URODA

Ultra Rapid Opioid Detoxification under Anesthesia

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Disclosures:

- No conflicts of interest or disclosures to make.
- Will be mentioning several ***off-label uses*** for discussion purposes today.

- ***No animals or opium poppies were harmed in the making of this presentation***

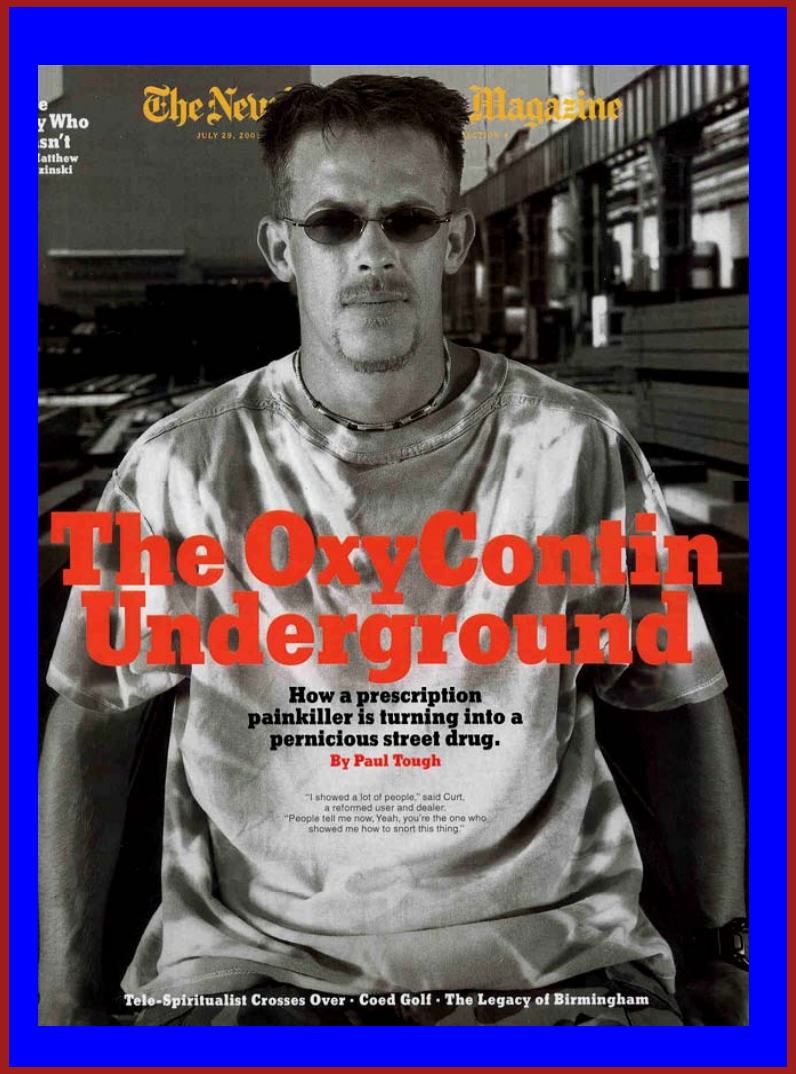
The views expressed herein are my own and are not meant to represent the interest or opinions of the US Army or the DoD.

Objectives

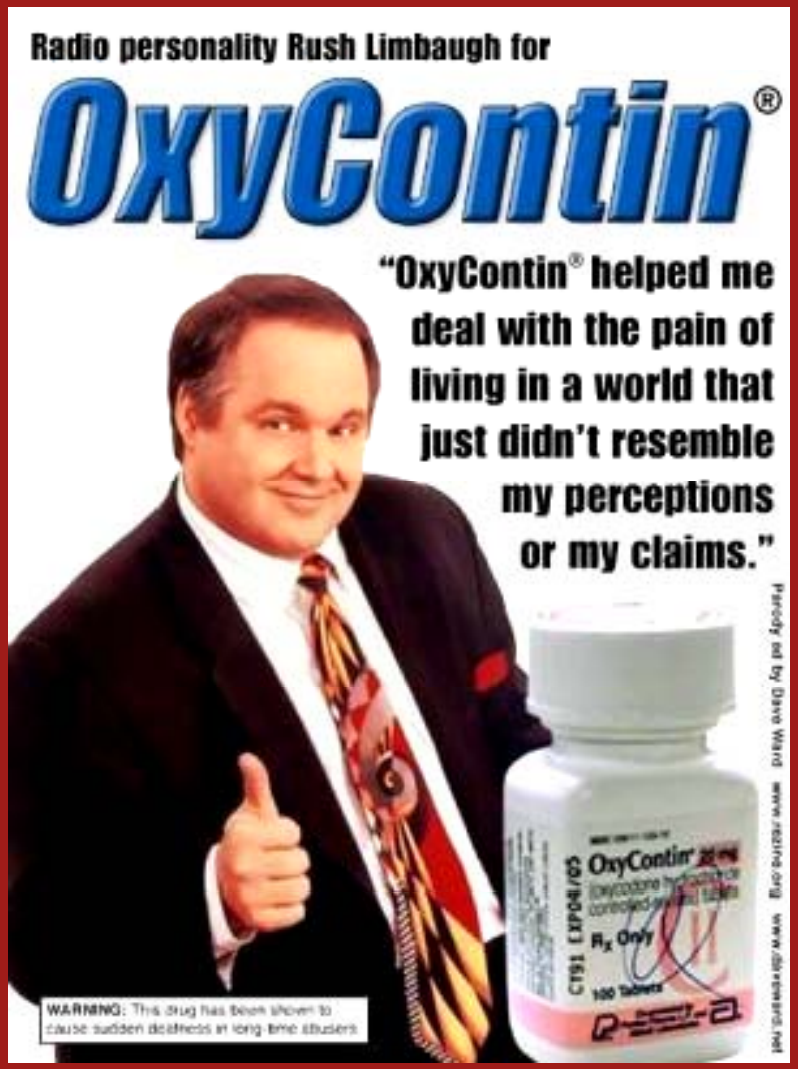
- Intro - pain, opioids, misuse of Rx meds
- Clarify - Opioid addiction vs. dependence
- Why URODA over conventional treatments ?
- Rationale - why now & why burn patients
- ISR Burn Center URODA Protocol
- Results - let the data speak for itself
- Discussion - The real McCoy?
- Future direction / plans

Scientific literature review: narcotics

The New Yorker Magazine



Paid advertisement



Soothes all that ails ya' & kids love it too !

Contained 1 grain (65 mg) of MSO_4 per fluid ounce !!!

Effectively ***quieted*** restless infants and small children

…no more noisy sniffling or pesky breathing…

Review of scientific literature

"There is arguably nothing worse than pain. Uncontrolled pain can take over your life. You just want it to stop. … [But] opioids have some nasty side effects"

» **Consumer Reports, April 2008**

Fascinating & enlightening

OIF / OEF Pain Stats

- Pain is a serious problem in the military
- 970 OIF / OEF vets from Southeastern VA
  - ~31 yr old white male served AD in Iraq
- 82% (n=793 / 970) had pain scores documented
- 47% (n=369 / 793) of these had pain > 1/10
- 28% (n=219 / 793) had moderate to severe pain
  - Pain rated > 4/10 (considered by VA national policy to be clinically significant pain)

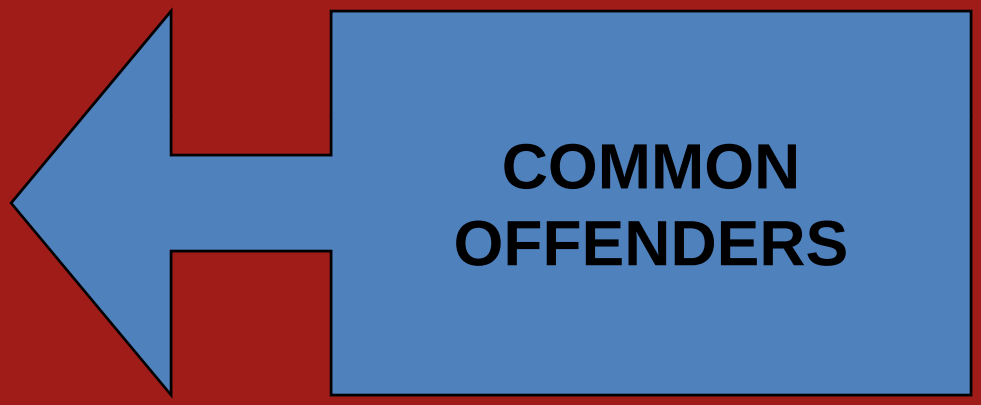
~60% of pt's with pain reported significant pain

(n=219 / 369)

– Gironda et al, Pain Medicine 2006: 7(4)

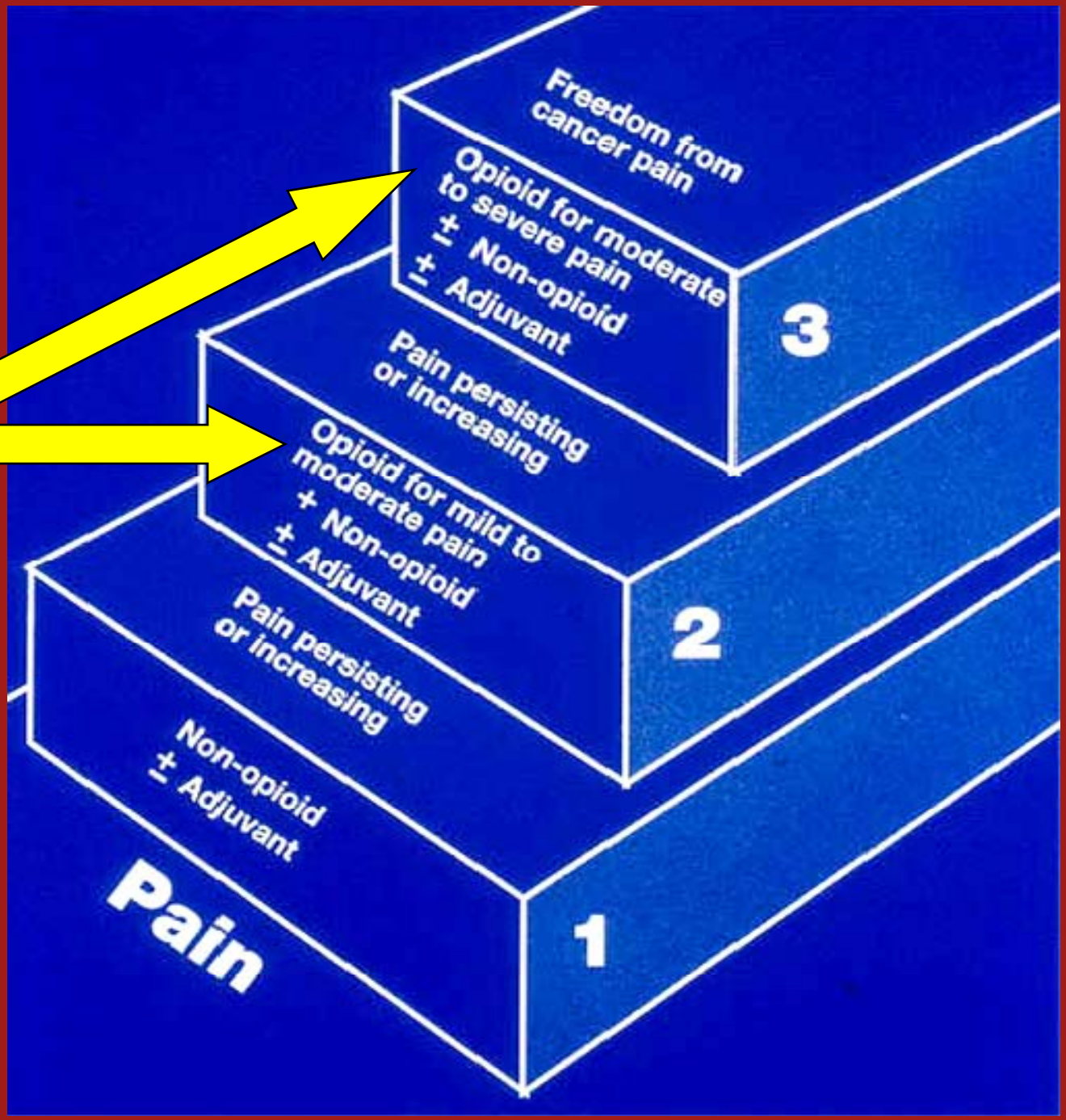
Introduction to Opioids – Pharm 101

- Narcotics are clinically used to manage pain
  - **Morphine**
  - **Codeine**
  - **Fentanyl**
  - **Hydromorphone**
  - **Percocet, Darvocet, Vicodin, Lortab**



- Opioids are often viewed as necessary evils

Opioids in the WHO Ladder of Analgesia for Cancer Pain



Intro to Opioids – Pharm 202

Opioid Receptor Classification

Receptor	*Prototypic drug*	*Proposed actions*
μ_1	Most endogenous, naturally-occurring or synthetic opioids	Supraspinal analgesia
μ_2	Morphine	Respiratory depression Cardiovascular effects
δ	Enkephalins	Spinal analgesia
κ	Ketocyclazocine and dynorphin	Spinal analgesia Sedation, miosis
σ	N - allylnormetazocine	Psychotomimetic effects

Taken from Goodman & Gilman's Pharmacology

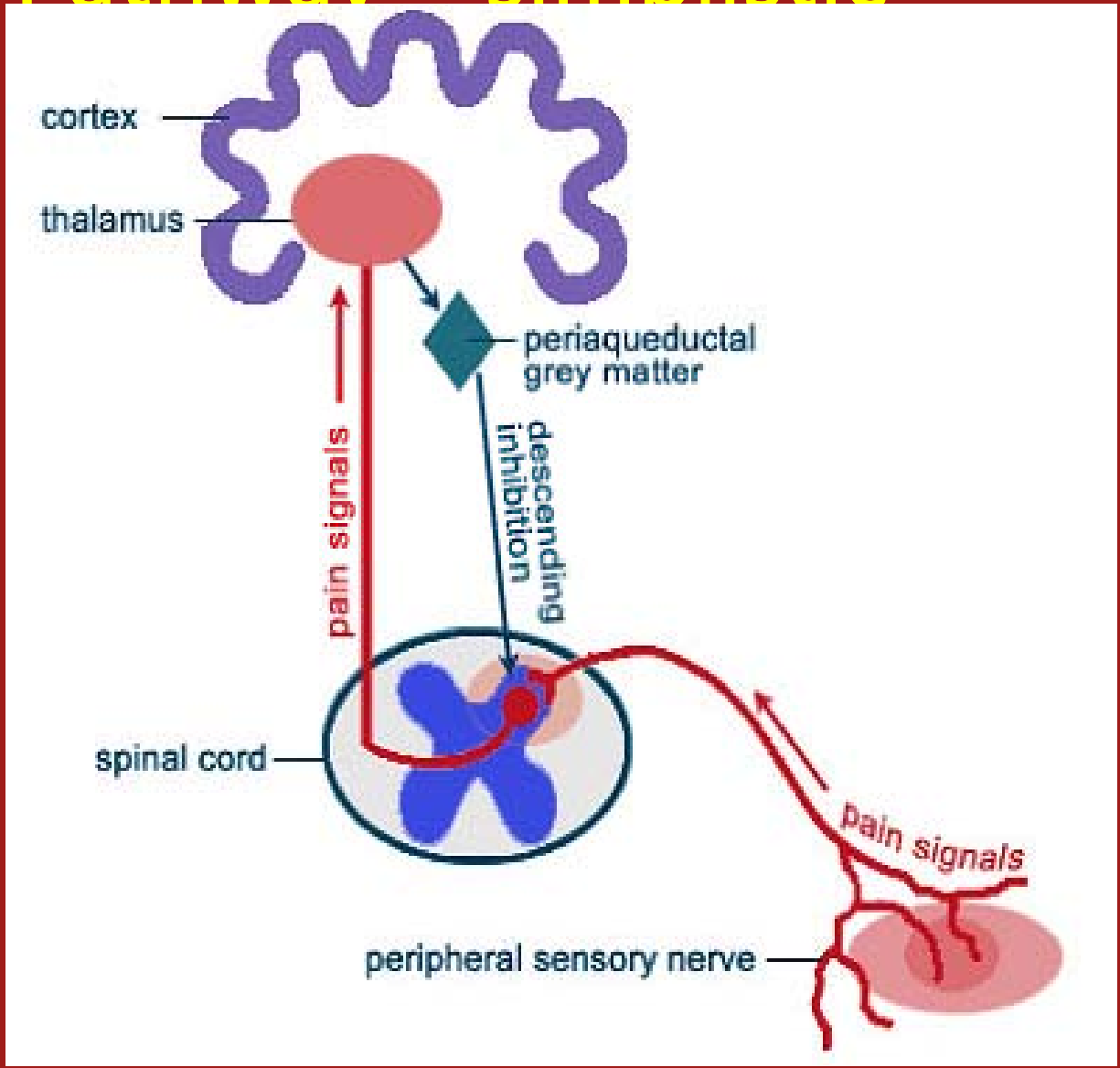
BLUF

The *mu* receptor is the one which is most relevant with regards to opioid abuse and treatment

- Analgesia
- Euphoria
- Addiction

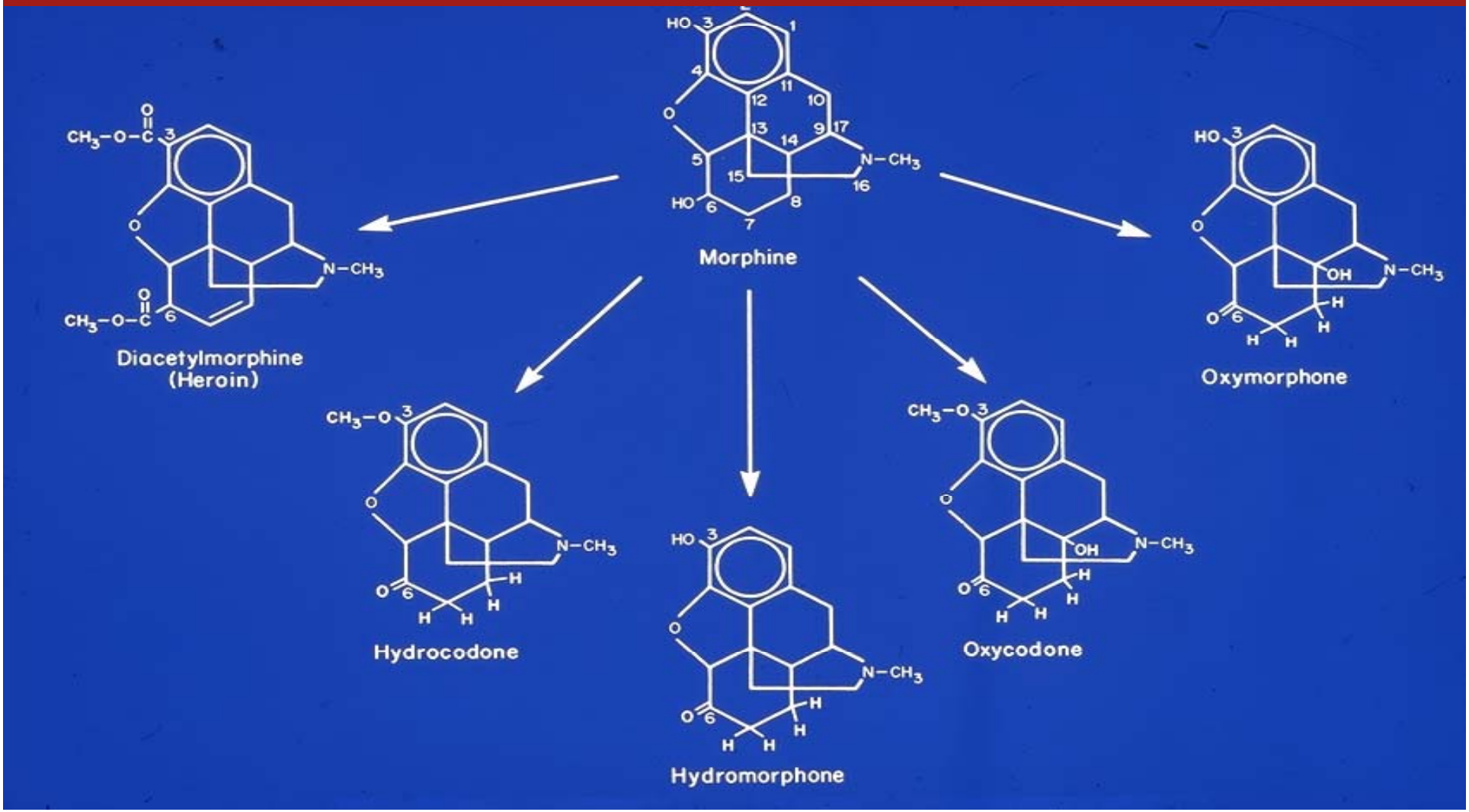
??? role of other opioid R's in addiction

Pain Pathway – simplistic



Intro to Opioids – Pharm 303

Semisynthetic Opioids



Effects of Opioids

- Sedation
- Pupil constriction
- Slurred speech
- Impaired attention/memory
- Constipation, urinary retention
- Nausea
- Confusion, delirium
- Slowed heart rate
- Respiratory depression

DSM criteria for opioid intoxication

Definitions

Opioid Tolerance

Opioid (Physical) Dependence

Opioid Addiction

Opioid Tolerance / Habituation

- With continued use, progressively more & more opioid is necessary to produce the same analgesic effect
  - There is no analgesic ceiling
- *Pharmacologic property* of a class of agents
- Not = across all effects

  TOLERANCE to analgesia but **tolerance** to constipation

Physical Dependence

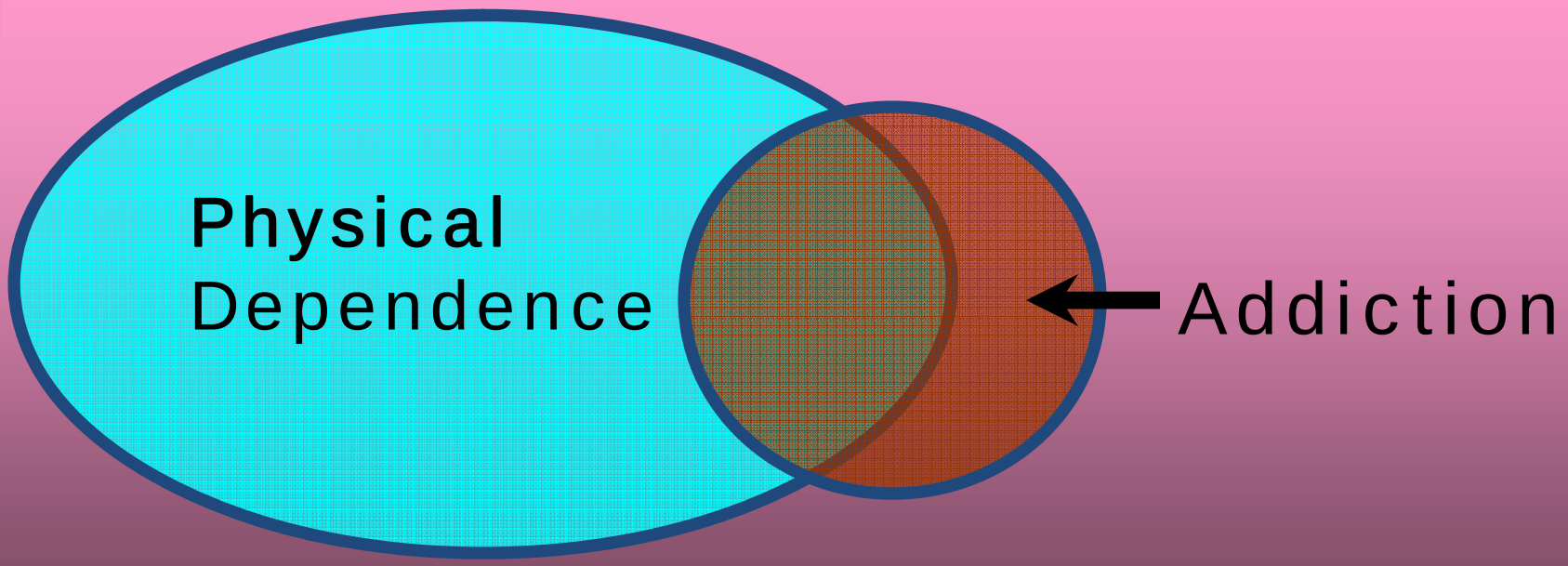
- *Not the same as tolerance or addiction !!!*

- **= When the abrupt discontinuation of narcotics or the administration of narcotic antagonists (naloxone / Narcan) produces physical withdrawal symptoms**

Addiction = Psychological Dependence

- *A behavioral state characterized by a compulsive desire to obtain a drug in order to experience its psychic effects, despite full knowledge of its harmful effects*
- Not a pharmacologic property of the drug
- Not synonymous with tolerance or physical dependence
  - BUT IS **OFTEN CONCURRENT**

Physical Dependence & Addiction



Pain vs. Addiction

	Chronic Pain	*Addiction*
Out of control with medications	**No**	**Yes**
Medications improve QOL	**Yes**	No
Continues use despite problem	No	Yes
Denial about any problems	No	**Yes**

Pain vs. Addiction

	Pain	*Addiction*
Self medicates / Rx misuse	**No**	**Yes**
Craves drug when not in pain	No	**Yes**
Requests specific opioids	No	Yes
Gets med from non-med source	No	**Yes**

Fatal Drug Poisoning

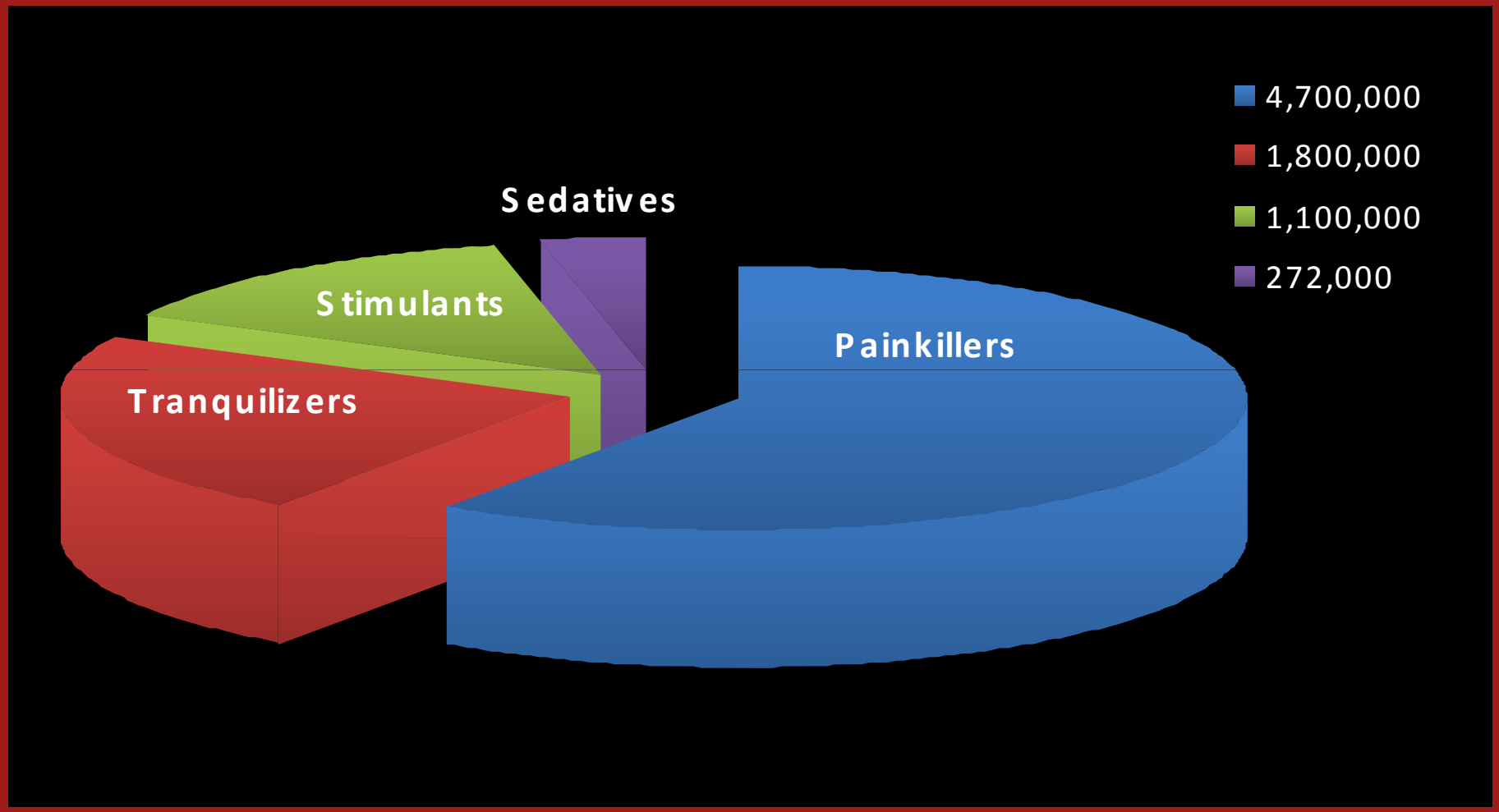
- Between 1999 & 2002, the number of opioid analgesic poisonings on death certificates rose 91.2%*
- During this time period, poisoning from opioid analgesics surpassed both cocaine & heroin poisoning as the most frequent type of drug poisoning found on death certificates in the U.S.*
- In Florida 2007, 3 times more deaths from prescription drugs than from all illicit drugs combined. **

* Source: Paulozzi, L.J., Budnitz, D.S., Xi, Y, 2006. Increasing deaths from opioid analgesics in the United States. Pharmacoedidemiology and Drug Safety 15, 613-7.

** New York Times, June 14, 2008.

Rx Drug Misuse in the U.S.

6.4 million aged 12+ used a Rx drug (non-medically) in the past year



NSDUH, 2006

SAMHSA Advisory

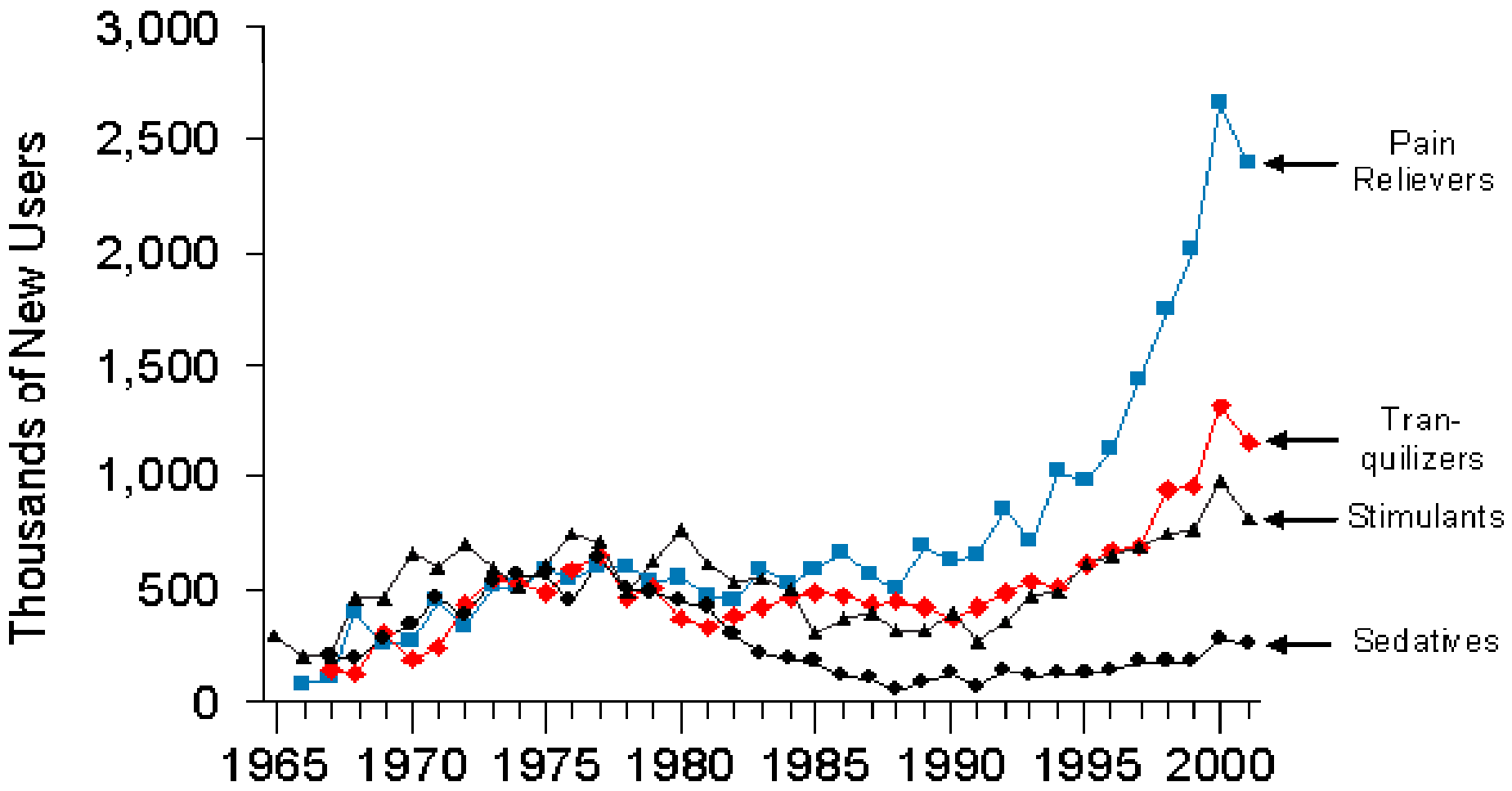
Substance Abuse and Mental Health Services Administration

- **"Federal Report Shows New Non-Medical Users of Prescription Pain Relievers Outnumbered New Marijuana Users Between 2002 and 2004"**

- **Prescription drug misuse / abuse**

http://www.samhsa.gov/news/newsreleases/061027_PainRelievers.htm

Number of New Non-medical Users of Therapeutics



Two Views of Opioid Dependence

Recognition of this problem has spurred a long-running debate that centers on two different views:

1. *Opioid addiction is a **disease** that requires long-term maintenance with medication.*

Or

2. *Opioid addiction which stems from weak will, lack of morals, or other psychodynamic factors or is a predilection **(character flaw)** that is rectified by criminalization of uncontrolled use and distribution and measures promoting abstinence.*

OPORD URODA

- Recognize the enemy - THE PROBLEM
- Identify the mission - THE TARGET
- Research for potential solutions - THE PLAN
  - Best fit for time, place, resources & personnel
    - DEFINE A COHORT
  - Compare friction points & potential risks
- Act with extreme malice - EXECUTE PLAN
- Regroup & AAR to improve the process
  - *Present findings at ATACCC and either cry in our beer or proudly re-hydrate with friends*

Problem

- Opioid addiction & opioid dependence is too costly
  - Healthcare $$$
    - Provider visits
    - Prescription refills
    - Complications of chronic opioid use
  - Time spent ***away*** from the family and society
    - Sedated – sleeping ~12-16 hrs a day (low quality sleep)
    - Preoccupied / distracted & moody / depressed
  - Productivity - ? RTD's, MOS reclassifications
  - BLUF : QALY's – Isn't this why we do what we do ?

Target

1. URODA safely; minimizing complications
   - naloxone, dexmedetomidine and ketamine
2. Reduce daily narcotic requirements of opioid dependent pain patients by 50%
3. Improve quality of life - QALY's
   - Fewer pills & polypharm / Less adverse effects
   - More awake / Less sedated
   - More time with family & friends / Less in hospital
   - Reduce daily VAS pain scores
   - Improve patient satisfaction

Plan: Research potential therapeutic options

- No intervention – status quo
- Quit Cold Turkey
- Outpatient behavioral health
  - +/- group therapy / hypnosis / acupuncture
- Inpatient behavioral health
- Methadone clinic
- ROD - Buprenorphine/Naloxone (Suboxone)
- RODA → UROD→ **URODA**

Cold Turkey Opioid Withdrawal

… that which doth not kill us makes us stronger…

Symptoms of opioid withdrawal:

- Diaphoresis
- Lacrimation
- Coryza
- Tachycardia
- Headache
- Abdominal cramps
- Nausea / Vomiting
- Diarrhea
- Insomnia / Restlessness

Why URODA ?

- It's riskier, more expensive, and wrought with very high relapse rates (15-80% at 18 mo) in prior studies.

- Why not rely on more conventional pharmacological interventions such as methadone tapers through outpatient clinics?

- Why not rely on the outpatient treatment that has stood the time honored test…
  - Of being a reason to "defer to network" ?

By far, the easiest road to take.

Why URODA ?

- URODA has been used successfully
- Avoids the protracted course of debilitating physical and psychological withdrawal symptoms
- Compressing the detoxification process into an abbreviated symptomatic period
- Precipitating withdrawal while under general anesthesia

- Favrat B, Zimmermann G, Zullino D, Krenz S, Dorogy F, Muller J, et al. Opioid antagonist detoxification under anaesthesia versus traditional clonidine detoxification combined with an additional week of psychosocial support: a randomised clinical trial. Drug Alcohol Depend. 2006 Feb 1; 81(2): 109-16. Epub 2005 Jul 15.
- Collins ED, Kleber HD, Whittington RA, Heitler NE. Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. JAMA. 2005 Aug 24;294(8):903-13

Aetna's policy on URODA

- The post-detoxification relapse rate for these techniques appears to be **quite variable**.
- The most suitable patients for these procedures **must still be defined**.
- **Possible aspiration and choking** from emesis may occur when an anesthetized or heavily sedated individual is detoxified while asleep.
- The approach must be regarded as **experimental** with both risks and benefits remaining uncertain.

- **NOT COVERED**

http://www.aetna.com/cpb/medical/data/300_399/0317.html

We tried RODA already …
it never worked before

But as you all know …

OUR PATIENTS ARE THE BEST THERE'S EVER BEEN!

And plus, in the military
we just grow them better !

Plan

"In times of change the learners will inherit the world…while the learned will find themselves beautifully equipped to deal with a world that no longer exists"

-Eric Hoffer

-American social philosopher

Decision Matrix - URODA

Pros	Cons
•Less work for patient *"I want to be completely out"* •No out of pocket costs •Just another admission •Short burst, then long haul (sense of accomplishment then determination)	•Staff & labor intensive for the acute care team •Expensive historically •Stigma of "drug rehab" •Slow, long haul (*"Look doc, last thing I wanna hear now is that 'slow & steady' wins the race…"*)

Previous study cohorts

Unfavorable risk-to-benefit ratios due to:

- Poor access to medical care
  - ie- only in exchange for research participation
  - Sub-optimal follow-up
- Significant out-of-pocket expenses (uninsured)
- Often little to no social support
  - Return to negative habit forming environments
- Patient composition
  - Homeless / Juveniles / IVDA's / minimally educated / questionably motivated / unknown baseline

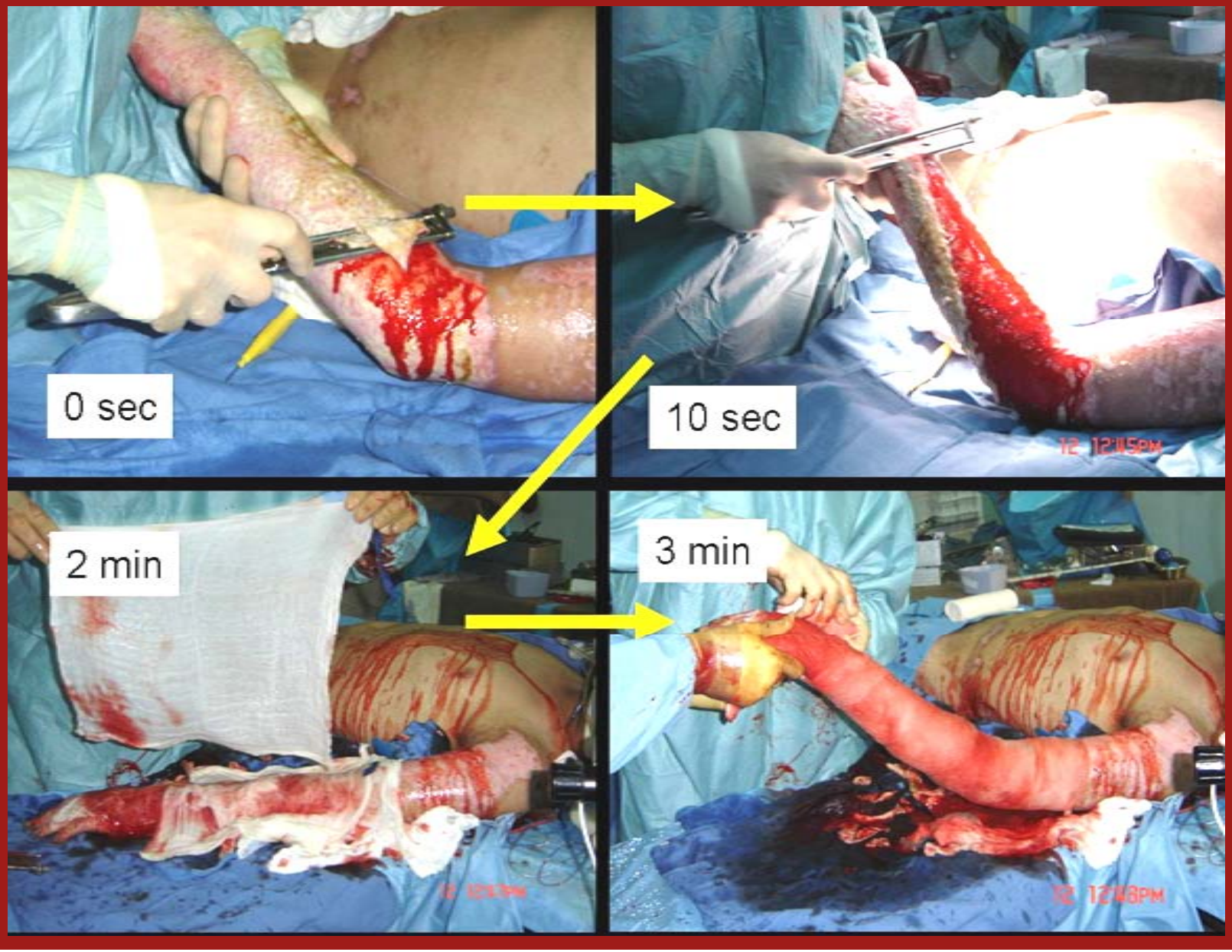
But the Military…

Favorable risk-to-benefit ratios due to:

- Access to medical specialists & MTF's
  - Promotes better follow-up
- Little financial cost for service-members
  - TRICARE
- Close-knit social support networks
  - Family - spouses, children, parents, …
  - Friends – old unit, WT unit, hospital staff
  - Camaraderie amongst Wounded Warriors
- WARRIOR ETHOS & strength of character
  - Highly motivated & high-functioning individuals

Are burns really that different ?

Is burn surgery really that different?



Is burn surgery really that different?

Execute

Keep in mind:

Change often occurs slowly.

"The journey of a thousand miles begins with a single step"

Background

- Since 2003, >800 military burn casualties have received comprehensive care at the U.S. Army Institute of Surgical Research Burn Center.
- The purpose of this case series was to review the management of burn patients who requested URODA - a multi-D PI project .
- The patient's hospital course was reviewed and their response to the treatment assessed.
- The rationale and multidisciplinary processes used to implement URODA at a contemporary burn center are described.

Execute -

This is a procedure guideline only. Variance will be in accordance with clinical judgment.

- Initial screening assessed potential candidates for URODA
  - Multidisciplinary medical specialists including anesthesiologists, physiatrists, surgeons, physician assistants, social workers, occupational therapists and the behavioral medicine team
- Each patient was referred and independently evaluated by the behavioral medicine team, a physiatrist, a senior burn surgeon and an anesthesiologist
- Exclusion criteria:
  - Age >65
  - ASA III's and IV's
  - Patients not willing to be assessed and follow-up as instructed

Execute -

This is a procedure guideline only. Variance will be in accordance with clinical judgment.

If selected & cleared for participation →

- Team discussion with attending burn surgeon to ensure no operative plans were imminent
  - minimize new opioid prescriptions post-URODA
- Each patient would also undergo extensive counseling with anesthesia team as well as behavioral health team
  - Written Informed Consent
  - Psychological assessments
    - **Comprehension & compliance**

Execute - day before procedure

This is a procedure guideline only. Variance will be in accordance with clinical judgment.

- Direct admit to the ward by Burn Team
  - Start PIV's
  - Start clonidine patch
  - Bowel prep
  - MIVF's while NPO
  - D/C all narcotics
    - Including transdermal fentanyl, and methadone
  - NPO after midnight except meds

Execute -

This is a procedure guideline only. Variance will be in accordance with clinical judgment.

- Transfer to ICU – day of procedure
  - GERD prophylaxis
  - Standard ASA monitors + BIS (awareness)
  - Initiate propofol and low-dose ketamine gtt's
  - Standard controlled induction / intubation
  - OGT placed to LIWS
  - Foley cath for bladder decompression / I&O's

Execute -

This is a procedure guideline only. Variance will be in accordance with clinical judgment.

- Escalating naloxone doses until sympathetic response abolished

  = mu receptor saturation

  = maximal opioid antagonism

- Maintenance naloxone gtt x ~24 hrs
  - to effect complete reversal of agonist ligands to the mu opioid receptors

Execute – after ~24 hours narcan gtt

This is a procedure guideline only. Variance will be in accordance with clinical judgment.

- D/C propofol
- D/C narcan
- +/- D/C ketamine
- Continue Dex through extubation
- D/C OGT & foley
- Extubate to supplemental O2 as able
- D/C precedex in ~12 hours
- ADAT and transfer to ward

Execute -

This is a procedure guideline only. Variance will be in accordance with clinical judgment.

- Acetaminophen 500-1000 mg QID
- Gabapentin - titrate to 1800+ mg/day
- TCA du jour
- Acupunture therapy
- Continue clonidine tts as tolerated
- Plan Toradol 30 mg IV Q8' x 7 days
  - Then convert to PO COX-2 NSAID (meloxicam)
- +/- Pregabalin (with neurontin)
- +/- Tramadol
- +/- Suboxone

Execute -

This is a procedure guideline only. Variance will be in accordance with clinical judgment.

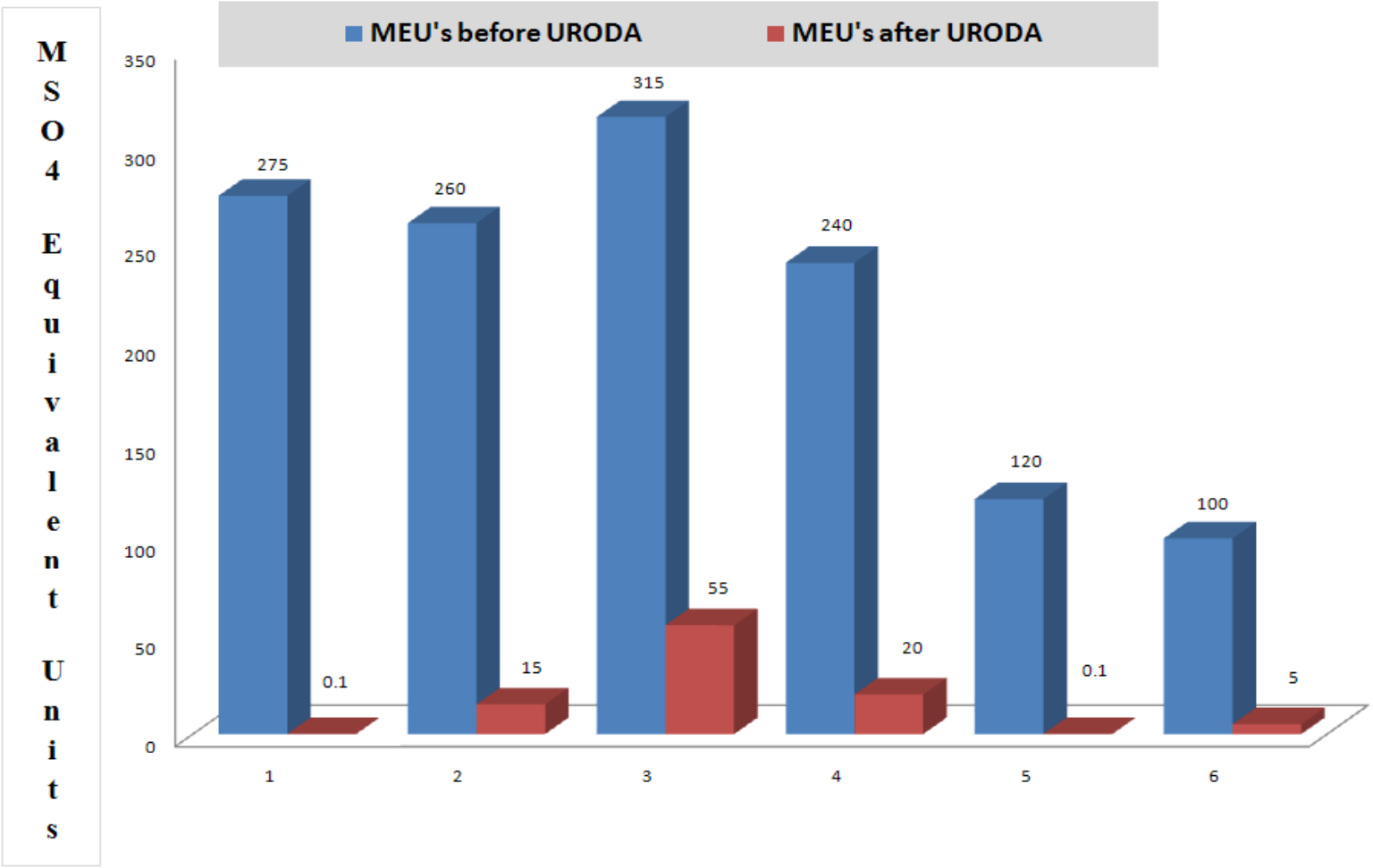
- Sleep hygiene protocols
- Continue patient and family education
  - Reinforce treatment goals and strategies
- Scheduled f-u appointments prior to discharge
  - Burn Clinic
  - Behavioral Health Team
  - Telephonic interview by Anesthesiologist

Results - Patient Characteristics prior to URODA.

~31 yo AD male s/p 38% TBSAB ~ 2yrs from DOI and with an avg daily 220 MEU's.
Mean ISS of 30.
The mean duration of narcotic use was 672 days [range 239-1156 days] or 1.9 years.

Patient	Age (yrs)	TBSA (%)	ISS	# Days Post-Injury	# of Opioid Days	Opioid Use – pre-URODA (MEU)	Opioid Use – post-URODA (MEU)
1	30	34	25	568	568	275	0.1
2	38	65	38	1156	1156	260	20
3	36	34	25	675	675	315	75
4	28	48	38	742	742	240	25
5	28	17	29	239	239	120	0.1
6	27	31	25	657	657	100	10
Avg.	**31.2**	**38.2**	**30.0**	**672.8**	**672.8**	**218.3**	**21.7**

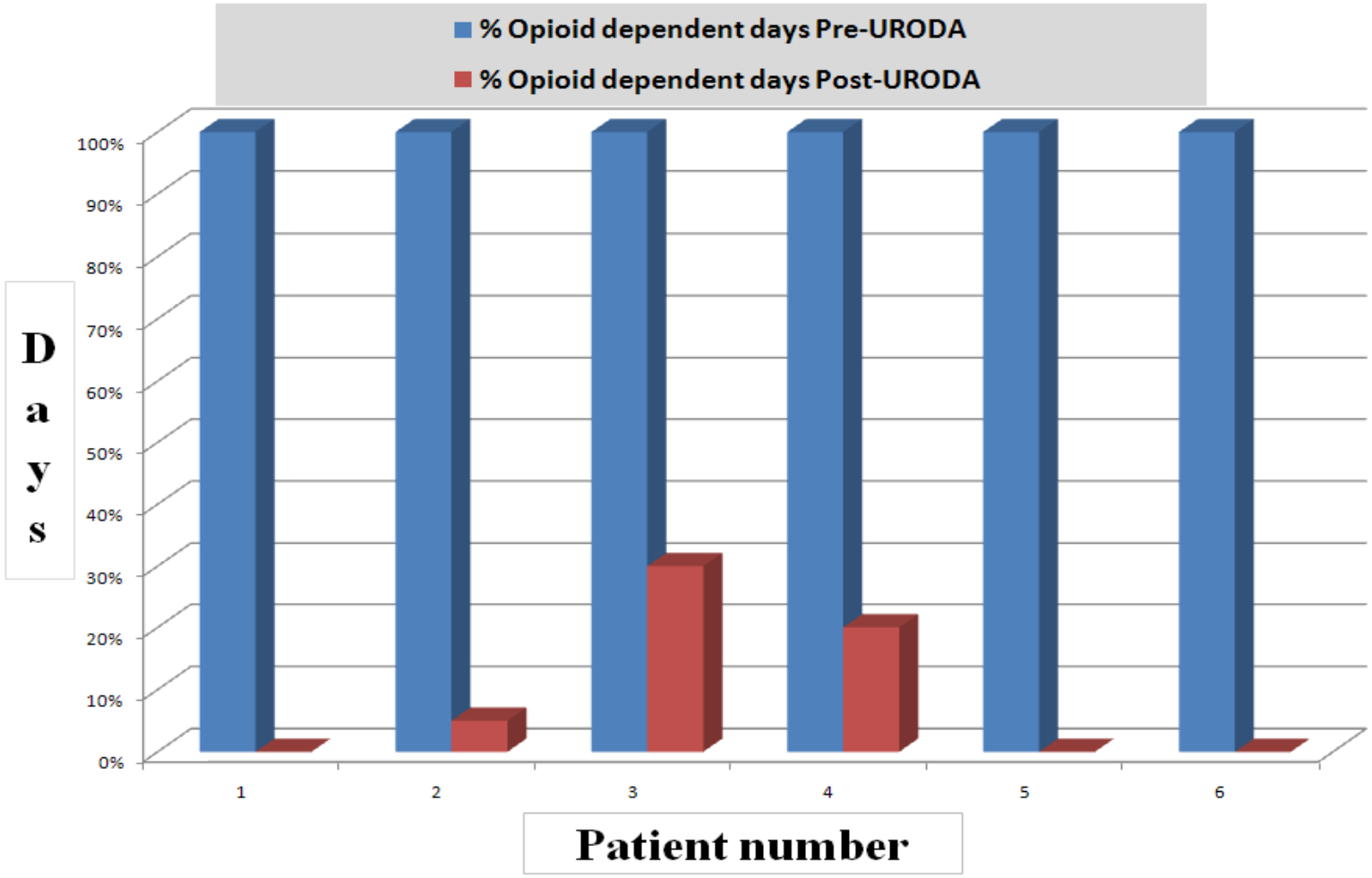
Figure 1 - Daily Consumption of Opioids



As expressed in morphine equivalent units (MEU's) both before and after URODA

Demonstrates statistically significant reduction in daily opioid consumption after URODA.
(*p = 0.0006)

Figure 2 - % Opioid-dependent Days



Demonstrates statistically significant reduction in opioid-dependent days after URODA.

*$p < 0.0001$

Discussion

Weaknesses

- Limited sample size
- Single-center experience
- Cost is not an issue; although it is eventually
- Long term follow-up pending
- Ultimate confounder of chronic pain
- Need for further surgical interventions
  - Likelihood of postop pain control with opioids
- System-wide notification s/p URODA
  - ? “OPIOID ALLERGY” vs medical alert bracelet

Pros

Although this small series of military burn patients had a much greater reduction in their opioid usage as calculated by daily MEU's, decreasing the opioid burden by as much as half would certainly make a profound difference in the well-being of most chronic pain populations.

Results

The post-procedure opioid consumption was less than 1/14th the pre-procedure value

(p-value of 0.0006)

Opioid-dependent days, as a % of total days compared before URODA (since initial injury) and after URODA, decreased markedly by 90%

(p-value less than 0.0001)

What patients are saying … and doing …

Can’t believe I finally got that monkey off my back !

<u>patient</u> → Wow, look at how big my kids are; feel like I ain’t seen ‘em in 2 years !

<u>wife</u> → Thanks for giving our family back my husband & their dad !

It’s like I’m seeing in color again, and I don’t have to read lips anymore !

References

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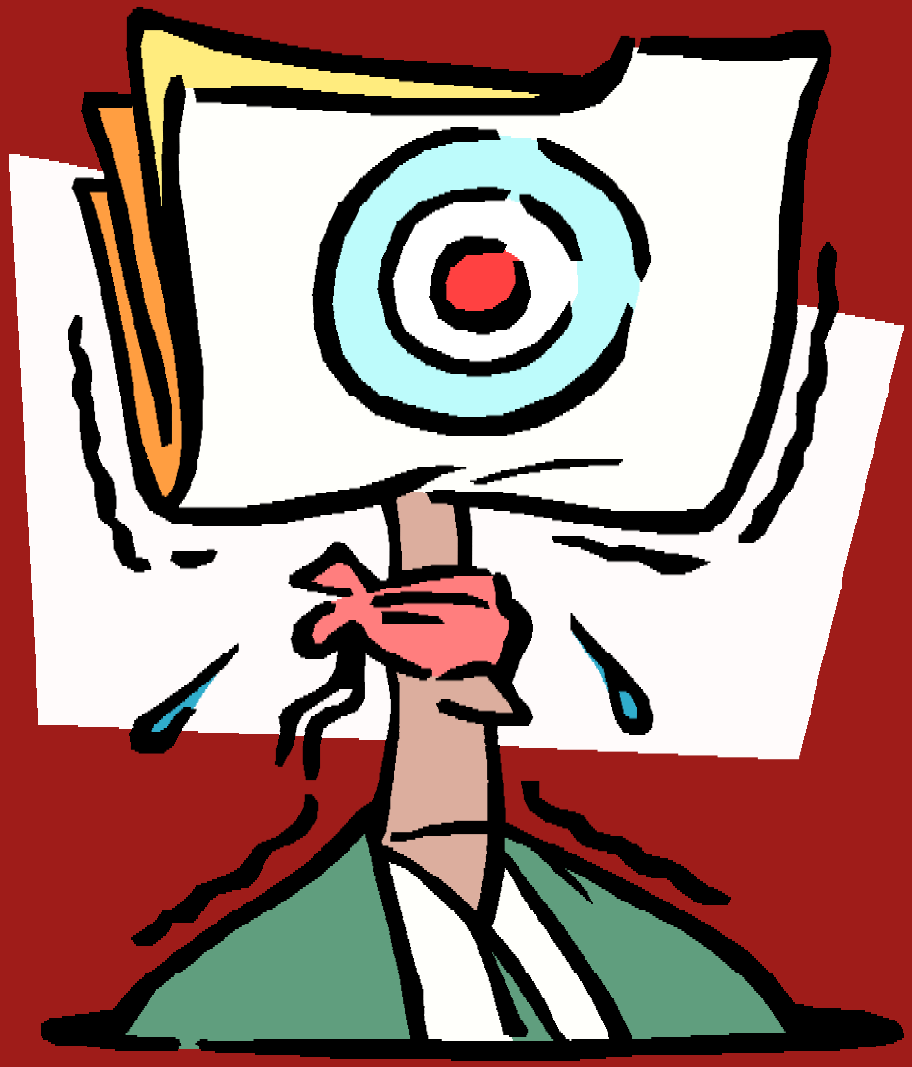
- Collaborators & research staff
- ISR Burn Center staff: the backbone of it all
  - docs, nurses, PA's, SWS's & the whole team
- Patients' families that provide the motivation & strength which fuels medical miracles daily
- Command that encourages us to think outside the box & be relentless in the quest to improve care for our Wounded Warriors & the CCCRP
- Patients that deserve and indeed oblige us to do just that

Before I hit the road, are there any questions, comments, or concerns ???