

Behavioral Pharmacology and Opioid Therapy: Beyond Pharmacokinetics and Pharmacodynamics

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Goals

- To differentiate the pharmacokinetic and pharmacodynamics of drugs
- To identify the variables that can influence the effectiveness of opioids
- Review how outcomes are measured
- To review the psychological and behavioral factors involved in opioid therapy for pain

Definitions

- **Pharmacokinetics:** the study of the movement of drugs in the body, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion (what the body does to the drug)
- **Pharmacodynamics:** the study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of their actions and effects with their chemical structure (what drugs do to the body)
- **Psychopharmacology:** the study of the effect of drugs on the mind and behavior
- **Behavioral Pharmacology:** the study of the physiological and behavioral effects of drugs on the mood and mind.

State Of The Painkiller Nation: Wide Variation In Prescription Rates: CDC

by SCOTT HENSLEY July 01, 2014

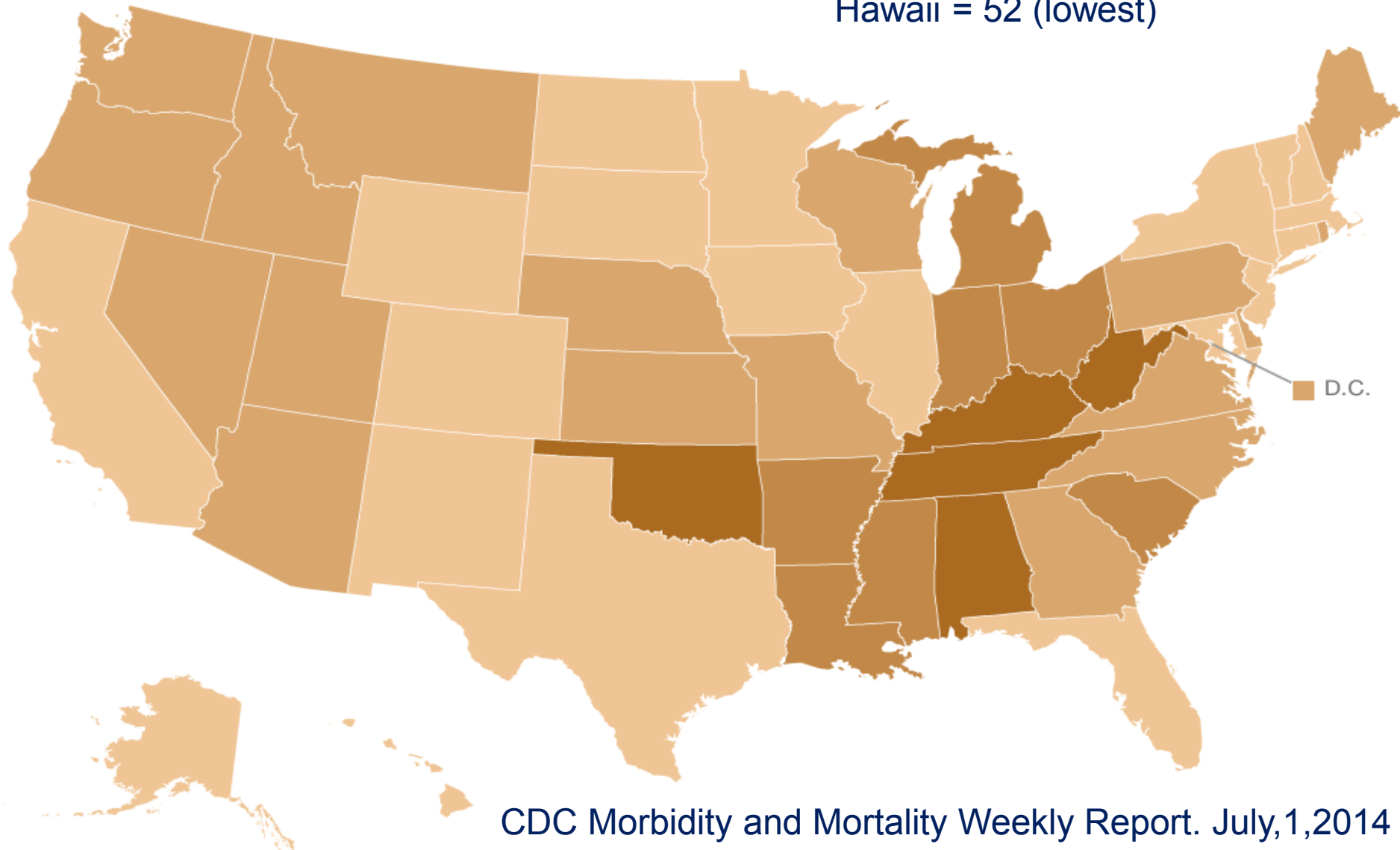
Prescriptions of opioid pain relievers
in 2012, per 100 people

50 75 100 125 150

National average = 82.5

Alabama = 142 (highest)

Hawaii = 52 (lowest)



CDC Morbidity and Mortality Weekly Report. July,1,2014

Chou et al. Systematic Review. Annals of Internal Medicine, 2015

- 40/4209 (< 1%) meet criteria; long-term was defined as > 3 months
- “...no study of long-term opioid therapy for chronic pain versus no-opioid therapy or nonopioid therapies that evaluated effects on pain, function, or quality of life at 1-year or longer” (p. 280)
- “Evidence is insufficient to determine the effectiveness of long term opioid therapy for improving chronic pain and function. Evidence supports a dose-response risk for serious harms (p. 276)
- “Despite these limitations, the lack of scientific evidence on effectiveness and harms of long-term opioid therapy for chronic pain is clear and is in striking contrast to its widespread use for this condition and the large increase in prescription opioid–related overdoses.” (p. 282) *(Does this reflect an appraisal of the evidence or bias of the authors?)*

Observations/Questions

- What is being published and why is it being published?
- Does lack of evidence=lack of effect?
- We do not understand the nature of opioids and the factors that influence their efficacy and effectiveness
- We do not know how to use opioids
- We do not have an adequate understating of the thing (Chronic pain) we are treating
- With the exceptions of greater details and specifics, there is little that was not foretold in Jerome Jaffe's chapter 'Narcotic Analgesics' (Goodman and Gilman (eds.) The Pharmacological Basis of Therapeutics, 1970, p.237-275)

What are we
measuring and why are
we measuring it?

All important things cannot be
measured and all things that can
be measured are not important.

Albert Einstein

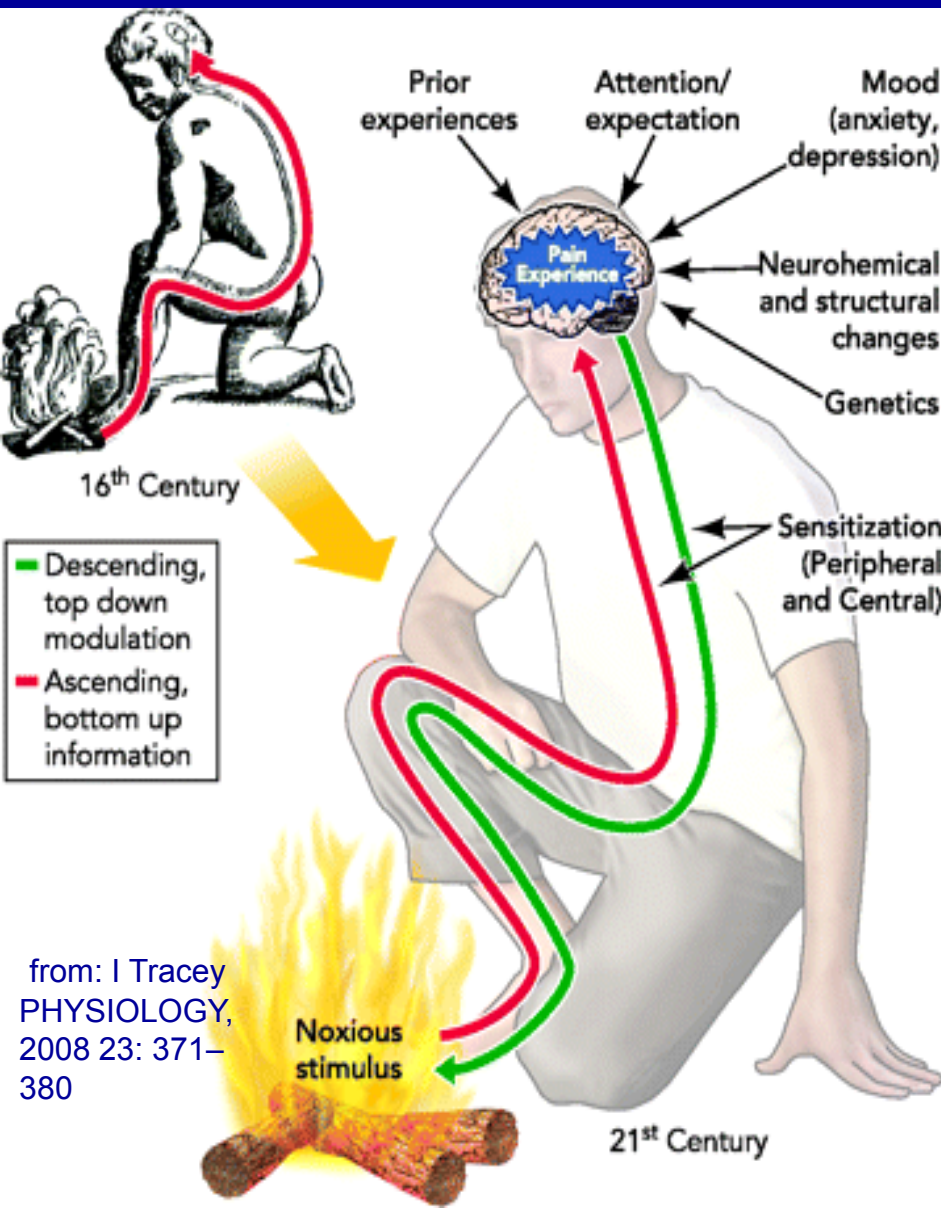
Nociception and Pain

In pain research, it is established that nociception (“the neural process of encoding Noxious stimuli”; IASP, 1994) is not sufficient to explain the conscious experience of pain and it has been repeatedly demonstrated that psychosocial factors can have important top-down effects on pain

(Hofbauer et al., 2004; Baumgärtner et al., 2006; Nikolajsen and Jensen, 2006; Lee et al., 2009)

Psychology of the Practitioner

Chronic Pain: Symptom or Disease?



Persistent Pain as a **Disease Entity**:
Implications for Clinical Management.”
(Siddall and Cousins, *Anesth Analg*, 2004,99, 510-520.)

“Chronic pain can be a **fatal disease** because of its association with suicide and with violence” (Gallagher & Verma, 2004, p147)

“Chronic **pain as a disease entity** in its own right” European Federation of IASP Chapters (EFIC) “Declaration on Pain” (Niv and Devor, *Pain Practice*, 2004, 4, 179-181)

“When this kind of hurt (neuropathic) continues, it is not symptomatic of some ongoing injury or another disease: it is itself **a disease of the nervous system ...**” (Basbaum, A & Julius, D. *Sci Am*, 2006, June, 61-67)

“...the realization that **pain is a destructive disease process** that should be treated” (Ballantyne, J. S *Med Jr*, 2006, 11, p1245)

Factors Related to Drug (Opioid) Seeking Behavior

- Pain patients have increased disease conviction, somatic preoccupation (Pilowsky, Chapman, & Bonica, 1977), and an externalized locus of control (Schug & Large, 1995), all of which may lead to increased opioid-seeking behaviors in the absence of increased nociceptive input. The nonanalgesic operant reinforcing effects of taking opioids (euphoria, anxiolysis, sense of well being) also may exacerbate opioid-seeking behavior (Jasinski, 1997).

Is Pain an Important Outcome Measure

- Positive outcomes without a reduction in 'pain'
 - Wicksell et al. Cog Behavior Therapy, 2008,37, 169-182
 - Wicksell et al. Eur J Pain, 2010, 14, 1059 e1-1059 e11
 - Woby et al. Eur Jr Pain, 2004,8, 201-210
- Lack of correlation between 'pain' and improvement in other outcome domains
 - McCracken et al. Eur Jr Pain, 2002, 6, 387-393
 - McCracken et al. Behavior Research an Therapy, 2011, 49, 276-274

Are Pain Ratings Relevant?

- NPR used by responding clinicians about 68% of the time on the initial visit and by only about 42% on each follow-up visit.
- The most common reason given using a NPR was justify prescribing analgesics.
- “...the complexity of the human pain experience reminds us that we neither have a clearly articulated nor widely accepted statement about what the pain intensity ratings represent” (p.1247).
- The authors compare the issue of the ‘objectivity’ of the NPR to that of blood pressure and heart rate. However, this comparison is legitimate only if the patient is asked to provide a verbal estimate of their BP and HR.
- A number of clinicians indicated they did not pay attention to or use pain scores rather they considered function and how the patient was doing overall.

Patient Satisfaction and Pain Intensity

- Despite **significant levels of pain and ineffective treatment**, greater than **90% of patients reported being satisfied** with pain management. (Comley AL, DeMeyer E J Assessing patient satisfaction with pain management through a continuous quality improvement effort. Pain Symptom Manage. 2001 Jan;21(1):27-40).
- Satisfaction was influenced by effectiveness of medication, **independent of pain intensity**, and by communication. Pain severity ratings near the time satisfaction was measured were more influential than earlier ratings. (Carlson et al. Is patient satisfaction a legitimate outcome of pain management? J Pain Symptom Manage. 2003 Mar;25(3):264-75)
- The **global satisfaction ratings** was found to assess something other than pain intensity or change in pain intensity and its use is recommended by experts in the field of pain assessment in clinical trials. (Jensen et al. Pain, 2004, 110, 480-487)

Role of Conditioning and Learning

Olfactory Cues and Morphine-Induced Conditioned Analgesia in Rats

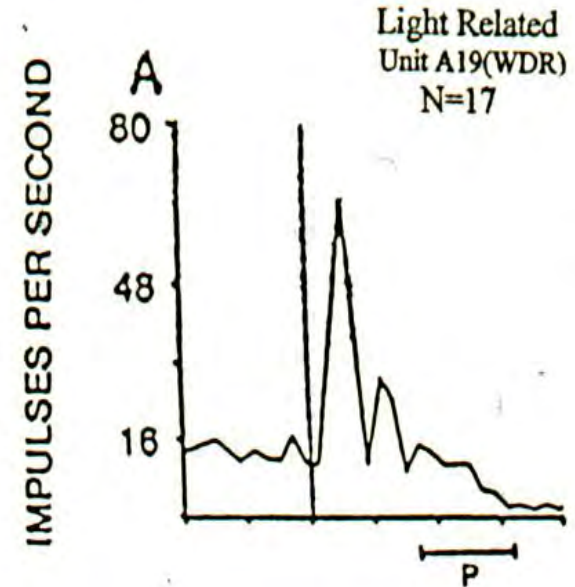
In a Pavlovian conditioning procedure, rats were exposed to an odor conditioned stimulus (CS) and then were given morphine with its effect serving as an unconditioned stimulus (UC).

After four CS-US pairings, the CS was tested alone and found to produce a morphine-like conditioned analgesic response (CR).

(Volcane et al. *Pharm Bio Behav.* 1998, 60 (1), 115-118)

(Duncan, Bushnell, Bates, & Dubner, Jr. *Neurophysiology*, 1987, v57)

Conditioned Nociception



6. Trial-continuation task-related responses (observed while the monkey waited for a thermal stimulus that triggered a rewarded motor response) were shown to be independent of the actual temperature of the thermal stimulus. In addition these trial-continuation task-related responses were also noted during trials without a thermal stimulus, in which the trigger cue was the onset of a light (in a visual task).

Pavlovian Conditioning and Heroin Overdose: Reports from Overdose Victims

Tested a Pavlovian conditioning model of tolerance, which emphasizes the contribution of an association between pre-drug cues (e.g., environment) and the systemic effects of the drug to tolerance

10 former heroin addicts who had survived an overdose were interviewed questioned about the circumstances of their overdose to ascertain the role of drug-associated cues.

Ss' reports were consistent showing that **overdose was more likely in *unusual circumstances*** related to the environment or to drug administration.

Findings suggest that the conditioning model may be relevant to some instances of overdose death among heroin addicts.

Siegel S, Hinson RE, Krank MS, McCully J: Heroin "overdose" death: Contribution of drug-associated environmental cues. *Science* 1982, 216:436-437.

Siegel S: Pavlovian conditioning and heroin overdose: Reports from overdose victims. *Bulletin of the Psychonomic Society* 1984, 22:428-430.

Tolerance

Associative (Behavioral)

- operant/classical conditioning (behavioral plasticity)
- acquisition/extinction
- drug-environment associations
- CCK-B

Non-associative (Pharmacological)

- NMDA activity, Ca, Mg, CCK, PKC, G-protein

Exteroceptive and Interoceptive Cues Associated with Drug Administration

- **SAC (self-administration cues)**: Exteroceptive and interoceptive cues incidental to self administration of a drug
- **DOC (drug onset cues)**: Exteroceptive and interoceptive cue incidental to the onset of a drug effect
- **CCR (conditional compensatory response)**: Drug compensatory responses elicited as conditioned response (CRs) mimicking the compensatory responses unconditionally elicited (UCR) by a drug. These CCRs represent the **homeostatic activity of a complex adaptive system** and may attenuate the effect of the drug and contribute to tolerance

(Siegel & Remos; Exp C & Kim; 2002. Sokolowska, Siegel, & Kim: Jr Exp Psyc: Animal Behavior Processes, 2002, 28,)

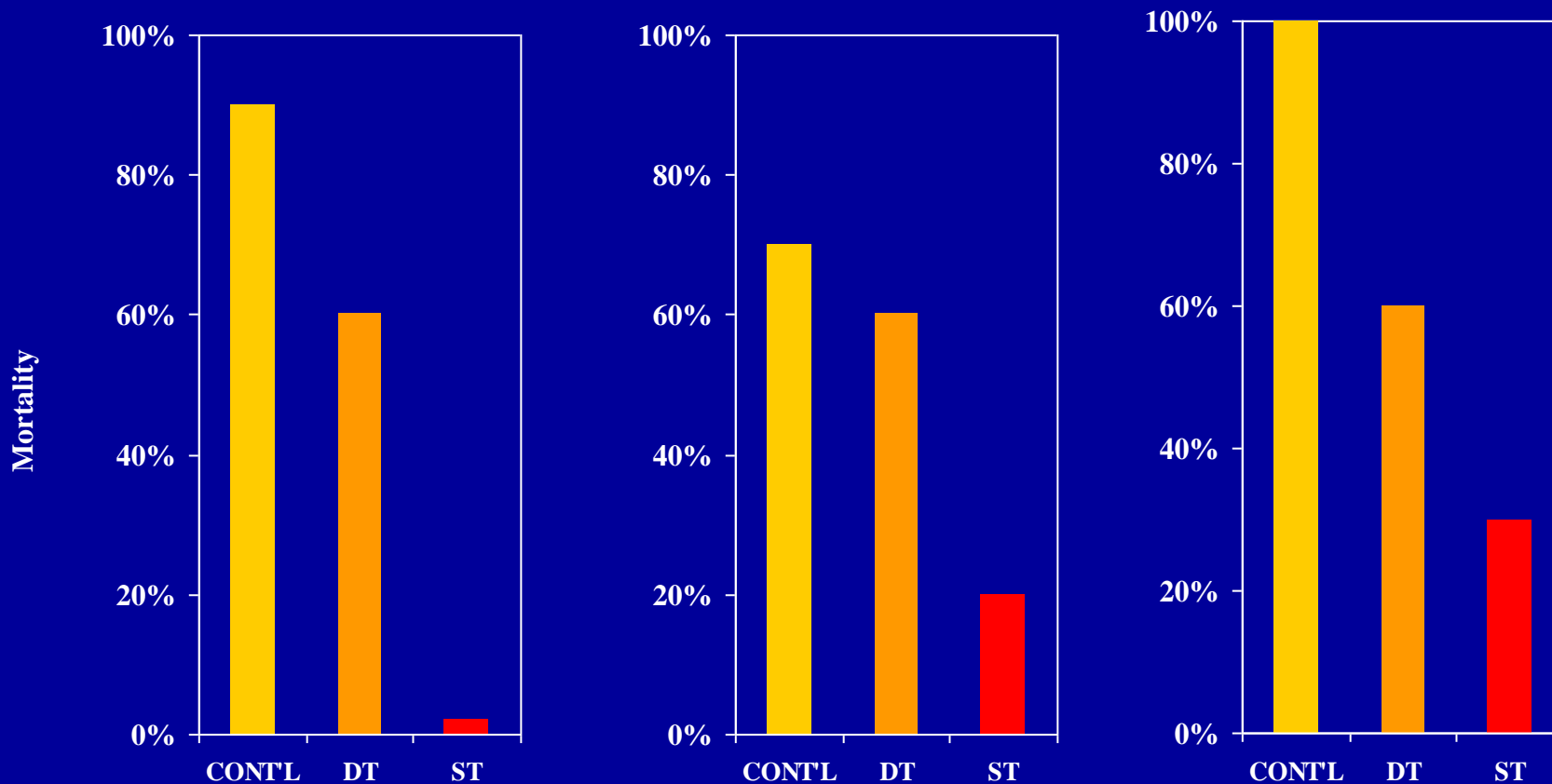
Conditional Compensatory Responses (CCR)

- Conditional compensatory responses (CCR; i.e. body responding as if the drug were administered) after pairings of the pre-drug conditional stimulus and pharmacological unconditional stimulus counteracting the drug effect and producing tolerance. With frequent administered the CCR grows in strength, the attenuation of the drug effect becomes more pronounced
- Situational specificity of drug tolerance: drug-associated cues elicit CCRs that attenuate the drug effect; thus tolerance is greater when assessed in the presence of drug-associated cues than in a novel situation
- Exteroceptive and interoceptive cues: animals that self-administer a drug by making a designated response (e.g., pressing a lever in an operant chamber) are more tolerant to the drug than are “yoked” animals that receive the same drug doses at the same time, but not contingent on their behavior. Self-administration cues function as conditional stimuli,

Self-Administration Cues (SAC) and Drug Onset Cues (COS)

- Self-administering subjects display more tolerance and more withdrawal symptoms than passive receipt subjects, when the instrumental response no longer leads to pharmacological reinforcement.
- When drug-onset cues reliably precede a later and larger drug effect; a small dose of morphine (4mg/kg) may serve as a cue for a larger dose (12 mg/kg) of the opiate and influence the display of morphine tolerance

Situation-Specific Tolerance



Mean mortality in rodents administered a high dose of a drug for the first time (CONTL), n-th time in the same environment (ST), n-th time in new/different environment (DT). IP injection of ethanol (panel 1), pentobarbital (panel 2), heroin (panel 3).

Locus and Mechanism of Action for Associative Morphine Tolerance

- Repeated administration of an opioid in the presence of specific environmental cues can induce tolerance specific to that setting (associative tolerance).
- Prolonged or repeated administration of an opioid without consistent contextual pairing yields non-associative tolerance.
- Microinjection of the cholecystokinin-B antagonist into the amygdala blocked associative tolerance.
- Conclusion: Cholecystokinin acting at the cholecystokinin-B receptor in the amygdala is required for associative but not nonassociative morphine tolerance.

Placebo/Nocebo Effect

Pain and Placebo Analgesia

- Perceived as a threat
- Expectation(s) of treatment outcome
- Desire for relief

D.D. Price “Psychological mechanisms of pain and analgesia”
AISP Press, Seattle, WA 1999.

Placebo: Classical/Contemporary View

- **Classical:**
- (a) **pharmacologically inert preparation** prescribed more for the mental relief of the patient than for its actual effect on a disorder;
- (b) an **inert or innocuous substance used in controlled experiments** testing the efficacy of another substance (as a drug).

Placebo: Classical/Contemporary View

- Contemporary:
- A placebo is a treatment with no specific therapeutic action and the placebo effect is the outcome following its administration
- The placebo effect is a psychobiological phenomenon and must not be confounded with other phenomenon such as spontaneous remission.
- The effects following administration of a placebo are due to the psychosocial context around the therapy (**contextual sensitive treatment**)
- A positive psychosocial context may induce a placebo effect whereas a negative context may led to a nocebo effect
- There is no single placebo effect but many, in different systems and with different mechanisms
- The placebo analgesic effect is often mediated by the endogenous opioid
- The nocebo hyperalgesic effect is mediated by anxiety-induced activation of CCK system
- If an analgesic treatment is administered covertly (hidden), the effects are smaller the when given overtly

Placebo (Latin for “Shall please”)

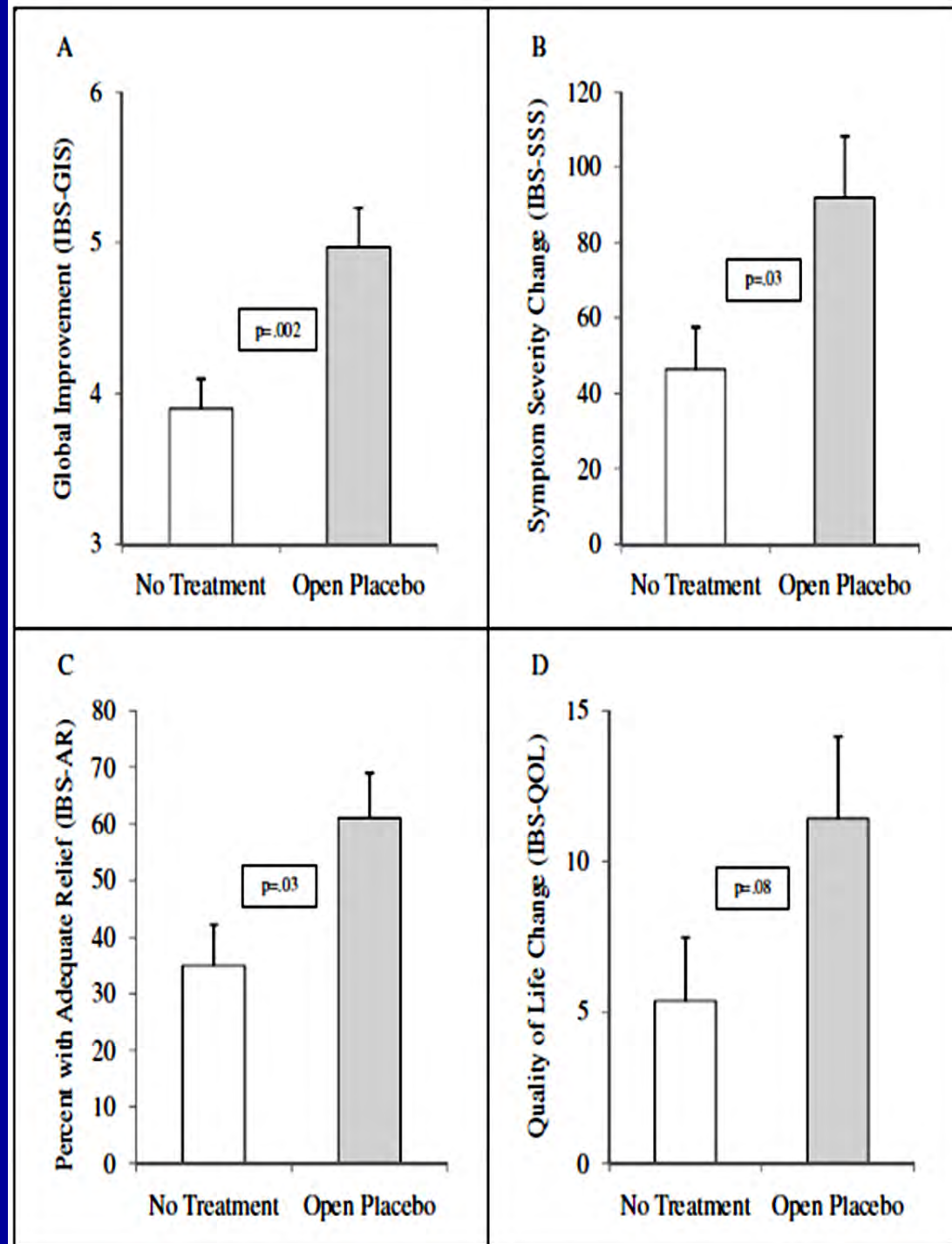
- *Contextual factors*:
 - doctor-patient relationship
 - emotions (i.e. anxiety)
 - memory/cognitive function (placebo effect less in Alzheimer’s patients)
 - verbal suggestion (expectancy: uncertain or deceptive, i.e. positive or negative, can account for 25-49% of variance in post-treatment pain ratings)
 - desire for relief (motivation)
 - conditioning (previous experience)
- *Responders/non-responders*: 30% (Beecher), 27% (Benedetti), 52% (Petrovic), 39% (Levine)
- *Responses*: pain, hormonal, immune, mood, movement (Parkinson’s)
- *Research Design*: ‘Open-hidden’ paradigm
 - open: treatment given in full view of the patient
 - hidden: physician not present, patient unaware treatment given i.e. automated infusion pump

Placebo (continued)

- Mechanism – Brain :
 - During anticipation: :increase DLPFC (cognitive control)
PAG, OFC (evaluative/reward processing), rACC
 - During treatment: decrease in ACC, Thalamus, IC (*pain matrix)
- Mechanism - Opioid vs. Non-opioid system:
 - Naloxone sensitive:: expectation, endogenous opioid system, can be regional (somatotopic)
 - Naloxone in-sensitive:: conditioning (classical), growth hormone, 5-HT, CCK (associated with negative verbal suggestion or expectancy)

Placebo Effect Without Deception

Before randomization the provider clearly explained that the placebo pill was an inactive (i.e., “inert”) substance like a sugar pill that contained no medication and then explained in an approximately fifteen minute a priori script the following “four discussion points:” 1) the placebo effect is powerful, 2) the body can automatically respond to taking placebo pills like Pavlov’s dogs who salivated when they heard a bell, 3) a positive attitude helps but is not necessary, and 4) taking the pills faithfully is critical.



Conscious Expectation and Unconscious Conditioning

- Placebo effect can be learned consciously or unconsciously
 - Consciously:** an increased **expectation** is likely to occur after repeated associations of contextual cues with the outcome
 - Unconsciously:** Pavlovian **conditioning** plays a crucial role in which contextual cues and outcomes are unconsciously associated because of their contiguity
- **Role in the placebo responses of human nonconscious involves physiological functions, whereas expectations replace conditioning when conscious perception is involved (e.g., pain and motor performance).**

(Benedetti et al. Jr Neuroscience, 2003, 23(10):4315– 4323)

Consultation



Two weeks later

% who got better

64

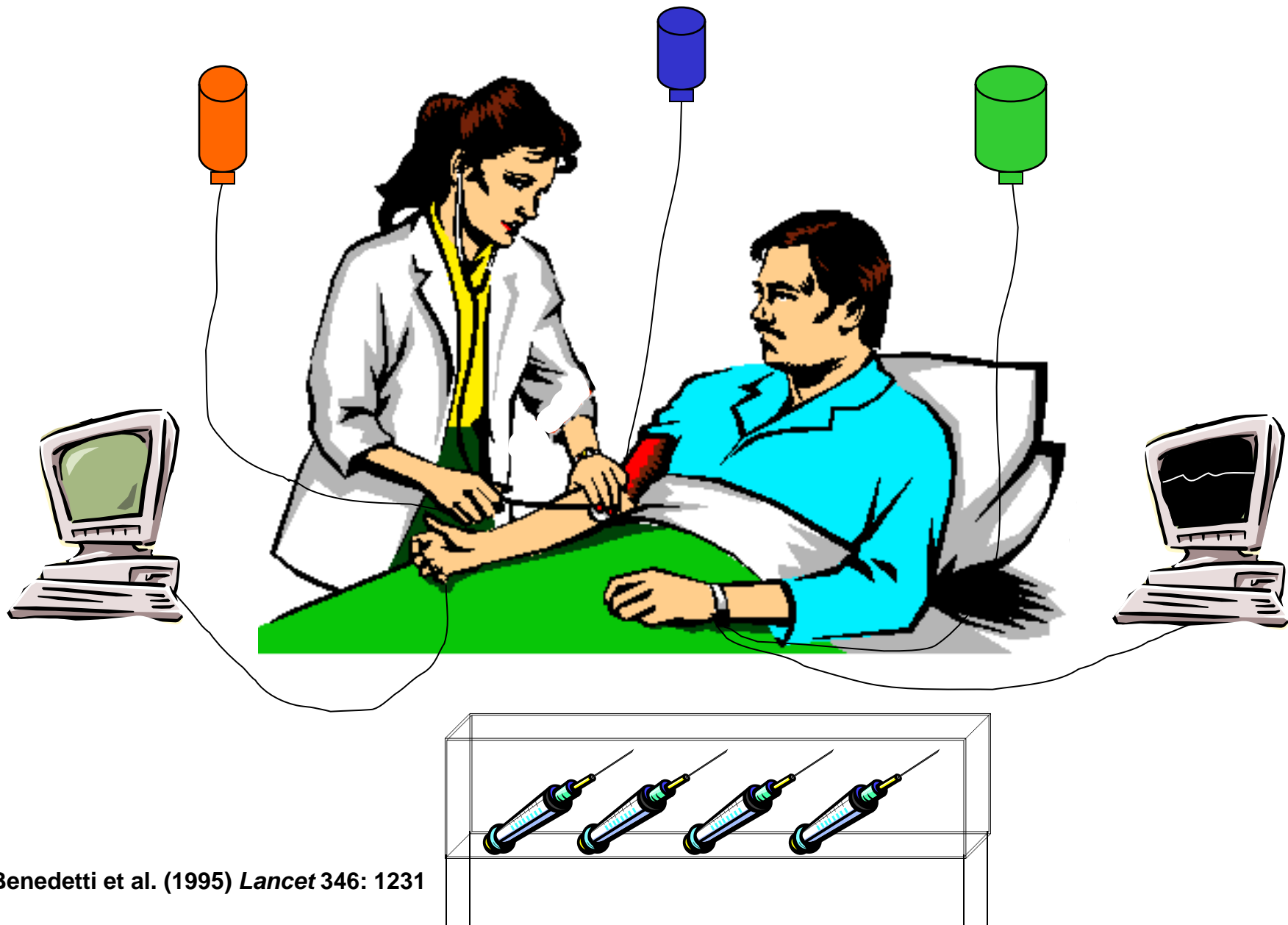


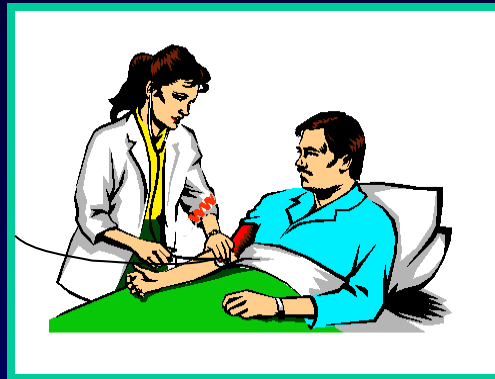
% who got better

39

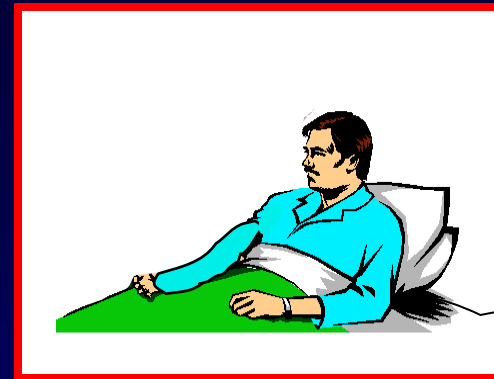
Thomas (1987)
Br Med J 294: 1200



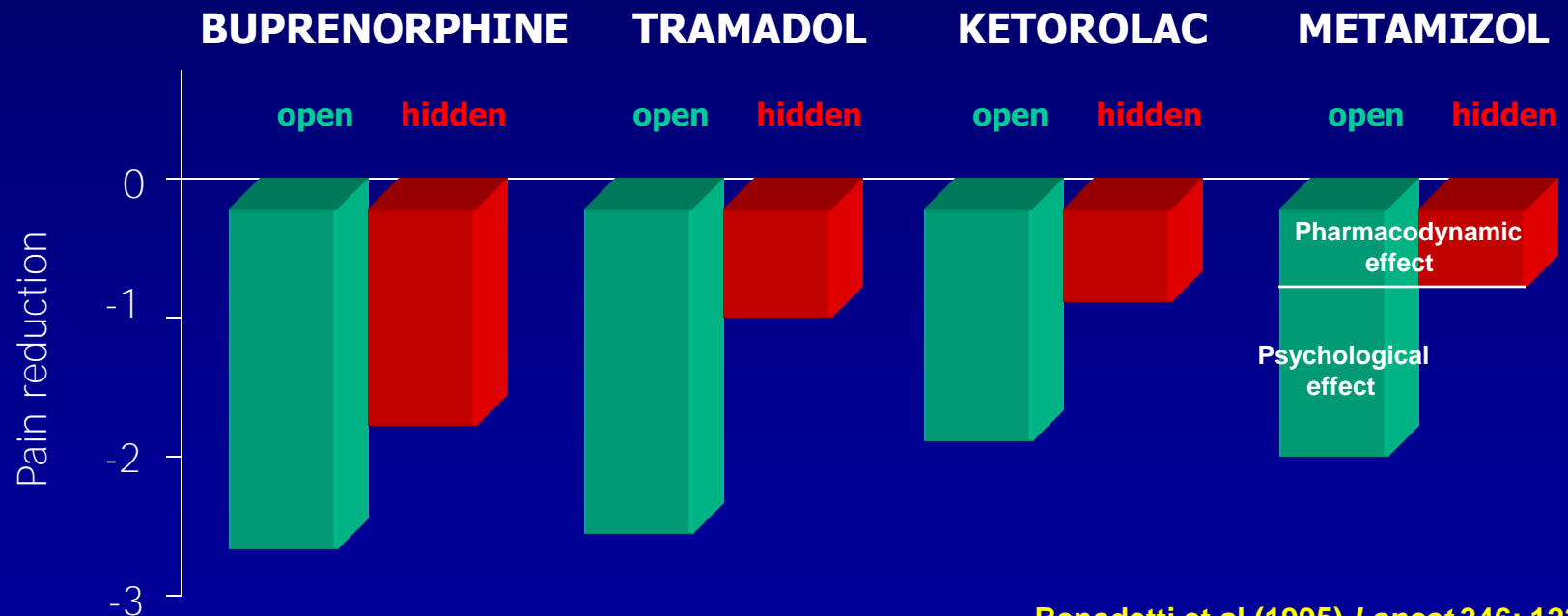




Open injection



Hidden injection



Benedetti et al (1995) *Lancet* 346: 1231
 Amanzio et al. (2001) *Pain* 90:205-15
 Colloca et al (2004) *Lancet Neurol.* 3: 679-684

Nocebo (“I will harm”)

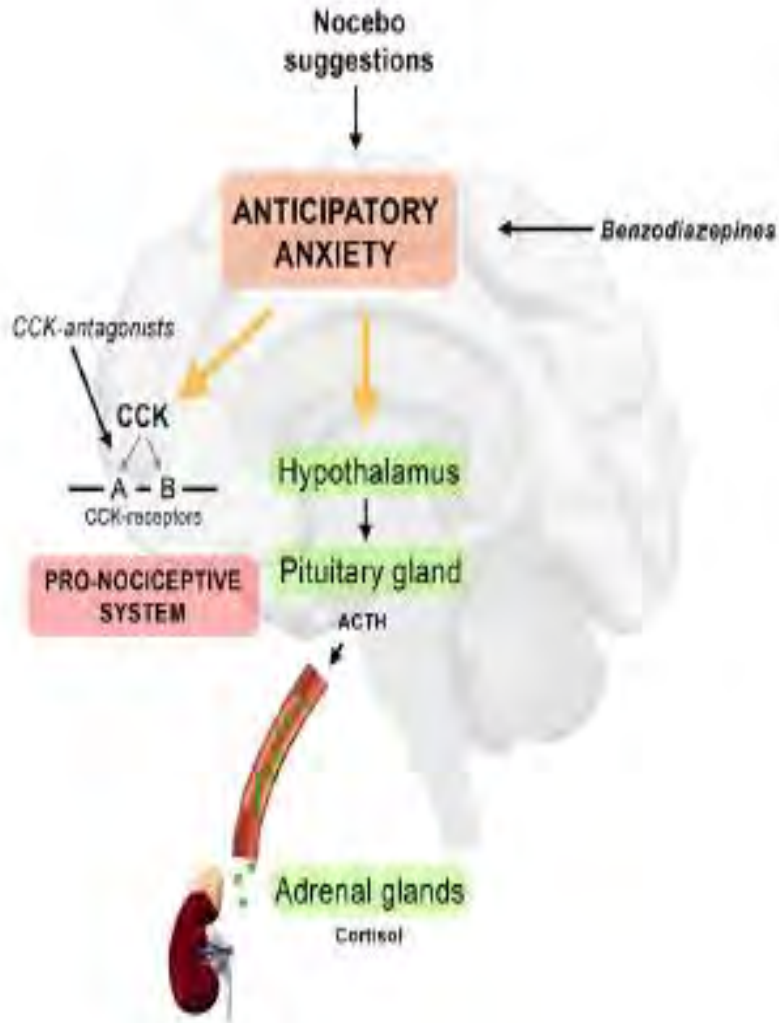


Figure 3. Mechanisms of the Hyperalgesic Nocebo Effect

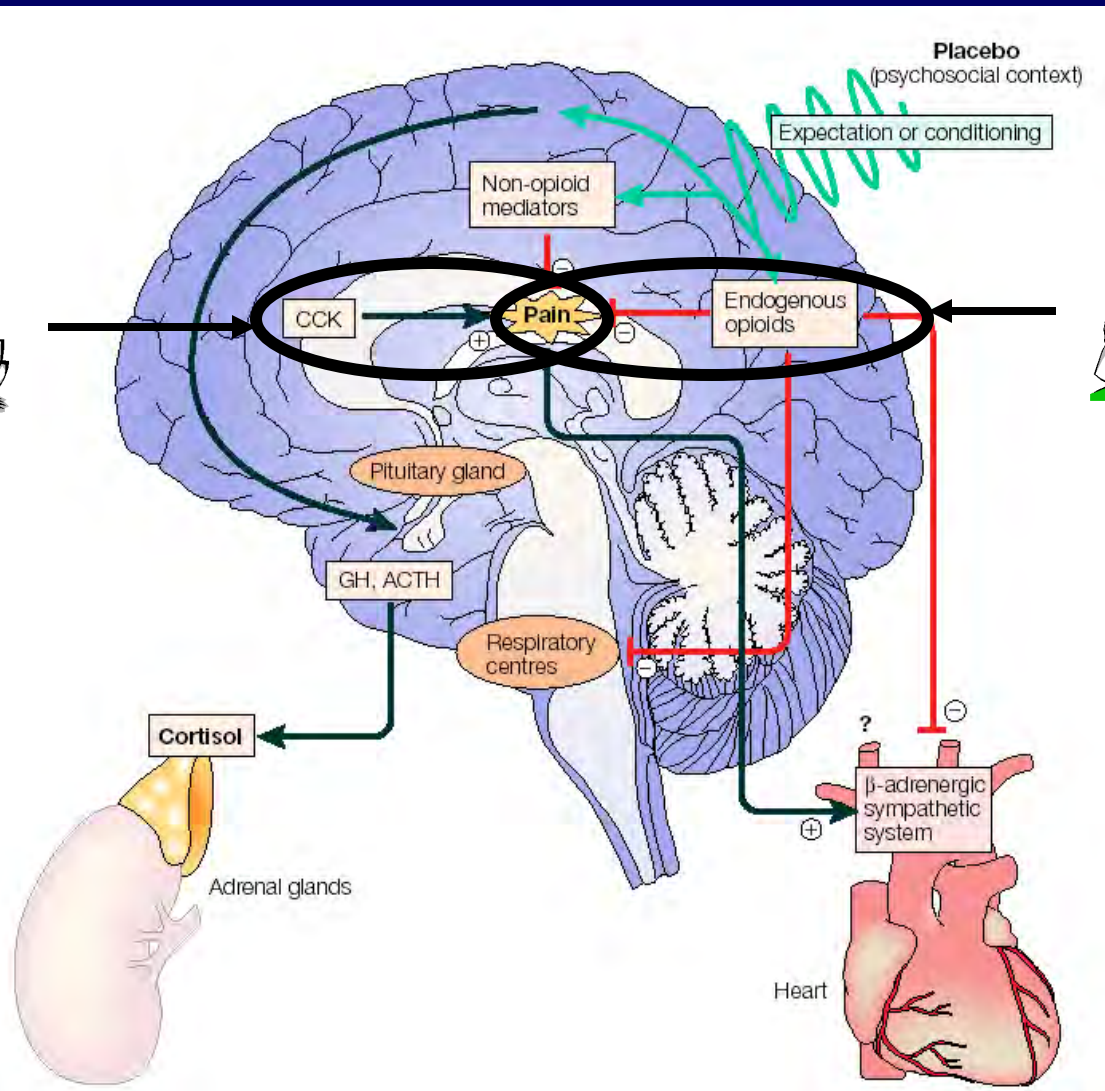
Nocebo suggestions induce anticipatory anxiety, which activates two independent pathways, the hypothalamus-pituitary-adrenal (HPA) axis on the one hand and a CCK-ergic pronociceptive system on the other hand. Benzodiazepines act on anxiety, thus blocking both the HPA hyperactivity and the CCK pronociceptive system. In contrast, CCK antagonists act on the pronociceptive system only, thus preventing nocebo hyperalgesia but not HPA-hyperactivity (Benedetti et al., 2006). Note: the main purpose of this sketch is to focus on neural substrates of the hyperalgesic nocebo effect which, in this case, takes precedence over anatomical accuracy.

Ethic Issue: Hyperalgesia and side-effects can potentially be manipulated by ‘informed consent’.

When informed of possible sexual dysfunction 43.6% reported if informed, only 15.3% of the uninformed (Mondaini et al, J Sex Med, 2004, 4). How much should patients be told?



Nocebo suggestions



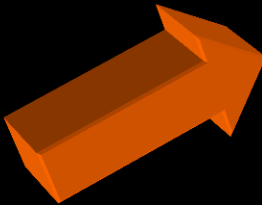
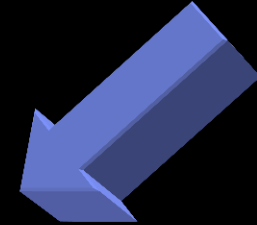
Placebo suggestions

Placebo effect = Context effect

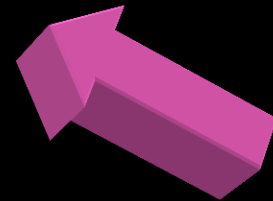
Sight



Words



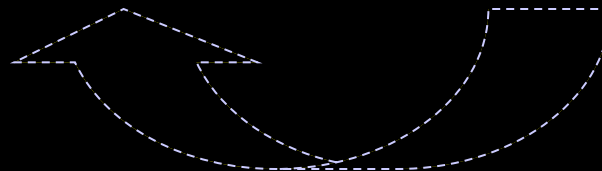
Smell



Touch



Dummy treatment



Conscious



Unconscious



PSYCHOSOCIAL CONTEXT

COGNITION

- Expectation
- Belief
- Trust
- Hope



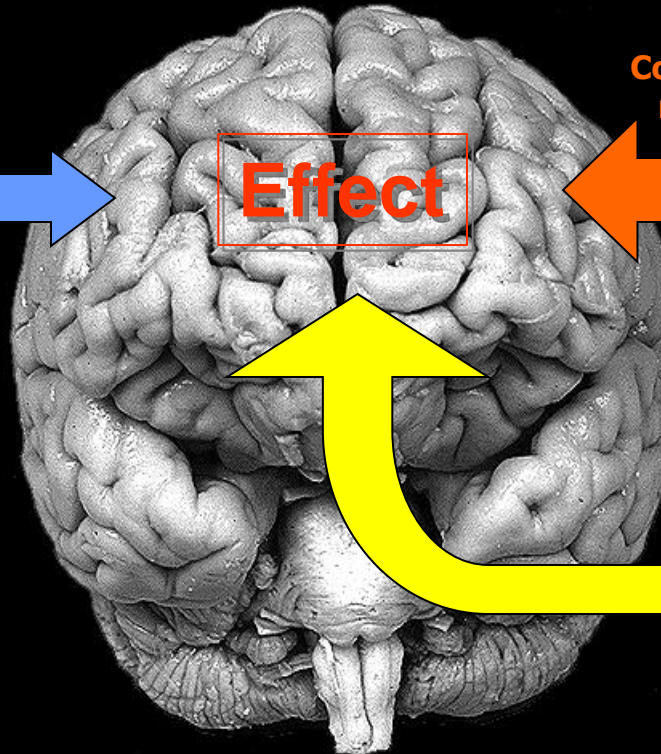
Effect

**Conditioned
response**



**Conditioned
stimulus**

**Unconditioned
stimulus
(e.g. drug)**



Behavioral/Psychological Influences

Chronic use of opioid analgesics in non-malignant pain: report of 38 cases

(Portenoy RK, Foley, KM. Pain, 1986, 25, 171-186)

Opioids: oxycodone = 12; methadone = 7; levorphanol = 5; 14 = others

Duration: 19 > 4 years; 6 > 7 years

Dosages: 67% < 20mg morphine/day; 4 > 40 mg/day

Results:

- 24/38 (63%) adequate/acceptable relief

- Limited gains in work/social function

- 2/38 had management issues (both history of drug abuse)

Conclusions: "...opioid therapy can be a safe, salutary and more humane alternative to the options of surgery or no treatment in those patients with non-malignant pain and no history of drug abuse" (p 171)

Chronic use of opioid analgesics in non-malignant pain: report of 38 cases

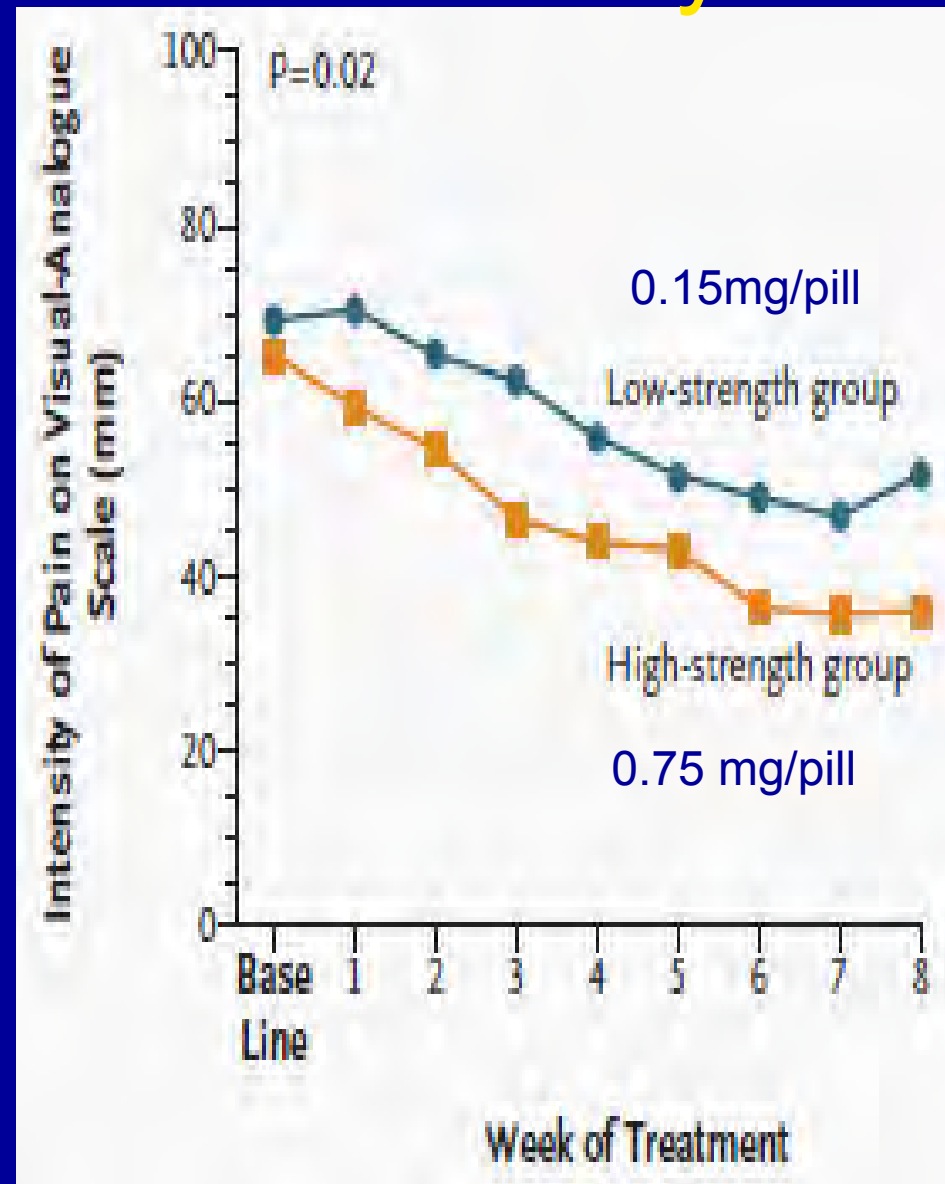
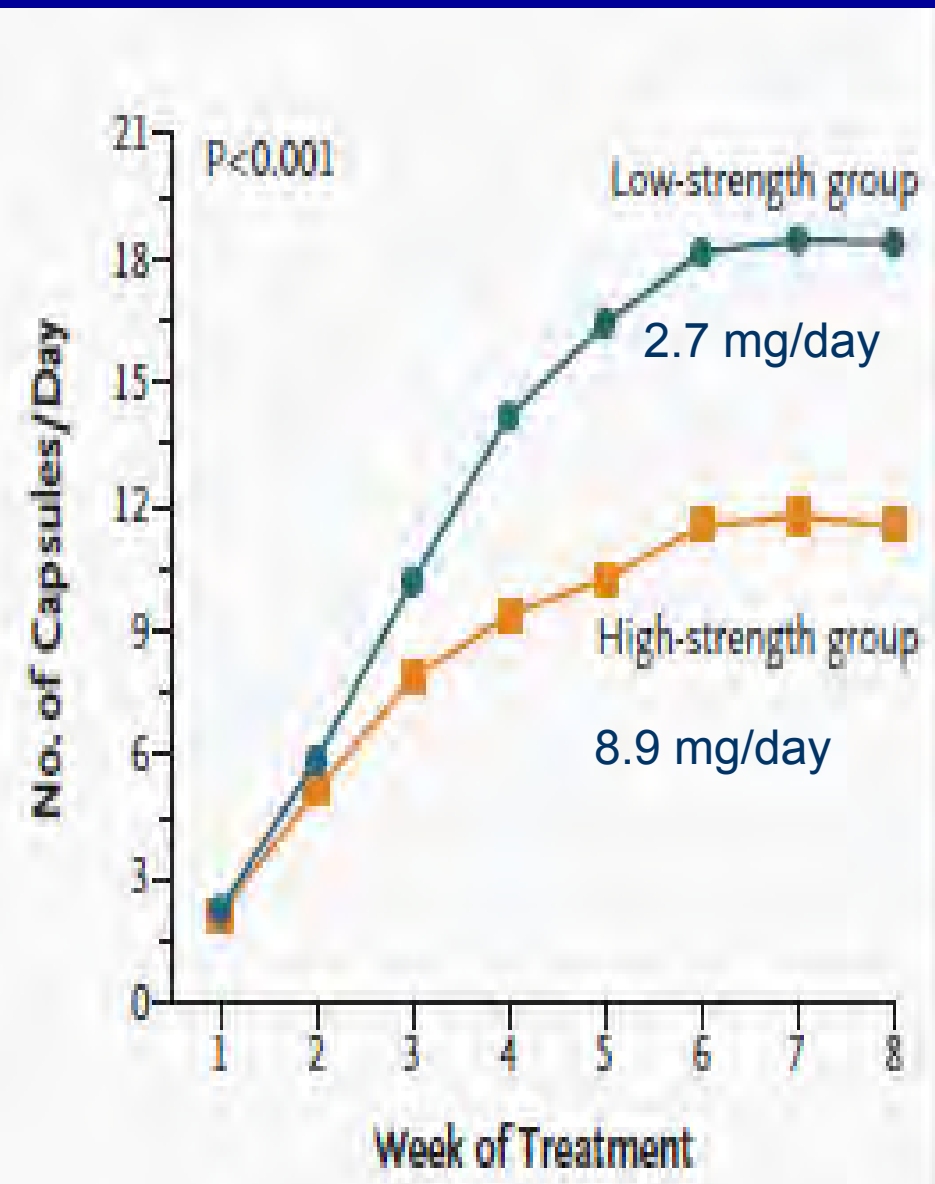
(Portenoy RK, Foley, KM. Pain, 1986, 25, 171-186)

- “It must be recognized, therefore, that the efficacy of this therapy and its successful management may relate as much to the **quality of the personal relationship between physician and patient** as to the characteristics of the patient, drug, or dosing regime.”

Unsupported Myths Re: Opioid Therapy

- **Leads to Addiction:** Especially if there is no history of drug abuse or genetic history
- **Route of Administration:** Addiction is not in the drug or route of administration
- **Agonist-antagonist drugs** will prevent addiction
- **Short acting drugs** are more likely to cause addiction than LA, SR, CR.
- **No ceiling:** Prescribe to effect/side-effect
- **Opioids** are appropriate for all types of pain
- **Opioids** should only be used for acute and cancer pain
- **SA opioids** should not be used for long term therapy

Effect of the Number of Pills/Day



Time-contingent vs Pain-contingent Opioid Dosing (Pain,2011,152,1255-62)

- Survey of 1,781 patients receiving COT for chronic noncancer pain in which 967 patients used time-scheduled opioid dosing and 325 pain-contingent opioid dosing only.
- Patients using time-scheduled dosing reported being more preoccupied with opioid use, less able to control their opioid use, and more worried about opioid dependence. They also were more likely to report that family or friends thought they may be dependent on opioids.

What is the Case for Prescribing *Long-Acting* Opioids Over *Short-Acting* Opioids for Patients with Chronic Pain? A Critical Review

- **Review:** 12 chronic pain studies comparing short- and long-acting opioids head-to-head. These were supplemented with representative studies from the chronic pain literature.
- **Results:** Although some patients with chronic pain appear to prefer short-acting opioids, many patients receiving long-acting opioid formulations show improved treatment responses and better perception of quality of life. In addition, the sustained reductions in pain seen with long-acting opioid formulations may promote patients' focus on daily activities rather than on their pain, thereby improving therapy adherence and reducing pain-related anxieties.
- **Conclusion:** Long-term clinical trials of these formulations are needed to allow clinicians to make informed decisions about which patient groups might benefit most from these formulations.

(Rauk, R. Pain Practice, 2009, 9, 468-479)

Opioid Dosing

(Doleys et al. Practical Pain Management, 2008)

- **Sample:** N = 47 **Pills/day:** 4.1 (range 3.1- 4.5) **Months:** 30.8 (range 12-96)
- **Overall improvement (0-100%):**
Pain: 56.8%
Qol: 64%

Satisfaction level:

Very satisfied: 14/47 (29.8%)

Satisfied: 31/47 (66%)

Not satisfied: 2/47 (4.2%)

Onset of relief:

Time Range	Percentage
0-20 minutes	36.2%
20-30 minutes	44.7%
45+	19.1%

DOC:

Outcome	Percentage
Decrease in pain	39.9%
Decrease/dulling of pain	37.8%
Energized	19.1%
Sleepiness	8.5%
Euphoria	0%

Duration of Relief (hours):

Hour Range	Percentage
2-3 hours	48.9%
4-5 hours	21.3%
1 or less hours	10.6%
1-2 hours	8.5%
3-4 hours	6.4%
5 hours +	4.3%
AVERAGE	3.2 hours

Patients report that **control-ability** of the medicine and **predictability** of the effect enhanced their pain control

Opioids and Hypogonadism

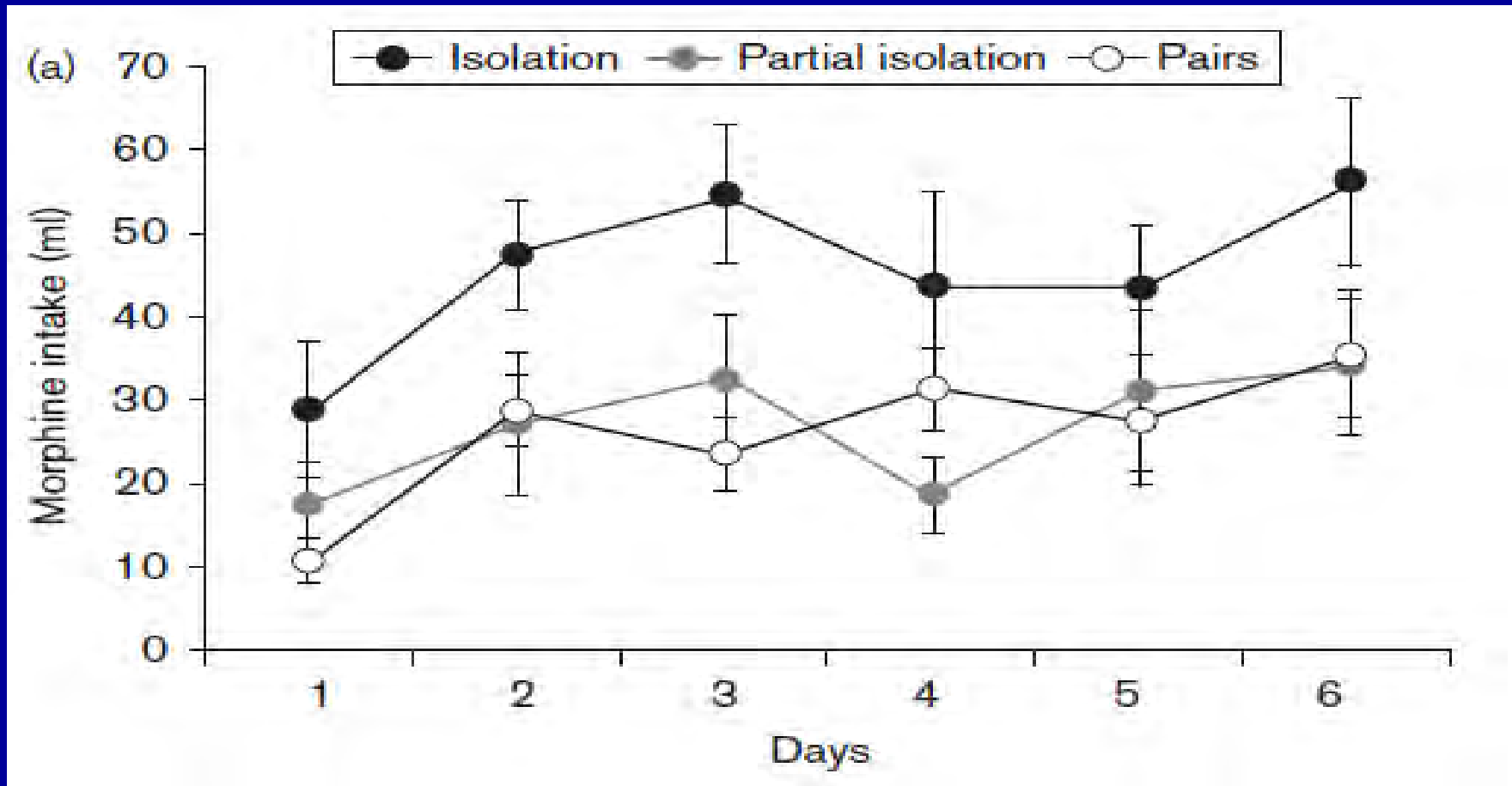
Examined: hydrocodone (25), oxycodone (8 CR, 10 IR), morphine CR (12), fentanyl patch (4), methadone (14), and buprenorphine (8).

Minimum of 90 days

Results:

- 57% of men were hypogonadal (testosterone level < 250 ng/dL; reference range 300-1195)
- 74% of men on long-acting formulations vs 34% short-acting formulations
- After controlling for dose and BMI patients receiving long-acting opioids had 4.78 times greater odds of becoming hypogonadal vs patients receiving short-acting opioids
- A high prevalence of hypogonadism was associated with duration of action, but not with total daily dose of the opioid.

Social Isolation and Morphine Consumption



Adult Wistar rats housed in short term isolation (21 days) consumed significantly more morphine solution (0.5 mg/ml) than rats living in pairs. No differences were found in their water consumption. This effect was observed in both males and females. As little as 60-min of daily social-physical interaction with another rat was sufficient to completely abolish the increase in morphine consumption in socially restricted animals. Environmental and situational factors influence drug intake in laboratory rats as they do in humans.

Opioid Use in a Hospital Setting

- “Narcotic utilization for back pain patients housed in private and semi-private rooms” Dolce JJ, Doleys DM, Raczynski JM, Crocker MF. Addictive Behavior, 1985, 10(1), 91-95

Patients in private rooms used more IM request-contingent narcotics than similar patients in semi-private rooms.

- “View through a window may influence recovery from surgery” Ulrich RS. Science, 1984 Apr 27;224(4647):420-1

Post-surgical patients in rooms with a view of a natural scene had shorter hospital stays, used fewer opioids than matched patients in rooms with windows facing a brick building wall.

Negative Affect and Opioid Therapy

- A double-blind, placebo-controlled study of extended-release (ER) hydromorphone among opioid-tolerant patients with chronic low back pain.
- Patients were grouped as Low, Moderate or High Negative Affect based on the Hospital Anxiety and Depression Scale (HADS). Numerical pain intensity measures at home and in the clinic, Roland-Morris Disability ratings, and measures of symptoms from the Subjective Opiate Withdrawal Scale (SOWS)
- **Results:** Patients in the Moderate and High Negative Affect groups
 - (a) higher drop-out rate because of the adverse effects or lack of efficacy
 - (b) reported significantly higher pain intensity scores
 - (c) greater disability on the Roland-Morris Scale
 - (d) more withdrawal symptoms
 - (e) High group had the most improvement in pain in the placebo condition
- **Conclusions:** Negative affect is associated with diminished benefit during a trial of opioid therapy and is predictive of dropout in a controlled clinical trial.

Opioids and Psychopathology

- **Level (L,M,H) of psychopathology:** based on BDI (depression), PASS (pain anxiety), NEO (neuroticism) scores
- **Results:**
 - High reported < analgesia vs Low
 - L = 65% relief vs 41% for high
 - L = 59% decrease vs H = 37%
 - H & M > placebo vs L (23%, 23%, Vs 7%)
 - Psych status, working, education accounted 31% of variance

Conclusion: High levels of psychopathology are associated diminished opioid analgesia

Depression and Pain

250 patients with low back, hip, or knee pain for 3 months or longer and at least moderate depression severity (Patient Health Questionnaire-9, score > 10)

The intervention consisted of 12 weeks of optimized antidepressant therapy (step 1) followed by 6 1-hour sessions of a pain self-management program over 12 weeks (step 2)

Medication priority: Venlafaxine, Fluoxetine, Sertraline, Citalopram, Bupropion, Mirtazapine, Nortriptyline

	% Treatment Group (n=123)	% Usual Care (n=127)
Depression (>50%)	37.4	16.5
Pain (>30%)	41.5	17.3
Global	47.2	12.0
Depression/Pain	26.0	7.9

Opioid use, misuse, and abuse in patients labeled as fibromyalgia.

Fitzcharles MA, et al. Am Med, 2011, 124, 955-960

METHODS:

A chart review of all patients referred to a tertiary care pain center clinic

RESULTS:

32% of 457 patients referred to a multidisciplinary fibromyalgia clinic, with over 66% using strong opioids. *Opioid use/abuse was more commonly associated with lower education, unemployment, disability payments, current unstable psychiatric disorder, a history of substance abuse, and previous suicide attempts.*

CONCLUSION:

Prolonged use of opioids in fibromyalgia may be associated negative health and psychosocial status and requires further evaluation.

Unraveling BPD

- SIB (self-injurious behavior): an nonsuicidal auto-aggression that terminated states of negative affect or inner tension
- Independent of nociceptive modality
- Stress leads to dissociative states and aversive arousal
- Peak dissociative states coincide with SIB
- Pain thresholds correlate with dissociation and aversive arousal
- Decrease volume in frontal/ prefrontal areas, 'soft' neurological signs suggest abnormal frontolimbic neurocircuitry



- The reduction in **nociceptive sensitivity** by SIB-induced antinociception contribute to further identity diffusion
- **Therefore, analgetic treatment in BPD may also trigger SIB** Am J Psychiatry. 2010 Aug;167(8):925-33. doi: 10.1176/appi.ajp.2010.09091348. Epub 2010 May 3.
- **Dysregulation of regional endogenous opioid function in borderline personality disorder.**
- Prossin AR1, Love TM, Koeppe RA, Zubieta JK, Silk KR (Mageri et al, Pain, 2012, 153, 575-584)

Alzheimer's, Dementia, TBI etc (cont)

- Results:

1. AD and controls showed open-hidden differences on 1st test;
2. At 2nd test difference remained while for AD the difference diminished (they also showed decreased MMSE & FAB (Frontal Assessment Battery) scores)
3. Lower FAB scores, <9, correlated with less effective open lidocaine;
4. Reduced prefrontal connectivity displayed greatest effect vs temporal-parietal-occipital regions

- Summary:

Reduced analgesia in AD patients appears to be secondary to the loss of placebo- and expectation- related mechanisms. A corresponding adjustment in opioid may be required.

(Benedetti et al, Pain, 2006,121, 133-144)

Assessing the Cognitively Impaired



- Altered central processing: - altered functional connectivity - impaired contextual appraisal
- Altered expression
- Altered fear or affective response
- Altered response to opioids secondary to disruption of the expectancy due to cognitive impairment
(Benedetti et al. Pain, 2006; Cole et al. Eur J Pain, 2011)



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Psychiatric Endogenous Opioid Dysfunction Syndrome: Premise

- Opiates were used to treat major depression in the United States until the mid-1950s.
- Treatment with opioids can produce a neuro-modulatory effect that is far beyond the consequences of mere analgesia and/or sedation
- The mu-opioid agonists (morphine, oxycodone, oxymorphone, and hydrocodone) have been shown to demonstrate sustained, robust, antidepressant, mood stabilizing, and antipsychotic effects without concomitant opioid abuse/tolerance—or the use of illicit substances

Psychiatric Endogenous Opioid Dysfunction Syndrome (PEODS): Evidence

- **Fibromyalgia:** Neuropsychiatric disorder exhibiting reduced mu-opioid receptor binding potentials
- **Depressive Spectrum Disorders:** Endogenous opioid neurotransmission on mu-opioid receptors is altered. Therefore, some chronic pain patients report improved mood and/or remission from depression when treated with opioids above and beyond any reduction of their pain symptoms
- **Sensitivity to social rejection:** Has been associated with a particular polymorphism of the mu-opioid receptor gene (OPRM1). Some patients may claim they function better socially while taking opioid pain medications (separate from the effects of analgesia).
- **Impulse Control Spectrum Disorders :** Endogenous opioids play a key role in the modulation of temperament and personality, as well as cognition and mood. Thus the proclivity for risk-taking behaviors in some chronic pain patients.
- **Borderline Personality Spectrum Disorders:** Abnormalities in their mu-opioid receptor concentrations and their endogenous opioid system response to negative emotional challenges

Psychiatric Endogenous Opioid Dysfunction Syndrome (PEODS): Conclusions

Chronic pain, in and of itself, can cause degenerative brain changes and may play a role in the genesis of certain cognitive and behavioral disorders. **Dysregulation of the endogenous opioid system may underly the propensity to exhibit aversive emotional responses or specific dysfunctional personality traits.** These include syndromes associated with a dysfunctional endogenous opioid system that may respond to exogenous opioid administration in the context of chronic opioid therapy.

Psychiatric endogenous opioid dysfunction syndrome (PEODS)—having predominantly depressive, anxious, obsessive/compulsive, impulsive or mood instability features—**can be used to document the diagnosis or presence of neuropsychiatric disorders that arise in whole, or in part, due to endogenous opioid dysfunction.**

Aberrant Drug Taking Behavior: 'Causes'

Addiction: Multiple unsanctioned dose escalations;
multiple prescribers; self-injecting oral formulations

Psychiatric Co-morbidity: Impulsive – Personality
Disorders; Self-medicating Sx ie anxiety, depression etc.

Cognitive: Dementia, TBI, IQ

Criminal Intent: For purpose of diversion

CONCLUSION: Aberrant behavior does not equal
addiction. It is a matter of type and extent.

(Passik & Kirsh; CNS Drugs, 2004,18,13-25)

Breakthrough Pain (?): Categories

1. End of dose
2. Disease progression
3. Incident:
 - Volitional (e.g. walking, bending, coughing, sitting, etc.)
 - Non-volitional (e.g. bowel/bladder distension, diurnal pater, etc.)
4. Weather sensitive
5. Psychosocial (e.g. depression, anxiety, conflict etc.)
6. Associative tolerance, nonassociative tolerance, OIH

Breakthrough Pain : Management

1. Detailed assessment: Patient Self- Monitoring
2. Treat underlying etiology; if known
3. “Rescue” meds; behavioral issues
4. Physical therapy
5. Education
6. Behavioral/ Cognitive behavioral therapy

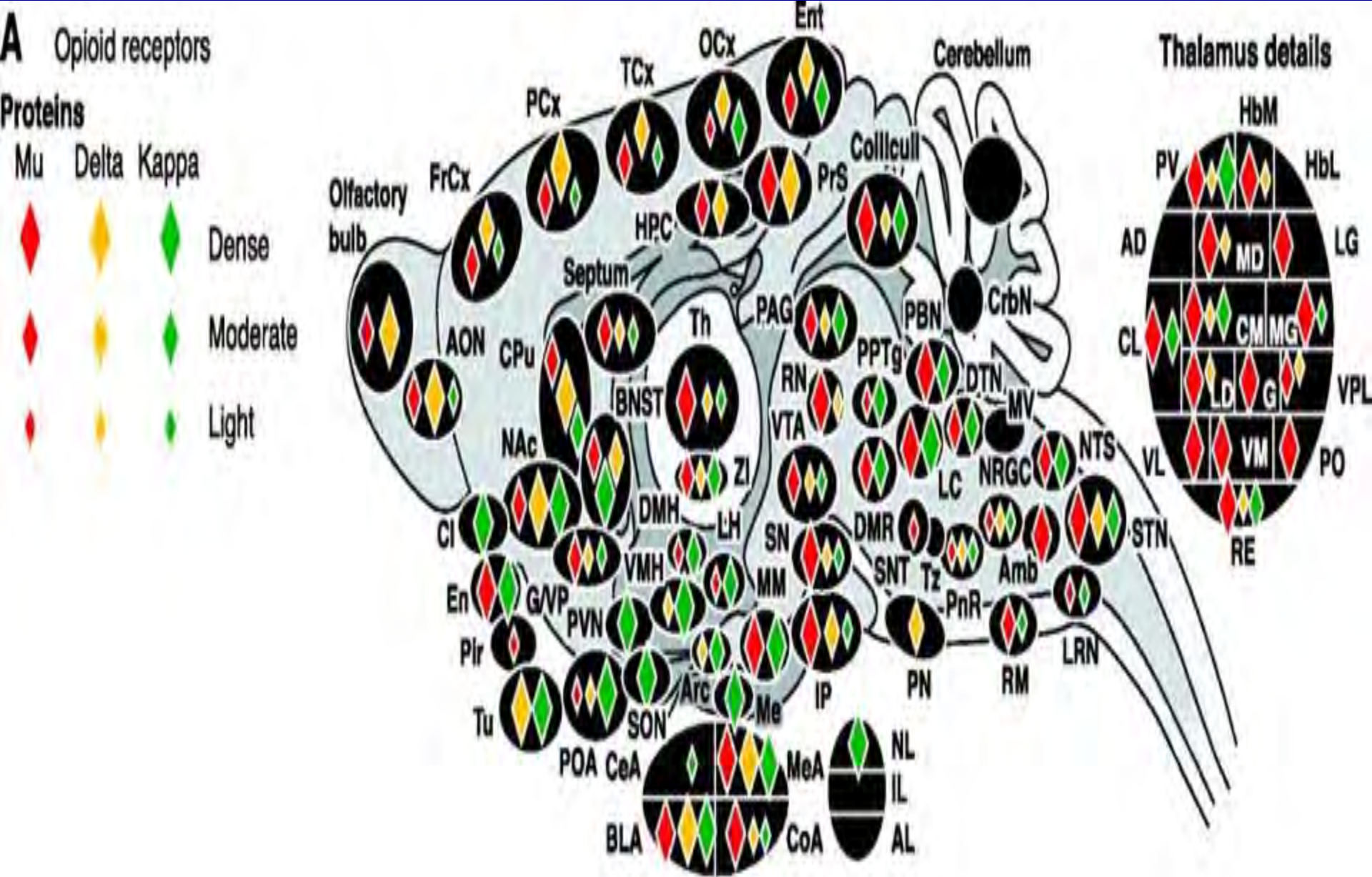
Why Patients Sue: Patient Attributes

(cont.)

- **In general:** affluent, higher education, angry, female
- **Odds** of affirming the desire to sue:
 - Litigation status (e.g. WC suit) x3
 - Feeling coerced x3
 - Anger x3.5
 - MD financially motivated **x8**
 - ‘Upset with health’ **x8** (acceptance)
- If **‘trusted’** their MD odds were **78% LESS**
- **“Satisfaction”:**
 - relationship of expectation to outcome
 - perception of the practitioner’s effort/involvement

(Fishbain et al. Pain Medicine, 2008, 9, 1130-1142)

Conclusions and Suggestions



Le Merrer et al Reward Processing by the Opioid System in the Brain
 Physiological Reviews, 2009, 89 (4).1379-1412 DOI: 10.1152/physrev.00005.200

Opioid Efficacy Determined By:

- Pharmacokinetics/Dynamics
- Route of administration
- Duration of treatment: acute vs chronic
- Type of pain: Nociceptive vs Neuropathic
- Conditioning factors
- Psychosocial factors: readiness, acceptance, mood, personality, addiction, psycho-pathology
- Outcomes measure (s) used
- Most variables are dynamic vs static

'Pain' Stimulating/Enhancing Factors

- Anticipation/expectation
- Uncertainty
- 'Imagined allodynia'
- Hallucinated pain
- 'Pain catastrophizing'
- Mood states
- 'Limbically augmented pain syndrome or LAPS'
- Conditioning and learning
- 'Conditioned nociception'
- Epigenetic



Implications and Applications

- BTP meds
- PO with IT therapy
- SA with CR/LA/SR
- Behavioral/psychological assessment/therapy
- 'Context' vs. content of treatment
- You have to know when to stop 'digging' a deeper 'hole'

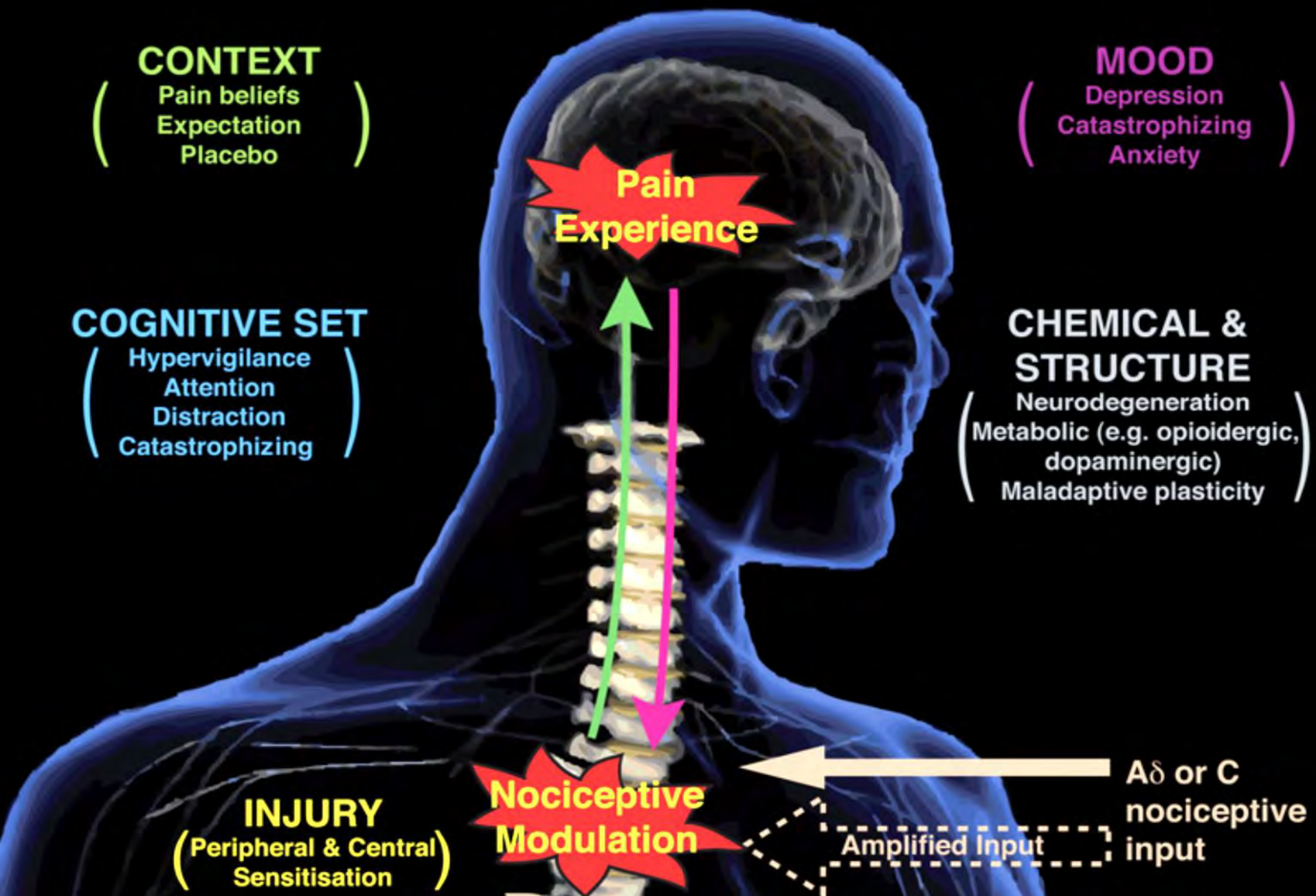


Purpose of Opioid Therapy?

- to improve pain
- to improve function
- to improve QOL
- to produce patients who
are content with their treatment

Key Concepts

- Expectations
- Acceptance
- Function
- FLOP (functional level of pain)
- Dispositional Optimism





- Pain is not an opioid deficiency
- Life is not a chemical deficiency
- Don't say yes if you can't say no
- Be the clinician the patient needs; not just the one they want

Thank You

