1. Pharmacotherapy: opioids, NSAIDs, adjuvants, and analgesic e...

Pharmacotherapy: opioids, NSAIDs, adjuvants, and analgesic equivalence

Ewan McNicol RPh, MSPREP
Tufts University

(c) 2007, Ewan D. McNicol, RPh.

2. Pharmacotherapy of Pain

Pharmacotherapy of Pain

Categories of analgesic drugs

- Opioid analgesics
- Nonopioid analgesics
- Adjuvant analgesics

(c) 2007, Ewan D. McNicol, RPh.
3. Mechanisms of Pain and Medication Activity Sites

4. Classes of analgesics

Choice of therapy dictated by
- Severity (WHO ladder)
- Source (nociceptive/neuropathic)
- Time course (chronic/acute)
- Patient’s age
- Comorbidities

(c) 2007, Ewan D. McNicol, RPh.
5. Severity: WHO analgesic ladder

(c) 2007, Ewan D. McNicol, RPh.

6. Pain Source

(c) 2007, Ewan D. McNicol, RPh.
7. Acute vs. chronic therapy

Acute vs. chronic therapy

Efficacy
Opioids: Effective for acute pain, may be less effective if administered chronically
NSAIDs: Effective for acute pain, need to be given at higher doses and for longer to reduce inflammation. Effectiveness may be reduced with chronic administration (tolerance?)
Adjuvants: Generally ineffective for acute pain

(c) 2007, Ewan D. McNicol, RPh.

8. Acute vs. chronic therapy

Acute vs. chronic therapy

Adverse effects:
Lessen with chronic therapy, e.g., opioid-related sedation
Increase with chronic therapy, e.g., NSAID-related ulceration
No change, e.g., opioid-related constipation

(c) 2007, Ewan D. McNicol, RPh.
9. Elderly Patients

Elderly Patients

- Reduced renal/hepatic function: reduce dose/frequency
- More susceptible to CNS adverse effects
- Beer's criteria:
  - Propoxyphene napsylate and acetaminophen, pentazocine, meperidine
  - Ketorolac, long-term NSAIDs
  - Muscle relaxants, amitriptyline, long acting benzodiazepines, clonidine
- Start low/go slow

10. Opioids

Opioids


(c) 2007, Ewan D. McNicol, RPh.
11. Positioning Opioid Therapy

Positioning Opioid Therapy

- Usually first-line therapy for:
  - Acute severe pain
  - Moderate to severe chronic pain related to cancer, AIDS, or life-threatening illness
- Use of long-term opioid therapy for diverse pain syndromes is increasing
  - Slowly growing evidence base
  - Acceptance by pain specialists


(c) 2007, Ewan D. McNicol, RPh.

12. Opioids: Mode of action

Opioids: Mode of action

- Opioid receptors found in ascending and descending pain pathways and in portions of the brain. Essential in pain-modulating system.
- Opioids bind to opioid receptors - mimic endorphins.

(c) 2007, Ewan D. McNicol, RPh.
13. Guidelines for Management of Opioid Therapy

Guidelines for Management of Opioid Therapy

- Comprehensive Assessment
- Drug selection
  - Age
  - Renal/hepatic function
  - individual differences/preferences
  - concurrent therapies
  - cost
- Route
- Likelihood of addiction/abuse/diversion

Sources:

(c) 2007, Ewan D. McNicol, RPh.

14. Opioid Agents

Opioid Agents

- Morphine-like agonists (oxycodone, codeine, hydromorphone, hydrocodone)
- Meperidine-like agonists (fentanyl)
- Methadone-like agonists (propoxyphene)
- Mixed agonist-antagonist
- Antagonists

(c) 2007, Ewan D. McNicol, RPh.
15. **Morphine**

- Still considered “Gold Standard” (WHO)
- Starting dose: 10 mg iv, 30 mg po, q3-4h
- Extensive first-pass metabolism
- Metabolites: M6G, M3G
- Reduce dose in renal failure
- Morphine sulfate controlled-release tablets, iv, MSIR, epidural (morphine sulfate extended-release liposome injection)

(c) 2007, Ewan D. McNicol, RPh.

16. **When to consider alternatives to morphine?**

- Allergy
- Lack of efficacy
- Development of intolerable side effects
- Change in patient status
- Practical considerations

(c) 2007, Ewan D. McNicol, RPh.
17. When to consider alternatives to morphine?

When to consider alternatives to morphine?

Allergy:
- Is it genuine? - often intolerable side effects
- If genuine, do not use drug from same class (hydromorphone, codeine, hydrocodone, oxycodone)

(c) 2007, Ewan D. McNicol, RPh.

18. When to consider alternatives to morphine?

When to consider alternatives to morphine?

Lack of efficacy:
- Often tied to intolerable side effects
- Try another drug from same class or from different class (fentanyl, methadone)

(c) 2007, Ewan D. McNicol, RPh.
19. When to consider alternatives to morphine?

When to consider alternatives to morphine?

Intolerable side effects:
- Not much evidence of differences in side effect profiles amongst opioids
- Nausea - hydromorphone, oxycodone lower?
- Hallucinations - oxycodone less?
- Constipation - fentanyl less?
- Hemodynamic effects - fentanyl less?

(c) 2007, Ewan D. McNicol, RPh.

20. When to consider alternatives to morphine?

When to consider alternatives to morphine?

Change in patient status:
- Renal dysfunction - reduce dose/frequency or switch to drug with lower risk of toxic metabolites (hydromorphone, methadone)
- Unable to swallow - consider fentanyl patch

(c) 2007, Ewan D. McNicol, RPh.
21. When to consider alternatives to morphine?

Practical considerations
- Cost - morphine cheap, but methadone cheaper
- Preference - within reason!
- Quicker onset/shorter action - e.g., for procedural pain: fentanyl (meperidine?)

(c) 2007, Ewan D. McNicol, RPh.

22. Transdermal Fentanyl

- Systemic concentrations reached within 12 hours post application - use a short-acting opioid during the first 8 to 12 hours after initial application
- Available in 12-100 mcg/hr patches
- Patches changed every 48-72 hrs
- Increased absorption with increased temp
- Contraindication: Doses exceeding 25 mcg at the initiation of opioid therapy in opioid naïve patients

(c) 2007, Ewan D. McNicol, RPh.
23. Mixed Agonist-Antagonists/Partial agonists

Mixed Agonist-Antagonists/Partial agonists

- Lower abuse potential?
- High psychotomimetic response due to Kappa stimulation
- “Ceiling” effect on both side effects and analgesia
- May cause pain or precipitate withdrawal
- Not first line drugs for severe pain

(c) 2007, Ewan D.McNicol, RPh.

24. Antagonists

Antagonists

- Bind competitively with agonists at opioid receptors
- Do NOT produce analgesic effects
- Used to reverse the toxic effects of agonists and or agonist-antagonists (respiratory depression, itch, constipation)

(c) 2007, Ewan D.McNicol, RPh.
25. Naloxone

Naloxone

- Respiratory depression:
  Mix one vial (400 mcg) in 10 cc NS. Push 0.5 cc every 2 min → prevent return of pain. Up to 800 mcg.
  Short half-life - may have to re-dose
- Itch:
  Mix one vial in 500 cc. Run over about 24 hrs (0.25 mcg/kg/hr)
- Will NOT reverse normeperidine-induced toxicity

Gen et al. Anesthesiology, 87(5),1997:1075-1081

(c) 2007, Ewan D. McNicol, RPh.

26. Medication Schedules

Medication Schedules

- Round-the-clock medication
  - Use for constant pain
- PRN medication
  - Pain meds available when patient needs relief - not constant pain
  - Premedication for procedures
    - Use short acting opioid prior to procedure to relieve pain, or use patient’s PCA bolus

(c) 2007, Ewan D. McNicol, RPh.
27. Opioid Selection: Poor Choices for Chronic Pain

Opioid Selection:
Poor Choices for Chronic Pain

- Meperidine
  - Poor absorption and toxic metabolite
- Propoxyphene
  - Poor efficacy and toxic metabolite
- Mixed agonists-antagonists (pentazocine, butorphanol, nalbuphine)
  - Compete with agonists → withdrawal
  - Analgesic ceiling effect

(c) 2007, Ewan D. McNicol, RPh.

28. Opioid-drug interactions

Opioid-drug interactions

- Meperidine-MAOIs/SSRIs: serotonin syndrome
- Phenothiazines/antidepressants/MAOIs: increased sedative/depressant effect
- Phenothiazines/antihistamines/antidepressants/amphetamines: increased analgesia
- NSAIDs: increased analgesia
- Meperidine-phenobarbital/phenytoin: increased clearance

(c) 2007, Ewan D. McNicol, RPh.
29. Routes of Administration

Routes of Administration

- Oral and transdermal: preferred
- Oral transmucosal: available for fentanyl and used for breakthrough pain
- Rectal, parenteral, intraspinal, sublingual, transbronchial, buccal, subcutaneous implanted
- Potential drug delivery advances
  - Transdermal iontophoretic - Fentanyl PCA


(c) 2007, Ewan D. McNicol, RPh.

30. Opioid Therapy: Dosing Guidelines

Opioid Therapy: Dosing Guidelines

- Initial dose based on prior opioid exposure, age, comorbidities, and pain severity
- No maximal or “correct” dose: gradually increased dose until pain relief is adequate or intolerable/unmanageable side effects occur
- If rescue (breakthrough) drug used, dose is usually 5% to 15% of the total daily dose
- Use same drug for standing and rescue


(c) 2007, Ewan D. McNicol, RPh.
31. Opioid Therapy: Dosing Guidelines

Opioid Therapy: Dosing Guidelines

- Dose increases 25% to 100% or amount equal to rescue doses
- Increase rescue dose as baseline dose increases
- Frequency of dose increases based on time to steady state, pain severity, and comorbidities


(c) 2007, Ewan D. McNicol, RPh.

32. Poor Opioid Responsiveness

Poor Opioid Responsiveness

- If dose escalation leads to side effects:
  1. Manage side effects
  2. Pharmacologic strategy to lower opioid requirement
     Spinal route of administration
     Add non-opioid or adjuvant analgesic
  3. Nonpharmacologic strategy to lower opioid requirement
     – If above fails consider “Opioid rotation”


(c) 2007, Ewan D. McNicol, RPh.
33. **Opioid Rotation**

Opioid rotation involves switching from one opioid to another to optimize analgesia and lessen side effects (or simply for financial savings or convenience)


(c) 2007, Ewan D. McNicol, RPh.

34. **How does this look?**

- 50-year-old male, 70 kg, post op, normal renal function, moderate pain.
- Hydromorphone 5 mg po/iv q8 hrs prn

(c) 2007, Ewan D. McNicol, RPh.
35. **Equianalgesic Conversion**

Equianalgesic Conversion

1) Total the 24 hr dose of current drug (including rescue doses)
2) Convert for drug and route
3) Divide total dose by schedule of drug
4) Reduce dose for incomplete cross-tolerance? (33%)
5) Calculate breakthrough dose

(c) 2007, Ewan D. McNicol, RPh.

36. **Tolerance**

Tolerance

- The need for a higher dose (or increased plasma concentration) to achieve the same pharmacological effect.
- Hallmark: Decrease in duration of analgesia per dose

(c) 2007, Ewan D. McNicol, RPh.
37. Incomplete cross-tolerance

Incomplete cross-tolerance

- When a patient who has developed tolerance to one opioid is switched to a different opioid, “cross tolerance” exists, but may not be as extensive as a greater than expected response may be observed from the new opioid.
- May require a reduction of 33-50% of calculated dose.

(c) 2007, Ewan D. McNicol, RPh.

38. Equianalgesic conversion

Equianalgesic conversion

- Reduce calculated equianalgesic dose by 33% to 50% to account for incomplete cross-tolerance, **but**:
  - Reduce *less*:
    - Severe or uncontrolled pain
    - Same drug by different route
    - Manufacturer’s recommendations may underdose fentanyl patch
  - Reduce *more*:
    - Medically frail
    - Methadone: 75% to 90%

*Mercadante S. *Cancer*, 1999;86:1856-66.)*

(c) 2007, Ewan D. McNicol, RPh.
39. Conversion Table

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parenteral</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>NA</td>
<td>20 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>100 mcg</td>
<td>15 mcg TD</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5 mg</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Methadone</td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

(c) 2007, Ewan D. McNicol, R.Ph.

40. Simple example

A patient is taking 30 mg oral morphine every 4 hrs around the clock. You wish to start them on twice daily oxycodone.

1) Total the 24 hr dose of current drug: 30 x 6 = 180 mg
2) Convert for drug and route
   180 mg oral morphine x 20/30 = 120 mg oral oxycodone

(c) 2007, Ewan D. McNicol, R.Ph.
41. **Simple example cont.**

3) Divide total dose by schedule of drug
   120/2 = 60 mg twice daily
4) Reduce dose for incomplete cross-tolerance? (33%)
   60 x 0.67 = 40 mg
5) Calculate breakthrough dose
   15% x 80 mg = 12 mg oxycodone IR
   Closest strength = 10 mg

(c) 2007, Ewan D. McNicol, RPh.

42. **Equianalgesic conversion example**

Mrs. E is a 37 year-old female with chronic low back pain s/p skiing accident. A trial of opioid therapy facilitated functional rehabilitation and return to full-time work. The patient's current opioid regimen consists of the following:

- **Long-acting oxycodone (OxyContin®)** 40 mg orally 3 times daily
- **Oxycodone/APAP 7.5/325 (Percocet®)** orally every 4-6 hours as needed for pain

The patient states, “Currently my pain is not interfering to any great degree with what I need to get done. However, I am constantly tired out and I have noticed that I get an upset stomach after taking my OxyContin®. Is there anything else that I can use that would not require me to take pills during the day? On average, I am taking about 3 Percocet® a day when the pain flares up”.


(c) 2007, Ewan D. McNicol, RPh.
43. Equianalgesic conversion example

Equianalgesic conversion example

Physician Plan of Care:
Convert the patient to an alternate long-acting opioid for baseline analgesia. This may decrease the need to take oral medications during the day at work and may also reduce some of the sedation and/or nausea (“stomach upset”) the patient is experiencing with the current opioid. Transdermal fentanyl will be prescribed to minimize the need to take oral medication while at work and may help decrease side effects.

a) Calculate the patch strength required for this patient
b) Calculate the breakthrough dose required if the patient is to receive Percocet 10 mg/325 mg tabs

(c) 2007, Ewan D. McNicol, RPh.

44. Equianalgesic conversion example

Equianalgesic conversion example

Step 1: Total the 24 hr dose of current drug
Total daily scheduled doses - 3 tabs/day of Oxycontin 40 mg:

\[
\frac{3 \text{ tabs}}{\text{day}} \times \frac{40 \text{ mg po}}{\text{day}} \times \frac{1.5 \text{ mg po}}{1 \text{ mg po}} = \frac{180 \text{ mg po}}{\text{day}}
\]

(c) 2007, Ewan D. McNicol, RPh.
Equianalgesic conversion example

Also add total number of breakthrough doses - 3 tabs/day Percocet 7.5/325

\[
\begin{align*}
3 \text{ tabs/day} \times \frac{7.5 \text{ mg po oxycodone}}{\text{tab}} \times \frac{1.5 \text{ mg po morphine}}{1 \text{ mg po oxycodone}} \times \frac{33.8 \text{ mg po morphine}}{\text{day}} \\
\end{align*}
\]

Add total morphine equivalents

\[180 \text{ mg} + 33.8 \text{ mg} = 213.8 \text{ mg}\]

(c) 2007, Ewan D. McNicol, RPh.

Equianalgesic conversion example

- **Step 2: Convert for drug and route**
  Convert to Fentanyl by halving daily dose:
  \[-213.8/2 = 106.9 \text{ mcg/hr}\]
- **Step 3: Divide total dose by schedule of drug**
  not required

(c) 2007, Ewan D. McNicol, RPh.
47. Equianalgesic conversion example

Equianalgesic conversion example

Step 4: Account for incomplete cross-tolerance
Subtract 33% for incomplete cross-tolerance:
-106.9 x 0.67 = 71.6 mcg/hr
Closest patch size = 75 mcg/hr

(c) 2007, Ewan D. McNicol, RPh.

48. Equianalgesic conversion example

Equianalgesic conversion example

Step 5: Calculate breakthrough dose - 10 - 20% of total daily dose
total calculated morphine dose = 213.8 mg:
0.15 x 213.8 = 30 mg morphine
convert to oxycodone (divide by 1.5)
= 20 mg oxycodone q4h prn or 2 tabs of Percocet 10/325

(c) 2007, Ewan D. McNicol, RPh.
49. **Nonopioid Analgesics**

Nonopioid Analgesics

- Acetaminophen (paracetamol)
- Aspirin
- Traditional NSAIDs
- COX-2 inhibitors

(c) 2007, Ewan D. McNicol, RPh.

50. **NSAIDs: Properties**

NSAIDs: Properties

- Nonspecific analgesics, but greater effectiveness likely in inflammatory pains (minimal for acetaminophen - appears to act mostly by a central mechanism)
- Dose-dependent effects, with ceiling dose
- Marked individual variation in response to different drugs

(c) 2007, Ewan D. McNicol, RPh.
51. Non-opioid analgesics

Non-opioid analgesics

- Primary mechanism of action: inhibition of cyclooxygenase (COX) enzymes, in turn preventing the synthesis of prostaglandins
- Drug-to-drug variation in toxicities partly determined by COX-1/COX-2 selectivity

(c) 2007, Ewan D. McNicol, RPh.

52. Non-opioid analgesics: WHO ladder

Non-opioid analgesics: WHO ladder

- Step 1: mild/moderate pain - alone or combined with adjuvant
- Step 2 and 3: moderate/severe pain - combined with opioid and/or adjuvant

(c) 2007, Ewan D. McNicol, RPh.
53. Positioning NSAID Therapy

Positioning NSAID Therapy

- Pain
  - Surgical, cancer, muscle, bone pain, menstrual pain
- Inflammation
  - Acute: surgery
  - Chronic: RA (OA) - provide symptomatic relief
  - Doses for inflammation are higher than those for pain

(c) 2007, Ewan D. McNicol, RPh.

54. Guidelines for Management of NSAID Therapy

Guidelines for Management of NSAID Therapy

- Comprehensive Assessment
- Drug selection
- Age
- Renal/hepatic function
- Individual differences/preferences
- Concurrent therapies
- Cost
- Route
- Likelihood of addiction/abuse/diversion


(c) 2007, Ewan D. McNicol, RPh.
55. NSAID with or without opioid?

NSAID with or without opioid?

- Evidence of combination efficacy demonstrated in clinical trials of acute pain - less so in patients with chronic disease
- Acetaminophen commonly combined with opioids - dose ceiling

(c) 2007, Ewan D. McNicol, RPh.

56. NSAID with or without opioid?

NSAID with or without opioid?

- Meta-analyses report similar NNT’s for certain NSAIDs vs. opioids in acute pain
- Recent large trial refutes conclusions, but confirms that combination of opioid and NSAID reduces side effects in acute pain

(c) 2007, Ewan D. McNicol, RPh.
57. NSAIDs - Adverse effects

NSAIDs - Adverse effects

- GI: upset/bleed/nausea - reduced by proton pump inhibitors, misoprostol, and possibly high-dose histamine-2 blockers
- Renal toxicity
- Bleeding diathesis
- Allergy
- Hypertension

(c) 2007, Ewan D. McNicol, RPh.

58. NSAIDs: drug interactions

NSAIDs: drug interactions

ACE inhibitors: NSAIDs block production of vasodilator/natriuretic PGs; hyperkalemia, bradycardia - syncope
Corticosteroids: increased risk of GI ulceration
Warfarin: increased risk of bleed
Warfarin, sulfonylureas, methotrexate: displacement from protein binding

(c) 2007, Ewan D. McNicol, RPh.
59. Which NSAID to choose?

Which NSAID to choose?

- No “Gold Standard” (cf. morphine)
- GI concern: coxib, acetaminophen, ibuprofen, naproxen
- Renal impairment: sulindac
- Bleeding: acetaminophen, coxib, nabumetone, trilisate

(c) 2007, Ewan D. McNicol, RPh.

60. Which NSAID not to choose?

Which NSAID not to choose?

- Renal: ketorolac
- GI concern: indomethacin, aspirin, ketoprofen
- CNS: indomethacin
- Hepatotoxicity: acetaminophen
- Bleeding: aspirin
- Elderly: ketorolac - reduce dose; monitor comorbidities; CNS effects

(c) 2007, Ewan D. McNicol, RPh.
61. NSAIDs: available agents

- Diclofenac
- Ketorolac
- Etodolac
- Nabumeton
- Ibuprofen
- Naproxen
- Indomethacin
- Oxaprozin
- Ketoprofen
- Piroxicam
- Sulindac

(c) 2007, Ewan D. McNicol, RPh.

62. NSAID Recommendations

- Do not use multiple NSAIDs at one time, e.g., IV ketorolac plus PO Ibuprofen
- Expect ceiling limitations
- Recognize the difference between analgesic vs. anti-inflammatory doses
- Drug selection should be influenced by drug-selective toxicities, prior experience, convenience, cost

(c) 2007, Ewan D. McNicol, RPh.
63. Coxibs - place in therapy

Coxibs - place in therapy

- Safety profile of these agents in the perioperative or acute setting may offset their higher cost.
- Risk reduction of coxibs in chronic therapy may be insufficient to justify their use except in an, as yet unspecified, subset of patients at “high risk” for adverse GI events and “low risk” for cardiac events.
- Further evidence of the coxibs’ safety profile will be required before recommending their routine administration.

(c) 2007, Ewan D. McNicol, RPh.

64. Adjuvant Analgesics

Adjuvant Analgesics

Source: http://www.mass.gov/age/events/

(c) 2007, Ewan D. McNicol, RPh.
65. **Adjuvant Analgesics**

- Defined as drugs with other indications that may be analgesic in specific circumstances
- Numerous drugs in diverse classes
- Sequential trials and combinations are often needed
- Can be used at any step of the WHO ladder

(c) 2007, Ewan D. McNicol, RPh.

66. **Adjuvant Analgesics - place in therapy**

- Multipurpose analgesics
  - neuropathic pain
  - musculoskeletal pain
  - cancer pain
  - headache
- Often added if trials of opioids/NSAIDs have failed
- Not generally effective acutely
- Lower doses may be effective than those required for their primary indication

(c) 2007, Ewan D. McNicol, RPh.
67. Adjuvant Analgesics

Adjuvant Analgesics

- Anticonvulsants
- Antidepressants
- Local anesthetics
- Corticosteroids
- Miscellaneous


(c) 2007, Ewan D. McNicol, RPh.

68. Risk factors for herpes zoster

Risk factors for herpes zoster

- Psychiatrists > dermatologists > pediatricians
  - Solomon et al., 1998
- Fewer social and occupational contacts with children
  - Thomas et al., 2002
- Adults living without (vs. with) children
  - Brisson et al., 2002

(c) 2007, Ewan D. McNicol, RPh.
69. Pharmacotherapy: Slide 69

70. Anticonvulsants

MOA: Blocking sodium channels?
- Analgesic effects established for phenytoin, carbamazepine, valproate, clonazepam, and lamotrigine
- Uses:
  - Neuropathic pain (PHN, DPN, phantom limb)
  - Trigeminal neuralgia

(c) 2007, Ewan D. McNicol, RPh.
71. Gabapentin/Pregabalin

- Modulates calcium influx in hyperexcited neurons
- Reduces neurotransmitter release
- Pharmacologic effect requires binding at this site
- The clinical significance of these observations in humans is currently unknown


(c) 2007, Ewan D. McNicol, RPh.

72. Gabapentin

- Favorable safety profile and positive RCTs in PHN/diabetic neuropathy
- Only FDA approved for PHN
- Usual effective dose: 600–3600 mg/d and sometimes higher
- Modulates alpha2-delta subunit of the voltage-gated calcium channel in CNS, but MOA unknown

Luo, J Pharmacol Exp Ther. 2002

(c) 2007, Ewan D. McNicol, RPh.
Pregabalin

- Next generation gabapentin?
- Also modulates alpha2-delta subunit
- Indicated for DPN and PHN
- Starting dose: 150 mg (divided bid/tid), gradually titrated upwards (1 week) to 300 mg (divided bid/tid)

Dworkin RH. Neurology 60 (2003) 1274-83

(c) 2007, Ewan D. McNicol, RPh.

Pregabalin

- Reduction in pain seen within 3 days in some patients
- No important drug interactions (additive CNS effects with other depressants)
- Adverse effects: dizziness, somnolence, peripheral edema, blurred vision

(c) 2007, Ewan D. McNicol, RPh.
75. **Pregabalin in neuropathic pain**

- 300/600 mg > placebo (PHN)
  Dworkin et al., 2003
- 150, 300 mg > placebo (PHN)
  Sabatowski et al., 2004
- 300, 600 but not 75 mg > placebo (painful DPN)
  Lesser et al., 2004
- 300 mg > placebo (painful DPN)
  Rosenstock et al., 2004
- 150, 300 mg > placebo (painful DPN)
  Richter et al., 2005
- 150-600, 600 mg > placebo (PHN + painful DPN)
  Freynhagen et al., 2005

(c) 2007, Ewan D. McNicol, RPh.

76. **Antidepressants**

- MOA: inhibit reuptake of 5-HT & NE
- Common agents
  - Amitriptyline
  - Trazodone
- Neuropathic pain
  - Diabetic neuropathy
  - Post-herpetic neuralgia
  - Phantom limb pain
- Side Effects: sedation, dry mouth, constipation, orthostatic hypotension - additive with other drugs

(c) 2007, Ewan D. McNicol, RPh.
Antidepressants

- Best evidence: 3<sup>th</sup> amine TCAs (e.g., amitriptyline)
- 2<sup>nd</sup> amine TCAs (desipramine, nortriptyline) better tolerated and also analgesic
- Some evidence for SSRI/SSNRIs/atypical antidepressants (e.g., paroxetine, maprotiline, bupropion, others) and these are even better tolerated
- Beer’s Criteria: TCAs not recommended in elderly (for depression) - lower doses often needed for pain

(c) 2007, Ewan D. McNicol, RPh.

Local anesthetics and oral analogues

MOA: block sodium channels
- IV/SQ lidocaine used as predictor of efficacy
- Oral therapy with mexiletine, flecainide
- Useful for any type of neuropathic pain
- Lidocaine patches

(c) 2007, Ewan D. McNicol, RPh.
79. Steroids

Steroids

- Dexamethasone
- Prednisone
- MOA: anti-inflammatory effects
- Uses: increased intracranial pressure, nerve compression, bone pain, soft tissue damage
- Side Effects:
  - GI disturbances
  - Increased appetite
  - Increase in blood sugar
  - Insomnia

(c) 2007, Ewan D. McNicol, RPh.

80. Alpha-2 adrenergic agonists

Alpha-2 adrenergic agonists

- Clonidine and tizanidine used for chronic pain of any type
- Tizanidine usually better tolerated
- Tizanidine starting dose 1–2 mg/d; usual maximum dose up to 40 mg/d
- Used in diabetic neuropathy
- Side effects: Orthostatic hypotension, rebound hypertension (not recommended in elderly)

(c) 2007, Ewan D. McNicol, RPh.
81. NMDA-receptor antagonists

NMDA-receptor antagonists

- N-methyl-D-aspartate (NMDA) receptor involved in neuropathic pain
- Commercially available drugs:
  - ketamine
  - dextromethorphan
  - amantadine
  - (methadone)
- Usually reserved for refractory cases

(c) 2007, Ewan D. McNicol, RPh.

82. Topical Analgesics/Anesthetics

Topical Analgesics/Anesthetics

Counterirritants (e.g., menthol, methylsalicylate)
- Supplied as liniments, creams, ointments, sprays, gels, or lotions
- May be effective for arthritic pain, but effectiveness is limited when pain affects multiple joints
- Can cause skin injury, especially when used with heat or with an occlusive dressing

Capsaicin Cream
- Derived from red peppers
- Depletes substance P, desensitizes nerve fibers associated with pain
- Main limitation is skin irritation
- Use routinely for optimal effectiveness. Begin with 0.025% and advance to higher concentration if necessary. Try 0.075% preparation for 6 weeks before declaring treatment failure

(c) 2007, Ewan D. McNicol, RPh.
83. Muscle relaxants

“Muscle relaxants”

- Refers to numerous drugs, e.g.,
cyclobenzaprine, carisoprodol,
orphenadrine, methocarbamol,
chlorzoxazone, metaxalone
- Centrally-acting analgesics
- Do not relax skeletal muscle
- Not recommended in elderly

(c) 2007, Ewan D. McNicol, RPh.

84. Miscellaneous drugs

Miscellaneous drugs

- Calcitonin
  - intranasal or intramuscular
  - RCTs in CRPS and phantom pain
  - Limited experience

- Baclofen
  - RCT in trigeminal neuralgia
  - 30–200 mg/d or higher
  - Taper before discontinuation (spasticity, sweating, tachycardia)

(c) 2007, Ewan D. McNicol, RPh.
85. Adjuvant Analgesics for Cancer Pain

Adjuvant Analgesics for Cancer Pain

• For bone pain
  – Bisphosphonates (e.g., pamidronate, clodronate), calcitonin, radiopharmaceuticals (e.g., Sr^89, Sm^153)

• For bowel obstruction pain
  – Anticholinergics or octreotide (reduce peristalsis and secretions), steroids

86. First-line medications for neuropathic pain

First-line medications for neuropathic pain

<table>
<thead>
<tr>
<th>Medication</th>
<th>Beginning Dosage</th>
<th>Titration</th>
<th>Maximum Dosage</th>
<th>Duration of Adequate Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salazosin</td>
<td>100-200 mg every night or 100-300 mg 5 times daily</td>
<td>Increase by 100-300 mg every 1-2 wk as tolerated</td>
<td>3,000 mg (1,200 mg x 3 times daily); reduce if low creatinine clearance</td>
<td>3-8 wk for titration plus 1-2 wk at maximum tolerated dosage</td>
</tr>
<tr>
<td>3% Lidoceaine patch</td>
<td>Maximum of 3 patches daily for a maximum of 12 h; 5-15 mg every 4 h as needed</td>
<td>None needed</td>
<td>Maximum of 3 patches daily for a maximum of 12 h</td>
<td>2 wk</td>
</tr>
<tr>
<td>Opioid analgesics*</td>
<td>Maximum of 3 patches daily for a maximum of 12 h</td>
<td>After 1-2 wk, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed</td>
<td>No maximum with caution; titration: consider evaluation by pain specialist at dosages exceeding 120-180 mg/d</td>
<td>4-6 wk</td>
</tr>
<tr>
<td>Tramadol hydrochloride</td>
<td>50 mg once or twice daily</td>
<td>Increase by 50-100 mg in divided doses every 3-7 d as tolerated</td>
<td>400 mg (100 mg x 4 times daily); in patients older than 75 y, 300 mg in divided doses</td>
<td>4 wk</td>
</tr>
<tr>
<td>Tricyclic antidepressants (e.g., amitriptyline hydrochloride or desipramine hydrochloride)</td>
<td>10-25 mg every night</td>
<td>Increase by 10-25 mg/d every 3-7 d as tolerated</td>
<td>75-150 mg/d; if blood level of active drug and its metabolite is &lt;100 ng/ml, continue titration with caution</td>
<td>5-8 wk with at least 1-2 wk at maximum tolerated dosage</td>
</tr>
</tbody>
</table>

*Dosages given are for morphine sulfate.

(c) 2007, Ewan D. McNicol, RPh.
87. Add the following?

Add the following?

Duloxetine and pregabalin

(c) 2007, Ewan D. McNicol, R.Ph.

88. Treatment Options

<table>
<thead>
<tr>
<th>Pain Source</th>
<th>Potential analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma/post-surgical/post-procedure</td>
<td>Opioids, NSAIDs, APAP, epidural analgesia</td>
</tr>
<tr>
<td>Acute exacerbation of sickle-cell or cancer pain</td>
<td>Opioids, NSAIDs, APAP, steroids</td>
</tr>
<tr>
<td>Chronic lower back pain</td>
<td>NSAIDs, muscle relaxants, opioids</td>
</tr>
<tr>
<td>Diabetic peripheral neuralgia</td>
<td>Antidepressants, anticonvulsants, capsaicin</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>Carbamazepine, baclofen, phenytoin</td>
</tr>
<tr>
<td>Post-herpetic neuralgia</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>Phantom limb pain</td>
<td>Carbamazepine, mexiletine, epidural analgesia</td>
</tr>
<tr>
<td>Cancer/HIV</td>
<td>Multiple combinations</td>
</tr>
</tbody>
</table>

(c) 2007, Ewan D. McNicol, R.Ph.
Summary

Opioids:
- Used at step 2-3 of WHO ladder
- Indicated for short term use in surgical and cancer pain
- Long term use controversial
- No ceiling effect
- Morphine still considered “gold standard”, but consider opioid rotation when intolerable side effects/lack of efficacy

(c) 2007, Ewan D. McNicol, RPh.

Summary

Equianalgesic conversion of opioids:
1) Total the 24 hr dose of current drug
2) Convert for drug and route
3) Divide total dose by schedule of drug
4) Reduce dose for incomplete cross-tolerance? (33%)
5) Calculate breakthrough dose

(c) 2007, Ewan D. McNicol, RPh.
91. NSAIDs: Summary

NSAIDs: Summary

- Use at any step of WHO ladder alone or in combination with opioids/adjuvants
- Reduce pain and inflammation (except acetaminophen)
- Ceiling effect on analgesia but not ADRs
- Serious side effects include GI bleed, renal impairment
- Coxibs place in therapy undetermined: may reduce GI s/e’s but increase CV ADRs

(c) 2007, Ewan D. McNicol, RPh.

92. Summary

Summary

Adjuvant analgesics:
- Use at any stage of WHO ladder
- Often used after trial of opioid/NSAID has failed
- Place in therapy: chronic/neuropathic pain
- Includes: anticonvulsants, antidepressants, local anesthetics and steroids

(c) 2007, Ewan D. McNicol, RPh.
Pharmacotherapy: Slide 93