for quality of care, safety, and cost. Yet, old habits die hard, which is why physicians continue to prescribe docusate 3 years after a clinical trial showed it to be ineffective, and hospital formularies continue to support them. Nonbeneficial medications like docusate should be eliminated from hospital formularies so that patients can receive effective treatments in a more timely fashion.

Kanako Y. McKee, MD
Eric Widera, MD

Case continues…

Ms. Powell has been receiving cisplatin for her breast cancer, but has become increasingly nauseated and had more vomiting with each cycle. She is already taking dexamethasone, aprepitant (emend) and ondansetron (zofran) per her oncologist.

What can you offer her?

A) Haldol

B) Haldol

C) Compazine

D) I'm scared of all those medicines because of Q-T prolongation, I send them to cardiology for clearance or tell them they just have to suck it up


Six Flags

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting

Rudolph M. Navari, M.D., Rui Qin, Ph.D., Kathryn J. Ruddy, M.D., Heshan Liu, Ph.D., Steven F. Powell, M.D., Madhuri Bajaj, M.D., Leah Dietrich, M.D., David Biggs, M.D., Jacqueline M. Lafky, M.S., and Charles L. Loprinzi, M.D.

The study

- Double blind RCT
- 380 pts with no previous chemo
- Receiving either cisplatin or cyclophos-doxorubicin
- Randomized to take either olanzapine 10mg or placebo in addition to standard anti-emetic regimen on days 1-4 of chemo
- Results for primary outcome (nausea prevention):
  - 0-24 hours after chemo: 74% vs. 45%
  - 25-120 hours after chemo: 42% vs. 25%
  - Overall 120 hour period: 37% vs 22%

The study…continued

- Secondary outcome was complete response (defined as no emesis and no use of rescue medication) and was also higher in olanzapine group
- Biggest adverse effect in olanzapine group was sedation which was severe in 5% of olanzapine patients at day 2 (nobody stopped study due to sedation)
- TAKE HOME: Add olanzapine (or other anti dopamine agent?) to routine anti-emetic regimen of highly emetogenic chemo on days 1-4

Back to the case

- You see Ms. Powell about a month later, and while her pain is controlled, she complains of increasing shortness of breath. Review of the medical record reveals that she has worsening metastatic disease in her lungs.
- What can you offer her?
  A) Encourage her to use her opiates for dyspnea as well as pain
  B) Bedside fan
  C) Dexamethasone
  D) Just tell her to "chill out," because your new O2 sat monitor said she is at 98% and those machines are the gold standard for patient dyspnea

Original Article

Dexamethasone for Dyspnea in Cancer Patients: A Pilot Double-Blind, Randomized, Controlled Trial

David Hui, MD, MSc, Kelly Kilgore, BS, Susan Frisbee-Hume, MS, Minjeong Park, PhD, Anne Tsao, MD, Marvin Delgado Guay, MD, Charles Lu, MD, William William Jr., MD, Katherine Pisters, MD, George Eapen, MD, Frank Fossella, MD, Sapna Amin, PharmD, and Eduardo Bruera, MD

Departments of Palliative Care and Rehabilitation Medicine (D.H., K.K., S.F.-H., M.D.G., S.A., E.B.); Biostatistics (M.P.); Thoracic Medical Oncology (A.T., C.L., W.W., K.P., F.F.), and Pulmonary Medicine (G.E.), M. D. Anderson Cancer Center, Houston, Texas, USA

*Double blind RCT (41 patients, outpatient clinic)
*Cancer patients with lung involvement
*Randomized to placebo or dexamethasone 8mg BID x 4 days then 4mg BID x 3 days (1 week course)
*Data collected on patient reports of dyspnea, spirometry, QOL scores, and toxicities (measured at 4,7 and 14 days)

The study

- Mainly done to test if carefully controlled trials for dyspnea can be done in seriously ill patients (primary outcome was the percentage of patients who complete the blinded portion of the study)
- 85% of patients completed the study (so, we can study this population after all, they will stay in the study)
- Although placebo group also improved, the time to improve took several days longer
  - Psychological benefit off/u from study staff?
- Patients with KPS < 40 excluded
- Patients with organ failure exacerbation, or other acute illness were also excluded

Results

- Dexamethasone associated with significant reduction in dyspnea numeric rating scale (on scale of 0-10) of 1.9 points by day 4, and 1.7 by day 7 (compared to 0.7 point reduction in placebo group at day 4, and 1.3 point reduction at day 7)-→
- Difference between dexamethasone group and placebo group not statistically significant (but not powered for this comparison).
- Drowsiness improved with dexamethasone
- No significant toxicities

Another case…

- Mr. Jones is a 65 yo male with recent diagnosis of AML. He is hospitalized for a hematopoetic stem cell transplant, and you have been consulted by the oncologist. Another specialist is surprised to see that you will be seeing the patient and says "This guys are usually cured, I'm not sure why they are consulting you…do you think it will really make a difference?

- You say:
  - (A) Yes, but no good data yet
  - (B) Yes, and there is good data
  - (C) I'm not sure, but it couldn't hurt
  - (D) No, probably not, but he is in the unit so I may be able to bill critical care time

JAMA | Original Investigation

Effect of Inpatient Palliative Care on Quality of Life 2 Weeks After Hematopoietic Stem Cell Transplantation

A Randomized Clinical Trial

Areej El-Jawahri, MD; Thomas LeBlanc, MD; Harry VanDusen, BS; Lara Traeger, PhD; Joseph A. Greer, PhD; William F. Pirl, MD; Vicki A. Jackson, MD; Jason Telles, NP; Alison Rhodes, NP; Thomas R. Spitzer, MD; Steven McAfee, MD; Yi-Bin A. Chen, MD; Stephanie S. Lee, MD, MPH; Jennifer S. Temel, MD

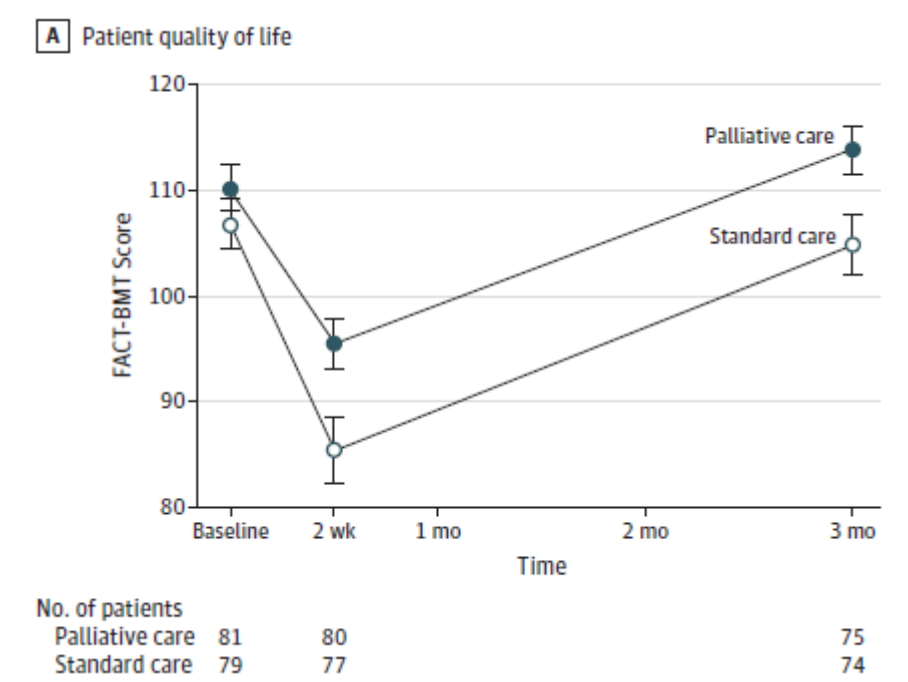
JAMA. 2016;316(20):2094-2103.

*Non blinded RCT
*160 adults with hematologic malignancies undergoing autologous/allogenic HCT and their caregivers
*Intervention: seen by palliative care clinicians at least twice a week during hospitalization (vs. usual care)
*Intervention was focused on management of physical and psychological symptoms

The study

- Primary outcome: change in patient QOL from baseline to week 2
- Secondary: patient assessed mood, fatigue, and symptom burden scores at baseline, 2 weeks and 3 months after HCT and caregiver assessed QOL at baseline and 2 weeks after HCT

Results



Those in palliative care group had a smaller decrease in QOL from baseline to week 2 compared to the usual care group

-Also less depression, anxiety, and symptom burden

Results

- Caregivers of patients receiving palliative care had a lower increase in mean depression scores in the first 2 weeks (although no significant change in QOL)
- Three months after the transplant, patients in the PC group had higher QOL scores and less depression symptoms than those assigned to usual care (no difference in anxiety, fatigue, or symptom burden)
- Only 2 people in the control group received PC consults despite protocol that allowed patients, caregivers, or clinicians to request PC involvement
- Take home: Strong evidence that integrating specialized PC into usual care not only helps those with life limiting illness, but also those undergoing potentially curative therapies

Back to Ms. Powell…3 years later

- You receive news that Ms. Powell has died, and call her husband to express your condolences
- Mr. Powell says "My shrink says I have persistent maladaptive thoughts, dysfunctional behaviors, and poorly regulated emotions"
- You immediately diagnose him with complicated grief, and ask how he is doing. He states he is receiving complicated grief therapy, but wonders if there is a "pill" that will help. You recommend say:

A) No, this is tough, just keep up with the therapy
B) Yes, you should be on trazadone
C) Yes, you should be on citalopram
D) By now you know to never pick D

JAMA Psychiatry. 2016;73(7):685-694.

Original Investigation

Optimizing Treatment of Complicated Grief
A Randomized Clinical Trial

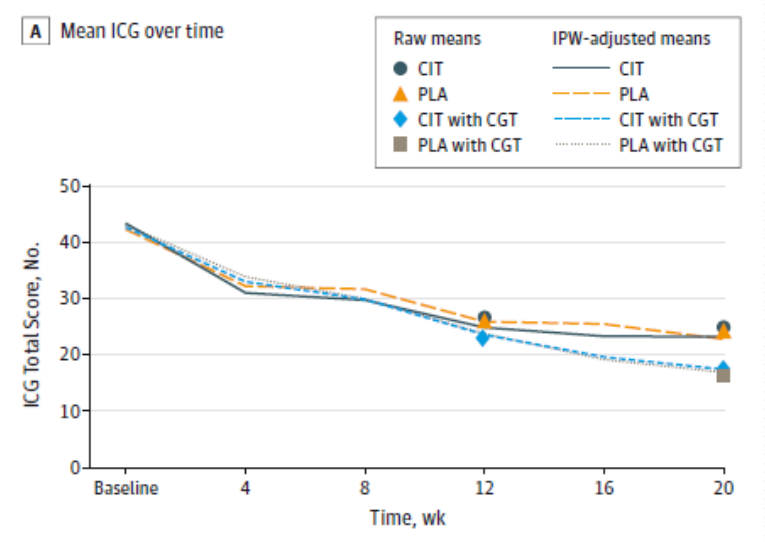
M. Katherine Shear, MD; Charles F. Reynolds III, MD; Naomi M. Simon, MD, MSc; Sidney Zisook, MD; Yuanjia Wang, PhD; Christine Mauro, PhD; Naihua Duan, PhD; Barry Lebowitz, PhD; Natalia Skritskaya, PhD

*Double blind, randomized, placebo-controlled trial
*395 patients randomized to citalopram or placebo with or without complicated grief therapy (16 weekly sessions)
*Median time since loss was 2.3 years (range 0.5-58 years)
*4 academic centers
*exclusion criteria: Current addiction, psychosis, mania, SI, cognitive impairment, or current therapy or psychiatric medication

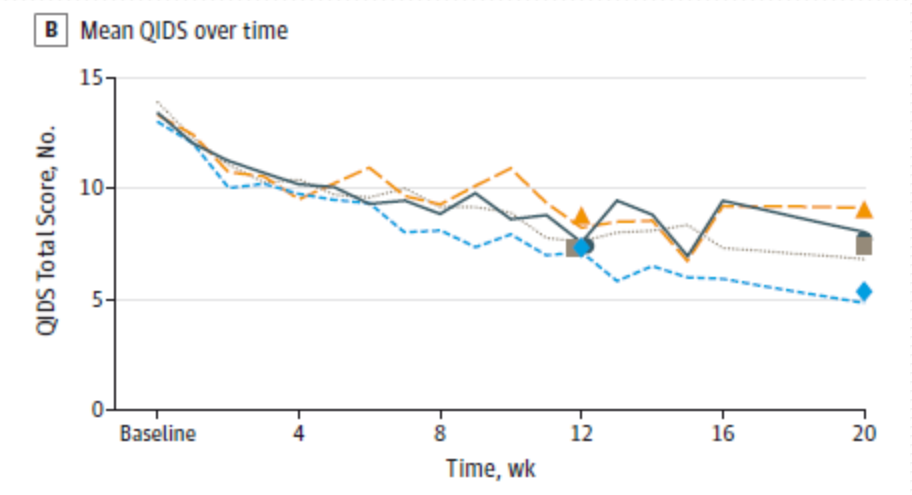
The study

- Primary outcome: CG treatment response rate at 12 and 20 weeks
- Secondary outcomes: reduced depressive, suicidal symptoms

Results



Pts better with thearpy than placebo, but citalopram did not improve complicated grief outcomes



Improvement of depressive symptoms was greater with citalopram

Bottom line

- CGT is the best treatment for patients meeting criteria for complicated grief
- For those with significant codepressive symptoms, the addition of citalopram provided symptom relief

Conclusions

- Morphine is better than weak opioids (tramadol and codeine) for moderate cancer pain. Consider skipping "step 2" of the WHO 3 step ladder
- Morphine and oxycodone work equally well. If one isn't working, switch to the other.
- Stop using docusate, get it off your formulary
- Add olanzapine (or other anti dopamine agent?) to routine anti-emetic regimen of highly emetogenic chemo on days 1-4…or remind your colleagues to.
- Studies in seriously ill cancer patients with dyspnea can be done, and maybe a week of steroids can help

Conclusions (continued)

- Palliative care should be getting more integrated with patients with potentially curative therapies such as bone marrow transplants
- In patients with complicated grief, make sure they are getting cognitive grief therapy and if they have depressive symptoms consider citalopram


THANK
YOU