The Pharmacotherapy of Chronic Pain

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Mary Lynch MD

Pharmacology, Anesthesia, Perioperative Medicine & Pain Management, and Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada

Presenter Disclosures

Mary E Lynch

- Relationships with commercial interests:
  - Grant Research support: CIHR, InnovaCorp
  - Founding Member, President, Panag Pharm Inc.
  - Clinical trial: Cannimed
- Not-For-Profit Organizations:
  - Founding PI and Board Member, CCIC
  - Opioid committee Canadian Pain Society

Current Options for Management of Chronic Pain

- "Pain Management"
- Education
- Therapeutic exercise
- Psychological techniques
- Trials of modality based therapies
  - TENS
  - Acupuncture
- Complimentary Rx
  - Qigong
  - Osteopathy
- Pharmacotherapy
- NSAIDS
- Antidepressants
- Anticonvulsants
- Opioids
- Dual action (methadone, tramadol)
- Cannabinoids
- Topicals

Tricyclic and SNRI Antidepressants are Analgesic

- Over 40 RCTs in the literature
- Analgesic effect is independent of the antidepressant effect
- Analgesia occurs earlier and at lower doses than the antidepressant effect
- Effective in sharp, lancinating and chronic dysesthetic types of pain

Analgesic Antidepressants

ANALGESIC ANTIDEPRESSANTS											
DRUG	COMMON TRADE NAME	THERAPEUTIC RANGE FOR PAIN (MG/24H)	HALF-LIFE (H)	NEUROTRANSMITTER PROFILE		MOST COMMON SIDE EFFECTS (%)					
				NA	5HT	SEDATION	ORTHOSTATIC HYPOTENSION	WEIGHT GAIN	DRY MOUTH	CONSTI-PATION	GI DISTRESS NAUSEA DIARRHEA
TRICYCLICS											
amitriptyline	Elavil	10-150*	10-46	+++	+++	>30	>10	>30	>30	>10	>2
doxepin	Sinequan	10-150*	8-36	+++	++	>30	>10	>10	>30	>10	<2
trimipramine	Surmontil	10-150*	7-30	++	+	>30	>10	>10	>10	>10	<2
imipramine	Tofranil	10-150*	4-34	+++	+++	>10	>30	>10	>30	>10	>10
clomipramine	Anafranil	10-150*	17-37	+++	++++	>2	>10	>10	>30	>10	>10
desipramine	Norpramin	10-150*	12-76	+++++	++	>2	>2	>2	>10	>2	>2
nortriptyline	Aventyl	10-100*	13-88	++++	++	>2	>2	>2	>10	>10	<2
SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS											
venlafaxine	Effexor	37.5-225	3-7 (parent) 9-13 (metabolite)	++	++++	>10	>10	<2	>10	>10	>30
duloxetine	Cymbalta	60-120	10	++++	+++++	>10	<10	<2	>10	>10	>10

Anticonvulsants

- Good evidence for analgesic action in neuropathic pain
- On the basis of ability to ↓neuronal excitability "neuromodulators"
- Mechanisms of action vary among agents
  - Sodium or calcium channel blockade

Anticonvulsants

	Dose mg/day	Mech	Indication	SE	
Gabapentin	1200-3600 (1800-2400)	N-type voltage gated Ca++ blocker	PHN DN Mixed neuropathic	Dizziness Sedation Ataxia Confusion	Does not require metabolism in the liver
Pregabalin	150-600	N-type voltage gated Ca++ blocker	PHN DN FM Spinal cord injury	Dizziness Somnolence Nausea	Analgesic effect within 3 days, no liver metablism
Carbamazepine	200-2000 (400-800)	Na+ channel blocker	TN	Sedation Dizziness Rash	Do CBC and liver function
Lamotrigine	200-400	Na+ channel blocker	TN DN Post stroke pain Spinal cord injury	Mild rash to serious dermatologic reactions***	Do CBC and liver function
Oxcarbazepine *Ketoanalog of carbamazepine*	600-1200	Na+ channel blocker	TN	Sedation Headache Dizziness Rash	Do CBC and liver function
Topiramate (studies disappointing to date)	50-200	Na+ Ca++ channel blocker Potentiate GABA Blocks glutamate	Migraine prophylaxis (3 large negative trials in DN)	Paresthesia Fatigue Nausea Dizziness Ataxia Metab acidosis	Modest effect , only 1 less migraine per month in 3 large RCTs Monitor serum bicarb

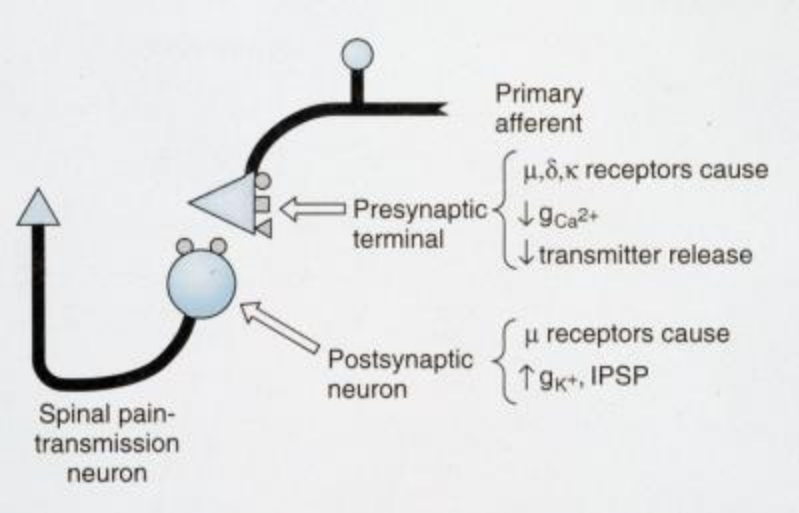
Anticonvulsants Summary

- Good when you suspect a neuropathic component, also approved for fibromyalgia
- Best evidence for gabapentin and pregabalin in PHN and DN
- Carbamazepine (maybe oxcarbazepine) is still best for treatment of trigeminal neuralgia
- Secondary role for Lamotrigine TN, DN

Opioids

- Critical in the management of acute and cancer pain
- Prevention of chronic pain
- Appropriate in 18% of people with chronic pain conditions

Opioids
Mechanism of Action



- Linked to G proteins (inhibit adenylyl cyclase activity)
- Close voltage gated Ca channels on presynaptic nerve terminals
  - ↓calcium influx
  - ↓neurotransmitter release
- Open K channels
  - Hyperpolarization
  - Decrease neuronal excitability
  - Inhibit postsynaptic neurons
- Overall effect is inhibitory

GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN

IMPROVING PRACTICE THROUGH RECOMMENDATIONS

CDC's Guideline for Prescribing Opioids for Chronic Pain is intended to improve communication between providers and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder and overdose. The Guideline is not intended for patients who are in active cancer treatment, palliative care, or end-of-life care.

DETERMINING WHEN TO INITIATE OR CONTINUE OPIOIDS FOR CHRONIC PAIN

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

CLINICAL REMINDERS

- Opioids are not first-line or routine therapy for chronic pain
- Establish and measure goals for pain and function
- Discuss benefits and risks and availability of nonopioid therapies with patient

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

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

Main editor

Jason Busse

Associate Professor, Department of Anesthesia
Associate Professor, Department of Health Research Methods, Evidence, and Impact
McMaster University, MDCL-2109
1280 Main St West, Hamilton, Ontario, Canada, L8S 4K1
bussejw@mcmaster.ca

National pain center

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"One Size Fits All" Doesn't Fit When It Comes to Long-Term Opioid Use for People with Chronic Pain

M. E. Lynch & J. Katz

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JAMA | Original Investigation

Opioids for Chronic Noncancer Pain
A Systematic Review and Meta-analysis

Jason W. Busse, DC, PhD; Li Wang, PhD; Mostafa Kamaleldin, MB BCh; Samantha Craigie, MSc; John J. Riva, DC, MSc; Sohail M. Mulla, PhD; Luciane C. Lopes, ScD, MSc; Nicole Vogel, PhD; Eric Chen, BHSc; Karin Kirmayr, MD; Kyle De Oliv Alka Kaushal, MBBS, DA; Luis E. Chaparro, MD; Inna Oyberman, MD; Amav Agarwal, MD; Rachel Couban, MA, MISt; Li Tommy Lam, MBBS; Per Olav Vandvik, MD, PhD; Sandy Hsu, BA; Malgorzata M. Bala, MD; Stefan Schandelmaier, MD; Sharil Ebrahim, PhD; Vahid Ashoorion, MD, PhD; Yasir Rehman, MD, MSc; Patrick J. Hong, BMSc; Stephanie Ross, PhD Regina Kunz, MD, MSc; Xin Sun, PhD; Norman Buckley, MD; Daniel I. Sessler, MD; Gordon H. Guyatt, MD, MSc

IMPORTANCE Harms and benefits of opioids for chronic noncancer pain remain unclear.

OBJECTIVE To systematically review randomized clinical trials (RCTs) of opioids for chronic noncancer pain.

DATA SOURCES AND STUDY SELECTION The databases of CENTRAL, CINAHL, EMBASE, MEDLINE, AMED, and PsycINFO were searched from inception to April 2018 for RCTs of opioids for chronic noncancer pain vs any nonopioid control.

DATA EXTRACTION AND SYNTHESIS Paired reviewers independently extracted data. The analyses used random-effects models and the Grading of Recommendations Assessment, Development and Evaluation to rate the quality of the evidence.

MAIN OUTCOMES AND MEASURES The primary outcomes were pain intensity (score range, 0-10 cm on a visual analog scale for pain; lower is better and the minimally important difference [MID] is 1 cm), physical functioning (score range, 0-100 points on the 36-item Short Form physical component score [SF-36 PCS]; higher is better and the MID is 5 points), and incidence of vomiting.

RESULTS Ninety-six RCTs including 26 169 participants (61% female; median age, 58 years [interquartile range, 51-61 years]) were included. Of the included studies, there were 25 trials of neuropathic pain, 32 trials of nociceptive pain, 33 trials of central sensitization (pain present in the absence of tissue damage), and 6 trials of mixed types of pain. Compared with placebo, opioid use was associated with reduced pain (weighted mean difference [WMD], −0.69 cm [95% CI, −0.82 to −0.56 cm] on a 10-cm visual analog scale for pain; modeled risk difference for achieving the MID, 11.9% [95% CI, 9.7% to 14.1%]), improved physical functioning (WMD, 2.04 points [95% CI, 1.41 to 2.68 points] on the 100-point SF-36 PCS; modeled risk difference for achieving the MID, 8.5% [95% CI, 5.9% to 11.2%]), and increased vomiting (5.9% with opioids vs 2.3% with placebo for trials that excluded patients with adverse events during a run-in period). Low- to moderate-quality evidence suggested similar associations of opioids with improvements in pain and physical functioning compared with nonsteroidal anti-inflammatory drugs (pain: WMD, −0.60 cm [95% CI, −1.54 to 0.34 cm]; physical functioning: WMD, −0.90 points [95% CI, −2.69 to 0.89 points]), tricyclic antidepressants (pain: WMD, −0.13 cm [95% CI, −0.99 to 0.74 cm]; physical functioning: WMD, −5.31 points [95% CI, −13.77 to 3.14 points]), and anticonvulsants (pain: WMD, −0.90 cm [95% CI, −1.65 to −0.14 cm]; physical functioning: WMD, 0.45 points [95% CI, −5.77 to 6.66 points]).

CONCLUSIONS AND RELEVANCE In this meta-analysis of RCTs of patients with chronic noncancer pain, evidence from high-quality studies showed that opioid use was associated with statistically significant but small improvements in pain and physical functioning, and increased risk of vomiting compared with placebo. Comparisons of opioids with nonopioid alternatives suggested that the benefit for pain and functioning may be similar, although the evidence was from studies of only low to moderate quality.

JAMA. 2018;320(23):2448-2460. doi:10.1001/jama.2018.18472

Opioids
For Chronic Non-cancer Pain
the Evidence:

- 96 RCTs involving 26,169 participants
- Evidence from high quality studies showed opioid use was associated with stat sig but small improvements in pain and physical functioning

Specific opioid agonists

- Phenanthrenes
  - Morphine, hydromorphone, oxycodone, codeine
- Phenylpiperidines
  - Fentanyl, sufentanyl, meperidine
- Phenylheptylamines
  - Methadone

Initiating a trial of opioid

- Which agent?
- Dosing:
  - Start low, go slow
  - Time contingent
  - Regular or long acting
  - Side effects:
    - Sedation
    - Constipation
    - Nausea, sweating,itching, swelling
    - Endocrine? HPG and HPA suppression, thyroid?

Adverse effects in context

- Addiction: In appropriately screened patients low risk
  - If no past history of substance use disorder low risk
  - Important to screen for risk and provide appropriate structure
    - Regular follow-up and documentation
    - If needed contracts, urine screening , daily dispensing

Liaison Committee on Pain and Addictions Definitions

Definitions Developed by Liaison Committee on Pain and Addiction (LCPA)

Term	
Addiction	A primary, chronic, neurobiologic disease, with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: • Impaired control over drug use • Compulsive use • Continued use despite harm • Craving
Physical dependence	A state of adaptation manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and /or administration of an antagonist
Tolerance	A state of adaptation in which exposure to the drug results in changes that result in a diminution of one or more of the drugs effects over time

Dual Action Opioids

- Tramadol
  - Weak opioid
  - Monoaminergic effects
- Methadone
  - Strong opioid
  - NMDA antagonist
  - Monoaminergic

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Combination pharmacotherapy for the treatment of fibromyalgia in adults

Cochrane Systematic Review - **Intervention** | Version published: 19 February 2018

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Joelle Thorpe | Bonnie Shum | R Andrew Moore | Philip J Wiffen | Ian Gilron

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- **RCTs of Combinations**
- Pregabalin+duloxetine in fibro, 2016
- Morphine +nortriptyline, 2015
- NTI+gabapentin in NP, 2009
- Morphine+gabapentin in NP, 2005

Topicals

NSAIDs	Pennsaid (diclofenac) Voltaren emugel
Capsaicin	Zostrix
TCA	Amitriptyline 2-4% & Ketamine (1-2%)
Cannabinoids	Topical A OTC Topical CBD/THC

Summary

- Pharmacotherapy should be used along with active strategies
- Medications for chronic pain
  - Acetaminophen and NSAIDS
  - Tricyclic and SNRI antidepressants
  - Anticonvulsants
    - gabapentin, pregabalin, carbamazepine
  - Opioids and Cannabinoids