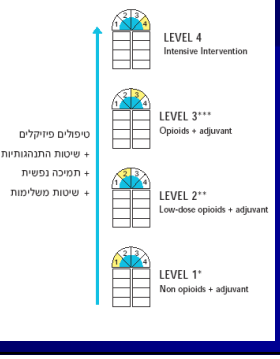
אופיואידים – אמיתות ואגדות

פרופ' פסח שורצמן
שירות שבוך באב – שירותי בריאות כללית – מחוז דרום
החטיבה לבריאות בקהילה
אוניברסיטת בן-גוריון בנגב
באר-שבע

The Pain Elevator:



Opioid analgesics and receptor selectivity

		μ	δ	κ
pure agonists	Morphine	+++	+	+
	Oxycodone	+++	+	+
	Hydromorphone	+++	+	+
	Methadone	+++	-	-
	Pethidine	++	+	+
	Fentanyl	+++	+	-
partial agonists	Buprenorphine	(+++)	-	++
antagonists	Pentazocine	+	+	++
	Naloxone	+++	+	++
	Naltrexone	+++	+	+++

+ : Affinity and intrinsic activity
(+) : Partial agonist
+ : affinity, no intrinsic activity
- : none / weak affinity

1. Rang et al., 2003

Opioid receptors and consequence of receptor binding

		μ	δ	κ
Analgesia	supra-spinal	+++	-	-
	spinal	++	++	+
	peripheral	++	-	++
Side effects	Miosis	++	-	+
	Respiratory depression	+++	++	-
	Reduction in GI motility	++	++	+
	Euphoria	+++	-	-
	Dysphoria	-	+	+++
	Sedation	++	-	++
	Physical dependency	+++	-	+

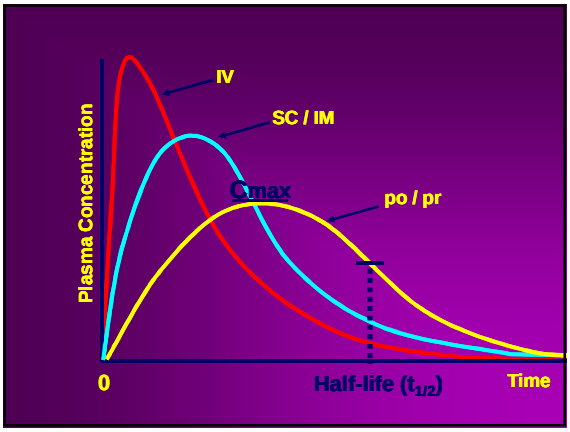
1. Rang et al., 2003

Immediate Release Opioids

- MIR (morphine sulphate)
- MSP(morphine sulphate)
- Percocet (oxycodone+..)
- Percodan (oxycodone+..)
- Oxycod (oxycodone)
- Aqtic(Fentanyl)
- Nopan (buprenorphine)
- Morphine (morphine hydrochloride)
- Palladone (Hydromorphone)
- Fentanyl
- Fentora (FBT-Fentanyl Buccal Tablets)

Opioid pharmacology . . .

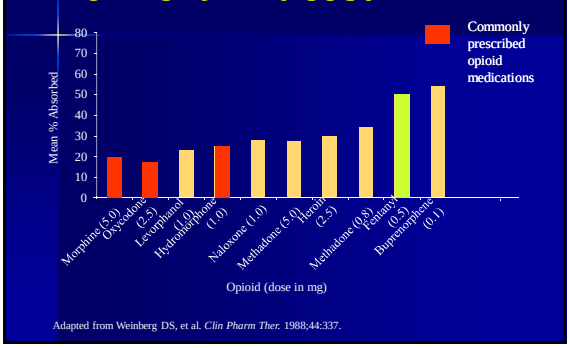
- Cmax after
  - –po ≈ 1 h
  - –SC, IM ≈ 30 min
  - –IV ≈ 6 min
- half-life at steady state
  - –po / pr / SC / IM / IV ≈ 3-4 h



. . . Opioid pharmacology

- Steady state after 4–5 half-lives
  - –steady state after 1 day (24 hours)
- Duration of effect of "immediate-release" formulations (except methadone)
  - –3–5 hours po / pr
  - –shorter with parenteral bolus

Absorption of Opioids from Oral Mucosa



Adapted from Weinberg DS, et al. *Clin Pharm Ther.* 1988;44:337.

ACTIQ Indication

- ACTIQ was FDA approved in April, 1999
- ACTIQ is indicated in the US for the management of breakthrough cancer pain in patients with malignancies who are **already receiving and who are tolerant* to opioid therapy for their underlying persistent cancer pain.**
- Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or equianalgesic dose of another opioid for a week or longer

Pharmacodynamics –

- Once in the bloodstream, fentanyl is rapidly distributed to the CNS (a process with a 3- to 5-minute half-life)
- Onset of pain relief may begin while consuming an ACTIQ unit (within 15 minutes)
- Full pain relief may not be felt for up to 45 minutes after consuming an ACTIQ unit
- Longer or shorter consumption times may produce less efficacy than reported in ACTIQ clinical trials

ACTIQ Package Insert. May 2003.

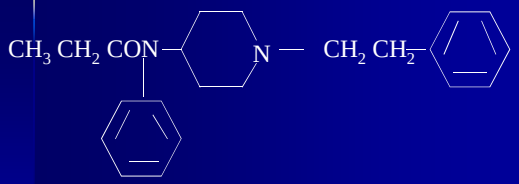
Extended Release Opioids

- MCR (morphine sulphate)
- Morphex CR (morphine sulphate)
- Oxycontin (oxycodone)
- Durogesic,Fenta (Fentanyl Patch)
- Adolan (Methadone)
- Butrans (Buprenorphine patch)
- Targin (Oxycodone/Naloxone)
- Jurnista (hydromorphone CR)

Routine oral dosing
extendead-release preparations

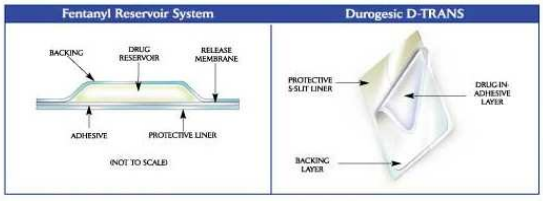
- Improve compliance, adherence
- Dose q 8, 12, or 24 h (product specific)
  - don't crush or chew tablets
  - may flush time-release granules down feeding tubes
    (not anymore in Israel)
- Adjust dose q 2–4 days (once steady state reached)

מבנה כימי של פנטניל :



- משקל מולקולרי < 1000
- מסיסות בשומן

Fentanyl –MATRIX



מטבוליזם של פנטניל :

- אין מטבוליזם עורי.
- המטבוליזם מתרחש בכבד.
- נורפנטניל - מטבוליט לא פעיל.
- 75%מהמטבוליט מופרש דרך הכליות.

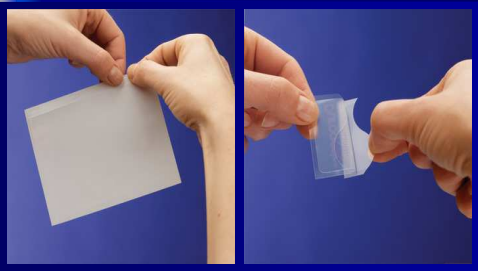
יתרונות פרמקולוגיים של פנטניל :

- שחרור מועט של היסטמין.
- ללא גירוי עורי.
- יציבות קרדיווסקולרית.
- זיקה גבוהה לקולטני mu.
- יעילות גבוהה.

Transdermal Fentanyl

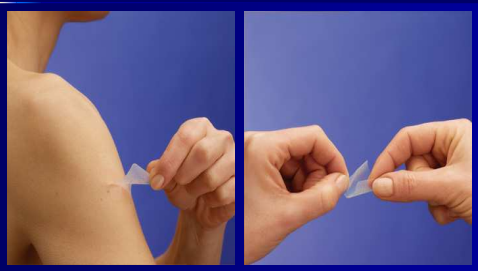
- Generally leveling 12-24 h
- Peak level 24-48 h
- After removal (50% falling) 17 h
- Range 13-22 h

שלב שני

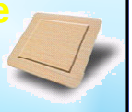


שלב שלישי

שלב אחרון



BuTrans patches: profile



- Active ingredient: Buprenorphine
- Three dose strengths: 5mcg/h, 10mcg/h, 20mcg/h
- Indicated for moderate to severe, opioid-responsive pain conditions which are not adequately responding to non-opioid analgesics.
- Can be used in OA patients when paracetamol and topical NSAIDs have failed to provide relief.

Buprenorphine pharmacology

- Strong opioid analgesic
- Partial mu agonist
- No observed analgesic ceiling effect

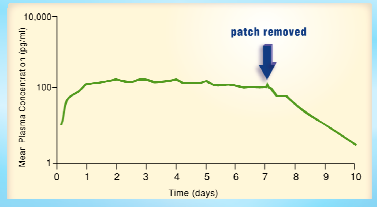
Buprenorphine: ideal for transdermal delivery

- Low molecular weight
- Highly lipophilic, semi-synthetic opioid analgesic
- Good skin penetration
- High analgesic potency
- Long duration of action

Pharmacokinetics

- Pharmacokinetics: **7**- day dosing
- Pharmacokinetics: patient populations

Pharmacokinetics: 7-day dosing



Pharmacokinetics: patient populations

- The three strengths of BuTrans patches are dose proportional
- Age* , race and gender do not significantly affect the pharmacokinetics
- No dose adjustment needed for elderly patients

*BuTrans patches are indicated for patients aged 18 years or over.

History of Methadone

- Synthesized in Germany in the late 1930's
- Developed as an alternative to morphine in WWII
- However, not used extensively as an analgesic during the war as poor dosing
- Caused ++ side effects
- Methadone became a spoil of war (property Allies)
- Rights purchased by Eli Lilly for $1
- Oral methadone approved US 1947 as analgesic and antitussive

History of Methadone

- First known as "Dolophine"
  "dolor" (pain) "fin" (end)
- Widely used in 1940's/50's … fatalaties children/adults … fell into disuse in the early 1960's
- Expanded into use for treating heroin addiction later in the 60's
- Renewed interest in methadone as an analgesic in last 10-15 yrs

Methadone Profile

- Synthetic opioid (1937)
- Indications: analgesic ,antitussive ,anti-addictive
- Metabolism: hepatic
- Half life: 24-36h
- Elimination half life variable: 15-60h (mean 22 h) up to 130h- 190h
- High bioavailibility

Two (2) stereo isomers

- R-methadone
  most potent stereoisomer (10x)
  affinity for opioid receptor (mu, delta)
- S-methadone
  NMDA receptor antagonist
  inhibits 5HT and norepinephrine uptake

- Br J Pharmacol 1997; 44:325-34 and J Palliative Med 2002; 5: 127-37

Methadone

- A mixture of (R)-methadone and (S)-methadone.
- (R)-methadone is 8 to 50 times more potent than (S)-methadone and is responsible for most of its actions.
- A mu-receptor agonist and a weak N-methyl-D-aspartate receptor (NMDA) antagonist.

Methadone Absorption

- Orally methadone has a quick onset of action. It is measurable in the plasma 15 to 45 minutes after administration.
- Peak plasma concentration occurs at 2.5 to 4.0 hours.
- Oral absorption is affected by gut motility, pH of gastric mucosa, gut perfusion and pharmacokinetic properties of the drug.

The pharmacology

- Extensive bioavailability
- Long half-life (96-130h)
- Lipophility
- Incomplete cross-tolerance
- Suggest that higher dose ratios are usually necessary

Metabolism

- Methadone biotransformed in liver (N-demethylation)
- Cytochrome P450 isoenzymes
- Inactive metabolites
- Less opioid-induced toxicity (myoclonus, delirium, …)
- Methadone, metabolites eliminated in urine & feces
- Dose adjustment not usually required in chronic and severe liver disease
- Dose adjustment not required in renal insufficiency
- Hemodialysis removes <1% daily methadone

Methadone When?

- Tolerance
- High Dose
- Renal Failure
- Neuropathic pain???
- Addiction

Tolerance

- Develops as result of compensatory increase in cyclic adenosine monophosphate activity and adenylcyclase levels due to influx of intracellular calcium ions and increased N-Methyl-D-Aspartate activity.

Why Not?

- Stigma
- Complex pharmacokinetics
- Long half life
- Equianlgesic relative
- Risks?
- Nonfamiliarity
- Taste
- Solution

RISK ?

To ECG or not to ECG

- It may cause prolongation of the QT interval.
- Generally associated with (but not limited to) a dosage exceeding 200 mg per day.
- Coadministration of drugs that decrease the metabolism of methadone (eg., erythromycin, amiodarone and guanidine) may increase the potential to cause QT prolongation.

Qt Interval

- The normal upper limit of QTc is 440 ms in males and 450 ms in females.
- If the baseline QTc is >450 ms in men and >460 ms in women, in the absence of interventricular conduction defects, all medication with potential of prolonging the QT interval should be avoided (Moss et al., 2001; Al-Khatib et al., 2003).

TARGIN

- TARGIN combines the analgesia of oxycodone with the peripheral antagonism of naloxone

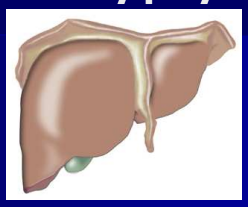
- Proven efficacy in chronic pain over many years
- Oral delivery prevents opioid binding peripherally and prehepatically
- Oral delivery does not antagonise central analgesia of oxycodone

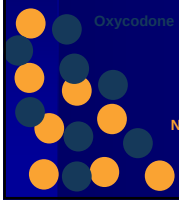
OIC a consequence of weak and discoordinated muscle activity

- Opioid μ receptor blockade results in:
- Weakened muscle contraction
- Discoordinated muscle contraction

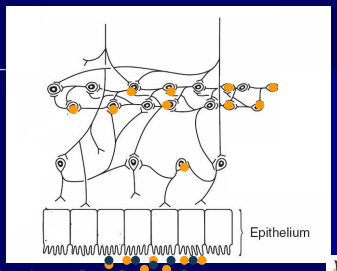
McMillan. Cancer Control 1999

The liver – a key player





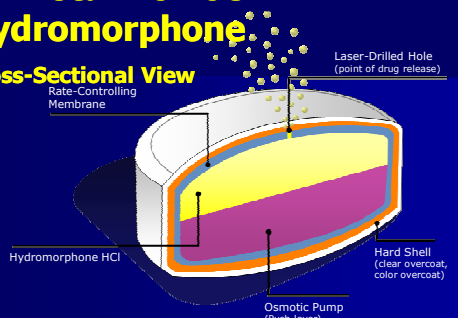
Oxycodone
Naloxone



TARGIN

Jurnista™ OROS® Hydromorphone

Cross-Sectional View



Data on file, ALZA Corporation.

Jurnista™ Steady-State Pharmacokinetic Profile

Parameter	Healthy Volunteers N=18	Chronic Pain Patients* N=5
Dose (mg)	16	16
C_{max} (ng/mL)	2.62 (0.83)	2.93 (0.6)
T_{max} (h)	14.7 (5.1)	9.8 (5.8)
C_{min} (ng/mL)	1.16 (0.47)	1.25 (0.31)
AUC_{0-24} (ng•h/mL)	45.6 (16.8)	46.1 (10.6)
Fluctuation (%)	83 (31)	89 (16)

* Chronic non-malignant or chronic cancer pain patients defined as those patients who required 32-300 mg morphine per day

Data on file, ALZA Corporation.

Jurnista™ Clinical Pharmacology

- The OROS® Push-Pull™ technology changes the drug profile of hydromorphone
- Constant drug delivery providing 24-hour analgesia with reduced peak-trough fluctuation
- Peak concentrations achieved at ~16 hrs
  - 80% of peak concentration achieved by ~6 hrs
  - Apparent half-life of Jurnista™ ~8-16 hrs
- Steady-state concentrations achieved after 2 days of dosing with no significant affect from food or alcohol
- Dose-proportional pharmacokinetics over all doses

Data on file, ALZA Corporation.

Guidelines for analgesic drug therapy

- "By the Elevator"
- "By the clock"
- "By the appropriate route"
- "By the patient/family"

שאלה 4

- עם החרפת הכאב מידי פעם ניתן לתת מנת הצלה
1. כל 4 שעות
2. כל שעתיים
3. עד כל שעה לפי הצורך
4 כל רבע שעה

שאלה 5

- מינון מנת ההצלה הוא:
1. 10-20% מסך המנה ל-24 שעות
2. שווה ערך למורפין 30 מ"ג
3. 5% מהמנה היומית

Routine oral dosing
immediate-release preparations

- Codeine, hydrocodone, morphine, hydromorphone, oxycodone
  - –dose q 4 h
  - –adjust dose daily
    - mild / moderate pain ↑ 25%–50%
    - severe / uncontrolled pain ↑ 50%–100%
  - –adjust more quickly for severe uncontrolled pain

Using Opioids for Breakthrough Pain

- Patient must feel in control, empowered
- Use aggressive dose and interval

Patient Taking Short-Acting Opioids:

- 50 - 100% of the q4h dose given q1h prn

Patient Taking Long-Acting Opioids:

- prn with short-acting opioid preparation 10 - 20% of total daily dose given q1h

Breakthrough dosing

- Use immediate-release opioids
  - –5%–15% of 24-h dose
  - –offer after Cmax reached
    - po / pr ≈ q 1 h
    - SC, IM ≈ q 30 min
    - IV ≈ q 10–15 min
- Do NOT use extended-release opioids

Equianalgesic doses of opioid analgesics

SC / IV / IM (mg)	Analgesic	po / pr (mg)
60	Codeine	100
-	Hydrocodone	15
1.5	Hydromorphone	4
5	Morphine	15
-	Oxycodone	10

Morphine Oral to Fentanyl Skin Patch Conversion

Oral Morphine, mg/24h	Fentanyl patch mg/hr
25-75	25
76-120	50
121-160	75
161-210	100
211-250	125
251-300	150

Conversion table from oral morphine to methadone for chronic administration

Total daily baseline oral morphine dose	Estimated daily oral methadone requirement as percent of total daily morphine dose	Estimated daily IV methadone as percent of total daily oral morphine dose*
<100mg	20%-30%	10%-15%
100-300mg	10%-20%	5%-10%
300-600mg	8%-12%	4%-6%
600-1,000mg	5%-10%	3%-5%
>1,000mg	<5%	<3%

* The total daily methadone dose derived from the table may then be divided to reflect the intended dosing schedule (i.e., for administration every 8h, divide the daily methadone dose by 3). Reproduced with permission from Drug Facts and Comparisons. (2007), p. 1082. St. Louis: Wolters-Kluwer Health.

. . . Changing opioids

- Cross-tolerance
  - –start with 50%–75% of published equianalgesic dose
    - more if pain, less if adverse effects
- Methadone
  - –start with 10%–25% of published equianalgesic dose

Changing routes of administration

- SC = IV = 1/3 PO

Clearance concerns

- Conjugated by liver
- 90%–95% excreted in urine
- Dehydration, renal failure, severe hepatic failure
  - ↓ dosing interval, ↓ dosage size
  - –if oliguria or anuria
    - STOP routine dosing of morphine
    - use ONLY prn

Not recommended . . .

- Meperidine
  - –poor oral absorption
  - –normeperidine is a toxic metabolite
    - longer half-life (6 hours), no analgesia
    - psychotomimetic adverse effects, myoclonus, seizures
    - if dosing q 3 h for analgesia, normeperidine builds up
    - accumulates with renal failure

Not recommended . . .

- Propoxyphene
  - –no better than placebo
    - low efficacy at commercially available doses
  - –toxic metabolite at high doses

. . . Not recommended

- Mixed agonist-antagonists
  - –pentazocine, butorphanol, nalbuphine, dezocine
    - compete with agonists → withdrawal
    - analgesic ceiling effect
    - high risk of psychotomimetic adverse effects with pentazocine, butorphanol

שאלה 6 נכון/לא נכון

- ניתן לרשום אופיואידים ל-10 ימים בלבד

15. <u>הגבלות ההספקה</u>

א) רוקח לא יספק סם מסוכן–

(1)על-פי מרשם רופא בצורה הגולמית של הסם
(2)יותר מפעם אחת על-פי אותה אסמכתה.
(3)על-פי מרשם רופא לאחר 15 יום מתאריך המרשם ובכמות העולה על המנות ל- 10 ימים.

ב) על אף האמור בתקנות משנה (א) רשאי רוקח לספק כמות סמים ל- 31 ימים, אם הרופא **הורה על כך במרשם בכתב ידו, באופן ברור, וציין הסיבה להגדלת הכמות.**

הנחיות לרישום מרשם עבור תכשיר אופיואידי על פי תקנות הרוקחים

מרשם רופא ישא את חותמת הרופא, מספר רישיונו ומען מרפאתו או
מרפאת המוסד הרפואי בו הוא מועסק. מס' טלפון בו ניתן להשיגו.
על הרופא לכתוב בכתב ידו, באותיות דפוס ובאופן ברור וקריא או להדפיס
מרשם עם לוגו של מוסד מוכר את הפרטים הבאים:

- שם המטופל, מענו ומס' תעודה מזהה, בצירוף שם התעודה.
- שם התכשיר, ריכוז ליחידת מינון וצורת המינון, כשהם מופיעים גם
  באותיות דפוס לטיניות.
- מס' מדבקות/כדורים לתקופה וסה"כ למרשם. כמויות אלו יצויינו הן בספרות והן במילים.

הנחיות לרישום מרשם עבור תכשיר אופיואידי על פי תקנות הרוקחים

- מספר ימי הצריכה במרשם יחיד הינם 10 ימים. קיימת אפשרות להגדלת ימי הצריכה עד ל-31 יום. במידה ורופא יורה על כך במרשם בכתב ידו ויציין את הסיבה להגדלת הכמות, לדוגמא: מרחק המטופל מהמרפאה, בן משפחה במילואים או אחר.
- ניתן לתת מנון אופיואידים ללא הגבלה אך יש לציין שמדובר בכאבים קשים (מחלה קשה)
- תוקף מרשם חודשיים מיום רישומו.

תקנות הסמים המסוכנים (תיקון) התשס"ט-2008

על פי תקנה 13 על הרופא רושם המרשם להוסיף במרשם גם את מספר הטלפון של המרפאה בה הוא עובד. וזאת על מנת לאפשר לרוקח לקבל הסברים במידת הצורך.

■האם קיימת הגבלה במינון אופיואידים?

תקנות הסמים המסוכנים (תיקון) התשס"ט-2008

כאשר הרופא מציין כי מדובר במתן סם מסוכן לחולה מחלה קשה, לאו דווקא סרטן, אין הגבלה על המינון היומי של הסמים המשמשים לשיכוך כאבים, לרבות מתדון.

תקנות הסמים המסוכנים (תיקון) התשס"ט-2008

לענין מתילפנידט:

א. ניתן לרשום מרשם עד למינון של 90 מ"ג ללא כל הגבלה.

ב. מרשם המורה על מתן של מתילפנידאט בכמות בין 90 מ"ג ל-
120 מ"ג חייב לעמוד בתנאים הבאים:

(א) הרופא נימק בכתב את המינון שרשם; נימוק יכול להיות
משקל גוף גדול או טיטראציה עולה של מינונים שאינה משפיעה אלא מעל 90 מ"ג וכיו"ב.

(ב) התקבל אישור המנהל הכללי של משרד הבריאות או מי
שהסמיך לעניין זה- או אישור המנהל הרפואי של המוסד

שאלה 8

- אופיואידים מפריעים לנהיגה

Opioids and driving

Chronic morphine use was associated with

- **Slower reaction times**
- **more mistakes**
- **slower ability to process visual information**

NON STATISTICALLY SIGNIFICANT!!!

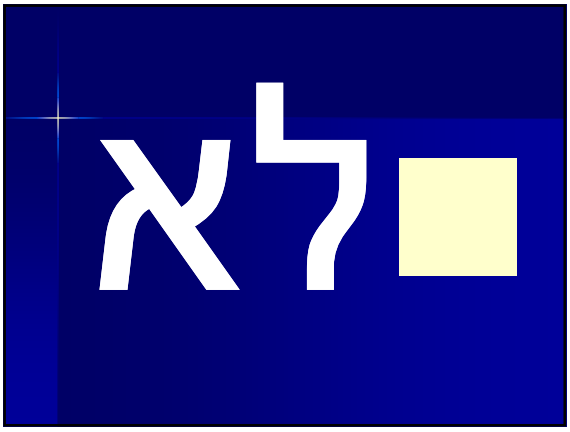
Driving

- Studies have shown that cognitive function, including the ability to drive and operate machinery, is preserved in patients taking stable, moderate doses of opioids for chronic pain. However, cognitive function may be impaired for up to seven days after an increase in the dose.

שאלה 9

האם אופיואיד יש אופיואיד אחד שטוב מהאחר
האם תופעת לוואי עם אופיואיד אחד מעידה על תופעות לוואי עם אחר

כן/לא



Tolerance

- Reduced effectiveness to a given dose over time
- Not clinically significant with chronic dosing
- If dose is increasing, suspect disease progression

Tolerance

- Tolerance to Side Effects occurs in 1st few months
  - nausea
  - fatigue
  - dizziness
  - CNS effect
  - respiratory depression
  - myoclonus
- Tolerance to constipation does not occur

Addiction . . .

- Psychological dependence
- Compulsive use
- Loss of control over drugs
- Loss of interest in pleasurable activities

Addiction . . .

- Continued use of drugs in spite of harm
- A rare outcome of pain a
  - –particularly, if no history of substance abuse

Physical dependence

- A process of neuroadaptation
- Abrupt withdrawal may → abstinence syndrome
- If dose reduction required, reduce by 50% q 2–3 days
  - –avoid antagonists

Side Effects of Opioids

- **Nausea**
- **Vomiting**
- **Sedation**
- **Constipation**
- **Urinary retention**
- **Pruritus**
- **Dysfunction of erection**
- **Endocrinological changes**
- **Respiratory depression**

Other Side Effects

- Confusion
- Hallucinations
- Night mares
- Urinary retention
- Multifocal Myoclonus
- Dizzines
- Dysphoria

Long Term Opioids

- The reported length of treatment is up to six years.
- In most cases, doses are in a moderate range (up to 195 mg of morphine or morphine equivalent per day)
- In two reports, higher doses were used (up to 360 mg in 52 patients, and up to 2 g in 23 patients).

NEJM

13/11/2003

Opioids Induced Hormonal Changes

- Decrease libido
- Aggression
- Amenorrhea
- Irregular menses
- Galactorrhea

Avoiding side effects of opioid therapy Mandatory Co-Medication

	Initially	Long term
Laxatives	+	+
Antiemetics	+	-
Antihistamine	(+)	-
Anticholinregics	(+)	

Abuse Rates

- 1/1000 cancer patients
- 3/2369 headache patients
- 0/10,000 burn patients
- 4/1182 hospitalized patients
- 3/133 rheumatoid arthritis patients
- 5-6/100 in general population

adapted from Mahowald, Snowmass Conference, 2000

Abuse

- Tampering with, improperly applying or improperly dosing an agent to achieve a non-medical or improper purpose with a significant risk of ill-effects or injury