New Opioid Formulations: Hope on the Horizon

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Outpatient: Critical Issues

- Utilize Optimal Opioids
- Optimize Route of Delivery
- Abuse-Resistant Formulations
- Safe Dosing/Prescribing
- Opioid Tolerance/Dose Escalation
Utilizing Optimal Opioids

- Avoid opioids with active metabolites
- Avoid untoward effects (e.g., histamine release)
- Match opioid half-life to indication to avoid lack of titration for acute pain and extended-release formulations for chronic pain
- Decreased respiratory depression
- Decreased physical dependence
- Decreased opioid tolerance
Optimize Route of Delivery

- Choose route that avoids poor bioavailability, thereby avoiding excess opioid loading
- Choose route that matches the opioid’s intrinsic characteristics
- Pick route of delivery to match indication
  (acute vs. chronic pain)
Need to Improve Bioavailability

Oral Route Bioavailability:

- Oral morphine (MSContin, Avinza) – 30%
- Oral oxymorphone (Opana IR, ER) – 10%
- Oral hydromorphone (Dilaudid) – 30-35%
- Oral oxycodone (OxyIR, OxyContin) – 60-80%

Other Routes:

- Fentanyl patch (IonSys, Duragesic) – 30-70%
- Fentanyl TM (Actiq, Fentora) – 50-65%
Double Trouble: Extended-Release Low Bioavailable Drug Formulations

IV dose: 0.2mg

10 X

Oral BA = 10%

Crushed IV dose: 10mg

50 X

Extended-Release

2mg pill

5 X

10mg pill
**Optimal Scenario:**
Methadone Resists Abuse

**IV dose:** 5mg

1 X

Oral BA = 90%

5mg pill

**Crushed IV dose:** 5mg

1 X

Extended-Release not necessary

5mg pill
Abuse-Resistant Formulations

- Need to avoid the ability to crush or rapidly extract drug with ethanol (OxyContin, Palladone)
- Remoxy – SABER technology (Durect/Pain Therapeutics/King Pharmaceuticals)
- Naloxone/Naltrexone additive
  - Suboxone (buprenorphine/naloxone)
  - Oxytrex (oxycodone/naltrexone)
Abuse-Resistance In Practice

Remoxy
Intact
Crushed

Oxycontin®
Intact
Crushed

No Rapid Release of Oxycodone = No Euphoria
Transdermal Opioids

- Due to delay in onset of plasma levels, this route appears best for chronic pain conditions.
- Opioids delivered transdermally:
  - Fentanyl (Duragesic, IonSys)
  - Sufentanil (Endo, in development)
  - Buprenorphine (Europe, Australia)
  - Hydromorphone (Altea, in development)
Outpatient Cancer Breakthrough
Pain

- Actiq, Fentora (buccal TM delivery of fentanyl)
- Rapinyl (sublingual fentanyl tablet)
- Many other fentanyl formulations in pipeline
- Saliva response results in at least half of the drug being swallowed, lowering bioavailability
- AcelRx sublingual sufentanil NanoTab™ formulation – above 90% bioavailability
Safer Dosing/Prescribing

- Scheduled drugs less trackable than UPS
- Patient reported usage, pill counting and urine testing only methods to determine opioid usage
- Need better tracking around opioid dosing history
- RFID chip on OxyContin bottles only helps track from manufacturer to pharmacy
- AcelRx electronic NanoTab™ dispensers will allow download of dosing history
Opioid Tolerance

- Opioid dose escalation at all time high
- Pain now the “5th Vital Sign”, fears slightly abating around high-dose prescribing
- Dose escalation driven by tolerance and disease progression
- Research into novel mechanisms to treat or avoid opioid tolerance are vital
- Until then, opioid rotation is only option
Opioid Tolerance

- Complex clinical phenomenon, not easy to study
- Studies not run long enough, nor detailed enough
- Recent studies suggest age plays important role
- Targets: NMDA antagonists, mu-receptor antagonists, bivalent mu/delta ligands, RGS protein modulators
Inpatient: Critical Issues

- #1 hospital medication error: Analgesics
- Most common mistake: Wrong Dose
- Patient-Controlled Analgesia (PCA)
  - IV PCA – misprogramming, basal rates, etc
  - IonSys – transdermal fentanyl on-demand
  - AcelRx – sublingual sufentanil NanoTabs™
  - with hand-held PCA dispenser
Is Morphine the Gold Standard?

- Morphine suffers from a number of pitfalls
- Relatively high-level of side-effects compared to other opioids
- Active metabolites, M3G and M6G, that build up particularly rapidly in the elderly
- M3G produces dysphoria, anxiety, anti-analgesia
- Often leads to overdosing and death due to perceived patient discomfort by nurse/MD
Post-Operative Pain
Is IV Route the Gold Standard?

- For acute pain, IV route of administration often held up as the gold standard
- However, IV opioids often achieve rapid, high plasma drug levels that can lead to respiratory depression
- Sublingual sufentanil NanoTabs™ offer rapid onset with safer drug plasma profile
Phase I Data in 12 Subjects

Human Clinical Study

Time (min)
0 10 20 30 40 50 60 70 80 90

Sufentanil Plasma Concentration (pg/ml)
0 2 0 4 0 6 0 8 0 1 0 0 1 2 0 1 4 0 1 6 0 1 8 0 2 0

10 mcg Sufentanil NanoTab
5 mcg Sufentanil NanoTab
2.5 mcg Sufentanil NanoTab
5 mcg IV infusion
Summary

- Need to pursue optimal opioids with optimal routes of delivery based on patient needs
- More aggressive tracking of patient dosing history in outpatient setting
- Pursue novel therapies to avoid or treat opioid tolerance to minimize dose escalation in chronic pain conditions
- Simplified patient-controlled opioid dosing
- Never avoid pursuing optimal pain therapies out of fear of abuse/diversion