Care of the Patient with Co-Morbid Pain and Anxiety

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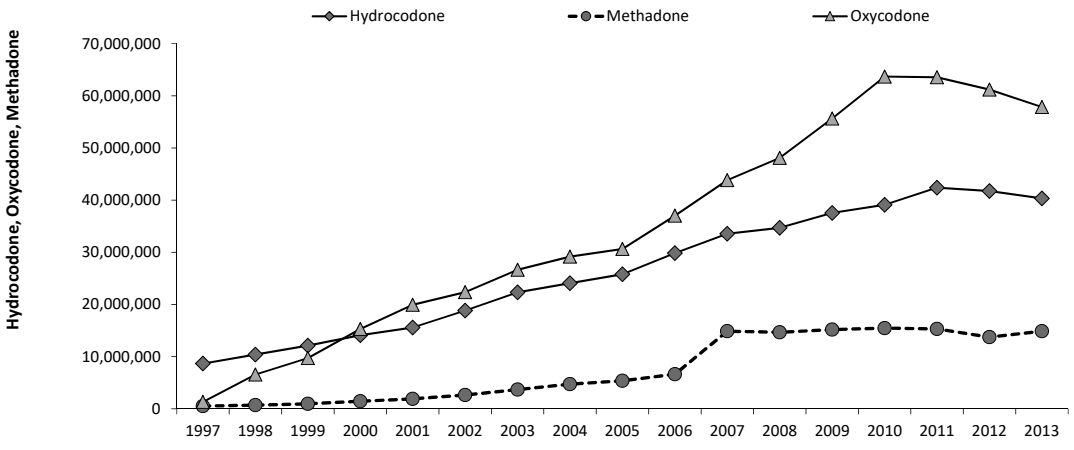
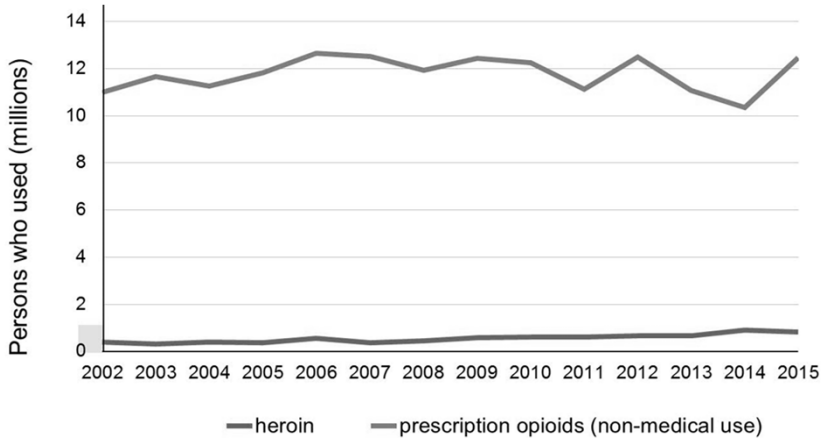
Outline

- Review the epidemiologic in context of psychiatry's role in the opioid problems.
- Chronic pain as a disease of the brain.
- The development of mood and anxiety secondary to chronic pain
- The problems of combining opioids and benzodiazepines.
- The association of depression, chronic pain and suicidality.
- Treatment of mood and anxiety in the chronic pain patient or opioid dependent patient.

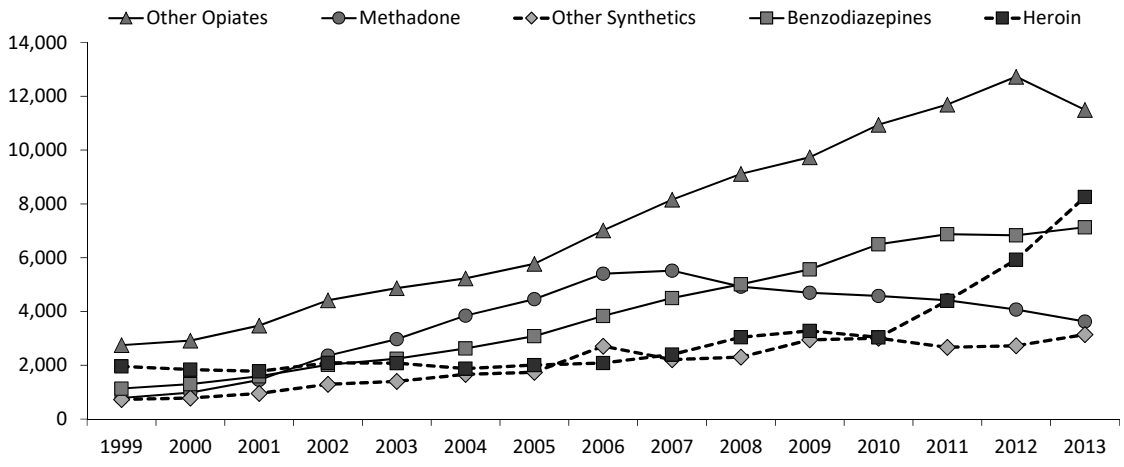
Grams of Selected Drugs Distributed per 100,000: DEA ARCOS 1997–2013[15]



U.S. Non-Medical Use of Opioids 2002-2015



Number of U.S. Drug Poisoning Deaths CDC 1999–2013[14]



Overdose Risk Factors

- Using more than 100 mg of oral morphine equivalents daily (Bohnert et al., 2011; Dunn et al., 2010)
- Mixing opioids with benzodiazepines, alcohol, other drugs (Powis et al., 1999)
- Medical conditions (renal, hepatic, pulmonary diseases, HIV)
- Hx of a OUD and recent release from controlled environment
  - Incarceration (Binswanger et al., 2013; Binswanger et al., 2007)
  - Treatment (Strang et al., 2003)
- Co-Morbid OUD and Depression

- Primary care physicians' adoption of opioid risk reduction strategies is limited, even among patients at increased risk of misuse.

Starrels JL, et.al., J Gen In Med 9, 958-964, 2011

CDC Guidelines (March 2016)

1. Nonpharm and nonopioid tx
2. Establish treatment goals
3. Discuss opioid risks
4. Start with mediate release opioids
5. Use the lowest effective doses
6. No greater quantity than needed
7. Evaluate benefits early/often
8. Evaluate risks often
9. Use the PMP
10. Use UDSs
11. Avoid co-Rx opioids and benzodiazepines
12. Offer MAT to patients thought to be dependent

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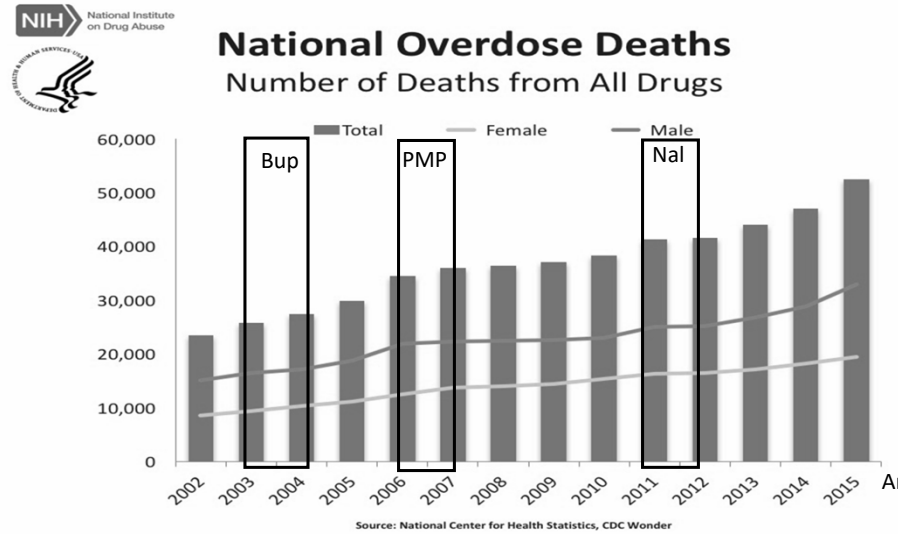
Current Interventions Effectiveness:
Are they not effective or are they just not being used?



Arthur Williams MD MBE

At Risk Patients for Opioid Misuse

- Past history of substance use disorder
- Emotionally traumatized
- Dysfunctional / alcoholic family
- Lacks effective coping skills
- Dependent traits
- Stimulus augmenters-deficit in hedonic tone

Pain

- In the past pain was typically viewed as an immediate and short-lived response to an injury or illness.
  - A warning sign to an emergent problem.
- It was generally accepted the pain would resolve as the injury or illness improved. There was also, potentially, an acceptance that the body would merely get used to the pain, or what we now think of as modulation.
- There was as much if at all a discussion of chronic pain as we talk about it today.
- Healthcare and society today is profoundly impacted with chronic pain conditions.
  - Prior to the 1990s SSDI enrollees had clearly delineated clinical disorders such as heart disease or cancer. Between 1996 and 2009, enrollment for workers in SSDI has expanded by 3.4 million people, or a growth of 77%.
    - 1.1 million can be attributed to a greater number of disabled with mental illness,
    - 1.2 million – a 137% increase – because of increases in musculoskeletal diseases.

Social Security Administration's Annual Statistical Report on the Social Security Disability Program, 2009 (published 2010).

Pain

- Perception of pain as a 4-step model
  - **Transduction**: Acute stimulation in the form of noxious thermal, mechanical, or chemical stimuli is detected by nociceptive neurons.
  - **Transmission**: Nerve impulses transferred via axons of afferent neurons from the periphery to the spinal cord, to the medial and ventrobasal thalamus, to the cerebral cortex
  - **Perception**: Cortical and limbic structures in the brain are involved in the awareness and interpretation of pain.
  - **Modulation**: Pain can be inhibited or facilitated by mechanisms affecting ascending as well as descending pathways.

Apkarian A., et.al. European Journal of Pain, Volume 9, Issue 4, page 463, August 2005
Zubieta J., Science 13 Jul 2001: Vol. 293, Issue 5528, pp. 311-315

Epidemiology of Pain

- Prevalence of Recurrent and Persistent Pain in the US
  - 1 in 10 Americans report having persistent pain of at least one year's duration
  - 1 in 5 individuals over the age of 65 report pain persisting for more than 24 hours in the preceding month
    - – 6 in 10 report pain persisting > 1 year
- Costs US economy estimated $100 billion/year
- JCAHO – Installs a Quality Standard on pain identification. (2001)

American Pain Foundation. http://www.painfoundation.org. Accessed March 2010.

Chronic Pain

- Chronic pain is often defined as pain that has lasted for more than three months. Officially it is pain that lasts beyond the "injury related healing process."

Merskey H, Bogduk N, editors. Classification of Chronic Pain. IASP Press; WA, USA: 1994.

- Multiple causes, most common are back pain and headache.

Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. 2011

How Chronic Pain Effects the Brain?

- A supraspinal problem?
- The main components of the brain network of <u>acute</u> pain:
  - primary and secondary somatosensory,
  - thalamus
  - insular,
  - anterior cingulate,
  - prefrontal cortices

How Chronic Pain Effects the Brain

- Advanced neuroimaging indicates chronic pain can result in structural changes in the brain.
  - Central nervous system changes secondary to a person's experiences, medications and health conditions including anxiety.

Henry DE, et.al., PM R. 2011;3:11161125

  - Chronic pain is associated with the reorganization of the nervous system.
    - observe regional degree changes with some unique properties to each type of chronic pain
    - chronic pain being a state of global randomization of functional interconnectivity

Mansour A., et.al.,Scientific Reports, Vol. 6, 34853, 11.10.2016

    - right parahippocampus gyrus connectivity predicts drug analgesia and also predicts placebo response.
    - There is evidence of the disruption of this response by active drug.

Tétreault, P., et.al., *PLoS Biology*, *14*(10)

How Chronic Pain Effects the Brain?

- Affective processing of pain involves the anterior cingulate and insular cortices
  - Changes with chronic pain: evidence of a thinning of the anterior cingulate and thickening of the insular cortices.

Apkarian AV, et.al., European Journal of Pain 9 (2005) 463–484

  - Alexithymia, “no words to emotions”,
    - cognitive alexithymia dimension showed significantly larger gray matter volumes of the right posterior insula,
    - affective dimension showed larger gray matter volumes in the right posterior medial cingulate cortex.

K.S. Goerlich-Dobre et al. / Neuropsychologia 53 (2014) 284–292

How Chronic Pain Effects the Brain?

- Endogenous opioids are mobilized during interpersonal acceptance in both controls and depressed patients, though not as persistently in the depressed patient. Conversely there is less resilience in the depressed patient during rejection.
- The μ-opioid receptor system has a role in the physiological regulation of affective experiences in humans. (Zubieta J, *Arch Gen Psychiatry.* 2003;60(11):1145-1153.)
- Regional activation of μ-opioid neurotransmission is centrally implicated in the suppression of the affective qualities of a pain stressor, as well as the negative internal affective states induced by pain. (Zubieta J, *Science.*2003;2991240- 1243)

Considerations in Chronic Opioids

- Chronic Opioid Use may result in hedonic homeostatic dysregulation.
  - Down regulation of natural drives, e.g. eating, copulation, affiliation, may be reorgainized around drug seeking behavior.
  - Heightened responsiveness to drug reward and decreased responsiveness to natural reward seen in opioid dependent individuals.
  - This may drive prescription opioid misuse and addiction.
  - Therapies are aimed at restructuring this reward.

Perceived Pain - Suffering

- At risk patients
  - Past history of substance use disorder
  - Emotionally traumatized
  - Dysfunctional / alcoholic family
  - Lacks effective coping skills
  - Dependent traits
  - Stimulus augmenters-deficit in hedonic tone

Modulation: Adaptation to pain

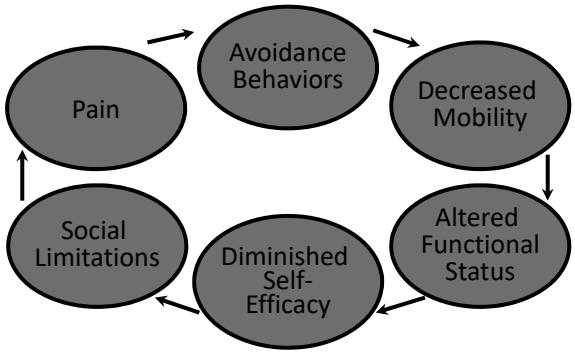
•Once the pain feedback system identifies the problem is no longer indicating a worsening problem the pain feedback mechanism modulates the response, the pain is isolated, and suffering is reduced.

•This can also occur through perception of pain by cognition and conditioning.

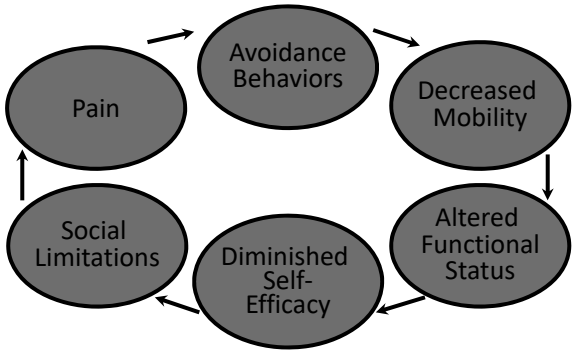
•Medications can augment these adaptations or disrupt them.

pain that lasts beyond the "injury related healing process."

Vicious Cycle of Uncontrolled Pain



Vicious Cycle of Uncontrolled Pain
(Would a Benzodiazepine help this or make it worse?)



Benzodiazepines

- Adverse effects:
  - Increased reaction time,
  - motor incoordination,
  - anterograde amnesia,
  - slurred speech,
  - restlessness, delirium,
  - aggression,
  - depression,
  - hallucinations,
  - paranoia.
- Unlike barbiturates, large doses of benzodiazepines are rarely fatal unless combined with other CNS depressant drugs, such as alcohol or opioids.
- Flumazenil can be administered by injection to reverse the adverse effects of benzodiazepines.

- FDA ,Drug & Chemical Evaluation Section, Jan. 2013

Benzodiazepines: Cognition

Results from the 13 studies in the meta-analysis:

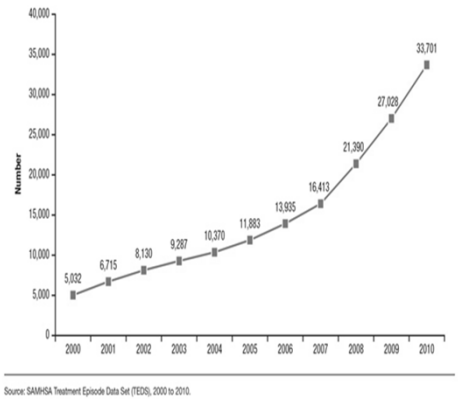
- Benzodiazepines use
  - the duration between 1 and 34 years (mean 9.9 years)
  - average dose equivalent was 17.2 mg/day of diazepam
- Results suggested decline in all the cognitive domains measured:

Barker MJ, Greenwood KM, and Jackson M. et al. Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. Arch Clin Neuropsychol. 2004. 19:437–454.

visuospatial,
attention/concentration,
problem solving,
general intelligence,
psychomotor speed,
sensory processing,
verbal memory,
non-verbal memory,
speed of processing,
motor control/performance,
working memory,
verbal reasoning.

Opioid/Benzodiazepine Treatment Admissions

- Treatment admissions reporting both benzodiazepine and narcotic pain reliever abuse increased 569.7 percent from 2000 to 2010.
  - 61.2 percent of benzodiazepine and opiate combination admissions reported daily use of any substance
    - compared with 34.6 percent of other admissions
  - 57.1 percent daily use of narcotic pain relievers
  - 45.5 percent reported daily use of benzodiazepines
  - 45.7 percent of benzodiazepine and narcotic pain reliever combination admissions reported a *co-occurring psychiatric disorder*
    - compared with slightly more than one quarter (27.8 percent) of other admissions



Source: SAMHSA Treatment Episode Data Set (TEDS), 2000 to 2010.

SAMHSA Treatment Episode Data Set (TEDS), 2000 to 2010.

Treatment of Anxiety

- First-line treatments:
  - selective serotonin reuptake inhibitors (SSRIs),
  - serotonin-noradrenaline reuptake inhibitors (SNRIs)
  - calcium channel modulator pregabalin.
- Second:
  - Tricyclic antidepressants (TCAs) are equally effective for some disorders, but many are less well tolerated than the SSRIs/ SNRIs.
- Treatment Resistant
  - Benzodiazepines, if no history of substance abuse disorders.
- Cognitive behavioural therapy (CBT) and other variants of behavior therapy have been sufficiently investigated and are recommended either alone or in combination with the above medicines.

Bandelow B. et.al., The World Journal of Biological Psychiatry, 2008; 9(4): 248312

Are they all unintentional overdoses?

- Dramatic increase in fatal poisonings involving opioid analgesics.
  - opioid related fatal poisonings tripled from 4,000 to 13,800 deaths from 1999 through 2006
  - 40% of all deaths by poisoning in 2006 involved opioids.

    Warner M, et.al., DMNCHS Data Brief. 2009 Sep; (22):1-8.
  - Results from the 2010 (SAMHSA) Drug Abuse Warning Network report opioid analgesics have become the common class of drugs associated with "unintentional", fatal poisoning, greater than heroin and cocaine. *SAMHSA, DAWN, 2007: Estimates of Drug-Related Emergency Department Visits.*
- How many are intentional death by suicide is undetermined due to misclassification or lack of classification of intent?
  - Between 2005 and 2007, emergency department visits for drug-related suicide attempts increased by 30% and there was an overall 55% increase in opioid related attempts. *SAMHSA, DAWN, 2007: Estimates of Drug-Related Emergency Department Visits.*

Suicide and Chronic Pain

- Assessment of suicidal behavior in adults with noncancer chronic pain (n=153)
  - 19% reported current passive suicidal ideation,
  - 13% had active thoughts,
  - 5% currently had a plan for suicide
  - 5% reported a previous suicide attempt.
  - 75% reported drug overdose as their plan

    Smith MT, et.al., Pain. 2004 Sep; 111(1-2):201-8.
  - A review of similar literature identified that the risk of successful suicide doubles with chronic pain. *Tang NK, et.al., Psychol Med. 2006 May; 36(5):575-86*
- Depression, Sleep and Catastrophizing are important mediators.

  Tang NK, et.al.,J Sleep Res. 2007 Mar; 16(1):85-95; Turner JA, et.al., Pain. 2002 Jul; 98(1-2):127-34; Edwards RR, et.al., Pain. 2006 Dec 15; 126(1-3):272-9.

Trauma and Stress in Chronic Pain and/or Concurrent Opioid Use

- Trauma and stress are risk factors for many forms of psychopathology, including depression, anxiety disorders, and substance abuse *Brady et al., in Nunes et al., Best Practices for Diagnosis and Clinical Treatment. Kingston, NJ: Civic Research Institute 2010*
  - Some studies indicate particularly high comorbidity of PTSD and OUD (relative to alcohol and other drugs).
    - reported 33% of those with OUD had PTSD *Meier A, et.al., Am J Drug Alcohol Abuse. 2014 Jul;40(4):304-11, 2014; Mills KL,et.al., . American Journal of Psychiatry, 163:652-8, 2006*
  - Among veterans, psychiatric diagnoses, particularly PTSD, were associated with increased risk of receiving opioids for pain, high risk opioid use and adverse clinical outcomes *Seal KH, et.al., . JAMA, 307: 940-7, 2012*

Treatments for anxiety and PTSD with chronic pain

- Psychotherapy:
  - Evidence-based psychotherapies:
    - Cognitive Behavioral Therapy (CBT),
      - including exposure-based CBT. CBT involves a combination of psychoeducation, relaxation and anxiety management techniques, cognitive techniques, in PTSD imagined and in vivo exposure to trauma-related stimuli, and relapse prevention *Gabbard G, Journal International Review of Psychiatry,19,1:5-12,2007*
    - Seeking Safety (SS) is a well studied non-exposure based treatments for co-occurring PTSD and SUD. *Hien et al., Journal of Consulting and Clinical Psychology, 77:607-19; 2009; Najavits and Hien, Jounral of Clinical Psychology, 69: 433-479, 2013*
      - a standard cognitive behavior treatment with both safety/trauma and substance use components integrated into each session. *Najavits et al., Journal of Traumatic Stress,11:437-56, 1998*

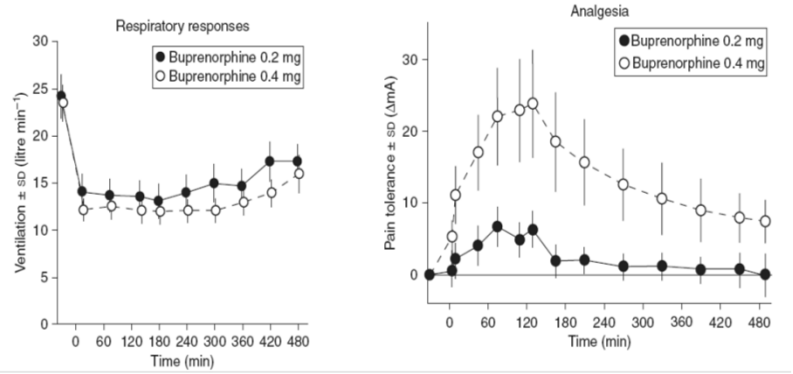
Treatments for anxiety and PTSD with chronic pain

- Pharmacotherapy:
  - Meta-analyses generally support the superiority of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) over placebo. Tricyclic antidepressants and monoamine oxidase inhibitors can improve in intrusive and depressive symptoms, but SSRIs are considered first-line in part due to safety profiles.
  - Mirtazapine and nefazodone have also be shown to be superior to placebo.
  - Prazosin has been found to be effective for PTSD-related nightmares and sleep disturbance.
  - APA guidelines recommended SSRIs as first-line. (2004)

Buprenorphine?

- A partial mu agonist and kappa antagonist.
  - Buprenorphine is a partial mu agonist opioid profile of effects similar to other mu agonists, but has less risk of respiratory depression and a lower level of physical dependence.
  - Kappa opioid receptors (KORs) belong to the G-protein coupled class of receptors (GPCRs).
  - They are activated by the endogenous opioid peptide dynorphin (DYN) and expressed at particularly high levels within brain areas implicated in modulation of motivation, emotion, and cognitive function.
  - Chronic activation of KORs in animal models; increases in behaviors that reflect depression, the propensity to engage in drug-seeking behavior, and drug craving.
  - Interest in selective KOR antagonists as potential therapeutic agents.
  - Both animal and human studies identifying the antidepressive effects including a reduction in suicidality. *Almatroudi A, et.al., J Psychopharmacol. 2015 Jul; 29(7): 812–821.; Yoram Yovell et al., American Journal of Psychiatry, 2015*

Buprenorphine Safety and Pain



An increase in the dose can improve analgesia but there is no change in respiratory depression.

Dahan A et al. Br J Anaesh 2006

Buprenorphine and Benzodiazepines

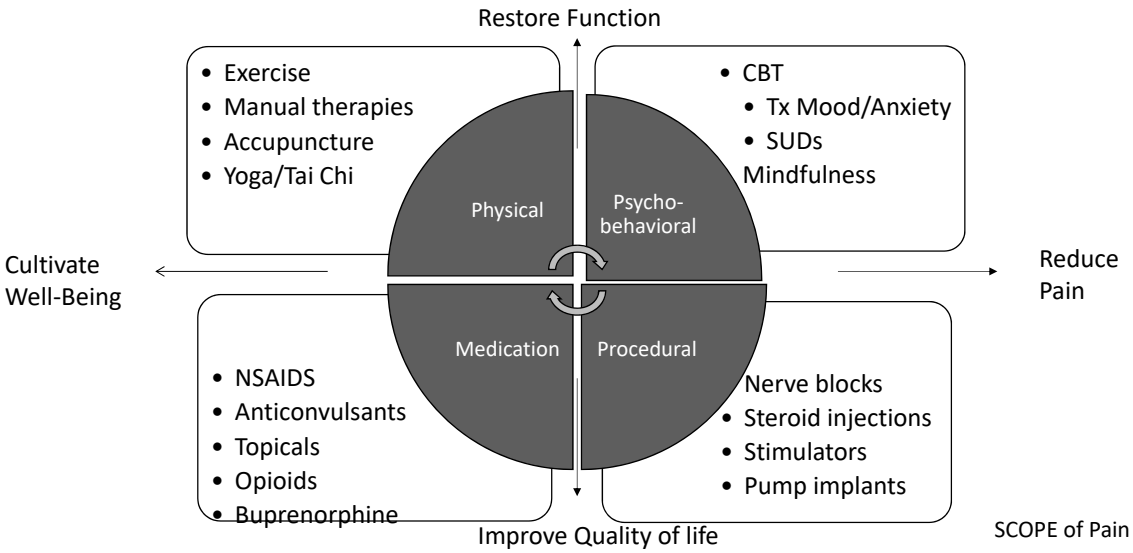
- Patients actively using benzodiazepines relapsed more often (70% vs. 42%, $p = .043$).
  - Of the 19 patients with anxiety disorders, 10 were found to have used benzodiazepines and 9 were not,
  - 10 out of 39 patients without anxiety diagnoses were found to have used benzodiazepines.
- However variables *significantly* associated with relapse when adjusted for age and gender:
  - higher buprenorphine maintenance doses (OR = 4.08, 95% CI = 1.64–10.13; $p = .002$);
  - comorbid anxiety disorders (OR = 4.16, 95% CI = 1.18–14.67; $p = .026$);
  - alcohol abuse during buprenorphine treatment (OR = 6.64, 95% CI = 1.22–36.05; $p = .030$).
- Those suggestive of a trend but *not statistically* significant associations:
  - a history of intravenous drug use (OR = 2.76),
  - *comorbid benzodiazepine use* (OR = 3.05),
  - history of residential substance abuse treatment (OR = 2.20)

- Ferri M, et.al. (2013) *American Journal on Addictions* 23(1): 62-67.

Promote Healthy Behaviors

- Promote healthy behaviors to reduce anxiety.
  - exercise;
  - sleep hygiene;
  - decreased use of caffeine, tobacco, alcohol, and other potentially deleterious substances.

Multidisciplinary Care



Summary

- Most people will have a period of chronic pain in their lifetime.
- Chronic pain just as other states, e.g. environmental, behavioral, chronic medication, can change the brain. Opioids can interrupt the natural modulation to chronic pain.
- Chronic pain can result in mood and anxiety problems.
- Benzodiazepines can cause added problems to the treatment of chronic pain.
- Strongly consider multimodal therapies in the treatment of pain.