

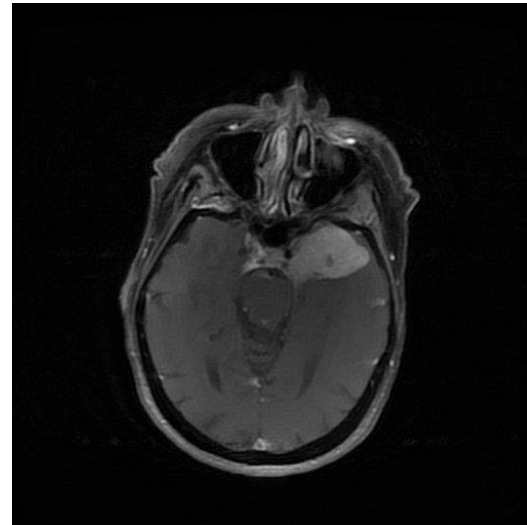
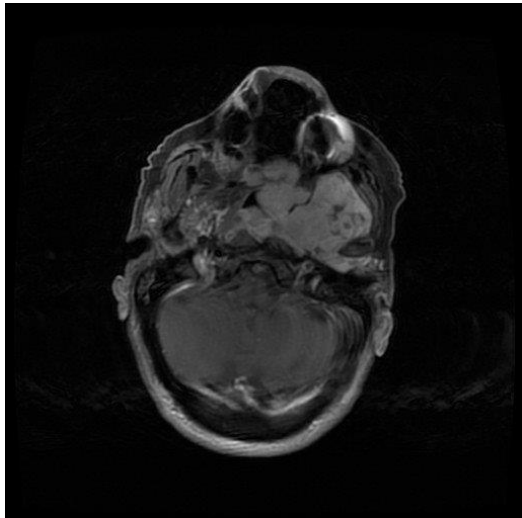
Symptom management in elderly cancer patients

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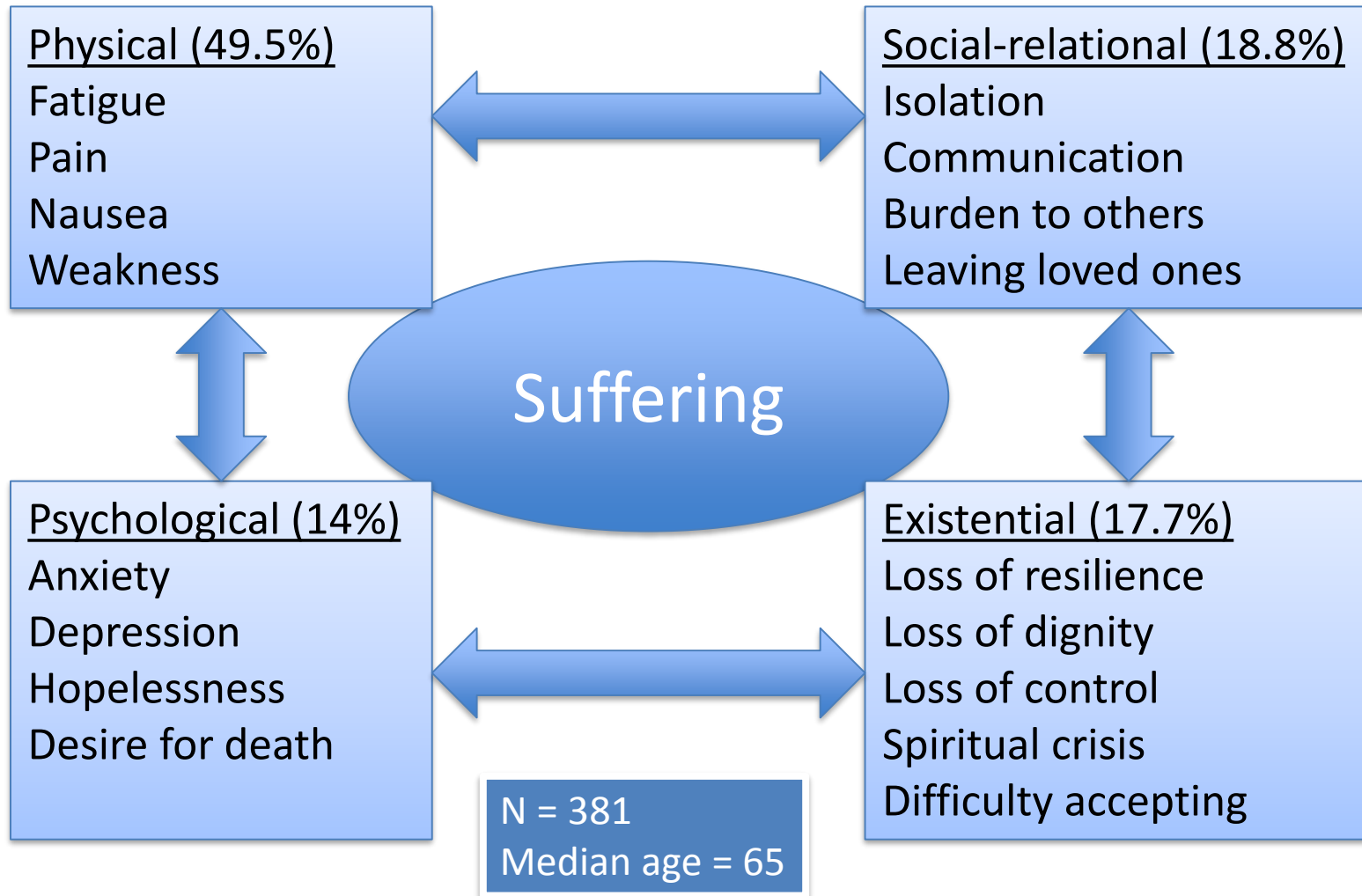
9 March 2018

Case 1

- 80 yo female with an enlarging nasopharyngeal adenoma presents to clinic.
- She has 5/10 pain over her left face and skull. It is aching and has a burning component to it. It does not radiate. Swallowing makes it worse. It keeps her up at night.
- She has good family support apart from an estranged son



Suffering in cancer pts



Prevalence and severity of cancer pain

- 122 studies (2005 – 2014)
- N = 63,533

Group	Pain (%)	Moderate-severe (%)
After curative tx	39.3	27.6
During tx	55.0	32.4
Advanced-metastatic	66.4	51.9

Worst Pain:
Head + Neck ca
Lung ca
Breast ca

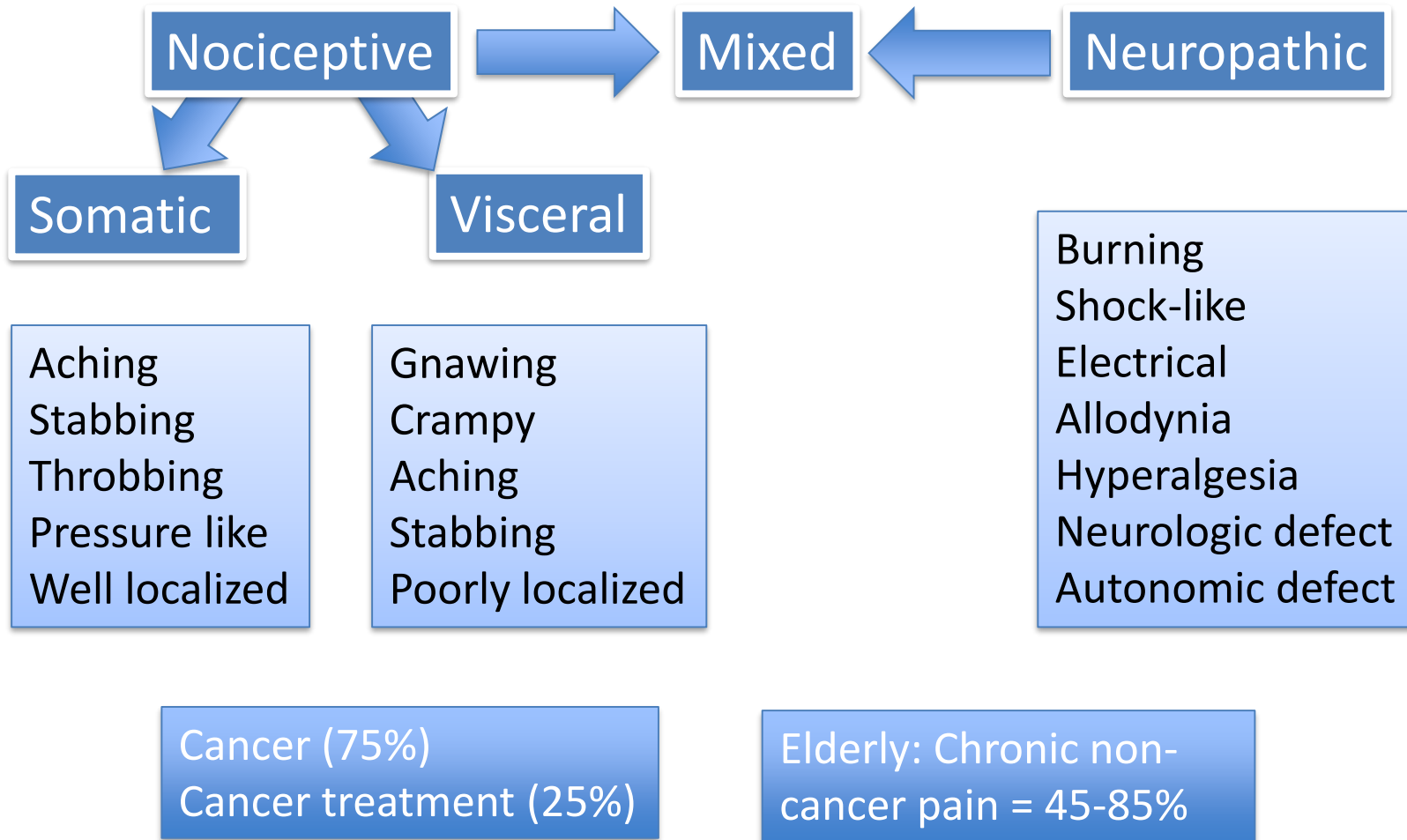
Age not
associated with
pain prevalence

Opioid prescriptions in elderly cancer pts based on pain severity: N = 219,535

Year	Moderate (%)	Severe (%)
2007	41.8	60.9
2008	38.0	52.8
2009	29.6	46.7
2010	27.6	45.4
2011	26.2	42.7
2012	25.4	42.6
2013	25.0	39.2

“a quality gap in the management of pain in [elderly] pts with cancer”

Classifying cancer pain



Classifying cancer pain: Edmonton Classification System of Cancer Pain

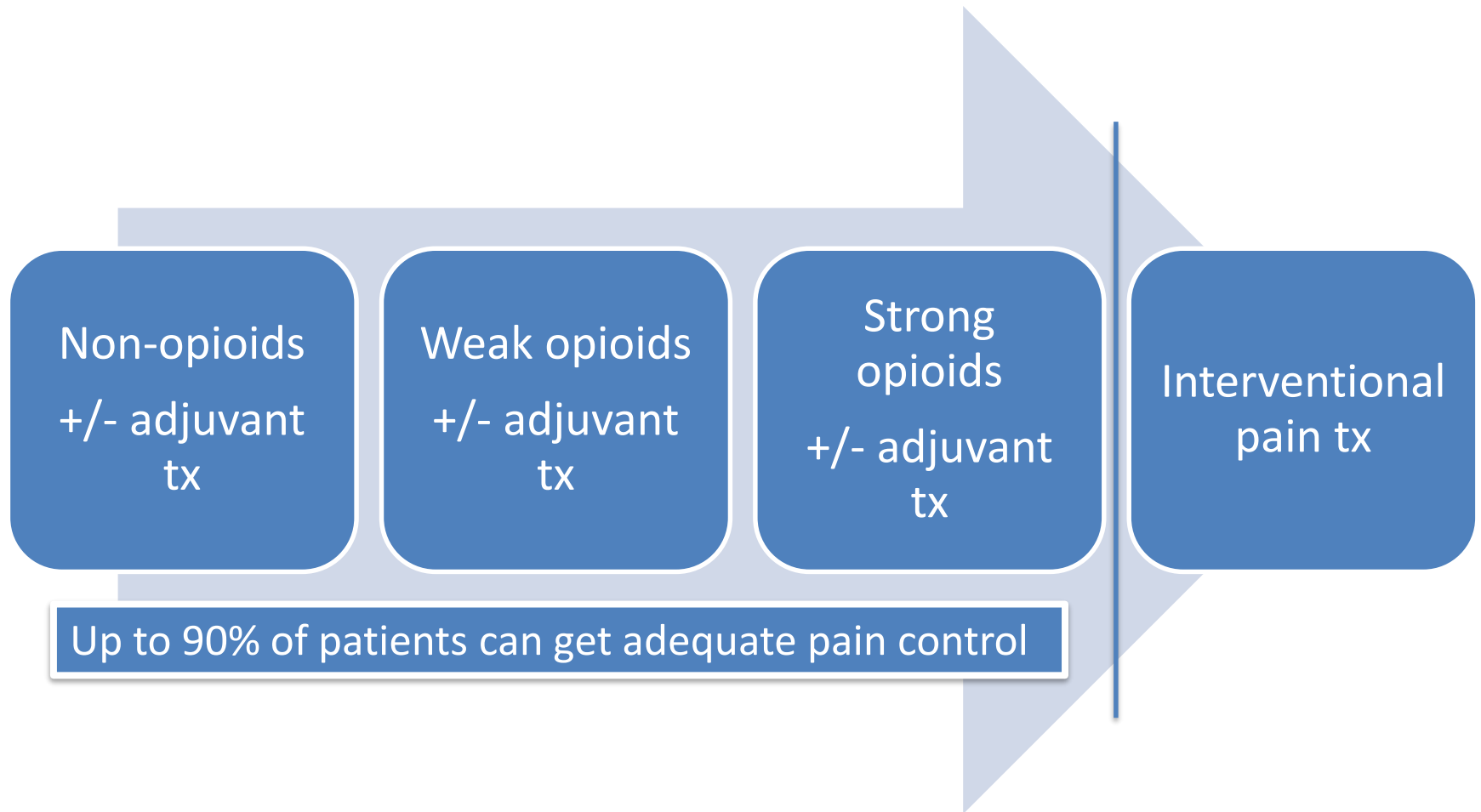
- Multinational validation study
- N = 1100, Mean age = 61 - 69

Variable	%	Time to pain control	Adjuvant analgesics	Total opioid dose
Nociceptive	67	↓	↓	↓
Neuropathic	27	↑	↑	↑
Incident pain	48	↑	↑	↑
Psychological distress	44	↑	↑	↑
Addictive behavior	11	↔	↔	↑
Impaired Cognition	21	↔	↔	↔

↓ or ↑ = P < 0.05

Age ≥ 60 ↓ time to pain control

World Health Organization Pain Ladder



Case 1 continued

- PMH: DM, HTN
- H/o falls, uses a walker
- Hard of hearing

- CrCl = 45
- Normal LFT's

- Currently on Acetaminophen

- Realistic about treatment goals.



Acetaminophen

- 3 studies, N = 122
- Low quality of evidence
- No studies looked at acetaminophen alone
- No evidence of benefit when combined with opioids
- No clear evidence of harm
- Elderly:
 - well tolerated, 1st line treatment, not habit forming, elimination not affected by age



NSAIDs

- 11 studies, N = 949
- Alone or in combination with opioids
- Significant improvement (within 1-2 weeks):
 - 26 – 51%
- Common side effects:
 - Thirst/dry mouth (15%), loss of appetite (14%), dyspepsia (11%), somnolence (11%)
- Treatment withdrawal:
 - Lack of benefit = 24%
 - Adverse event = 5%



NSAIDs: Elderly

- Toxicity ↑ in elderly
- Brief better than long term use
- Topical = ↓ toxicity
- Consider GI protection

- COX-2 inhibitors:
 - ↓ GI toxicity
 - ↑ CVD toxicity
- Naproxen = ↓ CVD risk



Common opioids

Mechanism	Opioid	Potency
Pure agonist	Morphine	1
	Hydromorphone	5 x
	Oxycodone	2 x
	Fentanyl	100 x
	Methadone	4-12 x
	Codeine	1/10 x
Agonist-antagonist	Buprenorphine	
Mixed mechanism	Tramadol	1/10 x
	Tapentadol	2.5 x

Similar efficacy

Common opioid toxicities

Adverse event	%
Constipation	25
Nausea +/- vomiting	21
Somnolence	23
Dry mouth	17
Decreased appetite	13
Dizziness	13
Fatigue	<5
Mood changes	<5
Insomnia	<5
Hallucinations	<5
Diarrhea	<5

Opioids have similar toxicity

Toxicity: Elderly > Younger

At least 1 significant adverse event = 11-77%

Pts Stopped therapy = 6-19%

Wiffen PJ, Wee B, et al: Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No.: CD012592

Wiffen PJ, et al: Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD011056

Schmidt-Hansen M, et al: Cochrane Database Syst Rev. 2017;8:CD003870

Hadley G, et al: Cochrane Database Syst Rev. 2013 Oct 5;(10):CD010270

Important considerations in the elderly

↑ comorbidities

↑ prescription meds

↓ organ perfusion

Δ in GI absorption (pH)

↑ adipose tissue

↓ body mass

Δ in volume of distribution



Implications for prescribing pain meds in the elderly

- ↓ 1st + 2nd pass metabolism
- ↓ renal excretion
- ↑ $\frac{1}{2}$ life
- ↓ time to peak analgesia
- ↑ metabolites

- ↓ therapeutic window



Prescribing pain meds in the elderly

- Check for drug-drug interactions
- Introduce 1 agent at a time
- Start slow and go slow (i.e. 1/2 regular dose)
- Increase interval between medication titration
- Monitor for toxicity more frequently

Prostran M, et al: Front. Aging Neurosci. 2016; 8:144

Pergolizzi J, et al: Pain Pract. 2008;8(4):287-313

Wiffen PJ, Wee B, et al: Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No.: CD012592

Wiffen PJ, et al: Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD011056

Schmidt-Hansen M, et al: Cochrane Database Syst Rev. 2017;8:CD003870

Hadley G, et al: Cochrane Database Syst Rev. 2013 Oct 5;(10):CD010270



Prescribing opioids in the elderly

- Start with short acting medication
- Weak evidence:
 - Oxycodone ↓ hallucinations
 - Fentanyl ↓ confusion + constipation
- Consider least invasive route
- Use long-acting formulations after adequate exposure
- Breakthrough dose \approx 10% of 24 hour needs
- Have lower threshold for rotating opioids

Opioid-Induced Neurotoxicity (OIN)

Cognitive dysfunction

Hallucinations

Myoclonus/seizures

Hyperalgesia/allodynia

High/prolonged opioid use

Advanced age

Comorbidities/ Renal failure

Poly-pharmacy

Look for other causes

Rotate opioids

Hydrate

Case 1 continued

- We started HM 0.5-1 mg po q2h prn pain.
- Over the next month the dose was titrated to HM C 6 mg po bid and HM 1-2 mg po q2h prn.
- She was worried about taking more and felt that it was making her fatigued.



Common adjuvant therapies: Neuropathic pain

Type	Studies	N	NNT	NNH
TCA's	15	948	3.6	13.4
SNRI's	10	2541	6.4	11.8
Pregabalin	25	5940	7.7	13.9
Gabapentin	14	3503	7.2	25.6
Tramadol	6	741	4.7	12.6
Strong opioids	7	838	4.3	11.7

NNT \geq 50% reduction in pain

Choosing adjuvant tx in the elderly

Type	Name	Clinical Pearls
Antidepressants	Nortriptyline	Preferred TCA Anticholinergic AE's
	Duloxetine	Preferred SNRI
Anticonvulsants	Gabapentin	Monitor renal function ↑ risk of falls
	Pregabalin	Monitor renal function ↑ risk of falls



Other adjuvants in elderly

Type	Name
Topical	Menthol 1.5-3%
	Capsaicin 0.025-8%
	Lidocaine 2-5%
	Diclofenac 1-3%
Antispasticity agents	Baclofen
	Dantrolene
	Tizanidine
Antispasmodic agents	Carisoprodol
	Cyclobenzaprine
	Methocarbamol
Steroids	Dexamethasone
NMDA antagonist	Ketamine

Case 1 continued

- We started a topical lidocaine ointment
- Later we felt there was a component of depression and initiated venlafaxine



Case 2

- 72 female with h/o metastatic endometrial ca
- She has visceral-nociceptive 4/10 abdominal pain despite morphine 10 mg po q1h prn. She has great social support.
- She does not want to start a long acting opioid
- She cries frequently in clinic. Depression screening (+)
- We started duloxetine
- At follow-up visit her depression is better. She continues to have pain. She wants to try Marijuana



Medical Marijuana

- CB receptors
 - CB1 = neuro-modulatory
 - CB2 = immune-modulatory

THC = psychoactive

CBD = non-psychoactive

Type	Onset (min)	Duration (h)	Enzyme inhibition
Smoked	5	2-4	3A4
Vaporized	5	2-4	3A4
Oral	30-60	8-12	3A4
Nabilone	60-90	8-12	
Dronabinol	30-60	4-6	3A4
Nabiximols	15-40	2-4	3A4

Cannabinoids

- RCT
- THC:CBD extract vs. THC extract vs. placebo
- N = 177, all pts on baseline opioids
- Median age = 60

Pain Outcome	THC:CBD	THC	Placebo
↓ VAS (10 point)	-1.37*	-1.01	-0.69
≥ 30% ↓ Pain	43%*	23%	21%
* P < 0.05 (THC:CBD vs. Placebo)			



Cannabinoids for medical use: A systematic review and meta-analysis- 2015

- Cancer and non-cancer patients (N = 6462)
- Moderate-quality evidence to support use in chronic pain
- $\geq 30\%$ improvement pain = 37% vs. 31%, OR 1.41 (0.99 – 2.00)
- \downarrow VAS vs. control arm - 0.47

The effects of cannabis among adults with chronic pain and an overview of general harms- 2017

- Cancer (N = 596, 3 RCTs)
- Significant methodological limitations
- Insufficient evidence

Systematic review and meta-analysis of cannabinoids in palliative medicine- 2018

- Cancer patients (N = 758)
- No significant improvement in:
Caloric intake, appetite, N/V, $> 30\%$ decrease in pain, sleep

Whiting PF, et al: JAMA. 2015;313(24):2456-2473

Nugent SM, et al: Ann Intern Med. 2017;167:319-331

Mucke M, et al: J Cachexia Sarcopenia Muscle. 2018, ahead of print.

Cannabinoid toxicity

Side effect	Odds ratio (95% CI)
Disorientation	5.41 (2.61 – 11.19)
Dizziness	5.09 (4.10 – 6.32)
Dry mouth	3.5 (2.58 – 4.75)
Nausea	2.08 (1.63 – 2.65)
Fatigue	2.00 (1.54 – 2.62)
Somnolence	2.83 (2.05 – 3.91)
Euphoria	4.08 (2.18 – 7.64)
Confusion	4.03 (2.05 – 7.97)
Hallucinations	2.19 (1.02 – 4.68)
Serious AE	1.41 (1.04 – 1.92)
Motor vehicle accident	1.35 (1.15 – 1.61)

Cannabis in the elderly

- Prospective study, out-pt cancer clinic
- Age \geq 65, cannabis tx for 6+ months
- N = 2736

- 43% used for 6+ months
- Oil (37%), smoking (24%), vaporizing (6.4%), oil + vaporizing (48.6%)

- Median pain scores: 8 \rightarrow 4
- 93.7% = overall improvement
- 41.9% = significant improvement
- 58.6% = QoL good or very good

- Side effects mild
 - Dizziness (9.7%), dry mouth (7.1%), somnolence (3.9%)



Case 3

- 82 yo male with metastatic bladder ca on the palliative care program.
- He has cancer-related pain that is managed with Fentanyl and morphine breakthrough.
- He has significant constipation despite PEG, senna, glycerin supps.
- Abd XRT + stool. Rectal = clear.



Constipation in the elderly

- More common
- Females > males

- Delayed colonic transit
- Pelvic floor dysfunction
- Psychosocial and behavioral factors



Causes of constipation

Cause	Examples
Constitutional	Immobility, dehydration, weakness
Metabolic	↑ca, ↓K, ↓Na, ↓Mg
Cancer	Tumor, radiotherapy, chemotherapy
Medications	Analgesics (opioids, NSAIDs) Anticholinergics TCAs Antihypertensives (CCB's, BB's) Antiemetics (ondansetron) Minerals (aluminum, ca, iron) Antihistamines Diuretics (HCTZ, furosemide)
Medical conditions	Renal disease, Dementia, DM, hypothyroidism, depression

Treatment

Category	Type	Route	Treatment line
Osmotic	Polyethylene glycol	PO	1 st
	Sorbitol	PO	1 st
	Lactulose	PO	1 st
	Mg hydroxide/sulfate/citrate*	PO	Caution
	Glycerin	PR	3 rd
	Phosphate*	PR	Caution
Stimulant	Senna	PO	2 nd
	Bisacodyl	PO/PR	2 nd
Lubricant	Mineral oil	PR	3 rd

Difficult to control constipation

Drug	Mechanism	RCT	RR	NNT
→ Methylnatrexone	PAMORA	6	0.62	3.4
→ Naloxone (oral)	Opioid antagonist	5	0.63	4
Naldemedine	PAMORA	4	0.65	5
→ Naloxegol	PAMORA	3	0.77	7
Lubiprostone	Type-2 chloride channel activator	3	0.90	15
Prucalopride	5-HT4 agonist	1	0.88	12

PAMORA = peripherally-acting Mu-opioid receptor antagonist

Case 4

- 67 yo female with metastatic pancreatic cancer on chemotherapy
- She has 9/10 visceral-neuropathic (mixed) pain despite Fentanyl 200 ug/h, morphine 80 mg po q1h prn, pregabalin and duloxetine.
- She has a friend who took methadone because she was a “drug addict” and does not want to take it.



Interventional therapies

Intervention	Example	Level of evidence
Autonomic nerve blocks	Celiac plexus Superior hypogastric plexus Ganglion impar	IIB
Neuroaxial infusion	Epidural/intrathecal	IIB
Vertebroplasty	Spine	IIIB
Peripheral nerve blocks	Paravertebral Intercostal Brachial plexus Gassesian ganglion	

Non-pharmacologic interventions

- RCT and meta-analysis benefits seen with:
 - Psycho-social interventions
 - Cognitive behavior therapy
 - Mindfulness-based therapy
 - Physiotherapy
 - Massage therapy
 - Yoga
 - Acupuncture



Zhang J, et al: Complement Ther Med. 2016;26:1-10
Gorin SS, et al: J Clin Oncol. 2012;30:539-547
Jara C, et al: Clin Transl Oncol. 2018;20:97-107
Lee SH, et al: Integr Cancer Ther. 2015;4:297-304

Cramer H, et al: Cochrane Database Syst Rev. 2017 Jan 3;1CD010802
Tao WW, et al: J Pain Symptom Manage. 2016;51(4):728-747
De Groef A, et al: Arch Phys Med Rehabil. 2015;96(6):1140-153

Electrical nerve stimulation

- Transcutaneous electrical nerve stimulation (TENS):
 - Cancer pts = 3 small RCT: no clear benefit
 - Chronic neuropathic pain
 - -1.58 (-2.08 to -1.09), $p < 0.01$
 - Very low quality of evidence = benefit unclear
- Scrambler therapy:
 - Preliminary reports (20) suggest benefit



Benefit of radiotherapy

- Improves pain (bone):
 - 90% have some pain relief
 - 50% have complete pain relief
- Can also be used to improve symptoms associated with:
 - Brain metastasis
 - Spinal cord compression
 - Bronchial obstruction
 - Bleeding (i.e. Lung, bladder, rectum, stomach)
 - Lymphadenopathy

How are clinic works

- Holistic approach
- Nurse
- Pharmacist
- Physiotherapist (CCMF grant)

- Early psychosocial intervention
- Frequent f/u via telephone
- Utilize integrative medicine



Conclusion

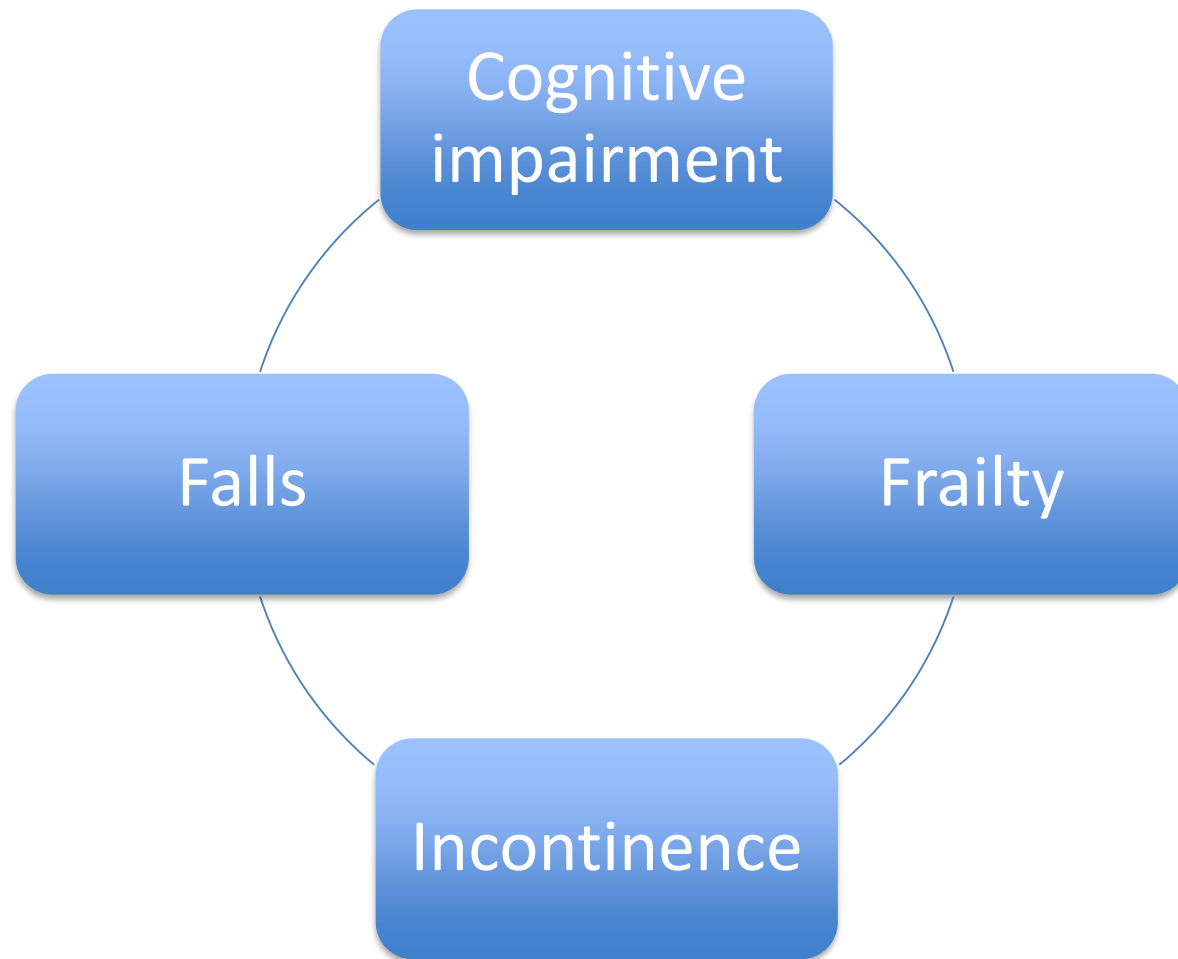
- Cancer related symptoms are common in the elderly
- Understanding factors influencing cancer pain is important
- Elderly pts have unique needs
- Many treatment options are available
- A multifaceted approach is essential to minimize toxicity and maximize benefit

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Symptom Management: Consider Geriatric Syndromes



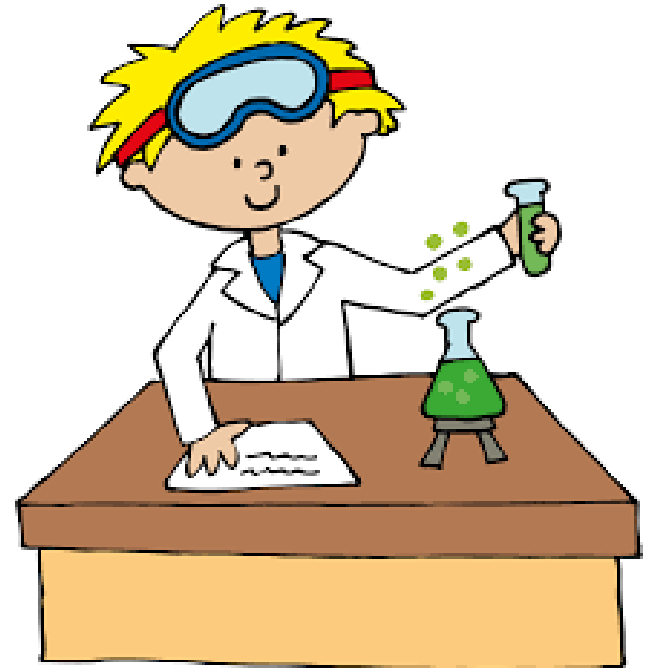
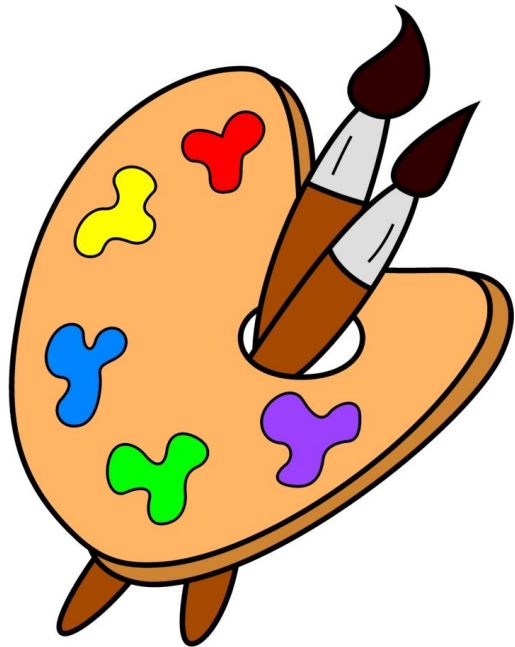
Under-treatment of cancer pain

- 26 studies (1994 – 2013)
- N = 18,384

Year	Undertreated (%)
1994 – 2000	46.6
2001 – 2007	41.5
2008 - 2013	31.8

↑ Economic level and cancer specific centers = Better pain control

Age not associated with under-treatment of cancer pain



Unique characteristics in elderly patients: Self reflection

- ↑ Life experiences
- Want to be listened too/respected
- ↑ Time to process
- Longer appointments