Pain management in older patients

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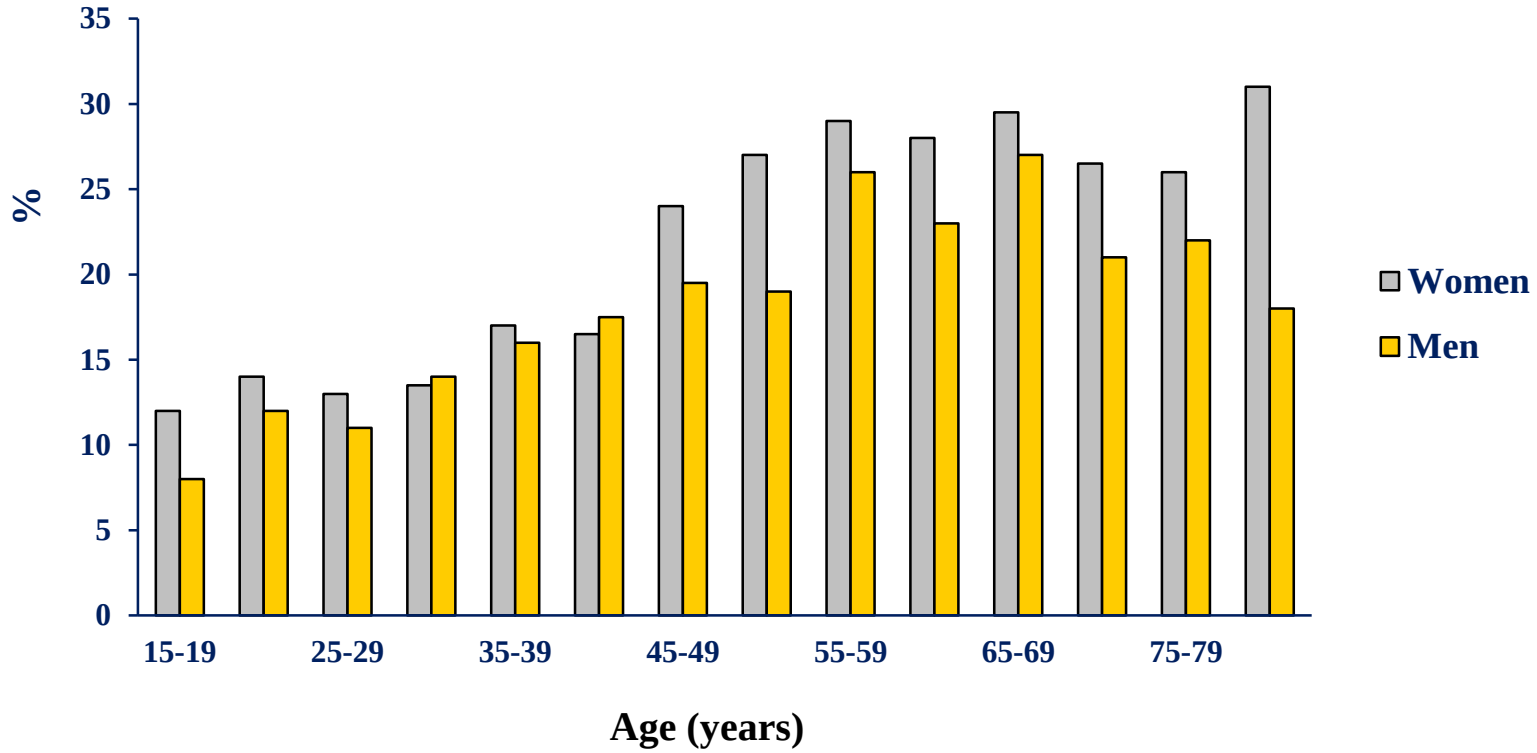
Pain

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"

(International Association for the Study of Pain)

Chronic pain prevalence

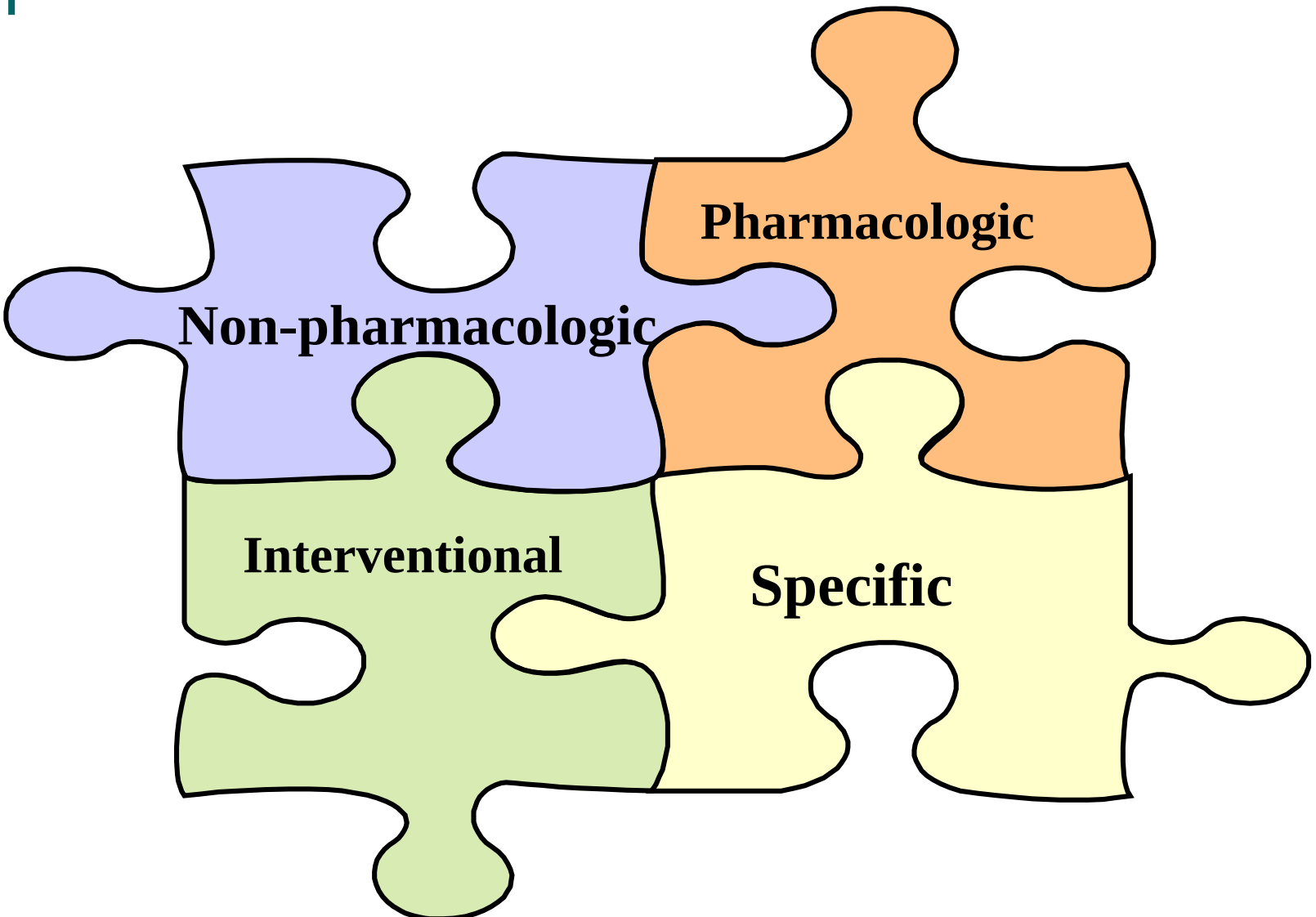


(Blyth et coll., 2001)

Pain management

FAVOR **ACTIVE** APPROACHES ENCOURAGING PATIENT **EMPOWERMENT** AND ENGAGEMENT IN HIS/HER PAIN MANAGEMENT

Pain management

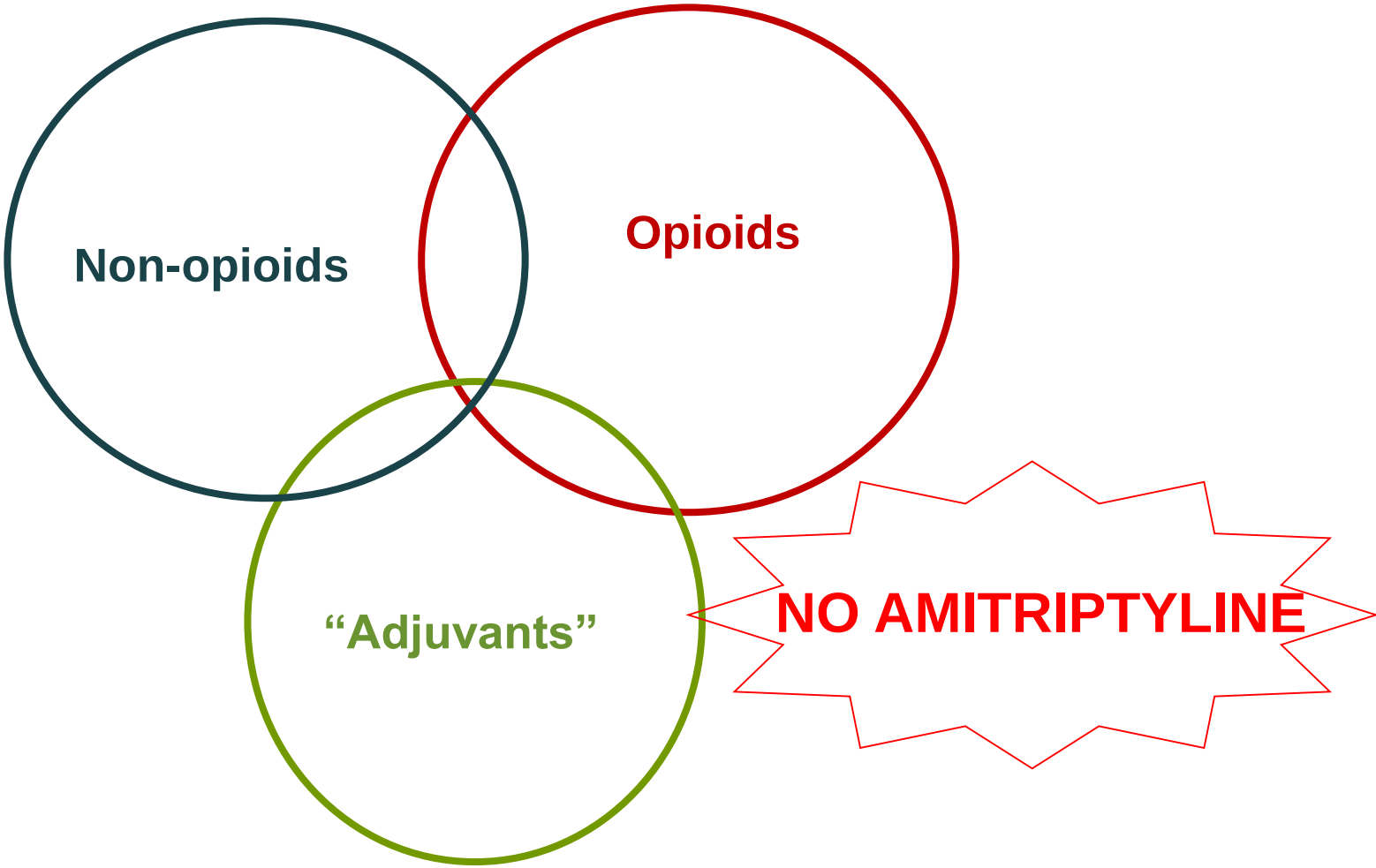


Pharmacological management

Pharmacological management

- Choose medications with the best efficacy : adverse effects ratio
- Discontinue medications with poor ratios
  - benzodiazepines
  - tricyclics
  - daytime gabapentinoids
- Use combination therapy rather than monotherapy
- **« Start low, go slow … but go somewhere »**

Pharmacological management



Acetaminophen

- ↑ half-life in older patients: qid rather than q 4 hours
- Sustained-release formulation 650 mg can be used bid-tid
  - Tylenol Arthritis, Tylenol Muscle Pains
- **Adverse effects**
  - renal toxicity with prolonged use
  - risk of liver toxicity with high doses
- **Caution with**
  - "**Back pain**" and "**Body Pain Night**": methocarbamol
  - "Night": diphenhydramine
  - "Headache": caffeine

Acetaminophen

- **Maximum doses :**
  - 4 g/d <10 days in healthy and well nourished patients
  - 3,2 g/d for prolonged use in healthy patients
  - **2,6 g/d** for prolonged use in patients at risk or > 65 years old

NSAIDs

Pharmacological Management of Persistent Pain in Older Persons

American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons

II) **Non-selective NSAIDs and coxibs may be considered rarely, and with extreme caution, in highly selected individuals**

(A) ***Patient selection***

- other (safer) therapies have failed
- evidence of ongoing therapeutic goals not met
- ongoing assessment of risks and complications outweighed by therapeutic benefits

VII) All patients taking non-selective NSAIDs or coxibs **should be routinely assessed** for

- gastro-intestinal toxicity
- renal toxicity
- hypertension
- heart failure
- drug-drug and drug-disease interactions

Opioids

- Opioids are rarely indicated as first-line treatment.
- It is usually accepted to initiate them
  - as second line, after acetaminophen and NSAIDs, for nociceptive pain
  - as second or third line for neuropathic pain

Collège des médecins du Québec, Douleur chronique et opioïdes : l'essentiel, Collège des médecins du Québec, Édition 2009.

Before prescribing an opioid

- Clarify patient's expectations
  - Reduce pain and its impacts rather than completely resolve pain
- Multimodal analgesia
  - Non-pharmacologic
  - Non-opioid analgesics
- Progressive dose titration
- Assess response
  - ↓ pain 30% or 2 on 0-10 scale
  - ↑ functional statis
- Prevent and treat adverse effects
- Be attentive to signs of inappropriate behavior

Follow-up of opioid prescription

At each follow-up of an opioid prescription, the following should be assessed and documented :

- pain relief
- adverse effects
- functional autonomy
- mobility
- mood
- Sleep
- inapproprite behavior

Collège des médecins du Québec, Douleur chronique et opioïdes : l'essentiel, Collège des médecins du Québec, Édition 2009.

The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain

Guideline for opioid therapy and chronic noncancer pain

Jason W. Busse DC PhD, Samantha Craigie MSc, David N. Juurlink MD PhD, D. Norman Buckley MD, Li Wang PhD, Rachel J. Couban MA MISt, Thomas Agoritsas MD PhD, Elie A. Akl MD PhD, Alonso Carrasco-Labra DDS MSc, Lynn Cooper BES, Chris Cull, Bruno R. da Costa PT PhD, Joseph W. Frank MD MPH, Gus Grant AB LLB MD, Alfonso Iorio MD PhD, Navindra Persaud MD MSc, Sol Stern MD, Peter Tugwell MD MSc, Per Olav Vandvik MD PhD, Gordon H. Guyatt MD MSc

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The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain

1. **First-line pain treatment**
   - **Optimize non-opioid pharmacotherapy** and non-pharmacological therapy, rather than a trial of opioids
     (**strong recommendation**)

2. **Persistent problematic pain despite optimized non-opioid therapy**
   - **Trial of opioids** rather than continued therapy without opioids
     (weak recommendation)

The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain

6. **Patients who are beginning longterm opioid therapy**
   - **Restrict prescribed dose to < 90 mg morphine equivalent/day** rather than no upper limit or a higher limit

     (strong recommendation)

Some patients may gain important benefit at a dose of more than 90mg morphine equivalents daily. Referral to a colleague for a second opinion regarding the possibility of increasing the dose to more than 90mg morphine equivalents daily may therefore be warranted in some individuals.

The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain

8. **Patients who are currently using opioids, and have persistent problematic pain and/or problematic adverse effects**
   - **Rotation to other opioids** rather than keeping the opioid the same

     (weak recommendation)

The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain

9. **Patients who are currently using ≥ 90 mg morphine equivalents/day**
   - **Taper opioids to the lowest effective dose,** potentially including discontinuation, rather than no change in opioid therapy

     (weak recommendation)

- Some patients are likely to experience significant increase in pain or decrease in function that persists for > 1 month after a small dose reduction.
- Tapering may be paused and potentially abandoned in such patients.

The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain

10. **Patients who are using opioids and experiencing serious challenges in tapering**
    - **Refer these patients to a formal multidisciplinary program**

      (strong recommendation)

Opioids in older patients

- Scarce data on pharmacokinetic and pharmacodynamic properties of opioids in older patients

- è Consider comorbidities and concomitant medications when choosing the most appropriate opioid for a patient

- è Avoid meperidine (Demerol®) and pentazocine (Talwin®)

Tramadol

- **3 mechanisms of action**
  - very weak agonist of μ opioid receptors
    - not pharmacologically defined as an opioid
    - not considered as a narcotic in Canada
  - noradrenaline and serotonin reuptake inhibitor
- Analgesic effect shown for noiceptive and neuropathic pain, including several studies with older subjects
- Less adverse effects than opioids (ex. ↓ constipation, ↓ somnolence)
- **Adverse effects**
  - Nausea/vomiting
  - Dizziness
  - Constipation
  - Sedation

Morphine

Advantages	Disadvantages
Metabolised via hepatic glucuronidation • no age-related changes • less drug-drug interactions	Renal clearance
	Lipophilic active metabolite that easily crosses blood-brain barrier
	↑ constipation

Oxycodone

Advantages	Disadvantages
Half-life unchanged	Renal clearance
Physiological effects unchanged	Drug-drug interactions via CYP2D6
	Pro-drug activated via CYP2D6 ?
Kappa agonist activity • ↓ sedation ?	Kappa agonist activity • euphoria

Codeine

Advantages	Disadvantages
	Pro-drug activated by CYP2D6
	Renal accumulation of codeine, morphine and norcodeine
	↑ nausea
	↑ constipation

Hydromorphone

Advantages	Disadvantages
Metabolised via hepatic glucuronidation • no age-related changes • less drug-drug interactions	↑ constipation
Metabolite has low affinity for opioid receptors	↑ sedation
Hydrophilic metabolite ➔ less easily crosses blood-brain barrier	

Long-acting opioids

- Indications
  - constant pain
  - frequent episodic pain
- **Most of the time, should only be used in patients who tolerate several daily doses of short-acting opioids**
- Better to start with several regular daily doses of short-acting opioids, and later convert to a long-acting opioid if well tolerated

Transdermal buprenorphine

Advantages	Disadvantages
No accumulation in renal failure	Lipophilic • ↑ volume of distribution • ↑ half-life
Metabolised via hepatic glucuronidation • no age-related changes • less drug-drug interactions	Highly protein bound → possible ↑ free portion in undernourished patients
Ceiling effect for respiratory depression	
Lower available dose can be given to opioid naive older patients	
Stable delivery for 7 days • ↑ compliance • ↓ nursing care	
Data on clinical efficacy and tolerability in older patients	

(Lussier 2013)

Transdermal fentanyl

Advantages	Disadvantages
No accumulation in renal failure	Lipophilic • ↑ volume of distribution • ↑ half-life
Stable delivery for 7 days • ↑ compliance • ↓ nursing care	Variable absorption and bioavailability
Dysphagic patients	Smallest available dose is too high ➔ **should never be prescribed to an opioid naive older patient**

Methadone

Advantages	Disadvantages
No accumulation in renal failure	Lipophilic • ↑ volume of distribution • ↑ half-life
Long duration of action	Long and variable half-life
Cheap	Linear equianalgesic doses
NMDA antagonist activity	Risk of QTc interval prolongation and torsade de pointes
No cross-allergy with morphine, codeine and oxycodone	Drug-drug interactions via CYP3A4
	Limited data on pharmacokinetics and pharmacodynamics in older patients

(Lussier 2013)

Long-acting opioids

- Lowest long-acting opioid doses available
  - BuTrans® (buprenorphine) 5-20 mcg/h q 7 jours
  - Kadian® (morphine) 10 mg die
  - Jurnista® (hydromorphone) 4 mg die

- Capsule can be opened and granules sprinkled on cold food or administered via jejunostomy/feeding tube
  - HydromorphContin® (3 mg bid)
  - M-Eslon® (10 mg bid)
  - Kadian® (10 mg die)

Equianalgesic doses

Maintenance treatment		
Morphine equivalents : other opioids		
Opioid	Equivalent dose (mg)	Conversion to morphine equivalents
Morphine	30	1
Codeine	200	0,15
Oxycodone	15	2
Hydromorphone	6	5
Methadone and tramadol	Variable morphine equivalents	

Equianalgesic doses

Maintenance treatment	
Morphine equivalents : fentanyl	
Opioid	
Transdermal fentanyl	60-134 mg = 25 µg/h 135-179 mg = 37 µg/h 180-224 mg = 50 µg/h 225-269 mg = 62 µg/h 270-314 mg = 75 µg/h 315-359 mg = 87 µg/h 360-404 mg = 100 µg/h

Adjuvants

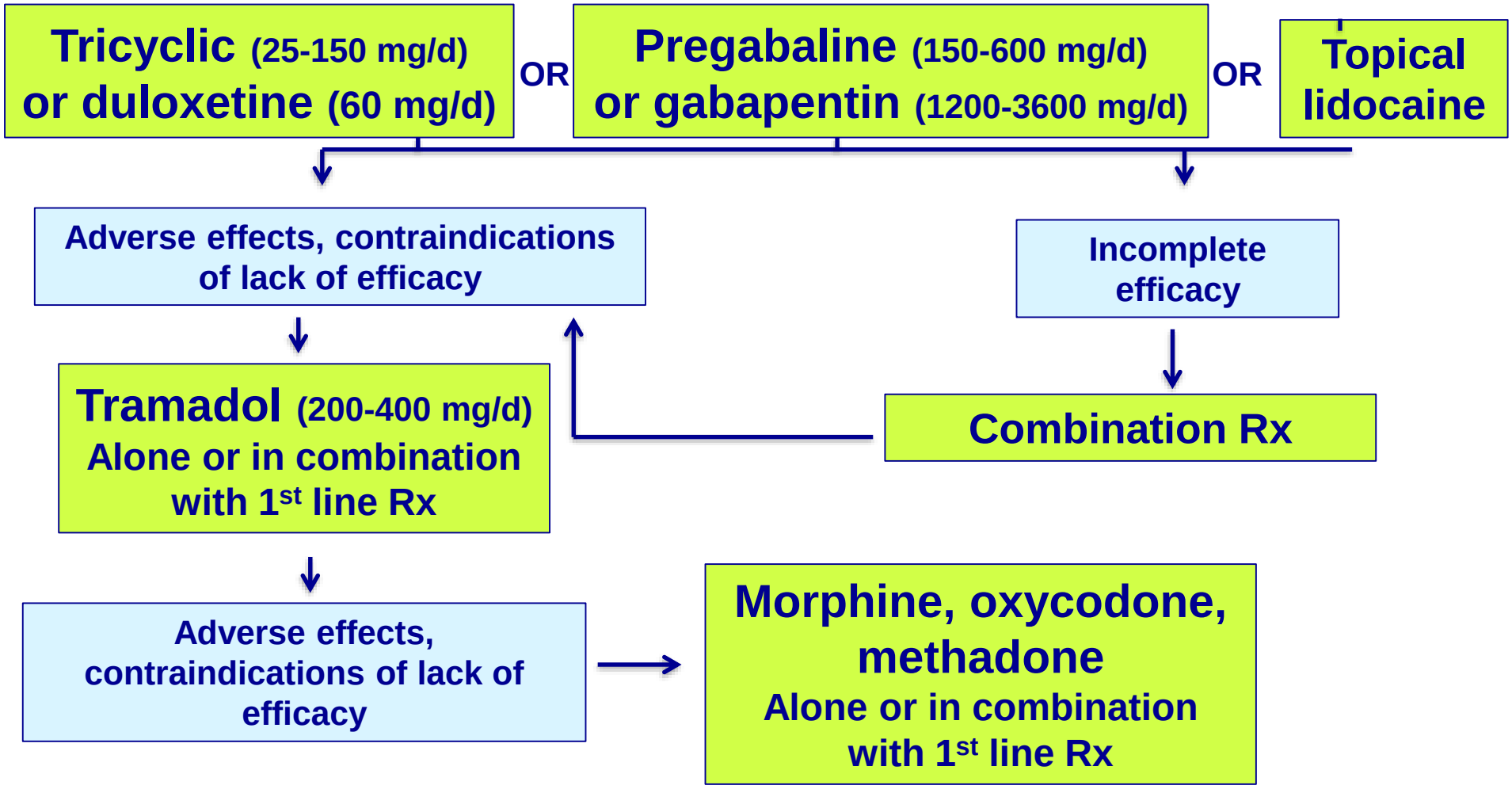
- "**Adjuvant**"
  - "Substance added to a medication to facilitate its action"
- "**Adjuvant analgesic**"
  - "Medication developed for an indication other than pain, but with analgesic properties in some circumstances"

(Lussier & Portenoy, 2003)

- Terms "adjuvant" and "coanalgesic" are obsolete and inappropriate
  - should be considered as "analgesics"

(Lussier & Beaulieu, 2010)

Neuropathic pain



Noradrenaline and serotonin reuptake inhibitors (NSRIs)

	Approved indications	Adverse effects	Interactions	Precautions
Duloxétine (Cymbalta®)	• Diabetic neuropathy • Fibromyalgia • Low back pain • Knee OA	• Nausea • Dizziness • Headache • Constipation • Fatigue • Somnolence	Numerous	• Adjust dose in renal failure • ↑ liver enzymes has been reported
Venlafaxine (Effexor®)		• Headache • Nausea • Somnolence • Sweating • High blood pressure		• Adjust dose in renal failure

Noradrenaline and serotonin reuptake inhibitors (NSRIs)

	Starting dose	Titration	Usual effective daily dose	Maximum daily dose	Delay to assess response
Duloxetine (Cymbalta®)	30 mg die	↑ to 60 mg die in 1-2 weeks	30-60 mg	60 mg	4 weeks
Venlafaxine (Effexor®)	37,5 mg die	75 mg q 1-2 w	37,5-150 mg	225 mg	4 weeks

Gabapentinoids

	Approved Indications	Adverse effects	Interactions	Precautions
Pregabalin (Lyrica®)	• Diabetic neuropathy • Post-herpetic neuralgia • Central neuropathic • Fibromyalgia	• Dizziness • Somnolence • Peripheral edema • Dry mouth • Ataxia • Weight gain • Confusion	None	• Adjust dose in renal failure • Caution if stage III-IV heart failure
Gabapentin (Neurontin®)			Antacids decrease absorption	

Gabapentinoids

	Starting dose	Titration	Usual effective daily dose	Maximum daily dose	Delay to assess response
Pregabalin (Lyrica®)	25-75 mg HS-bid	↑ q 3-7 days	150-300 mg	600 mg	3-4 weeks
Gabapentin (Neurontin®)	100-300 mg HS-tid	↑ par tranche 100 mg q 1-4 weeks	900-2400 mg	3600 mg	3-8 weeks

Other antidepressants

	Approved Indications	Adverse effects	Interactions	Precautions
Tricyclics/ tetracyclics **•amitriptyline** **•nortriptyline** **•desipramine**		**Central** •Fatigue •Sedation •↓ vigilance •Confusion **Peripheral** •Constipation •Blurry vision •Urinary retention •Tremors •Weight gain •Sexual dysfunction •Hypotension	Several	• Contraindicated if cardiac disorder (conduction, CAD, heart failure) or glaucoma • Risk of serotoninergic syndrome if associated to another antidepressant • **Avoid in older patients**
Bupropion (Wellbutrin®)		• Dizziness • Nausea • Somnolence • Headache	↓ seizure threshold if associated to another antidepresant	Contraindicated if feeding or seizure disorder

Other antidepressants

	Starting dose	Titration	Usual effective daily dose	Maximum daily dose	Delay to assess response
Tricyclics/ tetracyclics •amitriptyline •nortriptyline •desipramine	10 mg HS	↑ 10 mg q 3-7 jours	50-100 mg HS	150 mg	3-8 weeks
Bupropion (Wellbutrin®)	150 mg die	↑ to 300 mg after 2 weeks	150-300 mg	300 mg	4-6 weeks

Other anticonvulsants

	Approved Indications	Adverse effects	Interactions	Precautions
Carbamazepine (Tegretol®)		• Nausea • Fatigue • Somnolence	• Numerous	• Hepatiti • Stevens-Johnson syndrome • Bone marrow aplasia
Topiramate (Topamax®)				
Levetiracetam (Keppra®)				

Other anticonvulsivants

	Starting dose	Titration	Usual effective daily dose	Maximum daily dose	Delay to assess response
Carbamazepine (Tégrétol®)	50 mg die	100-200 mg/w	400-1200 mg (in 2-4 doses)	1200 mg	4 weeks
Topiramate (Topamax®)	15 mg bid	15-25 mg/w	200-400 mg (in 2 doses)	400 mg	
Levetiracetam (Keppra®)	250 mg bid	500 mg/d q 1-4 weeks	1000-3000 mg (in 2 doses)	3000 mg	

Other anticonvulsivants

	Approved Indications	Adverse effects	Interactions	Precautions
Oxcarbazepine (Trileptal®)		• Nausea • Fatigue • Somnolence	• Carbamazepine • Oxcarbazepine • Phenytoin • Valproic acid	
Lamotrigine (Lamictal®)				• Allergies • CNS effects • Skin reactions • Stevens-Johnson syndrome
Valproic acid				

Other anticonvulsivants

	Starting dose	Titration	Usual effective daily dose	Maximum daily dose	Delay to assess response
Oxcarbazepine (Trileptal®)	150 mg bid	300 mg/d q 1-4 w	900-1200 mg (in 2 doses)	2400 mg	4 weeks
Lamotrigine (Lamictal®)	25 mg bid	50 mg/d q 2-4 w	300-500 mg (in 2 doses)	500 mg	
Valproic acid	10-15 mg/k/j	5-10 mg/kg/d	1200-1800 mg (in 3 doses)	1800 mg (60 mg/k/d)	

Cannabinoids

	Approved Indications	Adverse effects	Interactions	Precautions
Nabilone (Cesamet®)		• ↓ concentration • Hypotension • CNS effects • Dry mouth • Dizziness	↑ effects of other CNS depressants	Caution in patients with psychiatric history
Dronabinol (Marinol®)				
Buccal THC/CBD (Sativex®)	• Multiple sclerosis • Cancer			

Cannabinoids

	Starting dose	Titration	Usual effective daily dose	Maximum daily dose	Delay to assess response
Nabilone (Cesamet®)	0,5-1 mg HS-bid	0,5-1 mg HS-bid q 1-4 w	1-2 mg HS	6 mg	2 weeks
Dronabinol (Marinol®)	2,5 mg bid	2,5 mg bid q 4 w		20 mg	
Buccal THC/CBD (Sativex®)	4 puffs	as tolerated	8 puffs (12 puffs q 4-6h)	12 puffs	

Cannabis

- 2 forms
  - **Cannabidiol (CBD)**
    - Anti-inflammatory and analgesic effects
  - **Tetrahydrocannabidiol (THC)**
    - Euphoric, dysphoric, antidepressive?, anxiolytic? effects

Cannabis

- **Administration routes**
  - Smoked
  - Inhaled
  - Oil
  - Gelule

- **Medical authorisation**
  - MD only authorizes use, does not prescribe it
  - Must be obtained from licensed producer

Cannabinoids

Summary of key statistics on the effectiveness of cannabinoids for chronic noncancer pain in randomised controlled trials.

Outcome	Pooled odds ratio (95% CI)	Pooled event rate (%), cannabinoid vs placebo	Number needed to treat to benefit (NNTB) (95% CI)
Pain outcomes			
30% reduction in pain	**1.46 (1.16-1.84)**	**29.0% vs 25.9%**	**24 (15-61)**
50% reduction in pain	1.43 (0.97-2.11)	18.2% vs 14.4%	*
Patient global impression of change			
Perceived "much" to "very much" improved	**1.62 (1.34-1.96)**	**18.9% vs 11.8%**	**38 (27-62)**
	Pooled odds ratio (95% CI)	**Pooled event rate (%), cannabinoid vs placebo**	**Number needed to treat to harm (NNTH) (95% CI)**
Adverse events			
All-cause adverse events	**2.33 (1.88-2.89)**	**81.2% vs 66.2%**	**6 (5-8)**
Study withdrawals—adverse events	**3.47 (2.64-4.56)**	**15.8% vs 4.6%**	**40 (35-49)**

Bold font indicates a statistically significant result. Only categorical outcomes with a moderate or higher GRADE rating are reported here.

Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies

Emily Stockings[a,*], Gabrielle Campbell[a], Wayne D. Hall[b,c], Suzanne Nielsen[a], Dino Zagic[a], Rakin Rahman[a], Bridin Murnion[d,e], Michael Farrell[a], Megan Weier[a], Louisa Degenhardt[a]

E. Stockings et al. • 159 (2018) 1932–1954 PAIN®

Cannabinoids

- "Seems unlikely that cannabinoids are highly effective medicines for chronic non-cancer pain"
- "Moderate to high-grade evidence supporting the use of nabiximols (Sativex®) to achieve modest reduction in pain as adjunctive therapy in multiple sclerosis-related pain"

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Cannabinoids

- "Minimal evidence that cannabinoids are effective improving other important domains in people with chronic non-cancer pain such as emotional and physical functioning"

- "Cannabinoids are unlikely to be a monotherapy for chonic non-cancer pain"

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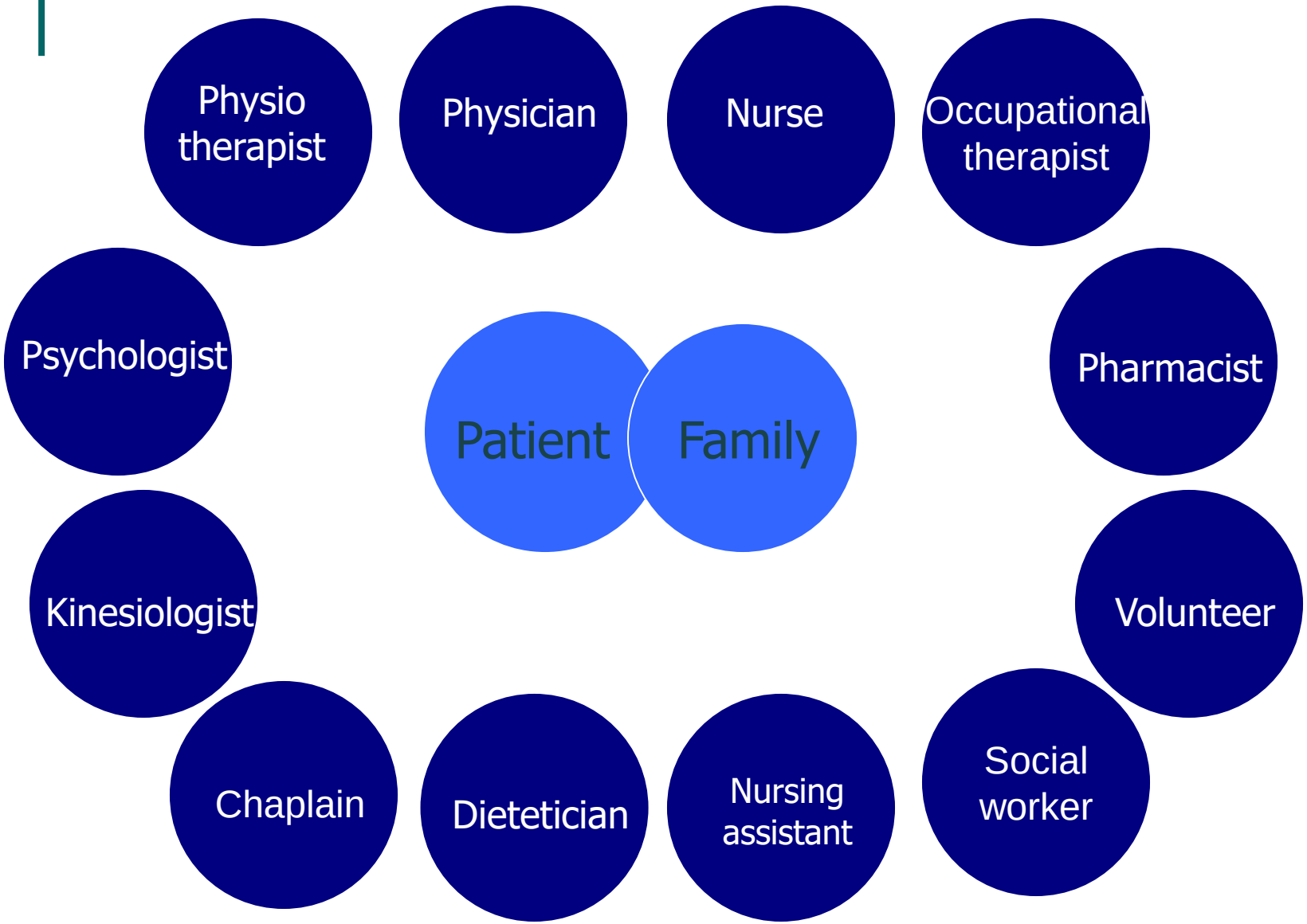
Interdisciplinary management



Conclusion

- Multimodal approach
- Favor medications with the best efficacy : adverse effects ratio
- Use several medications at small doses rather than one medication at high dose
- Treat comorbidities
  - Depression
  - Anxiety
  - Sleep impairment

Adapt the treatment to the patient