Critical Review of the Effectiveness of Opioids for Analgesia

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Global Consumption of Morphine
1972-1995

Total Kilograms in Thousands

Source: International Narcotics Control Board
Reasons for increased opioid use

- History of pain undertreatment
  - effective
  - no organ toxicity
  - recognition of addiction realities
- 1985: MS-Contin® release for cancer pain
- 1986: Foley and Portenoy promoted opioids for non-cancer pain
- 1994/96: Supreme Court ruling on Euthanasia
- 1997: Federation of State Medical Board guidelines for controlled substances use

Supreme Court Ruling on Euthanasia

- Supreme Court (O’Connor/Stevens, ‘95/’96): reaffirmed their opposition to a constitutional right to assisted suicide, however indicated that there is a right to receive adequate palliative care.
  - Deficiencies in end-of-life care
  - Endorsed concept of palliative sedation
- February 2006: US Supreme Court upheld State of Oregon’s Death with Dignity Act
Reasons for increased opioid use

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  - effective
  - no organ toxicity
  - recognition of addiction realities
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Federation of State Medical Boards

Model Guidelines for the Use of Controlled Substances for the Treatment of Pain

Adopted May 1997

www.fsmb.org
Office visits and analgesic Rx: 1980 vs. 2000


- Compared National Ambulatory Medical Care Survey Rx data for MS pain from 1980-81 (89,000 visits) to 1999-2000 (45,000 visits)
  - Acute and chronic
- Threshold for prescribing opioids has dropped

<table>
<thead>
<tr>
<th></th>
<th>1980</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID’s</td>
<td>19%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>29%</td>
</tr>
<tr>
<td>Opioids</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td>MS, Oxy/HC for chronic MS pain</td>
<td>2%</td>
<td>9%</td>
</tr>
</tbody>
</table>
Opioid Sales in 2004

- Oxycontin $1.6B
- Duragesic $880M
- Avinza $150M
- Kadian $100M
- Actiq
- Countless oxycodone, hydrocodone

Types of Pain
Somatic pain

- Discomfort arising from nociceptor stimulation due to mechanical, thermal or electrical stimuli
- Well-localized
- “achy”, “throbbing”, “constant”, “gnawing”
- Responds to endogenous/exogenous opioids

Visceral Pain

- Injury to sympathetically innervated organs, pain emanates from soft organs of thorax, abdomen and pelvis
- Poorly-defined
- Referred pain: dual innervation, central convergence of afferent impulses, chemical irritation by tumor-mediated algesics
- “deep”, “dull”, “vague”
- Opioid-responsive
Neuropathic Pain

- Damage to sympathetics, peripheral nerves or CNS or pathologic neurofunctional changes ("wind-up", abnormal NMDA receptor activation, abnormal sympathetic-somatic activation)
- Localized, with radiations following a dermatomal distribution
- "burning", "tingling", "shooting"
- Opioid-resistant (?)

Neuropathic Pain

- Diverse syndromes
  - Mononeuropathy (eg, Postmastectomy syndrome)
  - Radiculopathy (eg, HNP)
  - Polyneuropathy (eg, Diabetes)
  - Deafferentation syndromes (eg, phantom pain, pain in spinal cord injury, poststroke pain)
  - Complex Regional Pain Syndrome I and II (Reflex Sympathetic Dystrophy and Causalgia, respectively)
Alfentanil, but not amitriptyline, reduces pain, hyperalgesia, and allodynia from intradermal injection of capsaicin in humans

- 46 volunteers received 100mcg capsaicin ID
- Four groups
  - midazolam 4mg IM
  - amitriptyline 25mg IM
  - alfentanil IV using CACI to 50ng/ml and 200ng/ml
  - amitriptyline + alfentanil
- Results
  - Alfentanil reduced hyperalgesia and allodynia
  - Amitriptyline had no effect/potentiation


- Prospective, randomized, double-blind trial
- Adults with uncontrolled neuropathic pain given levorphanol 0.75mg or 0.15mg tabs po prn up to 21 pills/day
- Central pain after stroke less improved
- High dose pill group (avg = 8.9mg/d) had ↓ pain 36% vs 21% in low dose group (avg = 2.7mg/d)
  - Increased doses, increased side effects w/o decrease in secondary endpoints (e.g., QoL, improvement in cognitive/psychological function)
Combination therapy for neuropathic pain


- Randomized, double-blind, placebo-controlled (active), crossover trial
- Placebo (lorazepam), morphine-SR, Gabapentin, morphine-SR + Gabapentin
- Patient self dose escalation
- % change in pain intensity MS-G vs P (p = 0.03)
- Less morphine and gabapentin tolerated in MS-G
- Improvement in McGill SF-36 in active groups

Efficacy and Safety of Opioid Agonists in the Treatment of Neuropathic Pain

Eisenberg, McNicol and Carr. JAMA 293:3043-3052, 2005

- Meta-analysis of RCT’s assessing neuropathic pain
- 22 articles met inclusion criteria
  - 14 short term
    - Outcomes measured for < 24 hours
    - Demonstrated equivocal results
  - 8 intermediate term
    - Opioids administered for longer periods (8-56 days)
    - Demonstrated consistent opioid analgesic efficacy
Opioid Classification

**Agonists**
- Morphine
- Meperidine
- Fentanyl
- Codeine
- Oxy/hydrocodone
- Dextrometorphan
- Methadone
- Heroin
- Buprenorphine

**Agonists-Antagonists**
- Pentazocine (Talwin)
- Butorphanol (Stadol)
- Nalbuphine (Naline)

**Antagonists**
- Naloxone (Narcan)
- Naltrexone

Opioid receptor actions

- **MU**: analgesia, miosis, respiratory depression, euphoria, bradycardia
- **KAPPA**: analgesia, miosis, sedation
- **SIGMA**: analgesia, mydriasis, respiratory stimulation, psychotomimetic effects, tachycardia
Molecular Biology of Opioid Analgesia
Pasternak GW. J Pain Sympt Man 29:2-9, 2005

- Responses of patients vary to various mu-agonists
- 5mg/kg/d caused marked reduction in analgesia to morphine and codeine after 5d but no decrease in analgesia of methadone, M-6-G, fentanyl and heroin (Trends Pharm Sci 22:67-70, 2001)
- Synergistic interaction between opioids, e.g., MS and methadone (J Pharmacol Exp Ther 303:557-562, 2002)
- Multiple splice variants of the mu-opioid receptor
  - Cross tolerance
  - Patient sensitivity
  - Combinations

Concept of Opioid Rotation

Symptoms of opioid toxicity may be due to accumulation of specific opioid metabolites. Changing opioids periodically may reduce side effects while maintaining, or possibly, improving analgesia.

80 patients demonstrating cognitive failure, N/V, hallucinations, myoclonus, sedation and persistent pain were allowed to titrate doses of a different opioid.

Side effects were reduced at approximately 58% of the mean pre-existing dose with a different opioid.

Opioid Classification

**Natural (phenantrenes)**
- Morphine
- Codeine
- Papaverine

**Semi-Synthetic (benzolisoquinolines)**
- Heroin
- Dihydromorphone

**Thebaines**
- Oxycodone
- Hydrocodone

**Synthetics**
- Morphinan (butorphanol, levorphanol)
- Diphenylpropylamine (methadone)
- Benzomorphinan (pentazocine)
- Phenylpiperidine (meperidine, fentanyl, alfentanil, sufentanil)

Basic mode of action of opioid medications

Inhibiting the release of glutamate from peripheral nociceptors and postsynaptic neurons in the dorsal horn
NMDA receptor activation

- Windup: spinal neurons carrying pain are stimulated with less peripheral input
- Endorphins and exogenous opioids lose effectiveness
- Stimulates normal apoptotic mechanisms
- Neural remodeling
- Precipitate destruction and loss of cells (overstimulated NMDA receptors on adjacent postsynaptic cells)
- Rechannel connections
Sympathetic Insprouting of DRG

Centralization of Pain/Neurogenic Inflammation
Classification of Opioids

- Propoxyphene
- Codeine
- Morphine
- Oxycodone / Hydrocodone
- Hydromorphone
- Methadone (mixed mu/NMDA)
- Fentanyl
- Sufentanil
- Carfentanil (experimental)
- Lofentanil (experimental)

Greater Receptor Occupancy

The “Ideal” Opioid

- Various delivery routes
- No active metabolites
- Readily absorbed
- Does not induce own metabolism
- Facilitates *steady state* rapidly
- No side-effects
- Non-abusable
How Do You Know Which Opioid Delivery System to Choose?

- All day long
- Stable in intensity
- Isolated incidents
- Severe rapid onset of pain

Both long-acting AND short-acting opioid analgesics

Long-acting opioids

Short-acting opioids

Ideal: Slow Release + Immediate Release

Over Medication

Slow Release Medication

Ideal Breakthrough Medication

Persistent Pain

TIME

Over Medication
Opioid Routes of Administration

- Oral
- Intramuscular
- Subcutaneous
- Intravenous
- Rectal
- Oral transmucosal
- Transdermal
- Spinal (subarachnoid, epidural)
- Other (nebulized, intravaginal)

Oral Opioids

- Morphine
  - Short acting: morphine, MS-IR
  - Long acting: MS-Contin, Ora-Morph, Kadian, Avinza
- Oxycodone
  - Short acting: OxyFast, Percocet/-dan, Roxicet, Tylox, Percolone, etc…
  - Long acting: Oxycontin
- Hydrocodone: Vicodin, Lorcet, VicoProfen, etc…
- Hydromorphone: Dilauidid, Palladone
- Fentanyl: Actiq
- Methadone
Oral Morphine

- Readily absorbed from GI/SC/IM, rectum, lung
- 50% of PO-M in central compartment w/i 30min
- M6G anal >>> M3G
  - M6G excretion dependent on renal function
  - M3G responsible for myoclonus and hyperalgesia

Oral Morphine: long acting

- **MS-Contin®**
  - 50% of PO dose reaches central compartment in 1.5h
  - Peaks at 2.5 - 4h
  - Steady-state achieved in 24h, higher [peak] and lower [trough] with bid than equal M oral preparations
  - GI abs 82%, 42% passed through liver, bioavailability of 34%, 71% M6G formed through first-pass *Lotsch et al, Anesthesiology 90:1026-1038, 1999*
- b.i.d vs. t.i.d. dosing?
**Long acting morphine: Kadian®**

- **Kadian®**
  - Oral swallow, “sprinkle” use
  - No chewing/crushing
  - 16 French NGT
  - 20, 30, 50, 60, 100mg
    - No immediate release component
  - Peak level at 8 – 10h
    - peak (> 75% $C_{\text{max}}$) lasts 6h

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**Kadian qd vs MS-Contin bid (100mg/d)**

Graph 2 (Study # N02-0292): Dose normalized mean steady state plasma morphine concentrations for KADIAN® (once a day), and an equivalent dose of a 12-hour, controlled-release morphine tablet given twice a day. Plasma concentrations are normalized to 100 mg every 24 hours, (n=24).

Kadian® 50mg bid vs. MS elixir q6h vs MS-Contin® bid (100mg/d)

Graph 1 (Study # M03-1/08):
Mean steady state plasma morphine concentrations for KADIAN® (twice a day), controlled-release morphine tablet (twice a day) and oral morphine solution (every 4 hours); plasma concentrations are normalized to 100 mg every 24 hours, (n=24).

Long acting morphine: Avinza®

- Two components: immediate (10%) and extended release
- Spheroidal oral drug absorption system (SODAS)
- 30, 60, 90, 120 mg
- Max 1800 mg/d (fumaric acid buildup)
- Avinza pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Avinza® 60mg qAM</th>
<th>MS 10mg q4h</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng/mlh)</td>
<td>273.25 ± 81.24</td>
<td>279.11 ± 63.00</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>18.65 ± 7.13</td>
<td>19.96 ± 4.82</td>
</tr>
<tr>
<td>Cmin (ng/ml)</td>
<td>6.98 ± 2.44</td>
<td>6.61 ± 2.15</td>
</tr>
<tr>
<td>% FL</td>
<td>106.38 ± 78.14</td>
<td>116.22 ± 26.67</td>
</tr>
</tbody>
</table>
Alternative morphine routes

- Nebulized M, 5mg PO vs. 50mg AER, faster [peak plasma] with AER. Bioavailability 24% vs. 5%. *Br J Clin Pharm* 41:3:250-252, 1996
- AER-M bioavailability 20%, [C\text{max}], [T\text{max}] same as PO-M. *J Pharm Pharmacol* 48:1256-1259, 1996
- Intravaginal MS-IR and MS-C. *Pharmacotherapy* 18:863-865, 1998

Oxycodone

- Semisynthetic thebaine derivative
  - 50% bioavailable orally
- Metabolized in liver (CYP2D6) to noroxycodone, oxymorphone and their glucuronides
  - Elim t\text{1/2} 3.5h
- 7.7x potency of codeine
  - 5mg oxycodone = 40mg codeine
  - T\text{max} = 84 minutes
- Oxycodone oral preparations
  - Percocet® 2.5/325, 5/325, 7.5/325 and 500, 10/325 and 650
  - must be identified
  - Roxicodone 5mg, Roxicet 5/325, Tylox
  - Oxy – IR 5 mg, Percolone
  - OxyFast® elixir 20mg/ml
Oxycodone (Oxycontin®)

- [steady - state] achieved in 24 - 36h
- 10, 20, 40, 60, 80 and 160 mg
- Oxycontin 60 - 87% bioavailable
  - low first-pass
  - 30 – 40% immediate release component
- Rectal
  - Absorption, AUC 39% greater
  - $C_{\text{max}}$ 9% higher

Avinza® vs. Oxycontin® for Chronic Low Back Pain
(interim report, Rauck et al, APS 2005)

- Randomized, open-label, multicenter study
- Pts with LBP, VAS > 4/10, not on SRO
- Avinza once daily vs. Oxycontin bid
  - 3-6 week titration to achieve effective dose
  - Ibuprofen 200mg PO as rescue
  - 4 week stable dose assessment followed by 4 week physician directed titration
- VASpain (BPI) + PSQI
- Pts documented electronic pain diary 4 times daily
Avinza® vs. Oxycontin® for Chronic Low Back Pain  
(interim report, Rauck et al, APS 2005)

- 329 patients studied in this ongoing study
- Demographics: more African-Americans and neuropathic pain in Avinza group
- MSO4: Oxycodone equianalgesic ratio 1.5:1
- VAS and side effects similar
- PSQI improved in Avinza group*
- Less proportionate opioid requirement on the Avinza group (58mg vs. 82.5mg)

Consistent with Caldwell et al, J Pain Sympt Man 23:278-291, 2002; Rosenthal et al, APS 2005

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Oxycodone (Oxycontin®)

- [steady - state] achieved in 24 - 36h
- 10, 20, 40, 60, 80 and 160 mg
- Oxycodin 60 - 87% bioavailable
  - low first-pass
  - 30 – 40% immediate release component
- Rectal
  - Absorption, AUC 39% greater
  - $C_{\text{max}}$ 9% higher
Oxycontin®

- Coefficients of variation of $C_{\text{max}}$ and AUC with bid dosing less for Oxycontin than MS-Contin *(Am J Ther 8:231 - 236, 2001)*

Methadone

- Less first-pass results in a lesser O:P ratio of 2:1
- After PO, ± 4h $C_{\text{max}}$
  - 90% protein bound
  - biotransformed extensively in liver by N-demethylation
  - excreted in urine ($\uparrow$ with $\downarrow$ pH)/bile
  - P-450 metabolism (inhibits CYP3A4)
- Analgesia duration 4h; used as q.6-8h, terminal elimination $t_{1/2} = 0 - 96h$ (?)
"The Trouble with Methadone"

- Analgesic vs. addiction
- Discordance between analgesic duration and half-life
- Long respiratory depression
  - Requires at least 36 hour observation
- Metabolism
  - CYP 3A4 inducers (Rifampin, Protease inhibitors) cause decreased [meth], decreased AUC
  - CYP 3A4 inhibitors (Keto-, Fluconazole)
  - ↑ heroin/cocaine use in MMT pts, *Drug Alc Dep 66:2002*
- Induces zidovudine toxicity (*Am J Addict, 10:2001*)
- Cipro inhibits CYP1A2 and 3A4 (increases [meth])

<table>
<thead>
<tr>
<th>Effect on methadone plasma levels</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased methadone plasma levels</td>
<td><strong>CYP 1A2 inhibitors</strong></td>
</tr>
<tr>
<td></td>
<td>Cimetidine, fluvoxamine, ciprofloxacin, INH, zileuton</td>
</tr>
<tr>
<td></td>
<td><strong>CYP 2D6 inhibitors</strong></td>
</tr>
<tr>
<td></td>
<td>Amiodarone, cimetidine, fluoxetine, paroxetine, quinidine, propafenone, delviradine</td>
</tr>
<tr>
<td></td>
<td><strong>CYP3A4 inhibitors</strong></td>
</tr>
<tr>
<td></td>
<td>Amiodarone, ciprofloxacin, cimetidine, clarithromycin, erythromycin, diazepam, diltiazem, disulfiram, fluconazole, fluoxetine, fluvoxamine, grapefruit juice, itraconazole, ketoconazole, metronidazole, nefazodone, propoxyphene, verapamil, zafirlukast, zileuton</td>
</tr>
<tr>
<td></td>
<td>Other: tramadol</td>
</tr>
<tr>
<td>Decreased methadone plasma levels</td>
<td><strong>CYP- 450 enzyme inducers</strong></td>
</tr>
<tr>
<td></td>
<td>Barbiturates, carbamazepine, phenytoin, primidone, rifampin, spironolactone, protease inhibitors</td>
</tr>
<tr>
<td></td>
<td>Other: Ammonium chloride, naloxone, naltrexone, somatostatin</td>
</tr>
</tbody>
</table>
Methadone equianalgesic ratios

- 2.5:1 to 14.3:1 (median, 7.75:1) in 38 cancer patients converted from oral morphine to oral methadone (Ripamonti et al, J Clin Oncol. 1998 Oct;16(10):3216-21)

- 52 consecutive cancer patients evaluated using dose ratio of 1:4 (Me:Mo) in pts receiving < 90mg of Mo; 1:8 in pts receiving 90-300mg/d and 1:12 in pts receiving > 300mg/d. (Mercadante et al, JCO, 19:11: 2001: 2898-2904)

- In 17 cancer pts, methadone dose was calculated according to a 2-step conversion between TDF:oral morphine (1:100 ratio) and oral morphine:oral methadone (5:1 ratio or 10:1 ratio). (Benitez-Rosario et al, Cancer. 2004 Nov 4)

Newer Opioid Delivery Systems

Oral transmucosal and transdermal fentanyl
Oral Transmucosal Fentanyl (ACTIQ®)

Absorption of Opioids From Oral Cavity

Pharmacokinetics of Oral Transmucosal, IV and PO Fentanyl Delivery


### Table: Oral transmucosal fentanyl (Actiq®)

- **200, 400, 600, 800, 1200, 1600mcg**
- **50% bioavailable**
  - 25% through buccal mucosa
  - 75% enters enterohepatic circulation
    - 1/3 (25%) escapes first-pass elimination

<table>
<thead>
<tr>
<th>Dose</th>
<th>$T_{\text{max}}$ (min)</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$T_{1/2}$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200mcg</td>
<td>40</td>
<td>0.39</td>
<td>193</td>
</tr>
<tr>
<td>400mcg</td>
<td>25</td>
<td>0.75</td>
<td>386</td>
</tr>
<tr>
<td>800mcg</td>
<td>25</td>
<td>1.55</td>
<td>381</td>
</tr>
<tr>
<td>1600mcg</td>
<td>20</td>
<td>2.51</td>
<td>358</td>
</tr>
</tbody>
</table>
Distribution of successful dose levels

A Double-Blind, Placebo-Controlled Study of Oral Transmucosal Fentanyl Citrate (OTFC, Actiq®) for the Treatment of Breakthrough Cancer Pain

Company FDA Submission

Fentanyl Transdermal Delivery

Patch with or without rate-limiting membrane (fentanyl-containing silicone Adhesive, no subcutaneous depot)
Fentanyl transdermal delivery

- NOT FOR USE IN ACUTE PAIN
- No first-pass metabolism
- Consistent analgesia
  - improvement in sleep
- Pharmacokinetic considerations:
  - [fentanyl] steady-state 12 - 24h (1-2 ng/ml)
  - q.72h dose (q.48h with “tumor fever”, patient variability)
  - half-life ± 17h after patch removal

DURAGESIC® (fentanyl transdermal system) CII is indicated for patients in chronic pain who require continuous opioid analgesia and whose pain cannot be managed by lesser means such as acetaminophen-opioid combinations, nonsteroidal analgesics, or p.r.n. dosing with short-acting opioids.

BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC IS CONTRAINDICATED:
- In the management of acute or postoperative pain, including use in outpatient surgeries
- In the management of mild or intermittent pain responsive to p.r.n. or non-opioid therapy
- In doses exceeding 25 mcg/hr at the initiation of opioid therapy

(See CONTRAINDICATIONS section of full Prescribing Information for further information.)

SAFETY OF DURAGESIC HAS NOT BEEN ESTABLISHED IN CHILDREN UNDER 2 YEARS OF AGE. DURAGESIC SHOULD BE ADMINISTERED TO CHILDREN ONLY IF THEY ARE OPIOID-TOLERANT AND AGE 2 YEARS OR OLDER. (SEE PRECAUTIONS—PEDIATRIC USE SECTION OF FULL PRESCRIBING INFORMATION FOR FURTHER INFORMATION.)

DURAGESIC is indicated for treatment of chronic pain (such as that of malignancy) that:
- Cannot be managed by lesser means such as acetaminophen-opioid combinations, nonsteroidal analgesics, or p.r.n. dosing with short-acting opioids and
- Requires continuous opioid administration

The 50, 75, 100 mcg/hr dosages should ONLY be used in patients already on and tolerant to opioid therapy.

Please see full Prescribing Information, including Boxed Warning.

NOTE: Since elderly, cachectic, or debilitated patients may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance, they should not be started on DURAGESIC doses higher than 25 mcg/hr unless they are taking more than 135 mg/day of oral morphine or equivalent dose of another opioid.
Oral morphine (mg/24h) to TDF (mcg/h)

<table>
<thead>
<tr>
<th>Morphine (mg/24h)</th>
<th>TDF (mcg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-134</td>
<td>25</td>
</tr>
<tr>
<td>135-224</td>
<td>50</td>
</tr>
<tr>
<td>225-314</td>
<td>75</td>
</tr>
<tr>
<td>315-404</td>
<td>100</td>
</tr>
<tr>
<td>495-584</td>
<td>150</td>
</tr>
<tr>
<td>675-764</td>
<td>200</td>
</tr>
</tbody>
</table>

Oral Opioid Conversion Table

<table>
<thead>
<tr>
<th>Opioid</th>
<th>mg/d</th>
<th>mcg/h</th>
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</thead>
<tbody>
<tr>
<td>Hydro-, Oxycodone</td>
<td>22.5-67</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>68-112</td>
<td>50</td>
</tr>
<tr>
<td>Codeine</td>
<td>150-447</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>448-747</td>
<td>50</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>6-17</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>18-28</td>
<td>50</td>
</tr>
<tr>
<td>Morphine</td>
<td>45-134</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>135-224</td>
<td>50</td>
</tr>
</tbody>
</table>
TDF and Constipation

- Constipation and N/V less compared to oral MSO4 \(^{(\text{Semin Oncol 25:47-53, 1998})}\)
- Constipation and laxative use less than MS-C in cancer patients. \((\text{Pain 54:3:527-534, 1996; Anticancer Drugs 3:39-43, 1995})\)
- Incidence of constipation in chronic pain pts receiving TDF (29%) vs. MS-CR (48%). \((\text{BMJ 322:1154-1158, 2001})\)
- Constipation rates in chronic pain pts comparing oral oxycodone-CR (6.1%), morphine-CR (5.1%) and TDF (3.7%). \((\text{South Med J 97(2):129-134, 2004})\)

TDF and Low Back Pain

- 50 patients evaluated q.3d during titration and monthly during maintenance
- Pain: improvements in pain VAS and NPS
- Disability: Oswestry Disability Questionnaire (ODQ) and Pain Disability Index (PDI) improvement
- Sleep: fewer awakenings/night
- 82% demonstrated a TDF preference

Cancer Pain

Chronic, non-malignant pain

Acute pain

New patch strengths/formulations?

12.5 mcg/h TDF patch
Iontophoretic patch

- Polarity change of skin facilitates absorption of medication
- Amount absorbed // intensity of electrical stimulus
- Used clinically for Iontocaine® system

Iontophoretic fentanyl patch

- Lithium battery, LED (dose indicator) and integrated circuit in a credit card size adhesive patch.
- Electrical impulse of 170 microamps/2.75cm² anode delivers approximately 40 mcg (10mg patch)
- 40 mcg dose with 10 minute lockout, no basal
- Duration 24 hours or 80 doses
Tramadol (Ultram®, Ultracet®)

- Synthetic analogue of codeine, binds to *mu* receptors and inhibits NE and 5-HT$_3$ reuptake
- Analgesia due to tramadol + M1-metabolite (~6x potency)
- Well abs GI (bioavail 75%), 20% bound
- Metabolic pathways N- and O-demethylation/conjugation.
  - Formation of M1- dep on CYP-450.
  - 30% excreted unchanged.
- [peak plasma] at 2.3h, t$_{1/2}$ = 6.7h, liver impairment 1.9h and 13.3h
- Seizure risk ↑ with SSRI/MAOI/TCA/opioid use
- 50-100mg PO q4-6h, 400mg/24h, 37.5mg/325mg T/acetaminophen
Geriatrics, Opioids and Non-Malignant Pain

- Especially undertreated
- Higher rate of renal toxicity with NSAID’s
- GI bleed incidence higher
  - 3-4% vs. 1% in younger patients
- < 1% of MMP attendees


"Few things a doctor does are more important than relieving pain. . . pain is soul destroying. No patient should have to endure intense pain unnecessarily. The quality of mercy is essential to the practice of medicine; here, of all places, it should not be strained."

Marcia Angell, M.D.