



**UW PACC**

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

# DEPRESSION AND OPIOID USE DISORDER

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# GENERAL DISCLOSURES

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# GENERAL DISCLOSURES

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# SPEAKER DISCLOSURES

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# SPEAKER DISCLOSURES

- ✓ No conflicts of interest

# PLANNER DISCLOSURES

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# AGENDA

- Neurobiological background: physical pain, social pain, and endogenous opioid system
- Role of psychiatric disorders:
  - Starting on long-term opioid therapy
  - Staying on long-term opioid therapy
  - Getting off of long-term opioid therapy
- Lessons learned about: pain, suffering, and opioids



**“O just, subtle, and all-conquering opium!”**  
**-- Thomas De Quincey,**  
***Confessions of an English Opium Eater*, 1821**

# NEUROBIOLOGICAL BACKGROUND: PHYSICAL PAIN, SOCIAL PAIN, AND ENDOGENOUS OPIOID SYSTEM



# PHYSICAL PAIN



From Rene Descartes, *Treatise on Man*, 1650

# PHYSICAL PAIN (A BROKEN LEG)

- Implies that nociception causes chronic pain
  - But this is never the whole story
  - And rarely the most important part of the story
- We are drawn to “physical pain” because
  - It fits into the biomedical model of causation where diseases cause symptoms
  - It provides us with a picture of innocent suffering

# AN OBJECTIVE NEUROLOGICAL SIGNATURE OF PHYSICAL PAIN

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

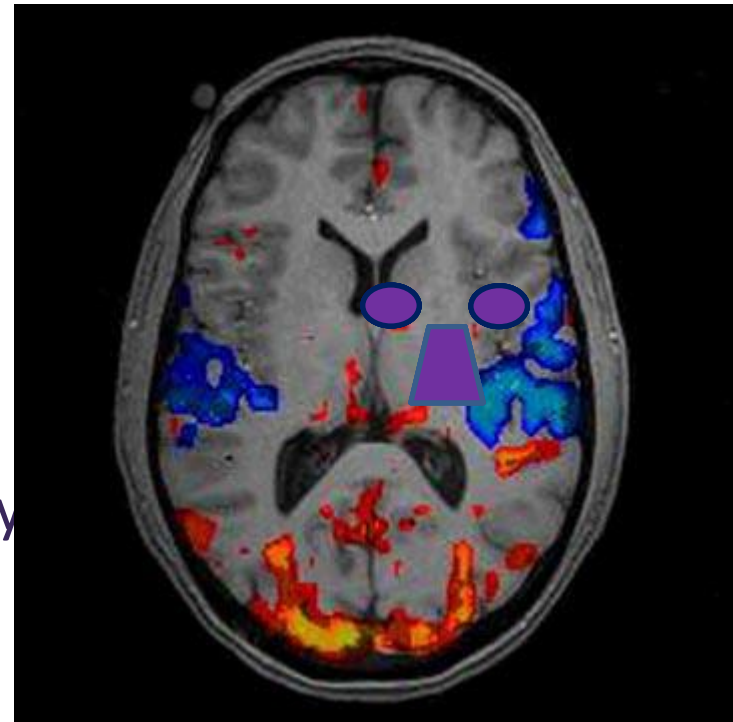
## An fMRI-Based Neurologic Signature of Physical Pain

Tor D. Wager, Ph.D., Lauren Y. Atlas, Ph.D., Martin A. Lindquist, Ph.D.,  
Mathieu Roy, Ph.D., Choong-Wan Woo, M.A., and Ethan Kross, Ph.D.

- N Engl J Med 2013;368:1388-97.

# PAIN CANNOT BE IDENTIFIED WITH ANY OBSERVABLE NEUROLOGICAL EVENT

- Pain is not peripheral tissue damage.
- Pain is not the activity of c-fibers.
- Pain is not the activity within the spinothalamic system.
- Pain is not the activity in the thalamus or in the somatosensory cortex.
- Pain is not the activity of a distributed network of sensory and affective brain regions.



There is no way to tell this brain is feeling pain unless it is attached to a person.

Brains do not suffer or communicate pain.

# SOCIAL PAIN (A BROKEN HEART)



It is a rare patient who would prefer a broken heart over a broken leg.  
--David Morris

# SOCIAL PAIN: NEW VIEWS

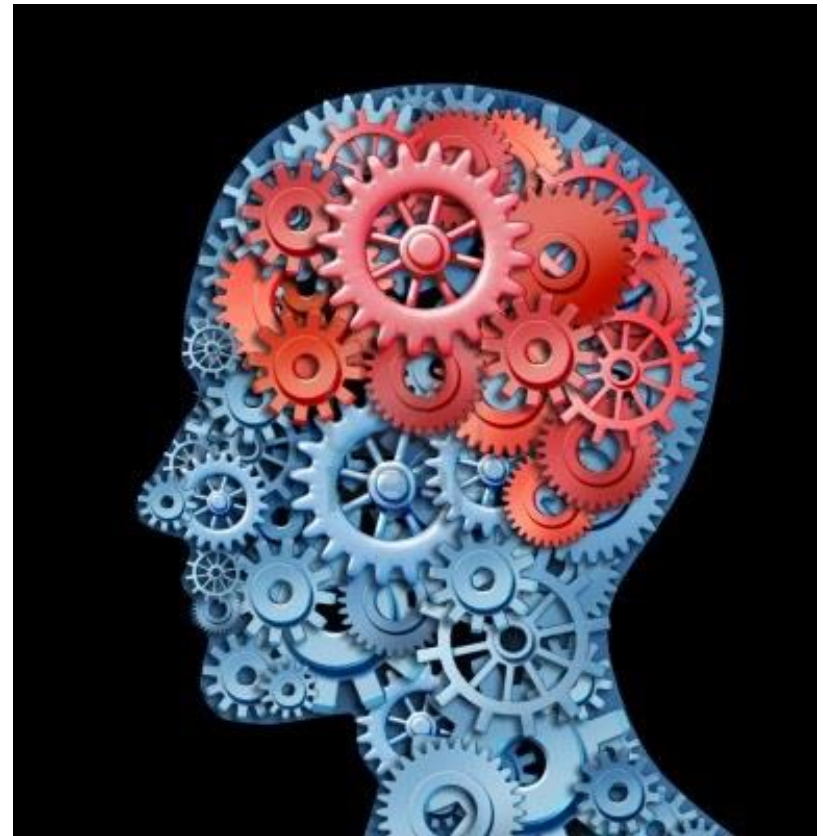
- All clinical pain has psychological elements
  - Threat more essential than nociception
  - Especially true of chronic pain which changes lives
- Experimental physical and social pain activate the same brain regions: rACC, anterior insula...
  - Same patients show sensitivity
  - Same medications provide relief
- Psychological trauma is real
  - Trauma can produce lasting brain changes and PTSD
  - Psychological healing more complicated

# SOCIAL PAIN AND OPIOIDS

- Opioids relieve distress of social separation and rejection (Panksepp 1978)
- In mammals, the social pain system has piggybacked onto the physical pain system of non-mammals to make social separation painful (because it is dangerous to survival) (Eisenberger 2012)
- In addiction, substances replace relationships  
In recovery, relationships replace substances

# FUNCTIONS OF THE ENDOGENOUS OPIOID SYSTEM

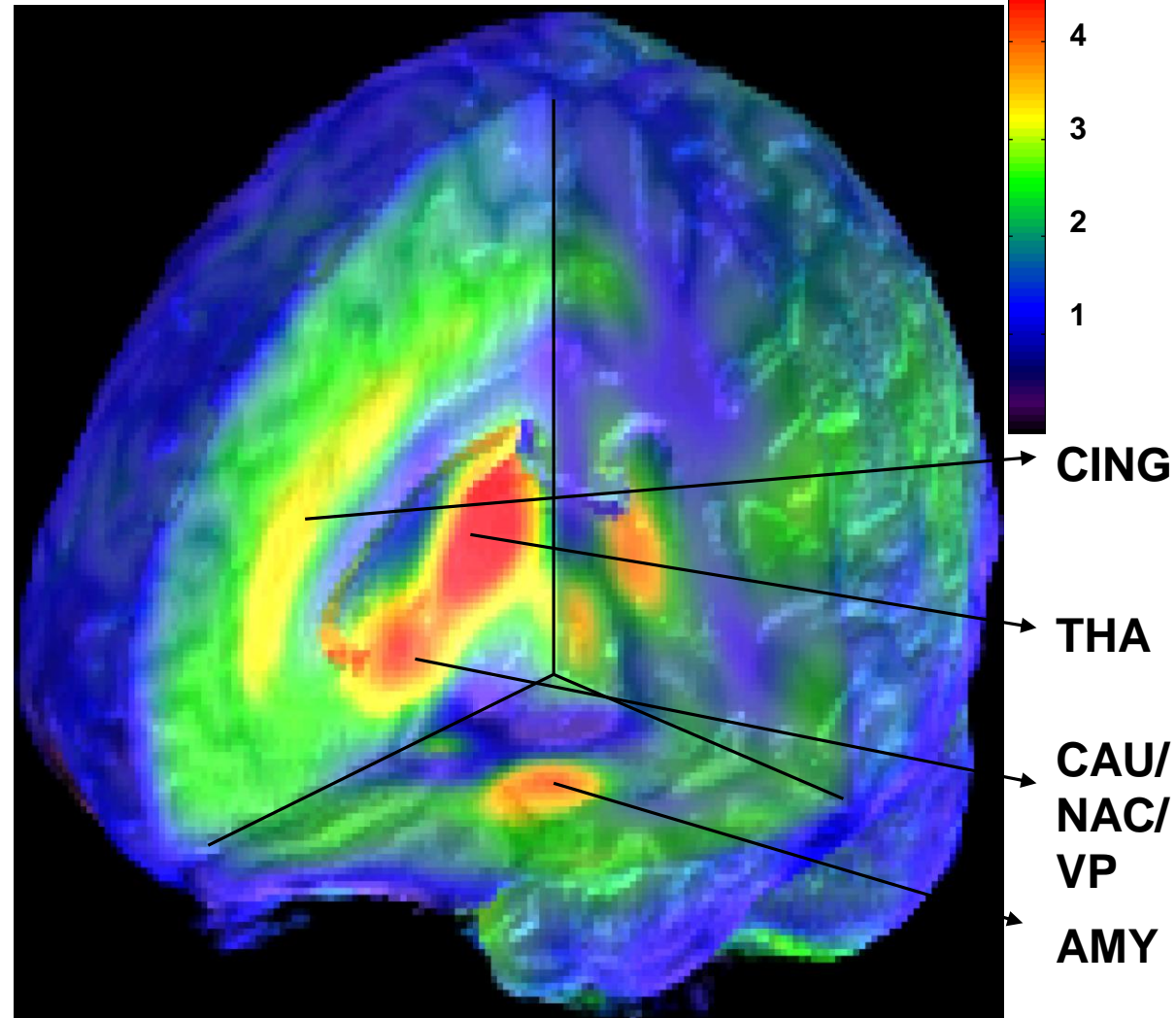
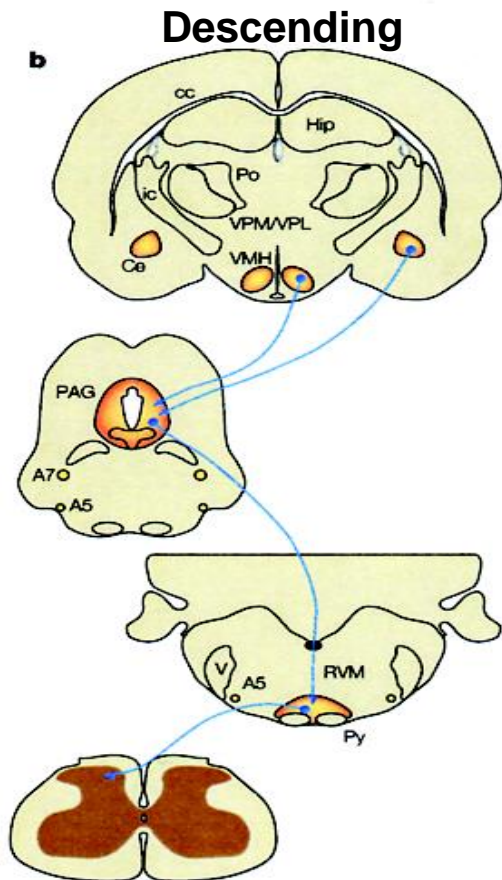
- Stress-induced analgesia
- Addiction: opioids, stimulants, alcohol, nicotine, cannabis
- Mental health: depression, stress, borderline PD, cognition, learning and memory
- Endocrine: fertility, sexuality, maternal-infant bonding, eating, drinking
- Gastrointestinal, renal and hepatic functions
- Cardiovascular responses, respiration, and immunological responses





# CNS Inhibitory Controls

## Mu Opioid Receptor-Mediated Neurotransmission



Distributed in pain regions but also “affective / motivational circuits” - neuronal nuclei involved in the assessment of stimulus salience and cognitive-emotional integration.

From Zubieta JK

# ROLE OF PSYCHIATRIC DISORDERS:

## STARTING LONG-TERM OPIOID THERAPY



# WHO RECEIVES LONG-TERM HIGH-DOSE OPIOID THERAPY?

- The vast majority of opioid therapy is short-term. (Noble 2010, Furlan 2006)
  - Most “ideal” candidates for opioid therapy discontinue before reaching 90 days
  - Three-fourths of patients started on ER/LA opioids will not fill a second prescription.
- Of patients prescribed opioids for chronic pain, those who go on to long-term therapy are a highly self-selected group (Morasco 2011, Seal 2012, Edlund 2013, Halbert 2016)
  - Depressed patients slightly more likely to be started on opioids, but twice as likely to progress to long-term use
  - PTSD patients more likely than other MH patients to get high-dose, long-term
  - SA and MH disorders much more common in long-term, high-dose users
  - Long-term opioid cohort progressively enriched with high-risk patients.
- ‘Adverse selection’:
  - combination of high risk patients with high risk med regimens
  - May link trends in use, abuse, and overdose

# WHO DISCONTINUES LONG-TERM OPIOID THERAPY?

- TROUP study of 'daily' COT recipients (Martin 2011)
  - Sample: used at least 90 days, no 32 day gap
  - Outcome: 6 months without any opioid Rx
  - In two diverse samples, 2/3 of patients remain on opioids years later
  - COT continuation predicted by: high daily dose (>120mg MED) and opioid misuse
- Nationwide VA study: >70% continue opioids (Vanderlip, 2014)
  - Continuation predicted by: high opioid dose, multiple opioids, multiple pain problems, tobacco use, but NOT other SA, MH disorders
- Other prospective studies show similar findings (Franklin 2009, Thielke 2014)

# ROLE OF PSYCHIATRIC DISORDERS:

## STAYING ON LONG-TERM OPIOID THERAPY



# LONG-TERM OPIOID THERAPY INDUCES MAJOR DEPRESSION

- Patients w opioid use > 30 days have incr. risk of new depression episode indep. of pain.
- Opioid use doubles risk of depression recurrence for patients with past episodes
- Long term opioid therapy interferes with depression treatment, increasing risk of treatment resistant depression by 50%
- [Scherrer et al, 2014, 2015, 2016, 2017]

# ROLE OF PSYCHIATRIC DISORDERS: GETTING OFF LONG-TERM OPIOID THERAPY



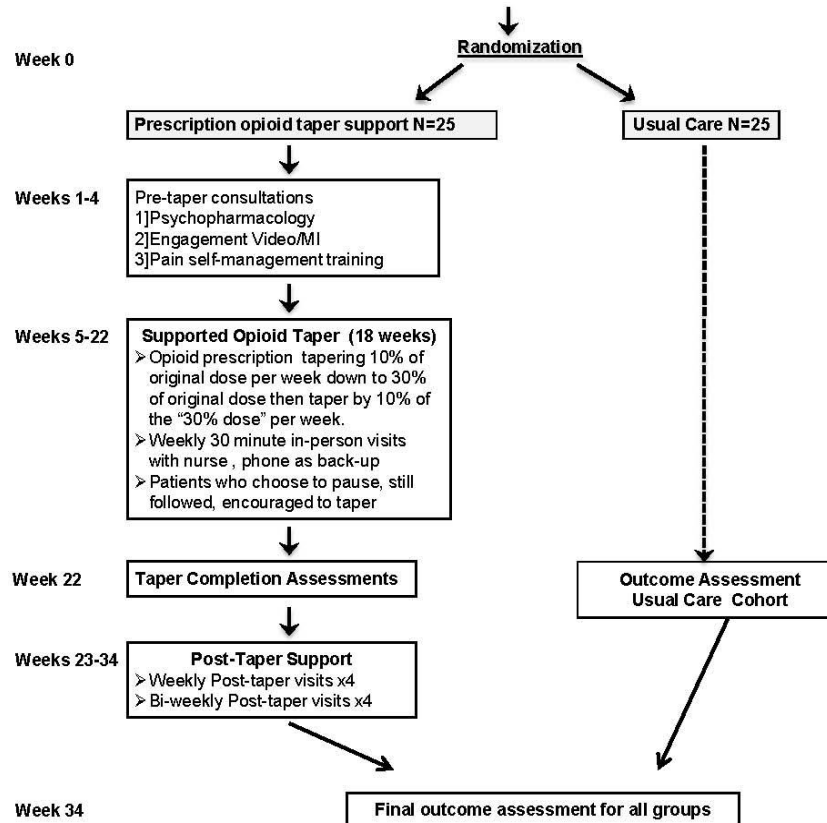
# OPIOID TAPER: ROLE OF PSYCHIATRIC SYMPTOMS

- Physical symptoms of opioid withdrawal:
  - Aches, rhinorrhea, gooseflesh, nausea, diarrhea
  - Usually absent in slow taper, easily treated
- Psych symptoms of opioid withdrawal:
  - Anxiety, depression, insomnia, craving, anhedonia
  - These may be significant despite slow taper, especially when psychiatric disorder preceded or followed opioid therapy



# WHAT CAN BE DONE TO SUPPORT OPIOID DISCONTINUATION?

<b>Screening Consent Baseline Data</b>	<ul style="list-style-type: none"> <li>&gt; All CPR patients on COT for CNCP (N=1500) complete PODS assessment, high scorers referred to trial</li> <li>&gt; Nurse case manager shows informational video, obtains informed consent from subjects</li> <li>&gt; Research Assistant collects baseline data then informs patients of randomization status</li> </ul>
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Prescription  
Opioid  
Taper  
Study

R34DA033384

# THEORY BEHIND POTS STUDY DESIGN

- Many patients on long-term opioid therapy are ambivalent: “would love to stop if I could”
- Fear of pain and withdrawal symptoms is more important than actual pain and withdrawal symptoms
- Transition to chronic pain self-management has two phases:
  - Establishing importance (engagement)
  - Establishing confidence and skills (training)

# POTS INTERVENTION

- Engagement
  - PODS, engagement video, MI
- Psychiatric/psychopharm consultation
  - Anticipate and treat pre-existing psych symptoms
  - Assess (PHQ9, GAD7, PC-PTSD) and Treat
- Skills training
  - adapted from pain CBT, delivered by PA
  - Pacing, relaxation training, flare management
  - Gradual taper: 10% per week, may be “paused”

# PODS: PRESCRIPTION OPIOID DIFFICULTIES SCALE

- PODS identifies problems attributed by patient to their opioid therapy in 2 domains:
- Psychosocial problems
- Opioid control concerns
  
- We use PODS answers to jump-start a discussion of the cons of opioid therapy from the patient's perspective

# ENGAGEMENT VIDEO

- Patients who have successfully tapered off prescription opioids describe their experience in two video segments
  - The end result: what is life like once you are off opioids?
    - pain level, emotions, “zombie”
  - The process: what are the challenges of going through opioid taper?
    - Pain, insomnia, anxiety, depression

# SAMPLE POTS STUDY SUBJECT FLOW SHEET #1

Baseline opioid regimen:

Other Medications:

Medication	Dose	Changes/date
Methadone	160	50mg 2/23
Dilaudid	32	Same
<b>Total Baseline MED:</b>	<b>2048</b>	1088

Medication	Dose	Changes/date
Diazepam	10mg	NO Diazepam use this past week
Venlafaxine	375 mg	1/26
Tizanidine	12 mg	
Trimethobenzamide	900 mg	Not needed

## Weekly Stats

Session Number	BL	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	we	24	we	28	we	32
Date	12/11	12/15	12/22	1/8	1/12	1/15	1/26	2/2	2/9	2/23	2/27	3/2	3/16	3/19									
phone (P), in-person (IP)	lp	lp	ip	IP	lp	p	ip	ip	lp	ip	P	lp	ip	P									
Methadone	160	140	120	100	90	90	60	60	60	55	50	50	50	50									
Dilaudid	32	32	32	32	32	32	32	32	32	32	32	32	32	32									
<b>Total MED</b>	<b>2048</b>	<b>1808</b>	<b>1568</b>	<b>1328</b>	<b>1208</b>	<b>1208</b>	728	728	728	678	628	628	628	628									
PHQ	16	20	16	19	14	22		11	6	10	12	17	21	23									
GAD	16	18	14	18	14	20		11	3	10	9	11	18	18									
Pain Intensity	6	7	8	6	7	7		5	2	4	2	5	4	2									
Pain Interference	8	6	6	6	7	8		4	0	3	1	4	3	2									
Benzo dose	Y	y	y	y	y	y	y	N	n	N	n	N	N	N									
Alcohol use	n	n	n	n	n	n	n	n	n	n	n	n	n	n									

**Baseline opioid regimen:**  
**Long-acting Oxycotin 60mg BID**  
**Short-acting Oxycodone 20mg QID**

**Other Medications:**  
**Doxepin 150mg**  
**Gabapentin 1800mg**  
**Prazosin 4mg**  
**Venlafaxine 150mg**

**Weekly Stats**

Session Number	BL	1	2 & 3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	24 week check in	28 week check in	32 week check in
Date	10/13	1/8	1/15	1/29	2/2	2/12	3/5	3/12	3/23	3/26	3/30	4/2	4/2	4/6	4/9	4/9	Pt no showed	4/23			
Phone (P) or in-person (IP)		IP	IP	ip	ip	lp	ip	lp	lp	lp	P	lp	ip	P	lp	ip		ip			
OxyContin	120	120	120	120	120	120	120	120	120	120	100	100	100	100	100			100			
Oxycodone	80	80	80	80	70	70	60	60	60	60	70	70	70	70	70			70			
Total MED	300	300	300	300	285	285	270	270	270	270	255	255	255	255	255			255			
PHQ		23	17	14	20	15	12	7	7	10	5		4	2	2			18			
GAD		15	15	21	16	16	19	21	8	14	3		4	5	1			20			
Pain Intensity		8	6	6	6	5	6	5	5	6	6		4	6	4			8			
Pain Interference		9	5	6	6	4	5	4	6	6	6		4	7	4			9			
Alcohol use	no	N	N	n	n	n	n	n	n	n	N		n	n	n						

**Notes**

- 2/26: She no showed to apt. on 2/26. No response. Daughter being treated for suicide attempt.
- 3/2: daughter now involuntary inpatient, pt feels she is in safe place and is feeling better. She did bring all her medications to visit and is on time. She has them very organized in a pill box each day. Did not want to reduce, as more pain associated with stressful situation, did not feel ready this week, but said she would like to reduce next week.
- 3/12 Still worried about her daughter who is inpatient. No change in dose.

# IMPRESSIONS FROM TRIAL PROCESS...

- Opioid cessation similar to smoking cessation
  - Difficult in the short-term, less so in long-term
- Insomnia and anxiety emerge during taper
  - Sometimes depression, PTSD, borderline PD...
- Nortriptyline often useful, sometimes SNRIs
  - Don't add benzos, don't taper, stable dosing
- Use early taper to build skills, confidence
- Patients limit their opioid taper for many reasons, but rarely due to pain increase



# PRELIMINARY TRIAL RESULTS

- 35/145 referred patients were randomized
  - Some ineligible, most declined as not ready, able
- 71% female, mean age 55, 83% white
- 11.5 years opioid tx, 55% HS or some college
- Baseline MED
  - 209mg MED Taper support
  - 244mg MED Usual care

# RCT RESULTS: OPIOID DOSE, PAIN

- By 22 weeks, adjusted mean daily opioid dose was 43mg MED lower in support group (p=.09)
  - Dose reduction from baseline:
    - 46% in taper support, 18% in usual care
- BPI pain intensity (adj. mean diff = 0.7, p=.30)
  - Taper support 5.7 -> 4.7/10
  - Usual care 6.3 -> 5.8/10

# RCT RESULTS: ACTIVITIES, SELF-EFFICACY

- BPI pain interference (adj. mean diff. -1.4, p=.05)
  - Taper support 6.0 -> 4.5
  - Usual care 6.6 -> 6.4
- Pain Self-efficacy (adj mean diff. 7.9, p=.02)
  - Taper support 30.6 -> 36.1
  - Usual care 31.9 -> 30.0
- PODS problems (adj. mean diff. -4.9, p=.02)
  - Taper support 12.7 -> 2.9
  - Usual care 12.0 -> 7.5

# PATIENT REPORTS OF TAPER EXPERIENCE

- “I am no longer a zombie.”
- “My husband is glad to have his wife back.”
- “My pain is the same, but my head is so much clearer.”
- “I was afraid my pain would go through the roof, but it hasn’t.”

# RCT RESULTS

- Outcomes not different between groups:
  - PODS concerns
  - Opioid craving
  - Opioid misuse
  - Insomnia severity
  - Somatic symptoms (PHQ15)
  - Depression (PHQ9)
  - Anxiety (GAD7)

# LESSONS FROM TRIAL

- Difficult to recruit into trial of “opioid taper”
  - Many interested, few willing to be randomized
  - May need to recruit for self-management support, later offering the option of supported taper
- Psychiatric symptoms are common
  - TCA useful because addresses pain, mood, sleep
  - Other patients needed SNRI started or adjusted
  - Prazosin useful for patients with PTSD

# LESSONS FOR CLINICAL TAPER PRACTICE

- Pledge you will not abandon patient
- No rush, allow patient to pause taper
- Taper long-acting opioids first
- Discourage concurrent tapers
- Offer pain self-management skills support
- Anticipate pain “flare-ups”

# CONCLUSIONS



- Opioids have diverse and important functions
  - Opioid use and taper affect many domains of experience and behavior
- Epidemiology of long-term opioid use suggests that opioids are treating various mental health and substance abuse problems
- It appears that opioid taper support can successfully facilitate opioid dose reduction without increasing pain intensity and may decrease pain interference



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