Avoiding Medication Mayhem

Penny Miller, BSc.(Pharm.), M.A.
Senior Instructor, Faculty of Pharmaceutical Sciences and Department of Family Practice, UBC
Pharmacotherapeutic Consultant, Lifemark Health Chronic pain Program

Disclosure

I have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

Goal: Provide the clinician with practical information to support the medication management of patients with chronic pain.

Learning Objectives:

At the end of this session, the clinician will demonstrate improved abilities to:

1. Describe the rationale, efficacy, benefits and risks associated with non-steroidal anti-inflammatory agents, opioids, antidepressants and anticonvulsants in the treatment of chronic pain.
2. Identify appropriate combinations of medications.
3. Outline the important reasons for slow upward titrations and slow tapers off medications.
4. Discuss effective monitoring for the efficacy and side effects of drugs to meet the outcomes of increased functioning, improved sleep and reduced pain.

Case of Ben

45 y.o., construction worker

- Low back pain x 7 months after a fall at work
- Constant throbbing ache in low back
- Radiates down right buttock & thigh, at times

extends to right ankle (burning, shooting, electric pain)

- Pain level on good day 5/10, on bad day 8/10, average 7/10 (over past week)
- Sleep 3 hours nightly interrupted 3 times.
- Diagnosis: Lumbar radiculopathy (neuropathy with nerve root impingement) possibly due to L5/S1 disc bulge (MRI inconclusive for disc herniation)
- Sole wage earner with wife and 3 young children
- Pain and stress impacting negatively on interpersonal relationships, especially with his spouse
- Prior history of depression following loss of brother 5 years ago

Goals of the Clinical Assessment

- Achieve diagnosis of pain
- Identify underlying causes of neuropathy
- Identify comorbid conditions
- Evaluate psychosocial factors
- Evaluate functional status (activity levels)
- Set treatment goals
- Develop targeted treatment plan (based on history of prior treatment)
- Determine when to refer to specialist or multidisciplinary team (pain clinic)

Assessment Tools

Assessment of neuropathic pain

- Neuropathic Pain Questionnaire (NPQ)
- Leeds Assessment of Neuropathic S/SX(LANSS)
- Pain Diagnostic Questionnaire (DN4)

Assessment of Mood:

- Anxiety – GAD-7 score
- Depression – PHQ – 9 Score (Beck)
- Pain catastrophyzing – PCS score

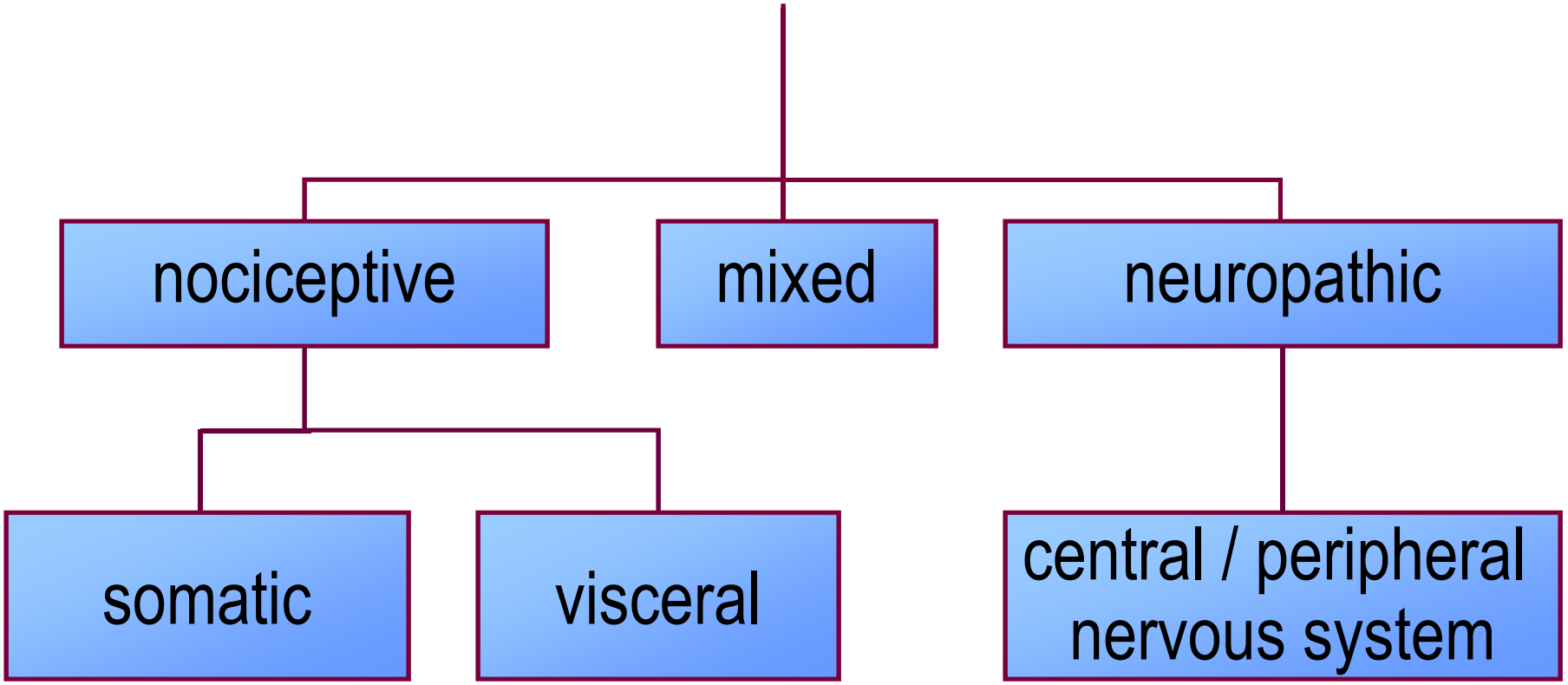
Assessment of pain interference:

- Brief pain inventory (BPI)

Case Study- Ben
Medication List

1. Arthrotec (diclofenac 75 mg/misoprostol 200 mg) one tablet twice daily
2. Aleve (naproxen sodium) 220 mg one tablet for headaches
3. Pantoprazole Mg (Tecta) 40 mg one tablet daily
4. Gabapentin 100 mg One capsule two to three times a day
5. Cyclobenzaprine 10 mg one tablet twice daily
6. Lorazepam 0.5 mg one tablet at bedtime
7. Tylenol #3 (Codeine, acetaminophen, caffeine) one tablet every 4 to 6 hours as required
8. Biofreeze (menthol 3.5%) topical once daily
9. Tadalafil (Cialis) 5 mg one daily as needed

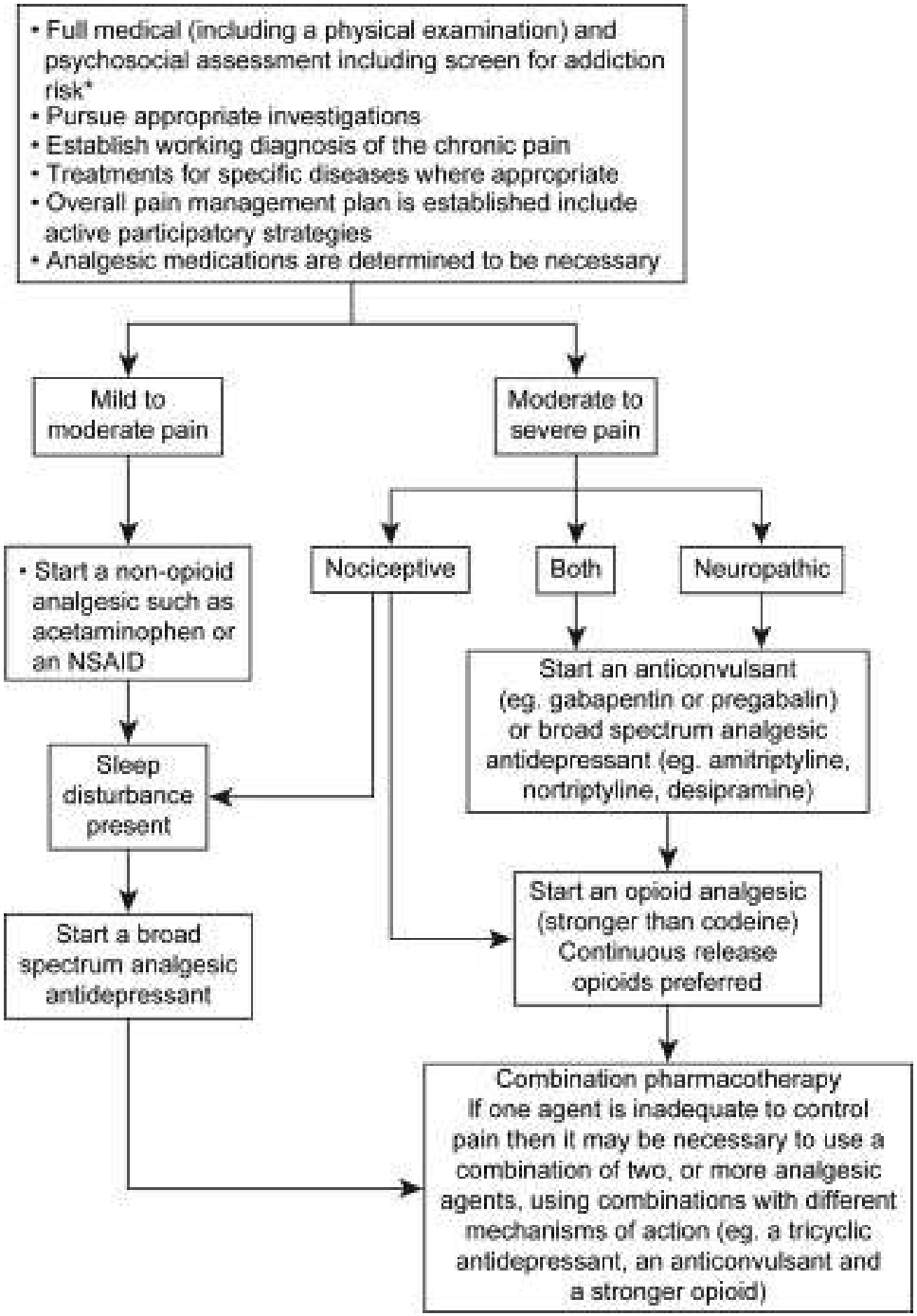
Types of Pain



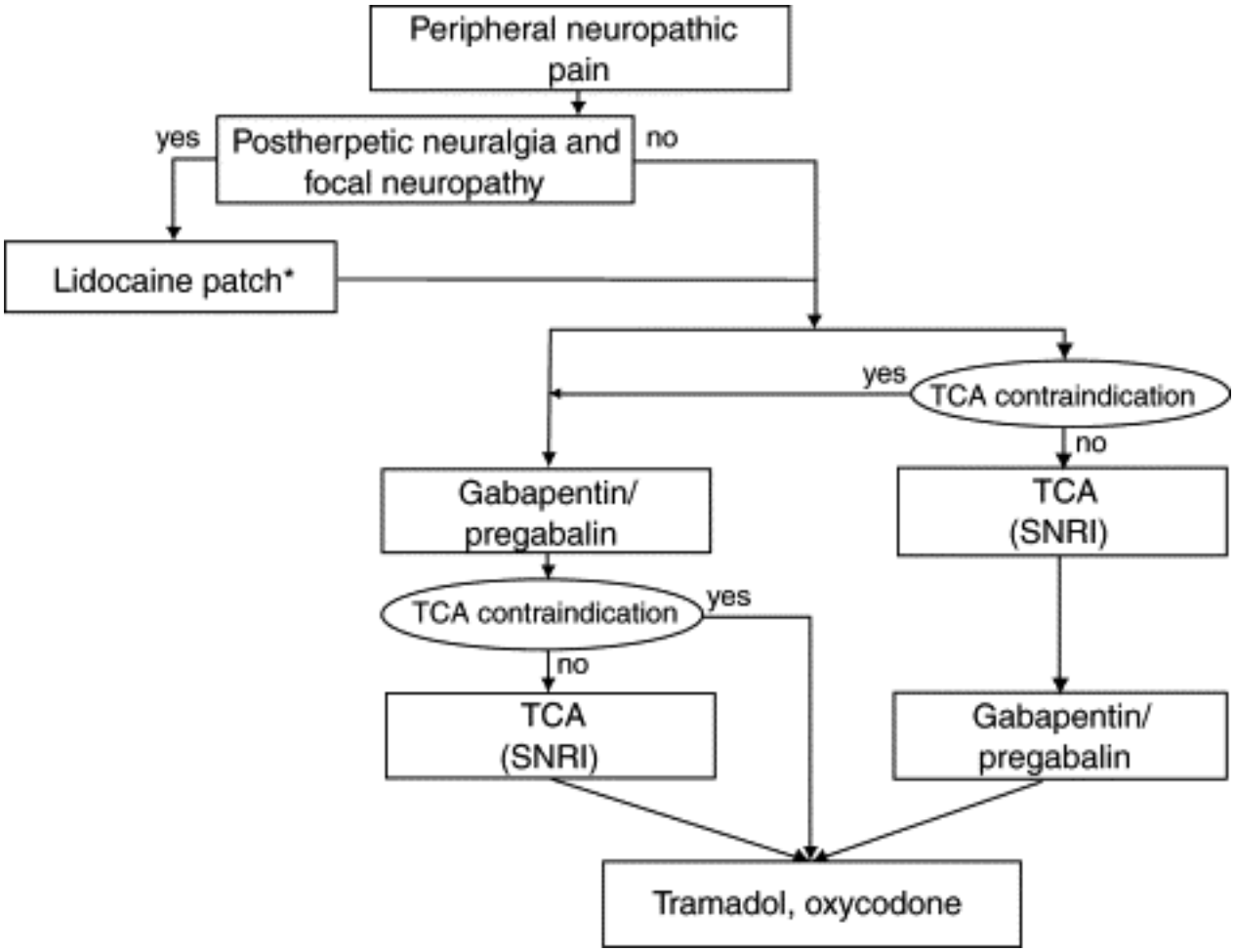
Pharmacologic agents to consider for neuropathic pain

- topical analgesics (capsaicin, *lidocaine 5% patch -USA*)
- anticonvulsants (gabapentin, pregabalin,lamotrigine)
- antidepressants (nortriptyline, desipramine)
- opioids (oxycodone, hydromorphone, morphine, codeine, tramadol)

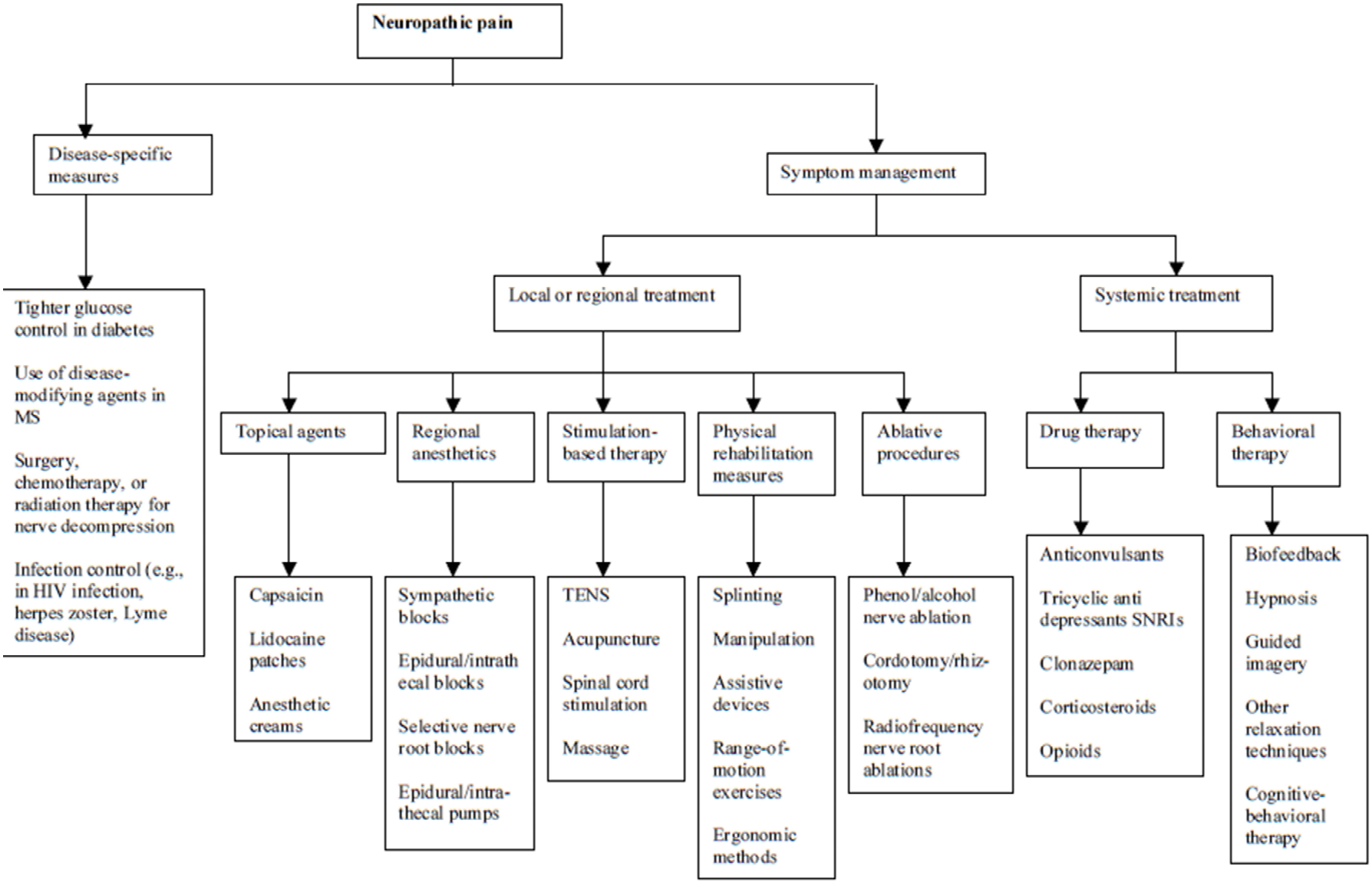
All are classes of agents with efficacy demonstrated in multiple, randomized, controlled trials for neuropathic pain


• Full medical (including a physical examination) and psychosocial assessment including screen for addiction risk*
• Pursue appropriate investigations
• Establish working diagnosis of the chronic pain
• Treatments for specific diseases where appropriate
• Overall pain management plan is established include active participatory strategies
• Analgesic medications are determined to be necessary
Mild to moderate pain
Moderate to severe pain
• Start a non-opioid analgesic such as acetaminophen or an NSAID
Nociceptive
Both
Neuropathic
Sleep disturbance present
Start an anticonvulsant (eg. gabapentin or pregabalin) or broad spectrum analgesic antidepressant (eg. amitriptyline, nortriptyline, desipramine)
Start a broad spectrum analgesic antidepressant
Start an opioid analgesic (stronger than codeine) Continuous release opioids preferred
Combination pharmacotherapy
If one agent is inadequate to control pain then it may be necessary to use a combination of two, or more analgesic agents, using combinations with different mechanisms of action (eg. a tricyclic antidepressant, an anticonvulsant and a stronger opioid)

Neuropathic pain algorithm

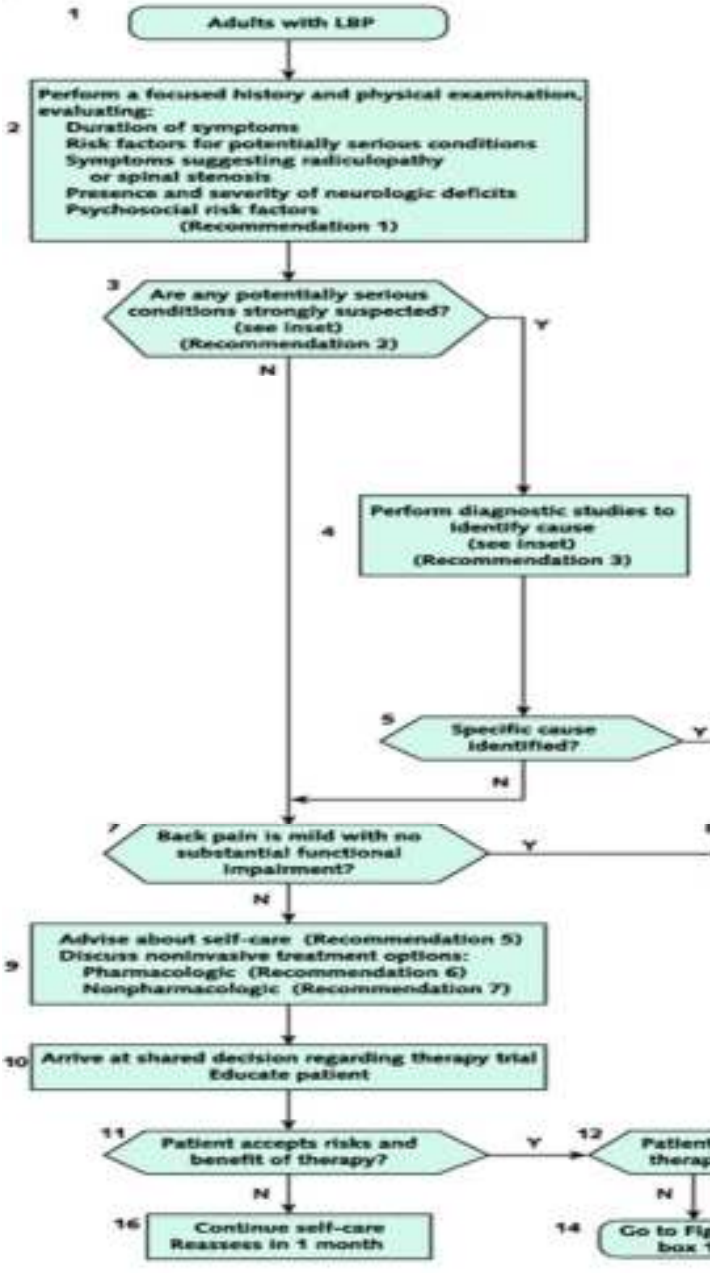


Appendix I – Neuropathic Pain Treatment Diag



ource: Belgrade, MJ. Following the clues to neuropathic pain. PostGraduate Medicine, 106(6), November 1999.

Annals of Internal Medicine

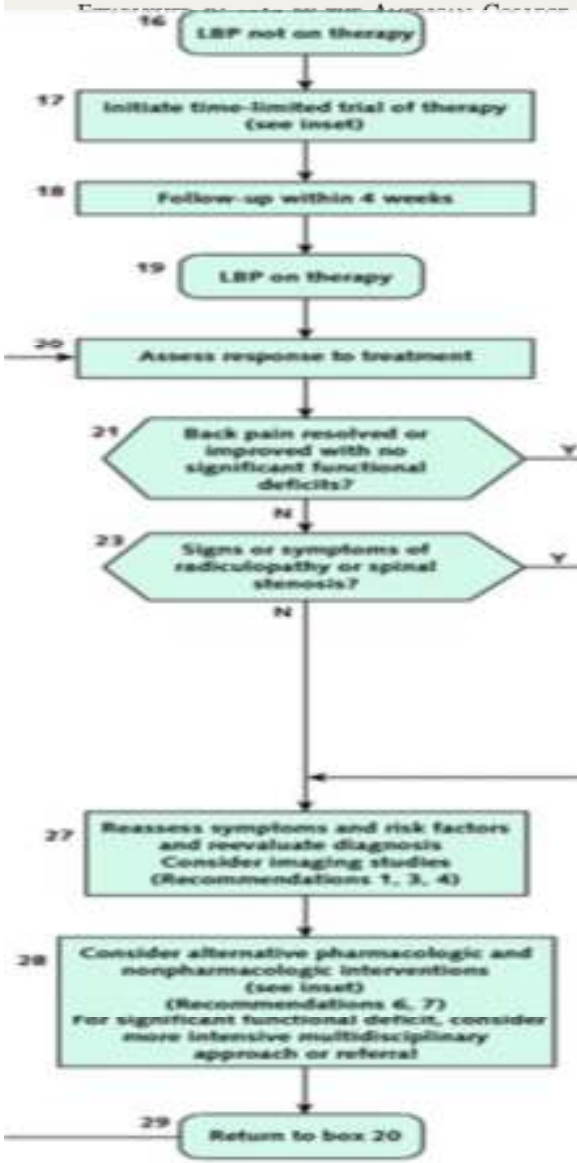


Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging*	Additional studies*
Cancer	History of cancer with new onset of LBP	MRI	ESR
	Unexplained weight loss Failure to improve after 1 month Age >50 years	Lumbosacral plain radiography	
	Multiple risk factors present	Plain radiography or MRI	
Vertebral infection	Fever Intravenous drug use Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	Urinary retention Motor deficits at multiple levels Fecal incontinence Saddle anesthesia	MRI	None
Vertebral compression fracture	History of osteoporosis Use of corticosteroids Older age	Lumbosacral plain radiography	None
Ankylosing spondylitis	Morning stiffness Improvement with exercise Alternating buttock pain Awakening due to back pain during the second part of the night Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Severe/ progressive neurologic deficits	Progressive motor weakness	MRI	Consider EMG/NCV
Herniated disc (Recommendation 4)	Back pain with leg pain in an L4, L5, or S1 nerve root distribution Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	Symptoms present >1 month	MRI	Consider EMG/NCV
Spinal stenosis (Recommendation 4)	Radiating leg pain Older age (Pseudoclaudication a weak predictor)	None	None
	Symptoms present >1 month	MRI	Consider EMG/NCV

*Level of evidence for diagnostic evaluation is variable.

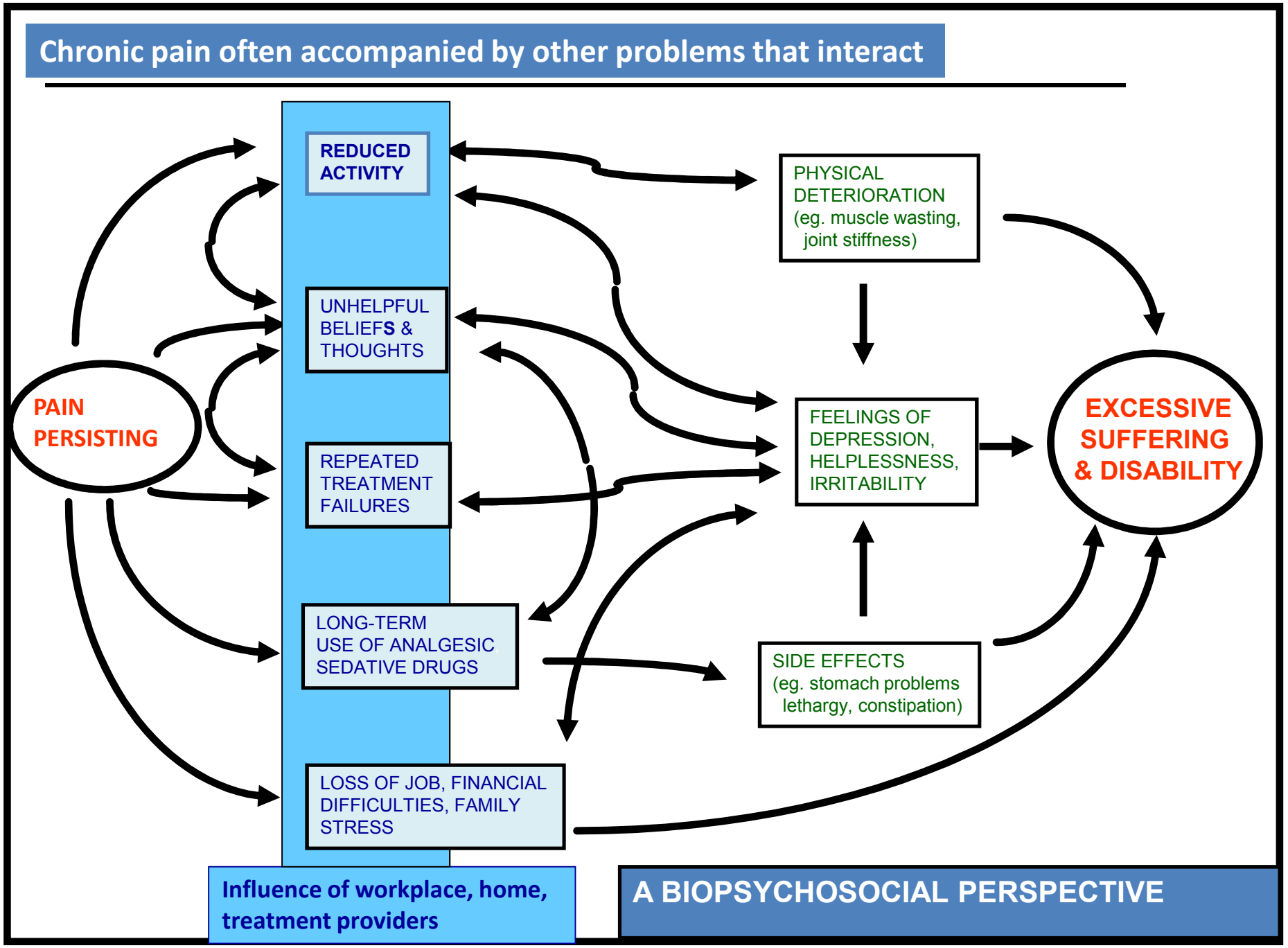
pain,
ate;



Interventions (Recommendations 5, 6, 7)

	Low Back Pain Duration	Acute < 4 Weeks	Subacute or Chronic > 4 Weeks
Self-care	Advice to remain active	•	•
	Books, handout	•	•
	Application of superficial heat	•	
Pharmacologic therapy	Acetaminophen	•	•
	NSAIDs	•	•
	Skeletal muscle relaxants	•	
	Antidepressants (TCA)		•
	Benzodiazepines	•	•
	Tramadol, opioids	•	•
Nonpharmacologic therapy	Spinal manipulation	•	•
	Exercise therapy		•
	Massage		•
	Acupuncture		•
	Yoga		•
	Cognitive-behavioral therapy		•
	Progressive relaxation		•
	Intensive interdisciplinary rehabilitation		•

• Interventions supported by grade B evidence (at least fair-quality evidence of moderate benefit, or small benefit but no significant harms, costs, or burdens). One intervention was supported by grade A evidence (good-quality evidence of substantial benefit).


Chronic pain often accompanied by other problems that interact
REDUCED ACTIVITY
UNHELPFUL BELIEFS & THOUGHTS
REPEATED TREATMENT FAILURES
LONG-TERM USE OF ANALGESIC SEDATIVE DRUGS
LOSS OF JOB, FINANCIAL DIFFICULTIES, FAMILY STRESS
PAIN PERSISTING
PHYSICAL DETERIORATION (eg. muscle wasting, joint stiffness)
FEELINGS OF DEPRESSION, HELPLESSNESS, IRRITABILITY
SIDE EFFECTS (eg. stomach problems lethargy, constipation)
EXCESSIVE SUFFERING & DISABILITY
Influence of workplace, home, treatment providers
A BIOPSYCHOSOCIAL PERSPECTIVE

Multimodal Therapeutic strategies for chronic pain and Associated disability

1. Pharmacotherapy

- **Opioids, nonopioids,**
- **adjuvant analgesics**

2.Physical Medicine and Rehabilitation

- **Assistive devices, electrotherapy**

3. Interventional Approaches

- **Injections, neurostimulation**

4. Psychological Support

- **Psychotherapy, group support**

5. Lifestyle Change

- Exercise, weight loss

6. Complementary and Alternative Medicine

Massage,supplements

- **Fine PG et al. *J Support Oncol*. 2004;2(suppl 4):5-22; Portenoy RK, et al. In: Lowinson JH, et al, eds. *Substance Abuse: A Comprehensive Textbook.* 4th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2005:863-903.**

Treatment Principles

- Select pharmacologic classes with efficacy demonstrated (ideally) in multiple RCTs
- Be aware that response will vary between patients
- Start with very low doses and titrate slowly
- If the medication is well tolerated, then continue to titrate to effective or acceptable pain relief
- Consider adding a second agent with a different mechanism of action if the first agent is providing partial relief yet pain remains > or = 4/10
- Consider side effects, drug interactions, cost and abuse potential
- Be aware of comorbidities such as depression, anxiety and insomnia
- Design a future plan to slowly taper off most medications for chronic pain
- Educate patients about their medications

Choosing Analgesics

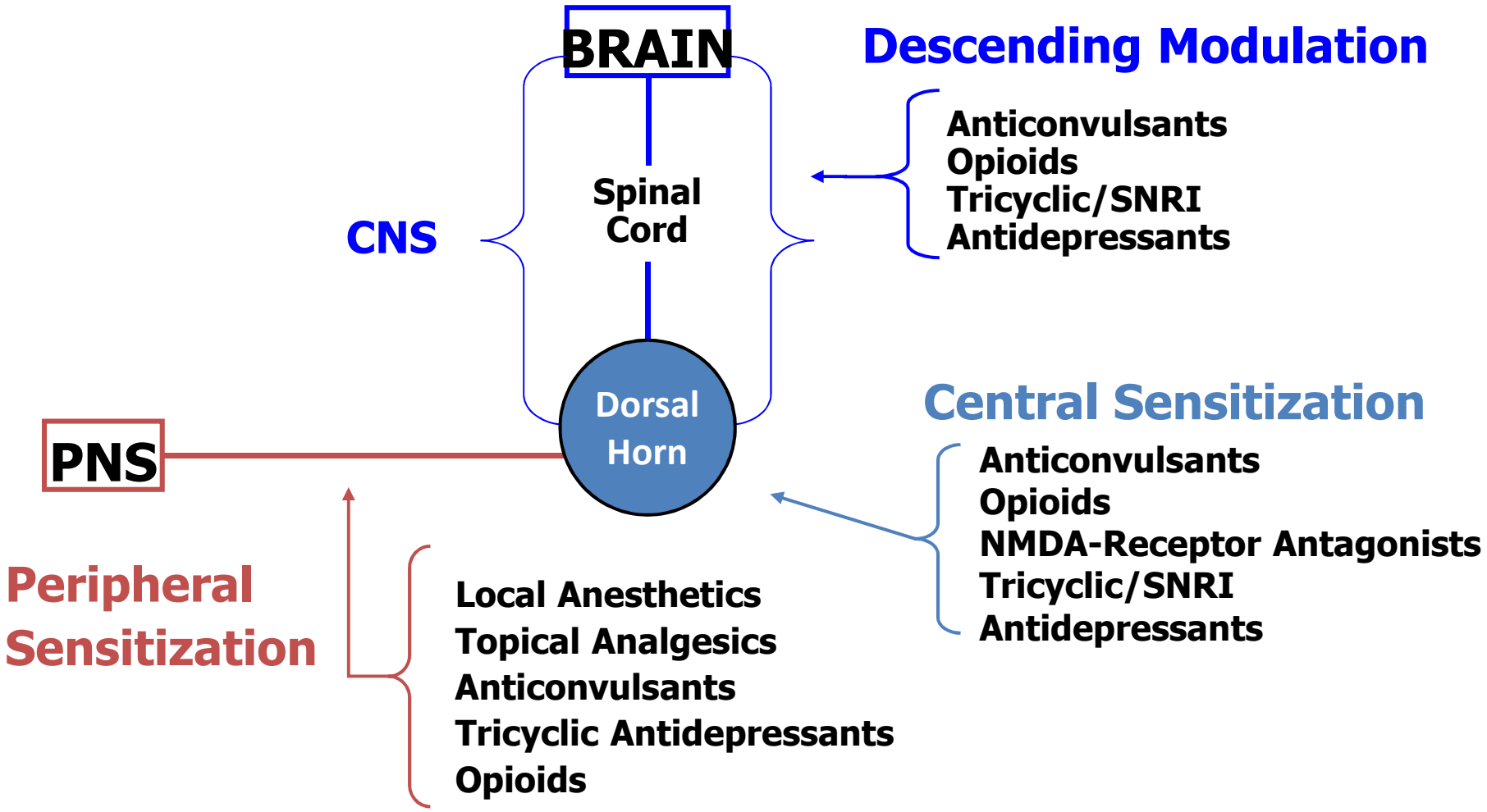
The choice of a pharmacologic agent is based upon the following factors:

- Indication/ type and intensity of pain
- Efficacy of agent for the specific indication(NNT)
- Safety and experience of the agent (NNH)
- Renal and hepatic function of patient
- Co-morbidities (e.g. constipation, cardiac disease)
- Drug interactions
- Cost
- Dosing Schedule
- Dosage forms (oral, topical, parenteral, etc.) & strengths available

NNT= numbers needed to treat

NNH- numbers needed to harm

Pharmacologic Agents Affect Pain Differently



Acetaminophen (*Tylenol®)*

Mechanism of Action: inhibits prostaglandin synthesis in CNS

- Analgesic, antipyretic (not anti-inflammatory)

Role in Therapy:

- Monotherapy for mild pain
- Combined with opioids and other adjuvants

Precautions:

- Hepatotoxic – liver disease, chronic and binge alcohol use
- Do not exceed 4 grams daily (avoid OTC combination products e.g. cough & cold, etc)

Advantages:

- No effect on platelet function or stomach lining

NSAIDs (Non-steroidal anti-inflammatory drugs)

Mechanism of action: Inhibit the synthesis of prostaglandin (cyclooxygenase- *COX*)

- anti-inflammatory, analgesic, antipyretic
- COX-2 selective or non-selective inhibitors

Role in Therapy:

- Monotherapy for mild to moderate pain
- Monotherapy for inflammatory conditions (osteoarthritis, rheumatoid arthritis, bursitis, tendonitis, gout, bony pain, low back pain)
- Combination therapy with opioids
- Also available topically (diclofenac), injectable

(ketorolac, ibuprofen)

NSAIDs

Precautions:

- **Gastrointestinal**- nausea, dyspepsia, GERD, erosions, ulcers, bleeding
  - Management: reduce dose or stop therapy; change to celecoxib; cytoprotective therapy with PPI or H2 antagonists, Helicobacter pylori eradication.
- **Renal toxicity** – hypertension, peripheral edema, CHF
- **Thrombosis** (cardiovascular events)-platelet effects
  - ASA 81 mg(low dose) is cardioprotective
  - Increased risk of MI and stroke with NSAIDs (especially Cox-2 selective inhibitors)
- **Allergies** – ASA-sensitive bronchospasm in asthmatics

Commonly used NSAIDs

Propionic Acids

- Naproxen (*Naprosyn®) 125 – 500 mg bid*
- Naproxen Na (*Aleve®) 220 – 440 mg bid*
- Ibuprofen (*Motrin®) 200 – 800 mg tid*

Phenylacetic Acid

- Diclofenac (*Voltaren®) 25 – 50 mg tid*

COXIB (COX-2 inhibitor)

- Celecoxib (*Celebrex®) 100 mg bid*

Carboxylic Acid

- Ketorolac *short term only* 10 mg qid (IM and po)

NSAID Monitoring

- Dyspepsia, GI complaints
- Stools (check for blood loss)
- Bruising or bleeding
- Blood pressure elevation
- Fluid status, edema (CHF)
- Renal function
- Potassium levels

Adjuvant Analgesics/ Co-analgesics
Anticonvulsants/Neuromodulators

Gabapentin (*Neurontin ®)* *NNT 4 NNH 26.1*

Mechanism of action: binds to presynaptic alpha-2- delta subunit of voltage-gated calcium channels in dorsal horn, which results in a decreased release of glutamate and substance P (excitatory neurotransmitters)

Role: a variety of neuropathic pain states (diabetic neuropathy, postherpetic neuralgia, mixed neuropathic states)

Adverse effects: sedation, ataxia, dizziness, visual blurring, memory impairment, confusion, peripheral edema

Dose: start at 100 mg at bedtime and increase slowly to 1800 – 3600 mg daily as tolerated (divided as three times daily)

- Adjust dose in renal impairment (clearance is decreased)
- Absorption variable with non-linear pharmacokinetics
  - Gabapentin 80% bioavailability with100 mg tid but 27% with 1600 mg tid

Gabapentin Dosing adjustments in Renal impairment (*Micromedex)*

CrCl (ml/min)	Dose
≥ 60	900 to 3600 mg per day given in three divided doses
30 – 59	400 to 1400 mg per day given in two divided doses
16 – 29	200 to 700 mg per day given once daily
15	100 to 300 mg given once daily
< 15	Reduce daily dose in proportion to the CrCl

*Gabapentin abrupt discontinuation and withdrawal symptoms

- Patients who have abruptly discontinued gabapentin have reported symptoms of anxiety, diaphoresis, irritability, agitation, confusion, tachycardia, myoclonus, and status epilepticus.
- The symptoms that have been associated with gabapentin withdrawal tend to mimic some of the same withdrawal symptoms associated with ethanol and benzodiazepine withdrawal, possibly because gabapentin augments GABA levels, as does ethanol and benzodiazepines. They are not relieved with benzodiazepines.
- http://www.medscape.com/viewarticle/722526_print

Adjuvant Analgesics/ Co-analgesics
Anticonvulsants/Neuromodulators

Pregabalin (*Lyrica ®) NNT 4.2 NNH 11.7*

- Similar to Gabapentin
- Linear pharmacokinetics (dose- response more predictable)
- Analgesic effect is seen within first week
- No generic products available
- **Dose**: start with 25 mg qhs and increase slowly as tolerated to 150 mg daily or 150 mg bid (Max 600 mg daily)
- **Taper to elimination to avoid seizures even with no history of convulsive disorder.**

Table 6. Dosage Adjustments of Pregabalin in Renal Impairment[1,25]

CrCl	*Total Pregabalin Daily Dose[a] (mg/day)*			*Dosing Regimen*
≥ 60 mL/min	150	300	600	Two or three times daily
30 to < 60 mL/min	75	150	300	Two or three times daily
15 to < 30 mL/min	25 to 50	75	150	Once or twice daily
< 15 mL/min	25	25 to 50	75	Once daily
Supplemental hemodialysis dose[b]	25 to 50 mg	50 to 75 mg	100 to 150 mg	

[a]Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

[b]The pregabalin daily dose should be based on residual renal function (eg, CrCl < 15 mL/min), with a supplemental dose administered immediately after each 4-hour hemodialysis session. Patients receiving 25 mg once daily should receive a supplemental dose of 25 or 50 mg, patients receiving 25 to 50 mg once daily should receive a supplemental dose of 50 or 75 mg, and patients on 75 mg once daily should receive a supplemental dose of 100 or 150 mg.

Hospital Pharmacy 2006;41:166

Adjuvant Analgesics/ Co-analgesics Anticonvulsants/Neuromodulators

- MONITORING:
  - Sedation
  - Dizziness
  - Cognitive side effects – word finding, memory
  - Ataxia, balance problems
  - Rash
  - Peripheral edema
  - (Aggression)

Anticonvulsant-
Risk of suicidal thoughts and behaviour

- Meta- analysis of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs (*antiepileptic drugs*) showed that patients randomized to one of the AEDs had approximately **twice the risk** (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomized to placebo.
- Evident as early as **1 week** after starting treatment
- 0.43% on AED versus 0.22% on placebo
- Risk is highest in Epileptic cases

Adjuvant analgesics/ Co-analgesics
Antidepressants

Tricyclic antidepressants (TCAs) *Average NNT 2.3 NNH 8.9*

Mechanism of action: inhibit the reuptake of norepinephrine and serotonin of descending pain pathway

Role in Therapy:

- Diabetic neuropathy, postherpetic neuralgia, central post-stroke pain, neuropathic pain, fibromyalgia, headache
- Useful in co-morbid conditions ie. insomnia, depression, anxiety
- Nortriptyline, Desipramine (secondary amines- greater Norepi reuptake inhibition) *NNT 2.6 NNH 20.4* preferred over amitriptyine (tertiary amine) *NNT 2.4 NNH 1.4* due to fewer side effects (*especially anticholinergic effects*)

Antidepressants/ TCAs

Adverse effects:

- Anticholinergic side effects (dry mouth, constipation, urinary retention, blurred vision, tachycardia, cognitive impairment)
- Sedation, postural hypotension
- Cardiac arrhythmias (especially in overdose)
- Weight gain

Precautions:

- Benign prostatic hypertrophy, closed angle glaucoma, CV disease
- Screening EKG for cardiac conduction abnormalities if > 40 yo)
- Risk of suicide by overdose

Dose: start with 10 mg at bedtime and titrate slowly

(analgesic response typically seen with 10 – 75 mg daily)

Effect of Combination drugs

- TCA + Codeine – TCA block hepatic cytochrome 2D6 isoenzyme so inhibit conversion of codeine to morphine (also, tramadol conversion to active metabolite)
- TCA +CNS depressants (alcohol, opioids)->sedation
- TCA + other anticholinergic – paralytic ileus
- TCA + SSRI (SNRI)or + Triptan= serotonin syndrome

Antidepressant (TCA) Monitoring

- Efficacy for improved sleep (immediate)
- Efficacy for improved pain control (1 -2 weeks

  Raskin et al *Pain Med 2005- Duloxetine*
- Pain benefit at therapeutic level is seen after 4 days of treatment.(Lynch,2006)
- Efficacy for improved mood (6 – 8 weeks)
- EKG baseline prior to initiation in patients over 40 years old
- Must taper off to avoid antidepressant discontinuation syndrome

Antidepressant Withdrawal (Discontinuation Syndrome)

"FINISH" Mnemonic

Flu-like symptoms	(e.g. chest discomfort, chills, fatigue, headache, malaise, myalgia, sweating)
Insomnia	(e.g. sleep disturbance including insomnia and nightmares)
Nausea	(e.g. gastrointestinal abdominal pain, diarrhea, anorexia)
Sensory disturbances	(e.g. neurologic such as tremor, akathisia, dizziness, dystonia, parathesia, **electric shock sensation**)
Hyperarousal	(e.g. psychiatric such as anxiety, aggressiveness, confusion, hallucinations, panic, hypomania)

Adjuvant analgesics/ Co-analgesics
Antidepressants- SNRI

SNRI- Serotonin- norepinephrine reuptake inhibitors

Mechanism of action: increase levels of norepinephrine (and serotonin) to stimulate the descending pain pathway

Duloxetine (*Cymbalta ®) NNT 5.2*

- Start at 15 mg once daily and titrate slowly up to 60 mg daily
- Dosage adjustment not necessary in renal dysfunction; caution with hepatic insufficiency

Venlafaxine *(Effexor ®) NNT 4.6*

- Start at 37.5 mg once daily and titrate slowly up to 150 mg (225 mg) daily
- Adverse effects: nausea, headaches, stimulation/sedation, sweating, increased blood pressure

  Minimal anticholinergic side effects

Other Antidepressants

- SSRIs (selective serotonin reuptake inhibitors)
  - NNT 6.7 Very weak Analgesic potential
- Bupropion (*Wellbutrin ®)* (dopamine/noradrenalin reuptake inhibitor) – single trial of analgesic benefit at 150 mg to 300 mg daily. No sexual dysfunction or weight gain. *Side effects*: insomnia, psychosis, seizures.
- Trazodone (serotonin-2 antagonist/reuptake inhibitor) – no analgesia. Very sedating so is useful as sleep aid. *Side effect*: priapism,rarely.

Serotonin Syndrome

Serotonin syndrome may occur with combinations of drugs affecting serotonin. Symptoms occur quickly within 24 hours when increasing doses or adding new drugs with serotonergic activity.

Signs and Symptoms

- restlessness
- confusion
- unsteadiness when walking
- fast heart beat
- increased body temperature (fever), shivering
- heavy sweating
- breathing quickly
- tremor
- muscle jerking
- rarely, convulsions

Treatment- should be immediate

Medications that may cause Serotonin Syndrome

Sleep and nerve pain medications		
Amitriptyline (Elavil)	Carbamazepine (Tegretol)	Desipramine (Norpramin)
Nortriptyline (Aventyl)	Trazodone (Desyrel)	Tryptophan (Tryptan)
Mood and anxiety medications		
Buspirone (Buspar)	Citalopram (Celexa)	Escitalopram (Cipralex)
Fluoxetine (Prozac)	Fluvoxamine (Luvox)	Lithium (Carbolith, Lithane)
Mirtazapine (Remeron)	Moclobemide (Manerix)	Sertraline (Zoloft)
St. John's wort	Venlafaxine (Effexor)	Buproprion (Wellbutrin)
Pain medications		
Meperidine (Demerol)	Methadone	Tramadol (Tramacet, Zytram XL)
Fentanyl (Duragesic)		
Migraine medications		
Naratriptan (Amerge)	Rizatriptan (Maxalt)	Sumatriptan (Imitrex)
Zolmitriptan (Zomig)	Eletriptan (Relpax)	Almotriptan (Axert)
Miscellaneous medications		
Dextroamphetamine (Dexedrine)	Dextromethorphan (e.g. Delsym, Robitussin DM, Benylin DM)	

Opioid Analgesics

Mechanism of action: bind to opioid receptors (mu, kapa, *delta*) present in CNS and periphery

- Alter the perception and emotional response to painful stimuli
- Pure opioid agonists, partial, mixed and antagonists

Role in therapy:

- Moderate to severe acute or chronic pain
- Cancer or non-cancer pain

Opioid use assessment Tools

1. To predict patient suitability for long term opioid use

Diagnosis, Interactability, Risk, Efficacy (D.I.R.E) score

2. To identify those at risk of opioid abuse prior to prescribing

- Opioid Risk Tool (ORT) - 5 questions
- Screener & Opioid Assessment for patients with pain (SOAPP) 5 – 24 questions
- Diagnosis, Interactability, Risk, Efficacy (D.I.R.E) score

3. To identify patients (already on opioids) who are abusing their opioid prescriptions:

- Current opioid misuse measure (COMM) -17 questions

High risk tend to have history of substance abuse, legal problems, medication craving, heavy smoking and/or mood swings.

Evidence for opioid efficacy in CNCP Canadian Guidelines McMaster

Effective in placebo controlled trials

- Diabetic neuropathy
- Peripheral neuropathy
- Postherpetic neuralgia
- Phantom limb pain
- Spinal cord injury with pain below level of injury
- Lumbar radiculopathy
- Osteoarthritis
- Rheumatoid arthritis
- Low back pain
- Neck pain

Not studied in placebo controlled trials

- Headache
- Irritable bowel syndrome
- Pelvic pain
- Temporomandibular jt dysfn
- Atypical facial pain
- Lyme disease
- Whiplash
- Repetitive strain injury

Evidence of opioid Efficacy Canadian Guidelines McMaster

- Nociceptive pain of musculoskeletal origin (e.g. low back pain, neck pain, osteoarthritis)
  - opioids **provide small to moderate** benefits in improving function & relieving pain.
  - Generally moderate doses are required (Use Tylenol, NSAIDs)
- Neuropathic pain
  - opioids **provide small to moderate** benefits in improving function & relieving pain.
  - Generally higher opioid doses are required (in combination with TCA or anticonvulsants.)

Opioid Analgesics

Adverse effects, Common:

- Respiratory depression
- Sedation
- Constipation, nausea, vomiting
- Dizziness
- Pruritis
- *Less Common*:
  - Endocrine abnormalities- decreased sex hormone levels
    erectile dysfunction, hypogonadism, amenorrhea
  - Neuropsychological effects – memory, cognition, decreased reaction times
  - Neurotoxicity (high dose opioids)

Opioids- Overdose

- **Signs of overdose**: slurred or drawling speech, emotional lability, ataxia, “nodding off” during conversation or activity.
- Patients at higher risk of overdose include: elderly, on benzodiazepines, renal or hepatic impairment, COPD, sleep apnea, sleep disorders and cognitive impaired.

Signs of opioid withdrawal seen with physical dependence

- Body aches, weakness, fatigue
- Diarrhea, Loss of appetite, Nausea/vomiting, Stomach cramps
- Goosebumps, Shivering, sweating
- Insomnia, irritability
- Runny nose, sneezing
- Tachycardia
- Uncontrollable yawning
- Fever

Treatment: clonidine 0.1 mg q 6 – 12 hours (*Clonidine is an α 2-adrenergic receptor agonist, that is effective at reducing the sympathetic nervous system hyperactivity)*

- The Opioid Manager is now available as an app from the Apple iTunes App store.

OPIOID MANAGER

The Opioid Manager is designed to be used as a point of care tool for providers prescribing opioids for chronic non cancer pain. It condenses key elements from the Canadian Opioid Guideline and can be used as a chart insert.

A Before You Write the First Script

Patient Name: _____

Pain Diagnosis: _____

Date of Onset: _____

Goals decided with patient:

_____

_____

_____

_____

_____

_____

_____

Initiation Checklist

	Y	N	Date
Are opioids indicated for this pain condition			
Explained potential benefits			
Explained adverse effects			
Explained risks			
Patient given information sheet			
Signed treatment agreement (as needed)			
Urine drug screening (as needed)			

Opioid Risk Tool

By Lynn R. Webster MD

Item (circle all that apply)	Item score if female	Item score if male
1. Family History of Substance Abuse:		
Alcohol	1	3
Illegal Drugs	2	3
Prescription Drugs	4	4
2. Personal History of Substance Abuse:		
Alcohol	3	3
Illegal Drugs	4	4
Prescription Drugs	5	5
3. Age (mark box if 16-45)	1	1
4. History of Preadolescent Sexual Abuse	3	0
5. Psychological Disease: Attention Deficit Disorder, Obsessive-Compulsive Disorder, or Bipolar, Schizophrenia	2	2
Depression	1	1
Total		

Total Score Risk Category:
Low Risk: 0 to 3, Moderate Risk: 4 to 7, High Risk: 8 and above

Overdose Risk

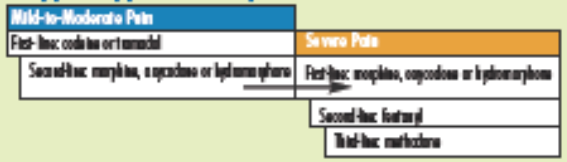
Patient Factors
- Elderly
- On benzodiazepines
- Renal impairment
- Hepatic impairment
- COPD
- Sleep apnea
- Sleep disorders
- Cognitive impairment

Provider Factors
- Incomplete assessments
- Rapid titration
- Combining opioids and sedating drugs
- Failure to monitor closely
- Insufficient information given to patient and/or relatives

Opioid Factors
- Codeine & Tramadol - lower risk
- CR formulations - higher dose than IR

Prevention
- Assess for Risk Factors
- Educate patients /families about risks & prevention
- Start low, titrate gradually, monitor frequently
- Careful with benzodiazepines
- Higher risk of overdose - reduce initial dose by 50%; titrate gradually
- Avoid parenteral routes
- Adolescents: addedy - may need concentration
- Watch for Misuse

Stepped Approach to Opioid Selection



B Initiation Trial

A closely monitored trial of opioid therapy is recommended before deciding whether a patient is prescribed opioids for long term use.

Suggested Initial Dose and Titration (Modified from Weaver M., 2007 and the e-CPS, 2008) Notes: The table is based on oral dosing for CINP. Brand names are shown if there are some distinct features about specific formulations. Reference to brand names as examples does not imply endorsement of any of these products. CR = controlled release, IR = immediate release, NA = not applicable, ASA: Acetylsalicylic Acid

Opioid	Initial dose	Minimum time interval for increase	Suggested dose increase	Minimum daily dose before converting IR to CR
Codeine (alone or in combination with acetaminophen or ASA)	15-30 mg q.4 h. as required	7 days	15-30 mg/day up to maximum of 600 mg/day (acetaminophen dose should not exceed 3.2 grams/day)	100 mg
CR Codeine	50 mg q.12 h.	2 days	50 mg/day up to maximum of 300 mg q.12 h.	NA
Tramadol (37.5 mg) + acetaminophen (325 mg)	1 tablet q.4-6 h. as needed up to 4/day	7 days	1-2 tab q. 4-6 h. as needed up to maximum 8 tablets/day	3 tablets
CR Tramadol	a) Zytram XL®: 150 mg q. 24 h. b) Tridural®: 100 mg q. 24 h. c) Ralivia®: 100 mg q. 24 h.	a) 7 days b) 2 days c) 5 days	Maximum dose: a) 400 mg/day b) 300 mg/day c) 300 mg/day	NA
IR Morphine	5-10 mg q. 4 h. as needed maximum 40 mg/day	7 days	5-10 mg/day	20-30 mg
CR Morphine	10-30 mg q.12 h. Kadian®: q.24 h. Kadian® should not be started in opioid-naive patients	Minimum 2 days, recommended: 14 days	5-10 mg/day	NA
IR Oxycodone	5-10 mg q. 4 h. as needed maximum 30 mg/day	7 days	5 mg/day	20 mg
CR Oxycodone	10-30 mg q.12 h. maximum 30 mg/day	Minimum 2 days, recommended: 14 days	10 mg/day	NA
IR Hydromorphone	1-2 mg q. 4-6 h. as needed maximum 8 mg/day	7 days	1-2 mg/day	6 mg
CR Hydromorphone	3 mg q. 12 h. maximum 9 mg/day	Minimum 2 days, recommended: 14 days	2-4 mg/day	NA

Initiation Trial Chart

		D / M / Y	D / M / Y	D / M / Y	D / M / Y
Date					
Opioid prescribed					
Daily dose					
Daily morphine equivalent					
	More than 200 (Watchful Dose > than 200)				
	Less than 200				
Goals achieved → Yes, No, Partially					
Pain intensity					
Functional status → Improved, No Change, Worsened					
Adverse effects	Nausea				
	Constipation				
0 = None 1 = Limits ADLs 2 = Prevents ADLs	Drowsiness				
	Dizziness/Vertigo				
	Dry skin/Pruritis				
	Vomiting				
	Other?				
Complications? (Reviewed: Y/N)					
Aberrant Behaviour (Reviewed: Y/N)					
Urine Drug Screening (Y/N)					
Other Medications					

To access the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain and to download the Opioid Manager visit https://nationalpaincentre.mcmaster.ca/opioid/

Feb 2011

C Maintenance & Monitoring

Morphine Equivalence Table

Opioid	Equivalent Doses (mg)	Conversion to MEQ
Morphine	30	1
Codeine	200	0.15
Oxycodone	20	1.5
Hydromorphone	6	5
Meperidine	300	0.1
Methadone & Tramadol	Dose Equivalents unreliable	
Transdermal fentanyl	60 – 134 mg morphine = 25 mcg/h 135 – 179 mg = 37 mcg/h 180 – 224 mg = 50 mcg/h 225 – 269 mg = 62 mcg/h 270 – 314 mg = 75 mcg/h 315 – 359 mg = 87 mcg/h 360 – 404 mg = 100 mcg/h	

Switching Opioids:	
If previous opioid dose was:	Then, SUGGESTED new opioid dose is:
High	50% or less of previous opioid (converted to morphine equivalent)
Moderate or low	60-75% of the previous opioid (converted to morphine equivalent)

Maintenance & Monitoring Chart

Date	D/M/Y	D/M/Y	D/M/Y	D/M/Y	D/M/Y	D/M/Y
Opioid prescribed						
Daily dose						
Daily morphine equivalent						
More than 200 (Watchful Dose > than 200)						
Less than 200						
Goals achieved → Yes, No, Partially						
Pain intensity						
Functional status → Improved, No Change, Worsened						
Adverse effects: Nausea						
Constipation						
Drowsiness						
Dizziness/Vertigo						
Dry skin/Pruritis						
Vomiting						
Other?						
Complications? (Reviewed: Y/N)						
Aberrant Behaviour (Reviewed: Y/N)						
Urine Drug Screening (Y/N)						
Other Medications						

0 = None
1 = Limits ADLs
2 = Prevents ADLs

D When is it time to Decrease the dose or Stop the Opioid completely?

When to stop opioids	Examples and Considerations
Pain Condition Resolved	Patient receives definitive treatment for condition. A trial of tapering is warranted to determine if the original pain condition has resolved.
Risks Outweighs Benefits	Overdose risk has increased. Clear evidence of diversion. Aberrant drug related behaviours have become apparent.
Adverse Effects Outweighs Benefits	Adverse effects impairs functioning below baseline level. Patient does not tolerate adverse effects.
Medical Complications	Medical complications have arisen (e.g. hypogonadism, sleep apnea, opioid induced hyperalgesia)
Opioid Not Effective	**Opioid effectiveness = improved function or at least 30% reduction in pain intensity** Pain and function remains unresponsive. Opioid being used to regulate mood rather than pain control. Periodic dose tapering or cessation of therapy should be considered to confirm opioid therapy effectiveness.

How to Stop – the essentials

How do I stop? The opioid should be tapered rather than abruptly discontinued.

How long will it take to stop the opioid? Tapers can usually be completed between 2 weeks to 4 months.

When do I need to be more cautious when tapering? Pregnancy:
Severe, acute opioid withdrawal has been associated with premature labour and spontaneous abortion.

How do I decrease the dose?
Decrease the dose by no more than 10% of the total daily dose every 1-2 weeks. Once one-third of the original dose is reached, decrease by 5% every 2-4 weeks. Avoid sedative-hypnotic drugs, especially benzodiazepines, during the taper.

Aberrant Drug Related Behaviour (Modified by Passik, Kirsh et al 2002).

Indicator	Examples
* Altering the route of delivery	• Injecting, linting or crushing oral formulations
* Accessing opioids from other sources	• Taking the drug from friends or relatives • Purchasing the drug from the "street" • Double-doctoring
Unsanctioned use	• Multiple unauthorized dose escalations • Binge rather than scheduled use
Drug seeking	• Recurrent prescription losses • Aggressive complaining about the need for higher doses • Harassing staff for faxed scripts or frequent appointments • Nothing else "works"
Repeated withdrawal symptoms	• Marked dysphoria, myalgias, GI symptoms, craving
Accompanying conditions	• Currently addicted to alcohol, cocaine, cannabis or other drugs • Underlying mood or anxiety disorders not responsive to treatment
Social features	• Deteriorating or poor social function • Concern expressed by family members
Views on the opioid medication	• Sometimes acknowledges being addicted • Strong resistance to tapering or switching opioids • May admit to mood-lowering effect • May acknowledge distressing withdrawal symptoms

* = behaviours more indicative of addiction than the others.

Mu and Kappa Receptor Activation

Response	Mu_1 (μ_1)	Mu_2 (μ_2)	Kappa
Analgesia	+++	++	+
Respiratory Depression		+	
Euphoria		+	
Dysphoria			+
Decrease GI motility		+	
Physical Dependence	+	+	
Miosis		+	+
Inhibition of ADH release			+

Receptor Binding at Mu receptor

Agonist	Morphine-like effect (e.g., heroin, weak binding except for Fentanyl)
Partial Agonist	Weak morphine-like effects with strong receptor affinity (e.g., buprenorphine)
Antagonists	No effect in absence of an opiate or opiate dependence (e.g., naltrexone)

Classes of Opioids

Phenanthrene Opioids

- Codeine
- Hydrocodone
- Hydromorphone
- Morphine
- Oxycodone
- (Oxymorphone)

NonphenanthreneOpioids

Piperidine Derivatives

- Fentanyl
- Meperidine
- Sufentanil

Other:

- Buprenorphine
- Methadone
- Tramadol
- Tapentadol

Opioids - Codeine

- 10 % caucasians cannot metabolize codeine to morphine for analgesic benefit (some are Super-metabolizers) (2D6 effects)
- Constipation is common and limits upper dosing of 350 mg daily.
- Combination products with acetaminophen and ASA, long acting and short acting products

Opioids-Morphine

- gold standard opioid
- Metabolism is complicated with several active metabolites that can accumulate (especially in renal impairment) to worsen nausea, sedation and CNS excitation
- Half-life of 2 – 4 hours
- Variety of dosage forms with short and long acting products

Opioids- Oxycodone

- Combined with acetaminophen or ASA
- Short and long acting products
- Presently high level of abuse
- Targets mu receptor and kappa receptors
- No active metabolites

ICIS. Org/pain

- **Black box warning on oxycodone**: the concomitant use of oxycodone hydrochloride controlled-release tablets with all **CYP3A4 inhibitors** such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole) and protease inhibitors (e.g., ritonavir) may result in an increase in oxycodone plasma concentrations and may cause potentially fatal respiratory depression. Patients receiving oxycodone controlled-release tablets and a CYP3A4inhibitors should be carefully monitored for an extended period of time and dose adjustment should be made if warranted.

Opioids - Hydromorphone

- No active metabolites
- Short and long acting products
- More potent than morphine (so lower doses used)

Opioids –Fentanyl (*Duragesic®)*

- Transdermal, parenteral
- Apply every three days to an opioid-tolerant patient (i.e. should have taken oral morphine 60 mg, oxycodone 30 mg , 8 mg hydromorphone for at least one week)
- Caution with elderly, cachectic or debilitated patients
- Need adequate subcutaneous tissue for absorption

Fentanyl patch

- Complicated pharmacokinetics making clinical switching and acute pain management difficult
- Onset of analgesia takes 12 hours
- Takes 24 hours to reach maximum effect
- Change patch every 72 hours
- Dosage change no earlier than six days on patch

- Suitable for stable pain only

Opioids - Buprenorphine

- Partial agonist of mu receptor, antagonist at kappa receptor
- Requires metabolism to an active analgesic
- Slow onset, poor oral bioavailability, extensive first pass metabolism
- highly bound to receptor so can displace morphine or other opioids to cause opioid withdrawal
- Ceiling effect – consider as a weak opioid
- Transdermal, oral, SL, Parenteral
- Transdermal – apply every 7 days; may be started at 5 mcg per hour in opioid-naïve patients.
- Dosage adjustments not required with renal or hepatic impairment.

- Butrans Patch 5, 10, 20 mcg/h

Methadone

- Supplied as a racemic mixture
  - L methadone is mu agonist
  - D methadone is NMDA receptor antagonist
- May have greater efficacy in neuropathic pain
- Half life variable but average is 24 hours – needs slow titration
- TID dosing needed for pain control
- Numerous, serious drug interactions
- Complicated pharmacokinetics (accumulation a problem)
- Most opioid-related deaths have been associated with methadone usage
- Requires a special licence in BC for use in chronic pain

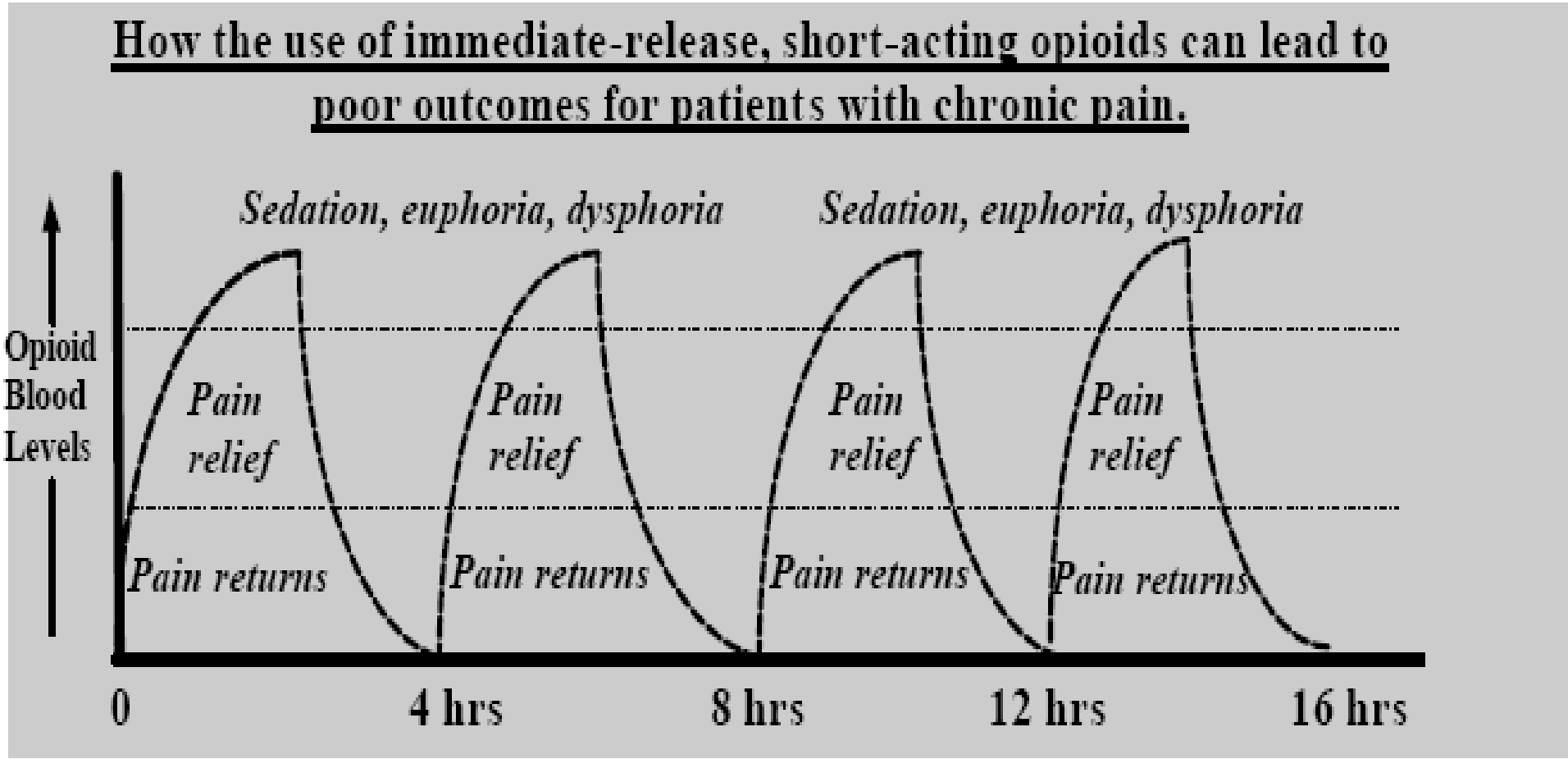
“Opioids/SNRI” – Tramadol; Tapentadol (*Nucynta)*

- Dual mechanism of action: inhibits reuptake of norepinephrine and serotonin plus opioid agonist
- Tramadol potency is about 1/3 that of morphine
- Tapentadol is more potent than tramadol
- Withdrawal reactions on discontinuation
- Caution in combination with SNRI, TCA, SSRI
- Lower seizure threshold

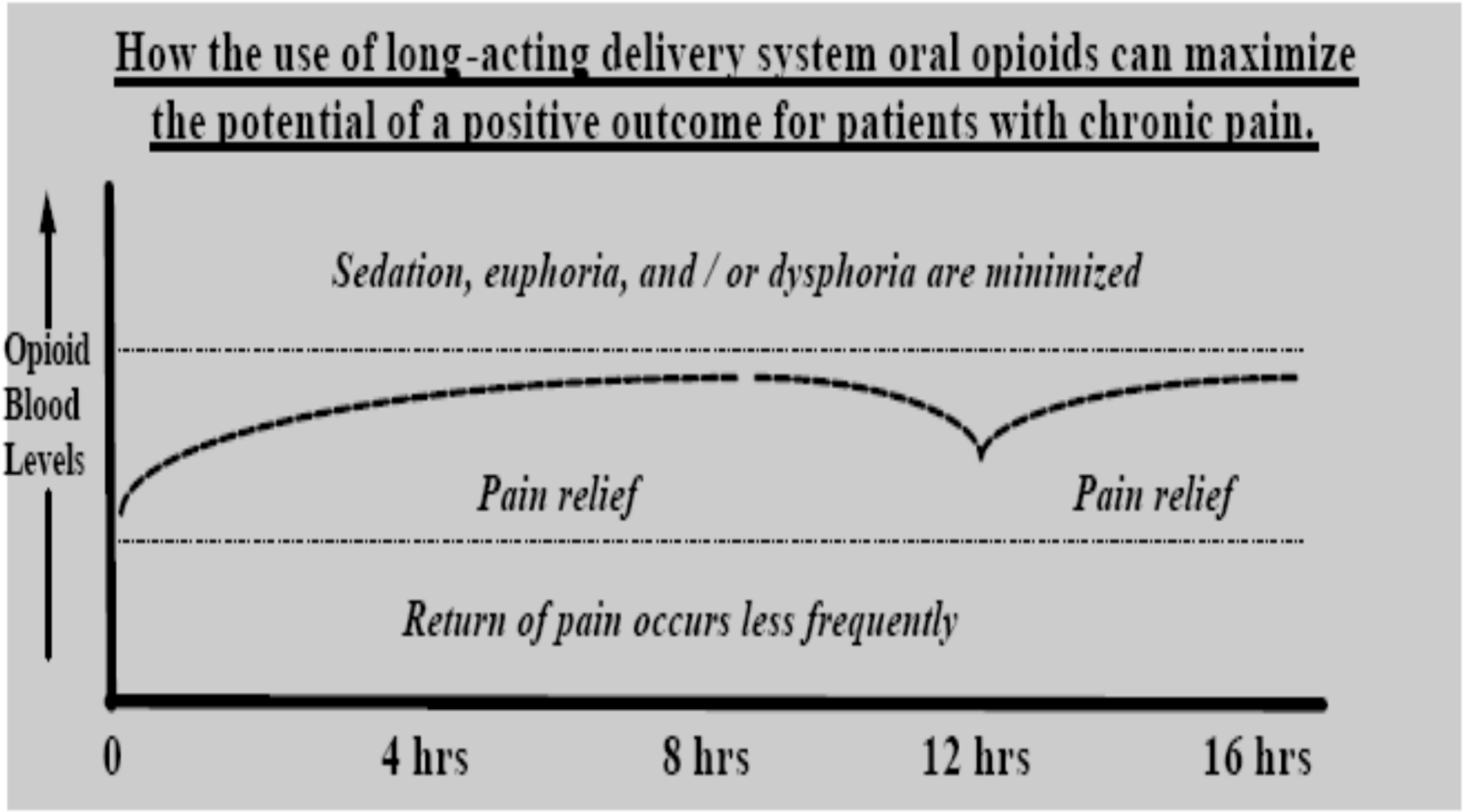
Opioids to avoid

- Meperidine (*Demerol ®)* – metabolite is a long acting inactive analgesic that accumulates to cause CNS excitation/seizures*;*
  - Very short duration of analgesic action 2 – 3 hours

Short acting opioids



Long acting opioids



Opioids for Chronic Non-cancer Pain Canadian Guidelines

1. What should be done prior to writing a prescription for opioids?

- Complete a thorough assessment of pain (DN4)
- Determine if opioids are indicated for this diagnosis
- Assess risk for opioid misuse or addiction (Opioid Risk Tool, CAGE, Urine screening)
- Set patient goals for pain reduction & functional improvement (these outcomes will measure opioid effectiveness)
- Ensure informed consent : review potential benefits, risks, adverse effects of opioid therapy
- Signed treatment agreement.

http://nationalpaincentre.mcmaster.ca/opioid/

Opioid Risk Tool

By Lynn R. Webster MD

Item (circle all that apply)	Item score if female	Item score if male
1. Family History of Substance Abuse:		
Alcohol	1	3
Illegal Drugs	2	3
Prescription Drugs	4	4
2. Personal History of Substance Abuse:		
Alcohol	3	3
Illegal Drugs	4	4
Prescription Drugs	5	5
3. Age (mark box if 16-45)	1	1
4. History of Preadolescent Sexual Abuse	3	0
5. Psychological Disease Attention Deficit Disorder, Obsessive-Compulsive Disorder, or Bipolar, Schizophrenia	2	2
Depression	1	1
Total		

Total Score Risk Category:

Low Risk: 0 to 3, Moderate Risk: 4 to 7, High Risk: 8 and above

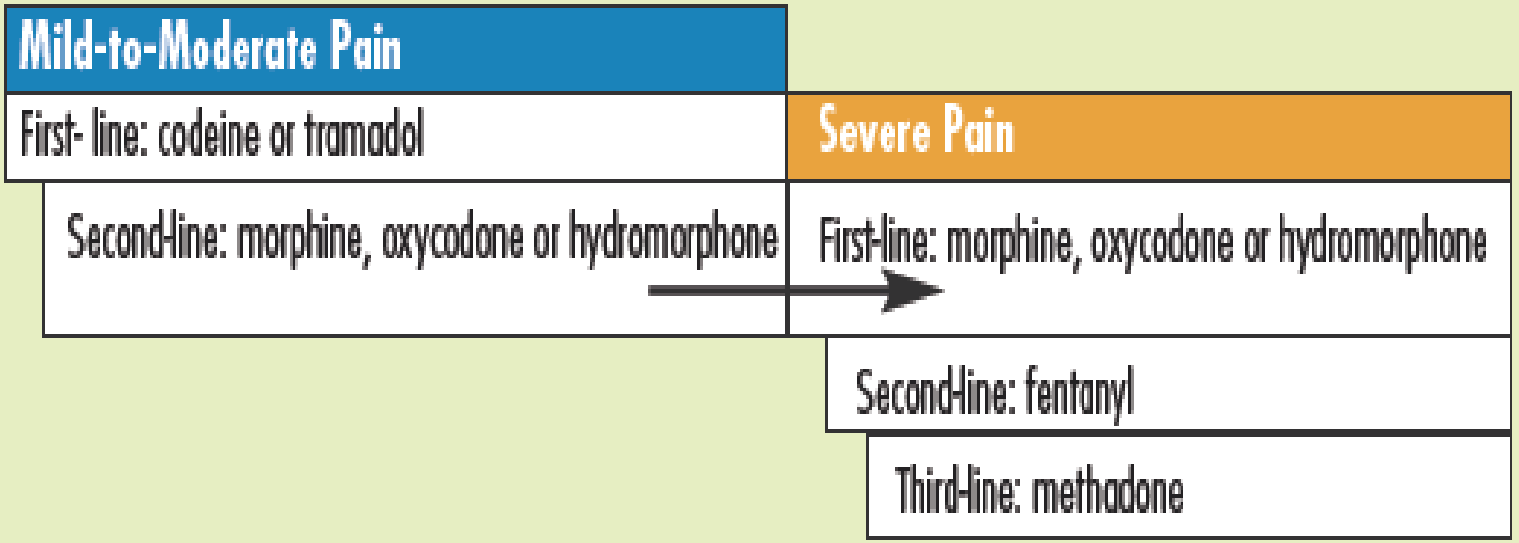
Opioids for Chronic Non-cancer Pain Canadian Guidelines

2. How should the opioid dosage be titrated?

- Start low, increase gradually while monitoring for improved function or pain reduction by 30%
- Track daily dose in morphine equivalents(< 200 mg daily). *Watchful dose.* Reassess if higher doses are needed.
- Optimal dose is reached when:
  - Function improved or pain reduced by at least 30%
  - Effectiveness has reached a plateau (no benefit with increased dose)
  - No major adverse effects or complications

http://nationalpaincentre.mcmaster.ca/opioid/

Stepped Approach to Opioid Selection



Morphine Equivalence Table

Opioid	Equivalent Doses (mg)	Conversion to MEQ
Morphine	30	1
Codeine	200	0.15
Oxycodone	20	1.5
Hydromorphone	6	5
Meperidine	300	0.1
Methadone & Tramadol	Dose Equivalents unreliable	
Transdermal fentanyl	60 – 134 mg morphine = 25 mcg/h 135 – 179 mg = 37 mcg/h 180 – 224 mg = 50 mcg/h 225 – 269 mg = 62 mcg/h 270 – 314 mg = 75 mcg/h 315 – 359 mg = 87 mcg/h 360 – 404 mg = 100 mcg/h	

Switching Opioids:	
If previous opioid dose was:	**Then, SUGGESTED new opioid dose is:**
High	50% or less of previous opioid (converted to morphine equivalent)
Moderate or low	60-75% of the previous opioid (converted to morphine equivalent)

Opioid converters when switching opiods. Allow for incomplete cross tolerance of the opioid so reduce the initial dose.

Apps: for I- Phone

- Opioid Converter (Opioid calculator by Dr. Cheryl Bernstein)

Computer:

http://www.globalrph.com/narcotic.cgi

- Also calculates varied Reduction for Incomplete cross tolerance

Opioid	Initial dose	Minimum time interval for increase	Suggested dose increase	Minimum daily dose before converting IR to CR
Codeine (alone or in combination with acetaminophen or ASA)	15-30 mg q.4 h. as required	7 days	15-30 mg/day up to maximum of 600 mg/day (acetaminophen dose should not exceed 3.2 grams/day)	100 mg
CR Codeine	50 mg q.12 h.	2 days	50 mg/day up to maximum of 300 mg q.12 h.	NA
Tramadol (37.5 mg) + acetaminophen (325 mg)	1 tablet q.4-6 h. as needed up to 4/day	7 days	1-2 tab q. 4-6 h. as needed up to maximum 8 tablets/day	3 tablets
CR Tramadol	a) Zytram XL®: 150 mg q. 24 h. b) Tridural™: 100 mg q. 24 h. c) Ralivia™: 100 mg q. 24 h.	a) 7 days b) 2 days c) 5 days	Maximum doses: a) 400 mg/day b) 300 mg/day c) 300 mg/day	NA
IR Morphine	5-10 mg q. 4 h. as needed maximum 40 mg/day	7 days	5-10 mg/day	20-30 mg
CR Morphine	10-30 mg q.12 h. Kadian®: q.24 h. Kadian® should not be started in opioid-naïve patients	Minimum 2 days, recommended: 14 days	5-10 mg/day	NA
IR Oxycodone	5-10 mg q. 6 h. as needed maximum 30 mg/day	7 days	5 mg/day	20 mg
CR Oxycodone	10-20 mg q.12 h. maximum 30 mg/day	Minimum 2 days, recommended: 14 days	10 mg/day	NA
IR Hydromorphone	1-2 mg q. 4-6 h. as needed maximum 8 mg/day	7 days	1-2 mg/day	6 mg
CR Hydromorphone	3 mg q. 12 h. maximum 9 mg/day	Minimum 2 days, recommended: 14 days	2-4 mg/day	NA

Opioids for Chronic Non-cancer Pain Canadian Guidelines

3. What should be done to ensure patient safety?

- Monitor : Use previously set goals for functional improvement and pain reduction to determine effectiveness of opioid *(Brief pain inventory) (Five A's- analgesia, adverse effects, activity ,adherence, aberrant behaviour)*
- Switch to different opioid if unacceptable adverse effects or insufficient effectiveness.
- Assess factors that could impair cognition or psychomotor ability (& driving ability)
- Watch for aberrant drug-related behaviours
- Refer for consultation if pain is unresponsive or addiction is suspected.
- Collaborate with pharmacist to improve patient education and safety

http://nationalpaincentre.mcmaster.ca/opioid/

Aberrant Drug Related Behaviour (Modified by Passik,Kirsh et al 2002).

Indicator	Examples
*Altering the route of delivery	• Injecting, biting or crushing oral formulations
*Accessing opioids from other sources	• Taking the drug from friends or relatives • Purchasing the drug from the "street" • Double-doctoring
Unsanctioned use	• Multiple unauthorized dose escalations • Binge rather than scheduled use
Drug seeking	• Recurrent prescription losses • Aggressive complaining about the need for higher doses • Harassing staff for faxed scripts or fit-in appointments • Nothing else "works"
Repeated withdrawal symptoms	• Marked dysphoria, myalgias, GI symptoms, craving
Accompanying conditions	• Currently addicted to alcohol, cocaine, cannabis or other drugs • Underlying mood or anxiety disorders not responsive to treatment
Social features	• Deteriorating or poor social function • Concern expressed by family members
Views on the opioid medication	• Sometimes acknowledges being addicted • Strong resistance to tapering or switching opioids • May admit to mood-leveling effect • May acknowledge distressing withdrawal symptoms

* = behaviours more indicative of addiction than the others.

Opioids for Chronic Non-cancer Pain Canadian Guidelines

4.**When should opioid therapy be stopped?**

- When opioid effectiveness is insufficient
- When adverse effects or risk outweighs benefit
- When medical complications have developed (e.g. sleep apnea, hypogonadism, opioid induced hyperalgesia)
- Use a tapering dose protocol to discontinue opioids

http://nationalpaincentre.mcmaster.ca/opioid/

Opioid Tapering Protocol

- Use controlled-release products for 24 hour coverage
- Decrease by 10% of total daily dose (ranging from every day to) every 1 to 2 weeks.
- Once one-third of original dose is reached, decrease by 5% every 2 to 4 weeks.
- Hold the dose when appropriate: The dose should be held or increased if the patient experiences severe withdrawal symptoms, a significant worsening of pain or mood, or reduced function during the taper
- Taper can usually be completed between *2 weeks*… to 4 months.

- http://nationalpaincentre.mcmaster.ca/opioid

Distinguishing between dependence, tolerance & addiction

- Physical dependence: withdrawal syndrome arises if drug discontinued, dose substantially reduced, or antagonist administered
- Tolerance: greater amount of drug needed to maintain therapeutic effect, or loss of effect over time
- Pseudoaddiction: behavior suggestive of addiction; caused by undertreatment of pain
- Addiction (psychological dependence): psychiatric disorder characterized by continued compulsive use of substance despite harm

How to convert opioids

1. Calculate total daily dose of opioid products
2. Convert dose to morphine
3. Convert morphine to opioid of choice
4. Individualize new dose

   -decrease daily amount by about 33% to account for cross tolerance

   -start daily amount as converted

   -slowly increase daily amount by 25- 30%

5. Follow up with patient within 3 to 10 days

6. If dose needs to be increased, increase daily long acting opioid by daily amount of PRN short acting opioid.

Clinical journal of Pain 2003;19:286-9

Combination Therapy

- In cases of partial but insufficient pain relief by a single drug, some combinations are more beneficial.
- Several placebo-controlled trials have confirmed the benefit of **gabapentin** *combined with* **nortriptyline** Lancet 2009;374:1252–61 or **morphine** N Engl J Med 2005;352:1324–34 versus monotherapy in a mixed group of patients with PDN and PHN, with either combination providing better efficacy at lower dosages without any increase in side effects

- In diabetic neuropathic pain, a combination of **gabapentin and oxycodone** was found superior to gabapentin alone.

  Eur J Pain 2008;12:804–13.

-

Muscle Relaxants

Systematic review (Cochrane Database Syst Rev. 2003;(2):CD004252)

- Only trials involving patients diagnosed with "nonspecific low back pain" were included[2]
- 30 trials included in review, 24 trials (80%) were on acute low back pain[2]
- Four trials studied benzodiazepines, 11 nonbenzodiazepines (including **cyclobenzaprine** and tinazidine), and 2 antispasticity muscle relaxants (including dantrolene) in comparison with placebo[2]
- The pooled relative risk for nonbenzodiazepines versus placebo after 2 to 4 days was 0.80 (95% confidence interval: 0.71 to 0.89) for pain relief and 0.49 (95% confidence interval: 0.25 to 0.95) for global efficacy[2]
- Adverse events were significantly more prevalent in patients receiving muscle relaxants and especially the central nervous system adverse effects (relative risk 2.04; 95% confidence interval: 1.23 to 3.37)[2]
- · The various muscle relaxants were found to be similar in performance[2]
- **REVIEWER'S CONCLUSIONS:**
- Muscle relaxants are effective in the management of non-specific low back pain, but the adverse effects require that they be used with caution. Trials are needed that evaluate if muscle relaxants are more effective than analgesics or non-steroidal anti-inflammatory drugs.

- **Acute treatment for 2 weeks.**

Skeletal muscle relaxants

- Pharmacotherapy. 2008 Feb;28(2):207-13.
- Skeletal muscle relaxants consist of both antispasticity and antispasmodic agents, a distinction prescribers often overlook. The antispasticity agents-baclofen, tizanidine, dantrolene, and diazepam-aid in improving muscle hypertonicity and involuntary jerks. Antispasmodic agents, such as cyclobenzaprine, are primarily used to treat musculoskeletal conditions. Much of the evidence from clinical trials regarding skeletal muscle relaxants is limited because of poor methodologic design, insensitive assessment methods, and small numbers of patients. Although trial results seem to support the use of these agents for their respective indications, efficacy data from comparator trials did not particularly favor one skeletal muscle relaxant over another. Therefore, the choice of a skeletal muscle relaxant should be based on its adverse-effect profile, tolerability, and cost.

Skeletal Muscle relaxants-combined with NSAIDs

- Skeletal muscle relaxants have also been studied as adjunctive therapy to analgesics in treating acute low back pain. In one open-label study (20 patients), the addition of cyclobenzaprine to naproxen (Naprosyn) resulted in a statistically significant decrease in muscle spasm and tenderness compared with naproxen alone.28 A Cochrane review analyzed three high-quality trials (560 total patients) that showed tizanidine plus analgesics was more effective in providing pain relief and decreasing muscle spasm than analgesics alone.17 Conversely, one low-quality open-label study (867 patients) comparing cyclobenzaprine alone (5 mg three times daily) versus combination with ibuprofen (Motrin; either 400 or 800 mg three times daily) showed that, although all groups improved at seven days, there was no statistical difference in outcomes among the groups.29 Nonetheless, the use of combination therapy has been supported in quickening recovery,17 with minimal overall risk of adverse effects (relative risk [RR] = 1.34; 95% confidence interval [CI], 0.67 to 2.67].20
- *Cochrane Database Syst Rev*. . 2003;(2):CD004252.

Topical -Menthol

Menthol generates analgesic activity through:

- Ca2+ channel blocking activity
- Binding to kappa opioid receptors
- Produces a cooling sensation; smells

J. Pain Symptom Manage, 33:342-55, 2007

Dermal Analgesics

Capsaicin(derivative of chili peppers)

Mechanism of action :Reduction in pain-related neuropeptides such as substance P, with blockade of afferent input.

Uses: Herpes Zoster, Diabetic neuropathy, osteoarthritis

NNT 5.7 (neuropathic pain) & 8.1 for MSK pain

Dosage: 0.025% or 0.075% cream (Zostrix) applied 4 times daily. Response occurs in 4-6 weeks.

SE: Burning sensation (80%) (may decrease with repeated applications)

Cannabinoids- third line treatments

- Nabilone (Cesamet)-(0.5, 1 mg) 1-2 mg bid
- Synthetic THC -Marinol (2.5, 5, 10) 5-10 mg bid
- THC extract (Sativex) buccal 2.7 mg bid
- Equivalent to codeine 60 – 120 mg daily (MS)
- Side effects: euphoria, anxiety, panic, paranoia, psychosis, sedation, dizziness, depression, ataxia, tachycardia, postural hypotension
- Evidence in MS and HIV neuropathies.
- Must apply for a license at:
- www.hc-sc.gc.ca/hecs-sesc/ocma/index.htm
- Also, see CMA Policy on Medical Marijuana 2011

Summary

- The complex task of pain management should be approached with a logical foundation:
  - A detailed history and physical
  - Any appropriate testing that can facilitate diagnosis and treatment
  - Establishment of realistic and desired common goals of further treatment and/or evaluation
  - Formulation of a treatment plan that includes a rational, evidence-based approach in the use and selection of medications
  - Flexibility in modification of treatment based on periodic re-assessment
  - Referral to a pain specialist when appropriate
  - **A trusting and caring relationship is an important imperative**

Key principles of care

Address the person's concerns and expectations when agreeing which treatments to use by discussing:

– benefits and possible adverse effects of each pharmacological treatment
– why a particular pharmacological treatment is being offered
– coping strategies for pain and for possible adverse effects of treatment
– that non-pharmacological treatments are also available

When selecting pharmacological treatments, take into account:

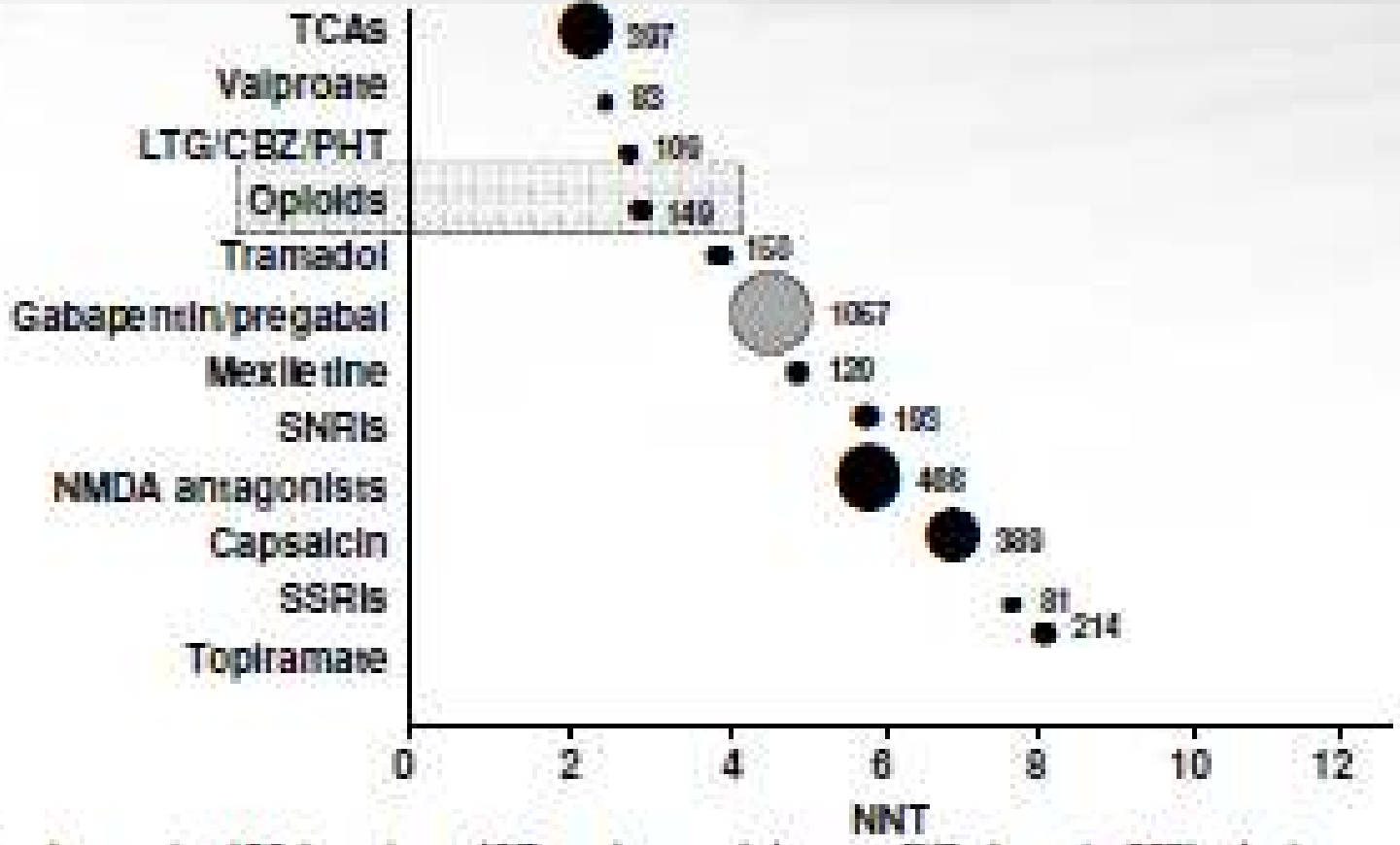
– the person's vulnerability to specific adverse effects because of comorbidities
– safety considerations and contraindications
– patient preference
– lifestyle factors (such as occupation)
– any mental health problems (such as depression and/or anxiety)
– any other medication the person is taking.

Explain both the importance of dosage titration and the titration process – provide written information if possible.

When withdrawing or switching treatment, taper the withdrawal regimen to take account of dosage and any discontinuation symptoms.

When introducing a new treatment, consider overlap with old treatments to avoid deterioration in pain control.

The NNT Map of Pharmacotherapy of Neuropathic Pain



CBZ, carbamazepine; LTG, lamotrigine; NNT, numbers needed to treat; PHT, phenytoin; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants. Finnerup NB et al. Pain. 2005;118:289-305. Finnerup NB et al. Pain. 2010;150:573-581.

- http://www.ashp.org/DocLibrary/MemberCenter/SHACCP/MCM08-Pain-Management-Workshop--Final-Handout.aspx
- Pocket guide

Opioid Induced Hyperalgesia OIH

- **Clinical features of opioid hyperalgesia:**
- *History*
  - Increasing sensitivity to pain stimuli (hyperalgesia).
  - Worsening pain despite increasing doses of opioids.
  - Pain that becomes more diffuse, extending beyond the distribution of pre-existing pain.
  - Can occur at any dose of opioid, but more commonly with high parenteral doses of morphine or hydromorphone and/or in the setting of renal failure.
- *Physical Examination*
  - Pain elicited from ordinarily non-painful stimuli, such as stroking skin with cotton (allodynia)
  - Presence of other opioid hyperexcitability effects: myoclonus, delirium or seizures

Opioid Induced Hyperalgesia OIH

- **Proposed mechanisms:**
- Toxic effect of opioid metabolites (e.g. morphine-3-glucuronide or hydromorphone-3-glucronide).
- Central sensitization as a result of opioid-related activation of N-methyl-D-aspartate (NMDA) receptors in the central nervous system.
- Increase in spinal dynorphin activity.
- Enhanced descending facilitation from the rostral ventromedial medulla.
- Activation of intracellular protein kinase C.

Opioid Induced Hyperalgesia OIH

- **Therapies:**
- Reduce or discontinue the current opioid.
- Change opioid to one with less risk of neurotoxic effects: fentanyl or methadone .
- Add an infusion of a non-opioid NMDA receptor antagonist such as ketamine .
- Add a non-opioid adjuvant such as acetaminophen or an NSAID.
- Initiate epidural, intrathecal, regional or local anesthesia and taper/discontinue systemic opioids.
- Increase hydration if clinically appropriate.

- http://www.eperc.mcw.edu/EPERC/FastFactsIndex/ff_142.htm

References for Opioid- induced Hyperalgesia

- Tompkins DA, Campbell CM. Opioid-induced hyperalgesia: Clinically relevant or extraneous research phenomenon? Curr Pain Headache Rep 2011; 15:129-136
- Lee M, Silverman S, Hansen H, et al. A comprehensive review of opioid-induced hyperalgesia. Pain Physician 2011;14:145-161.
- Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology 2006;104:570-87.

Guidelines - neuropathic pain

- Moulin et al. Pharmacological management of chronic neuropathic pain-consensus statement and guidelines from the **Canadian Pain Society**. Pain Res Manage 2007;12(1):13-21.
- R.H. Dworkin et al. Pain 2007; 132 : 237–251 IASP (**International Association for the Study of Pain**) Pharmacologic management of neuropathic pain: Evidence-based recommendations
- Attal et al. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2010; 17:1113-1123. (European Federation of Neurological Societies)

Other references

- Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, Kent JL, Krane EJ, Lebel AA, Levy RM, Mackey SC, Mayer J, Miaskowski C, Raja SN, Rice AS, Schmader KE, Stacey B, Stanos S, Treede RD, Turk DC, Walco GA, Wells CD. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc 2010;85(3 Suppl):S3–14.
- Attal N, Cruccu G, Haanpää M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P; EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006;13:1153–69.
- Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain 2010;150:573–81.

New products

- Tapentadol = Nucynta CR (50,100,150,200,250 mg)
- Hydromorphone prolonged release *Jurnista* (4,8,16,32 mg) once daily
- Oxycodone +naloxone *Targin for constipation*
- Buprenorphine + Naloxone (*Suboxone) 2, 8mg*
- Buprenorphine *Butrans Patch 5, 10, 20 mcg/h*
- *Naloxone (Narcan) nasal spray (30 ‘ duration)*

Tramadol – Chronic low back pain

- Cochrane Review of opioids (3 RCT; 914 patients, 150 – 240 mg /day for 1 – 3 months)
- Pain intensity reduced by 10.8 (0=100 scale)
- Function improved by 1.0 (0- 24 scale)

Cochrane Database of Systematic Reviews 2007, Issue 3. Ar.No.:CD004959. DOI:10.1002/14651858.CD004959.pub3

- Tramadol 50 mg qid vs Celecoxib 200 mg bid 52% vs 63% pain improvement
- And 13.4% and 10.6% withdrawal rates
- J Int Med Res 2009;37:1789-1802

Tramadol – neuropathic pain

- Cochrane Nov 2008- significant reduction
  - 5 RCT (tramadol 100 to 400 mg /day vs placebo) ; 374 patients; 4 to 6 weeks
  - NNT 3.8 (95% confidence interval 2.8 to 6.3) to reach 50% pain relief
  - NNH 8.3 (95% confidence interval 5.6 to 17)
- Comparative trials to morphine (40 patients) or clomipramine (21 patients)- insufficient data to draw conclusions of effectiveness
- (Canadian Pain Society Guidelines 2007 –
  - third line)

- Cochrane database of systematic reviews 2006, Issue 3. Art. No.:CD003726. DOI:10.1002/14651858.CD003726.pub3

Tramadol – Dosage titration

For moderate to moderately severe chronic pain not requiring rapid onset of analgesia.

Adults (17 +) 25 mg/day qam, then add separate 25 mg dose q3days to reach 25 mg qid. Then increase by 50 mg /day every 3 days to reach 50 mg qid. Max 400 mg/day

For rapid onset of analgesia (increased side effects):

50 to 100 mg q 4 to 6 hours (max 400 mg /day)

Extended-release 100 mg/day and increase by 100 mg every 5 days to max 300 mg/day

Tramadol - Dosing

- Elderly – maximum of 300 mg/day (regular release)
- Renal impairment – if CrCl<30 ml/min, then have 12 hour dosing interval and maximum 200 mg/day
- Hepatic impairment (Cirrhosis)
  - 50 mg q12 h (Extended release should not be used in severe hepatic impairment))

Tramadol Dependence

- Withdrawal (chronic use up to 400 mg): anxiety, restlessness, autonomic dysfunction, abdominal cramping, diarrhea, myoclonic activity of extremities (not entirely relieved with morphine)
- Am J Psychiatry 2004;161 (12):2326-27
- Stop gradually after long treatment periods

Tramadol Abuse potential

- Tramadol has 1/10 the analgesic potency of morphine but only 1/20 potency for subjective CNS effects J Clin Pharm Therap 2008;33:101-8.
- Chronic non-cancer pain Positive scoring on Abuse index within 12 months(11,352 patients)
  - Hydrocodone 4.9% ($p<0.01$)
  - Tramadol 2.7%
  - NSAIDs 2.5%

  J Pain Symptom Manage 2006;31:465-76
- Surveillance program (Ortho-McNeil Funded):
  - Over 3 years, 454 cases of abuse (1-3 cases per 100,000 pts)

  J. Fam Pract 2005;54:73.

Tramadol Side effects

- Mild Respiratory suppression (less than morphine)
- GI – constipation, nausea(40%), vomiting (20%), dry mouth
- CNS – drowsiness, dizziness, fatigue, headache, **seizures** < 1% (especially when combined with TCA, SSRI, MAOI, opioids, head trauma, past stroke)
- Urinary frequency or retention, diaphoresis, pruritis
- **Elderly are more sensitive to SE**

Pharmacotherapy 2000;20:1423-31 ; Clin Pharmacokin 2004;43:879-923

Tramadol- Adverse effects

- Serotonin syndrome combined with serotonergic agents:
  - Cognitive-behavioural changes
  - Neuromuscular hyperactivity
  - Marked rigidity
  - Rhabdomyolysis
  - Coma

Seizures are managed with benzodiazepines or barbiturates

AHFS Drug Information. ASHP 2006;2133-4

Tramadol in overdose

- Doses >500 mg
- Respiratory depression, CNS depression, hypertension, tachycardia, seizures, coma
- Naloxone does not reverse all of manifestations
- Mild Serotonin Syndrome – agitation, confusion,Tachycardia, hypertension
- Symptoms resolve within 24 hours

Tramadol-precautions

Use with caution in patients with:

- Renal and/or hepatic impairment
- Respiratory depression
- Seizure risk (SSRI, TCA, opioids)
- Concomitant CNS depressants (PTZ, sedatives, opioids, MAO I, alcohol)

Contraindicated

- History of seizure disorder

Tramadol- drug interactions

- CYP inducers – carbamazepine – see significant increase in tramadol metabolism
- CYP 2D6 inhibitors- fluoxetine, paroxetine, quinidine . See decreased conversion to active metabolite and perhaps decreased analgesia.

Tramadol Uses

- No more effective than combination opiate products for mild to moderate pain
- Not as effective as more potent analgesics for severe acute pain
- May be useful for chronic, moderate – to severe pain
- Best tolerated when dosage is slowly increased
- Watch interacting drugs and dosage
- May be misused