Managing Common Pain Co-morbidities: Current Practice and Future Directions

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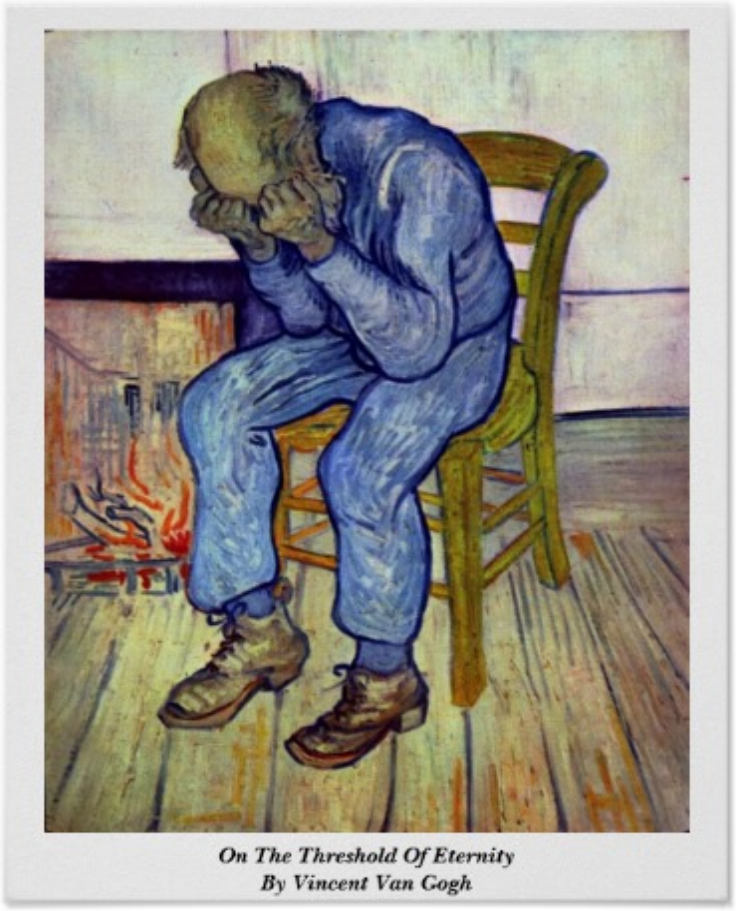
Conflict of interest

- MDC has no conflict of interest related to the topic of this presentation

Chronic Pain Comorbidites

- Mood Disorders
- Anxiety Disorders
- PTSD
- Sleep Disorders
- Personality Disorders
- Secondary Medical Conditions

Pain, Mood and Anxiety Disorders



On The Threshold Of Eternity
By Vincent Van Gogh

PAIN

Pain 106 (2003) 127–133

www.elsevier.com/locate/pain

Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample

Lachlan A. McWilliams[a,b,*], Brian J. Cox[b], Murray W. Enns[b]

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Received 4 March 2003; received in revised form 10 July 2003; accepted 18 July 2003

- **National Comorbidity Survey to evaluate the association between chronic pain and common mood and anxiety disorders**
- **Participants (n= 5877) completed the Composite International Diagnostic Interview based on the DSM**

Diagnosis	Number of participants meeting diagnostic criteria (% in parentheses)		Inferential statistics	
	Chronic pain ($n = 382$)	General population ($n = 5495$)	χ^2	p
Any mood disorder	83(21.7)	551(10.0)	32.16	<0.0001
Depression	77(20.2)	510(9.3)	26.53	<0.0001
Dysthymia	20(5.2)	128(2.3)	5.48	<0.01
Any anxiety disorder	134(35.1)	992(18.1)	21.54	<0.0001
Generalized anxiety disorder	28(7.3)	144(2.6)	9.10	<0.005
Panic disorder with or without agoraphobia	25(6.5)	103(1.9)	7.84	<0.01
Simple phobia	60(15.7)	456(8.3)	8.70	<0.01
Social phobia	45(11.8)	428(7.8)	5.91	<0.05
Agoraphobia with or without panic	32(8.4)	182(3.3)	6.52	<0.05
Posttraumatic stress disorder	41(10.7)	182(3.3)	16.29	<0.001

Diagnoses were made using the *Composite International Diagnostic Interview*. Psychiatric diagnostic categories were not mutually exclusive.

Pain, SUD and Suicidal Ideation

- **There is robust literature that there is a high prevalence of SI in patients with pain ranging from18% to > 50%**

Hitchcock L, Ferrell B, McCaffery M. The experience of chronic nonmalignant pain. *J Pain Symptom Manage* 1994; 9: 312-318.

Stenager EN, Stenager E, Jensen K. Attempted suicide, depression and physical diseases: a 1-year follow-up study. *Psychother Psychosom* 1994; 61: 65-73.

Fishbain DA, Goldberg M, Rosomoff RS, Rosomoff H. Completed suicide in chronic pain. *Clin J Pain* 1991; 7: 29-36.

Fishbain DA. The association of chronic pain and suicide. *Semin Clin Neuropsychiatry* 1999; 4: 221–227.

Smith MT, Edwards RR, Robinson RC, Dworkin RH. Suicidal ideation, plans and attempts in chronic pain patients: Factors associated with increased risk. *Pain* 2004; 111: 201-208.

Braden JB, Sullivan MD. Suicidal thoughts and behavior among adults with self-reported pain conditions in the national comorbidity survey replication. *J Pain* 2008; 9:1106-1115.

Ilgen MA, Zivin K, McCammon RJ, Valenstein M. Pain and suicidal thoughts, plans and attempts in the United States. *Gen Hosp Psychiatry* 2008; 30: 521-527.

Ratcliffe GE, Enns MW, Belik SL, Sareen J. Chronic pain conditions and suicidal ideation and suicide attempts: an epidemiologic perspective. *Clin J Pain* 2008; 24 : 204-210.

Substance Abuse and Mental Health Services Administration Office of Applied Studies. *Drug Abuse Warning Network, 2007: Estimates of Drug-Related Emergency Department Visits*. Rockville, MD; 2010.

Racine M, Choinière M, Nielson WR. Predictors of Suicidal Ideation in Chronic Pain Patients: An Exploratory Study. *Clin J Pain*. 2013 Jul 24. [Epub ahead of print]

Cheatle M, Wasser T, Foster C, Olugbodi A, Bryan J. Prevalence of suicidal ideation in patients with chronic noncancer pain referred to a behaviorally based pain program. *Pain Phys*, in press.

Edwards RR, Smith MT, Kudel I, Haythornthwaite J. Pain-related catastrophizing as a risk factor for suicidal ideation in chronic pain. *Pain* 2006;126 : 272-279.

- **A systematic review by Tang and Crane revealed that the risk of successful suicide was doubled in patients with CP as compared to non-pain controls**

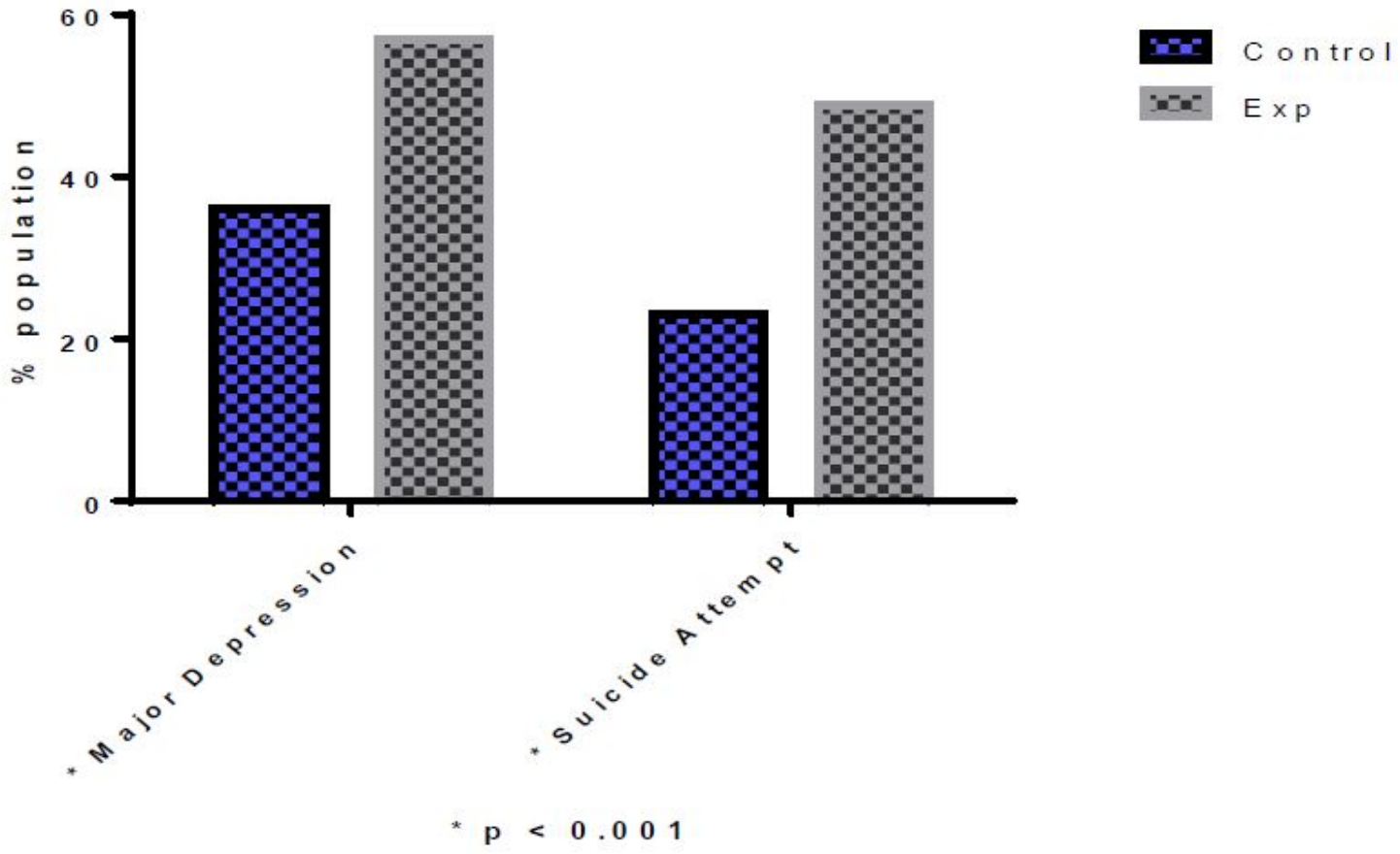
Tang NK, Crane C. Suicidality in chronic pain: A review of the prevalence, risk factors and psychological links. *Psychol Med* 2006; 36 :575-586.

Suicidal Ideation and Behavior and SUD

- **Approximately 40% of patients seeking treatment for substance use disorders report a history of suicide attempts [1-3]**
- **Compared to the general population, those with alcohol use disorders are almost 10 times more likely to die by suicide and those who inject drugs are about 14 times more likely to commit suicide.[4]**

1)Roy A, Janal MN. Risk factors for suicide among alcohol-dependent patients. Arch Suicide Res. 2007; 11:211–217; 2) Roy A. Characteristics of cocaine dependent patients who attempt suicide. Arch Suicide Res. 2009; 13:46–51;3). Roy A. Risk factors for attempting suicide in heroin addicts. Suicide Life Threat Behav. 2010; 40:416–420; 4) Wilcox HC, Conner KR, Caine ED. Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. Drug Alcohol Depend. 2004; 76:S11–S19.

% of Population



Cheatle et al Clinical and genetic characteristics of opioid addiction in patients with chronic pain 1R01DA032776-01 NIH/NIDA

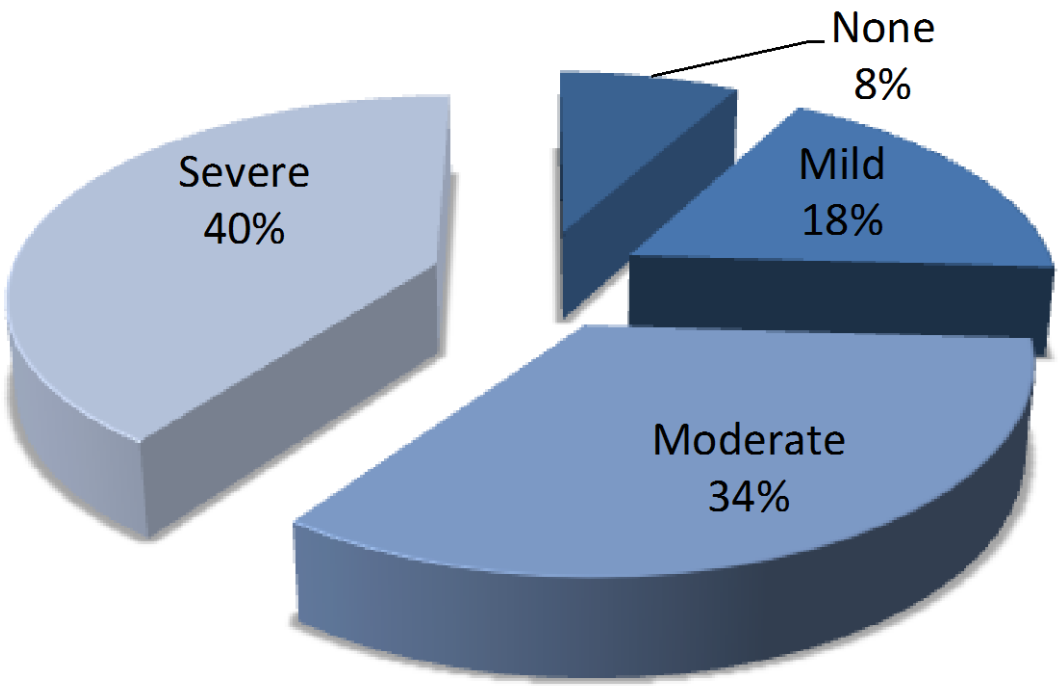
Pain and Sleep Disorders

Pain and Sleep Disorders

- **Chronic pain is associated with multiple symptoms that may impair a patient's quality of life, including emotional distress, fatigue and sleep disturbance.**
- **Studies have demonstrated that 50% of patients with a number of different chronic pain conditions complain of sleep disturbance, with estimates as high as 70%-88%.**

Cheatle MD, Foster S, Pinkett A, Lesneski M, Qu D, Dhingra L. Assessing and Managing Sleep Disturbance in Patients with Chronic Pain. Anesthesiol Clin. 2016 Jun;34(2):379-93

% Population Sleep Disturbance (n= 1038)



Cheatle M et al "Clinical and Genetic Characteristics of Opioid Addiction in Chronic Pain" 1RO1DA032776-01 NIH/NIDA unpublished data

Untreated or Undertreated Insomnia

Patients with chronic pain and sleep disturbance report:

- **Increased pain**
- **Excessive fatigue**
- **Poorer mood**
- **Higher rates of disability**

Cheatle MD, Foster S, Pinkett A, Lesneski M, Qu D, Dhingra L. Assessing and Managing Sleep Disturbance in Patients with Chronic Pain. Anesthesiol Clin. 2016 Jun;34(2):379-93

Experimental Studies

Short term:

- **Sleep deprivation or disruption increases pain & inflammation; dampen mood and pain inhibitory response**

Long term:

- **Development of depression, anxiety, widespread pain, diabetes, hypertension, CHD**

Cheatle MD, Foster S, Pinkett A, Lesneski M, Qu D, Dhingra L. Assessing and Managing Sleep Disturbance in Patients with Chronic Pain. Anesthesiol Clin. 2016 Jun;34(2):379-93

Pain and sleep are bidirectional

Pain and sleep are bidirectional

- Koffel E, Kroenke K, Bair MJ, Leverty D, Polusny MA, Krebs EE. The Bidirectional Relationship Between Sleep Complaints and Pain: Analysis of Data From a Randomized Trial. Health Psychol. 2015 Jun 15. [Epub ahead of print]
- Sivertsen B, Lallukka T, Petrie KJ, Steingrímsdóttir ÓA, Stubhaug A, Nielsen CS. Sleep and pain sensitivity in adults. Pain. 2015 Aug;156(8): 1433-1439.
- Haythornthwaite JA, Hegel MT, Kerns RD. Development of a sleep diary for chronic pain patients. J Pain Symptom Manage. 1991 Feb;6(2):65-72.
- Chiu YH, Silman AJ, Macfarlane GJ, Ray D, Gupta A, Dickens C, Morriss R, McBeth J. Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study. Pain. 2005 Jun;115(3):316-321.
- Moldofsky H, Lue FA, Eisen J, Keystone E, Gorczynski RM. The relationship of interleukin-1 and immune functions to sleep in humans. Psychosom Med. 1986 May-Jun;48(5):309-18.
- Onen SH, Alloui A, Gross A, Eschallier A, Dubray C. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. J Sleep Res. 2001 Mar;10(1):35-42.
- Boakye PA, Olechowski C, Rashiq S, Verrier MJ, Kerr B, Witmans M, Baker G, Joyce A, Dick BD. A Critical Review of Neurobiological Factors Involved in the Interactions between Chronic Pain, Depression, and Sleep Disruption. Clin J Pain. 2015 May 28. [Epub ahead of print]

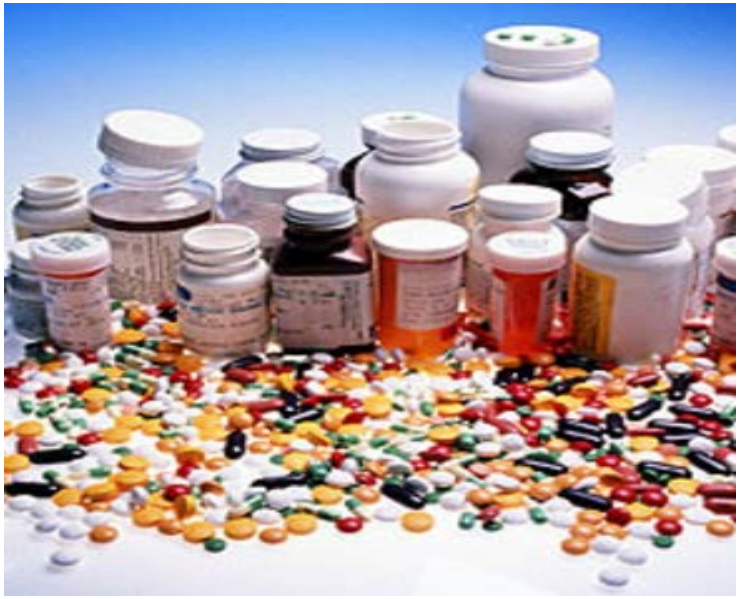
Pain and Sleep: Mechanisms of Action

- Reduced pain tolerance
- Pro inflammatory process
- Increased anxiety/lower mood

Cheatle MD, Foster S, Pinkett A, Lesneski M, Qu D, Dhingra L. Assessing and Managing Sleep Disturbance in Patients with Chronic Pain. Anesthesiol Clin. 2016 Jun;34(2):379-93

Treatment Approaches

- **Pharmacologic**
- **Psychosocial and CAM**



Antidepressant medication

- The role of antidepressant medication may relate, in part, to the high prevalence of co-occurring depression in chronic pain
- There is evidence of the analgesic properties of tricyclics and certain SNRIs
- TCAs, SNRIs like opioids are used to modulate descending inhibitory pain pathways

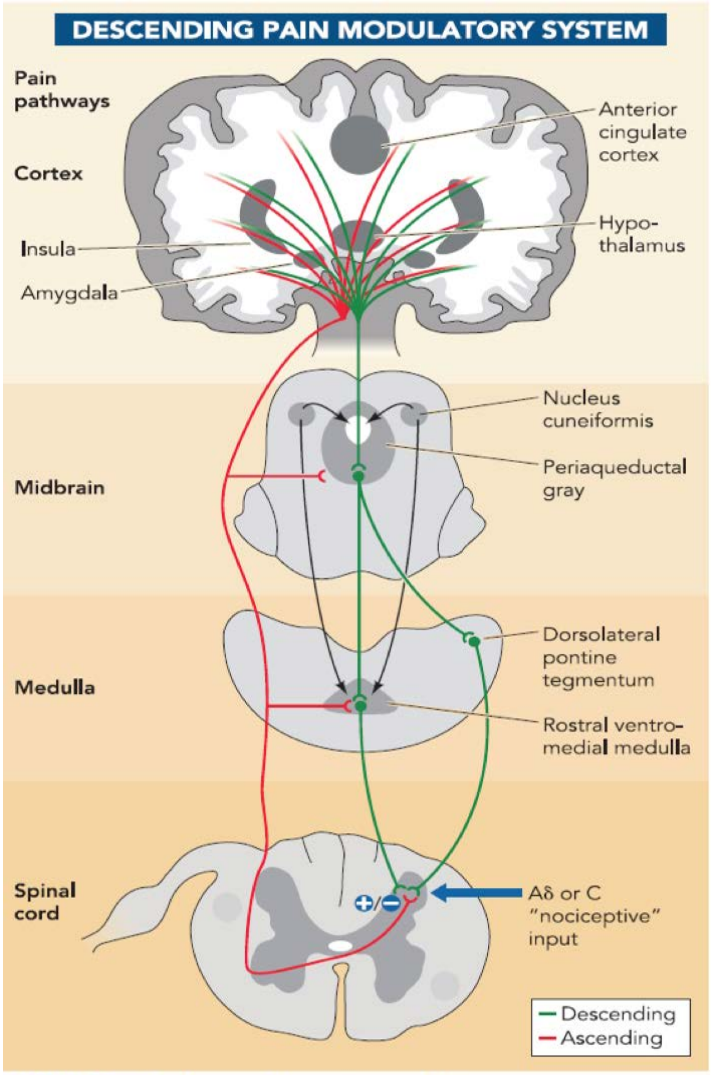


FIGURE 3. The descending pain modulatory system
+/- indicates both pro- and anti-nociceptive influences, respectively.

Jensen *et al. Molecular Pain* 2012, **8**:32
http://www.molecularpain.com/content/8/1/32

MOLECULAR PAIN

RESEARCH Open Access

Patients with fibromyalgia display less functional connectivity in the brain's pain inhibitory network

Karin B Jensen[1,2*], Rita Loitoile[1,2], Eva Kosek[3,4], Frank Petzke[5], Serena Carville[6], Peter Fransson[3], Hanke Marcus[7], Steven CR Williams[8], Ernest Choy[9], Yves Mainguy[10], Olivier Vitton[10], Richard H Gracely[11], Randy Gollub[1,2], Martin Ingvar[3,4] and Jian Kong[1,2]

- **28 matched FM pts compared to 14 healthy volunteers**
- **FM patients required significantly less pressure stimulus to reach a 50/100mm on a VAS**
- **Hypo-connectivity between the rostral anterior cingulate cortex and the amygdyla, hippocampus, and brainstem in healthy volunteers compared to FM patients**
- **Evidence that there is a dysfunction of the descending pain modulatory network**

- **Fibromyalgia patients endogenous opioid activity may be elevated at baseline (i.e. already working at full levels and thus can't increase with new pain stimuli)**
  - CSF of FM patients show higher enkephalins compared to controls
  - High Baseline occupancy of opioid receptors in FM patients who have never received exogenous opioids
  - Opioids usually ineffective in most patients with FM
  - Naltrexone-blocking endogenous release of opioids
- **Unlike the opioid system the serotenergic/noradrenegric system is hypofunctional**
  - Decreased norepinephrine and serotonin metabolites in CSF
  - Efficacy of compounds that raise serotonin and norepinephine may be effective
    - Duloxetine, Venlafaxeine, TCA, ?tramadol
    - Exercise and TENS units help potentiate this descending inhibition

Antidepressant Selection and Dosing

Priorty	Drug	Class	Indications and Precautions	Initial Dose	Possible Increases
1	Venlafaxine (Effexor)	SNRI	Avoid if CV disease, ABN ECG, poorly-controlled HTN	75	150, 225
2	Fluoxetine (Prozac)	SSRI	SSRI of choice	20	30, 40
2	Sertraline (Zoloft)	SSRI	SSRI of choice in patients with CV disease	50	100, 150
3	Citalopram (Celexa)	SSRI	Use if failed with first SSRI	20	30, 40
4	Bupropion (Wellbutrin)	Other	Use if obese, have unacceptable weight gain with other agent, or if sexual AEs reported	200	300, 400
4	Mirtazapine (Remeron)	Other	Use if insomnia a problem; avoid if obese	15	30, 45
5	Desipramine	TCA	Avoid with CV disease, advanced age, ABN ECG, poorly-controlled HTN	25	50, 100

Kroenke K et al JAMA 2009; 301 (20): 2099-110

How modest is the effect?

Drug	RCT / participants	30% pain reduction (drug vs placebo, %)	Drop out rate due to adverse events, (drug vs placebo, %)
duloxetine	5 / 1,884	46.8 vs 34.0	18.7 vs 10.4
milnacipran	5 / 4,110	36.4 vs 28.1	21.5 vs 11.0
SSRIs	7 / 414	36.4 vs 20.6	9.5 vs 7.0
TCAs	9 / 542	48.3 vs 27.8	5.2 vs 6.5
pregabalin	5 / 3,259	40.0 vs 29.1	19.4 vs 11.0

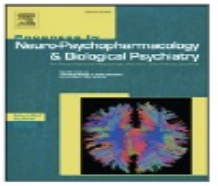
Arthritis Research & Therapy (2014) 16:201

Progress in Neuro-Psychopharmacology & Biological Psychiatry 75 (2017) 128–134

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp



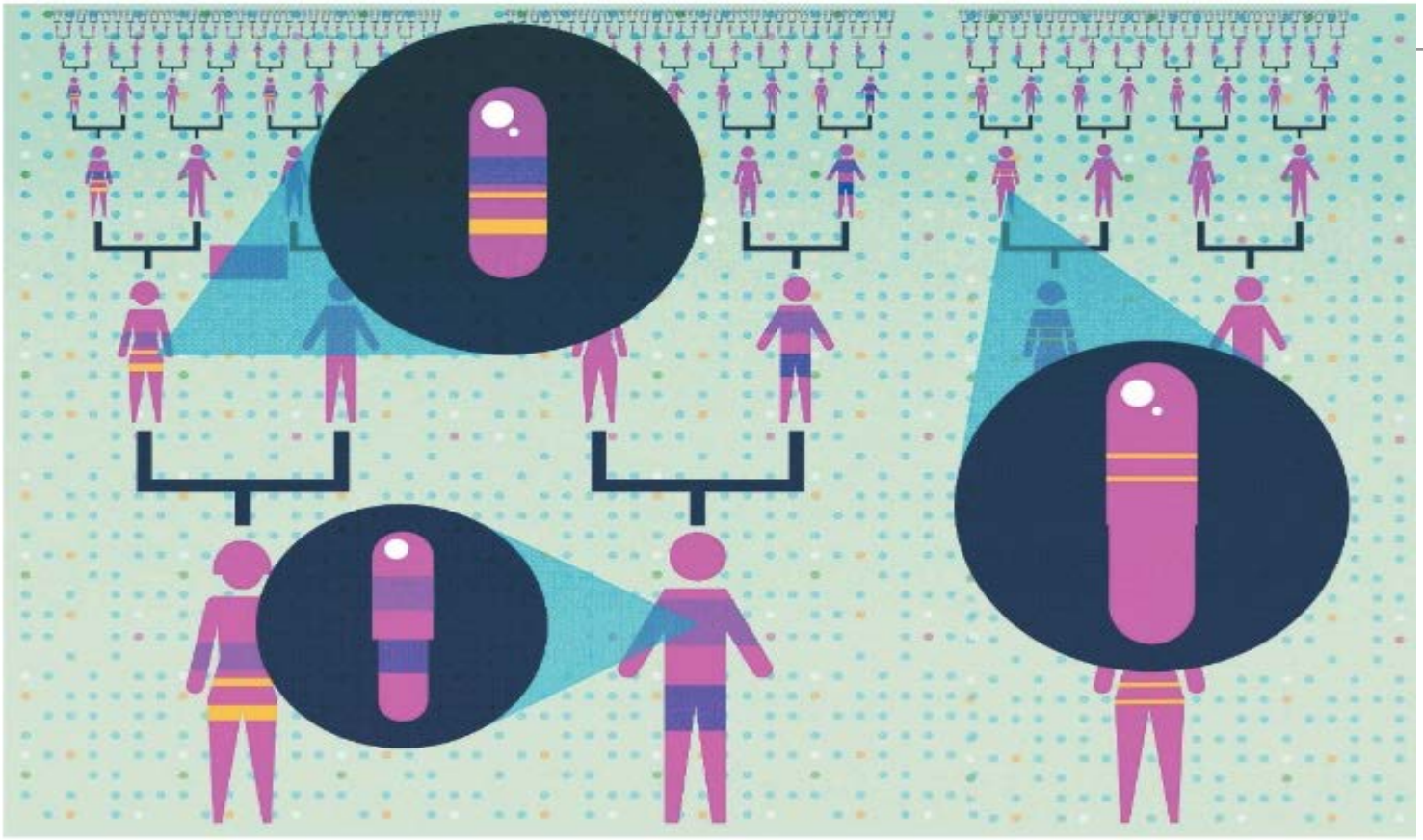
Pharmacogenetics of antidepressant response: A polygenic approach

Judit García-González [a], Katherine E. Tansey [b], Joanna Hauser [c], Neven Henigsberg [d], Wolfgang Maier [e], Ole Mors [f,g], Anna Placentino [h], Marcella Rietschel [i], Daniel Souery [j], Tina Žagar [k], Piotr M. Czerski [l], Borut Jerman [k,m], Henriette N. Buttenschøn [n], Thomas G. Schulze [o], Astrid Zobel [e], Anne Farmer [a], Katherine J. Aitchison [p], Ian Craig [a], Peter McGuffin [a], Michel Giupponi [q], Nader Perroud [r], Guido Bondolfi [s], David Evans [t], Michael O'Donovan [u], Tim J. Peters [v], Jens R. Wendland [w], Glyn Lewis [x], Shitij Kapur [a], Roy Perlis [y], Volker Arolt [z], Katharina Domschke [aa], Major Depressive Disorder Working Group of the Psychiatric Genomic Consortium[1], Gerome Breen [a], Charles Curtis [a], Lee Sang-Hyuk [a], Carol Kan [a], Stephen Newhouse [a], Hamel Patel [a], Bernhard T. Baune [ab], Rudolf Uher [ac], Cathryn M. Lewis [a,*,2], Chiara Fabbri [a,ad,2]

Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants

JK Hicks[1], JJ Swen[2], CF Thorn[3], K Sangkuhl[3], ED Kharasch[4], VL Ellingrod[5,6], TC Skaar[7], DJ Müller[8], A Gaedigk[9] and JC Stingl[10]

Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2016 Dec 20.



PHARMACOGENETICS

The right drug for you

Personalized prescribing is gaining momentum, but is there enough evidence for it to become standard clinical practice?

Drew L. Pharmacogenics: The Right Drug for You Nature. 2016 Sep 8;537(7619):S60-2.

Pharmacologic Approaches to Sleep Disorders

- Benzodiazepine and Receptor Agonists (BzRAS)
- Non-benzodiazepine receptor agonists
- Melatonin receptor agonists
- Sedative antidepressants
- Atypical antipsychotic medications,
- Antiepileptic Drugs

Benzodiazepine and Receptor Agonists (BzRAS)

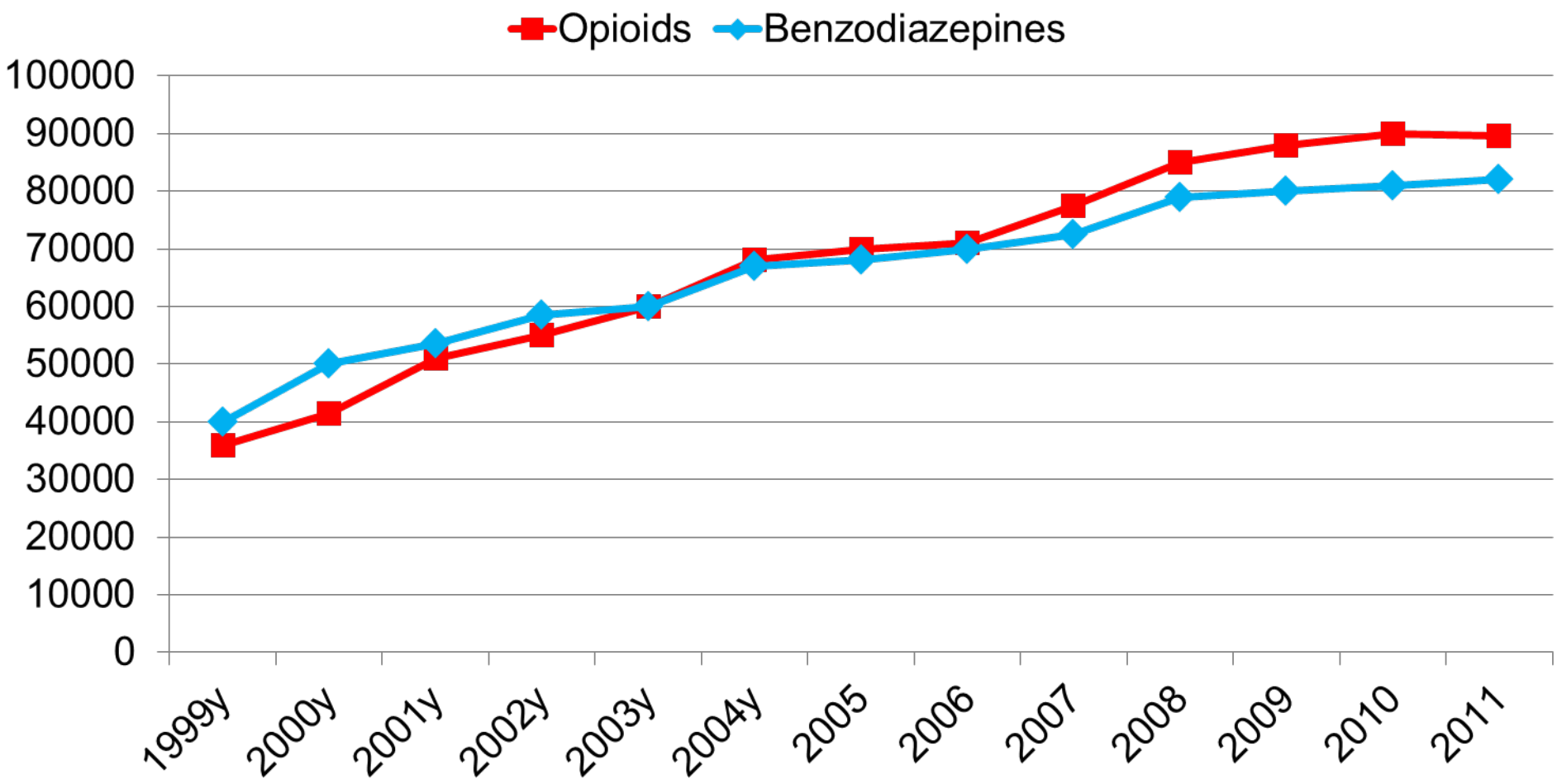
- **BzRAS include benzodiazepines (example Temazepam, Triazolam) and a newer class of non-benzodiazepine drugs (for example, Zolpidem).**
- **This class of drugs binds to GABA-A receptors and induces sedative/hypnotic, amnestic, anxiolytic and anticonvulsant effects.**
- **Many short term clinical trials show that BzRAS improve sleep quality, sleep latency, wakefulness after sleep onset and total sleep time.**
- **Most benzodiazepines (excluding Triazolam) have intermediate to long half-life, helping patients fall asleep and stay asleep longer.**

- **Benzodiazepines may work well in short-term efficacy trials, but there is a paucity of data on long-term use and there are many documented adverse effects:**

  - **Cognitive impairment**
  - **Decreased attention**
  - **Anterograde amnesia**
  - **Depressive symptomatology with cognitive and psychomotor slowing**
  - **Abruptly discontinuing benzodiazepines may lead to rebound insomnia, seizure activity**

- ***Given these multiple safety concerns, benzodiazepines have fallen out of favor as a class of drugs for use in sleep disorders.***

Drug Misuse and Abuse



Spiller HA. What every clinician needs to know about overdoses - poison center surveillance. Presented at: The 2012 National Rx Abuse Summit. April 10 – 12, 2012; Orlando, FL. http://www.slideshare.net/OPUNITE/henry-spiller-edited

Non-Benzodiazepine Receptor Agonists (NBzRAS)

- **Non-benzodiazepine receptor agonists include Ambien (Zolpidem), Sonata (Zalepon), and Lunesta (eszopiclone) are the newest class of FDA approved hypnotics used for insomnia.**
- **These class of drugs improve sleep latency and have potential for fewer daytime side effects, given their short half-life and receptor binding profile.**

Antidepressants

Antidepressants

- **Sedative antidepressants, such as tricyclic antidepressants mirtazapine and Trazodone, are useful in treating chronic pain patients with insomnia.**

- **These classes of drugs help to relieve:**
  1. Insomnia
  2. Any associated depression that negatively influences pain perception
  3. The pain condition itself

- **Tricyclic antidepressants have pro-serotonergic, noradrenergic, dopaminergic and sodium channel blocking effects that may account for their efficacy in pain and depression, along with anticholinergic and antihistaminic effects that lead to sedation.**

AEDs

- Gabapentin and pregabalin often used to treat chronic pain conditions with comorbid insomnia.
- In multiple studies of patients with neuropathic pain and fibromyalgia, self-reported sleep outcomes suggest positive effects on sleep latency and wakefulness after sleep onset, as well as increased deep sleep.
- Both have adjunctive effects on depression and anxiety.
- Pregabalin showed increased efficacy in promoting sleep in patients with diabetic neuropathy, compared to amitriptyline in a recent study.
- Adverse effects include dizziness, next day sedation, GI symptoms and peripheral edema.

Psychosocial and CAM Interventions

- Acupuncture
- Neurofeedback & Biofeedback
- CBT
- Physical Therapy
- Massage
- 12-step programs
- Herbs
- Manipulation
- Mindfulness
- Yoga

CBT

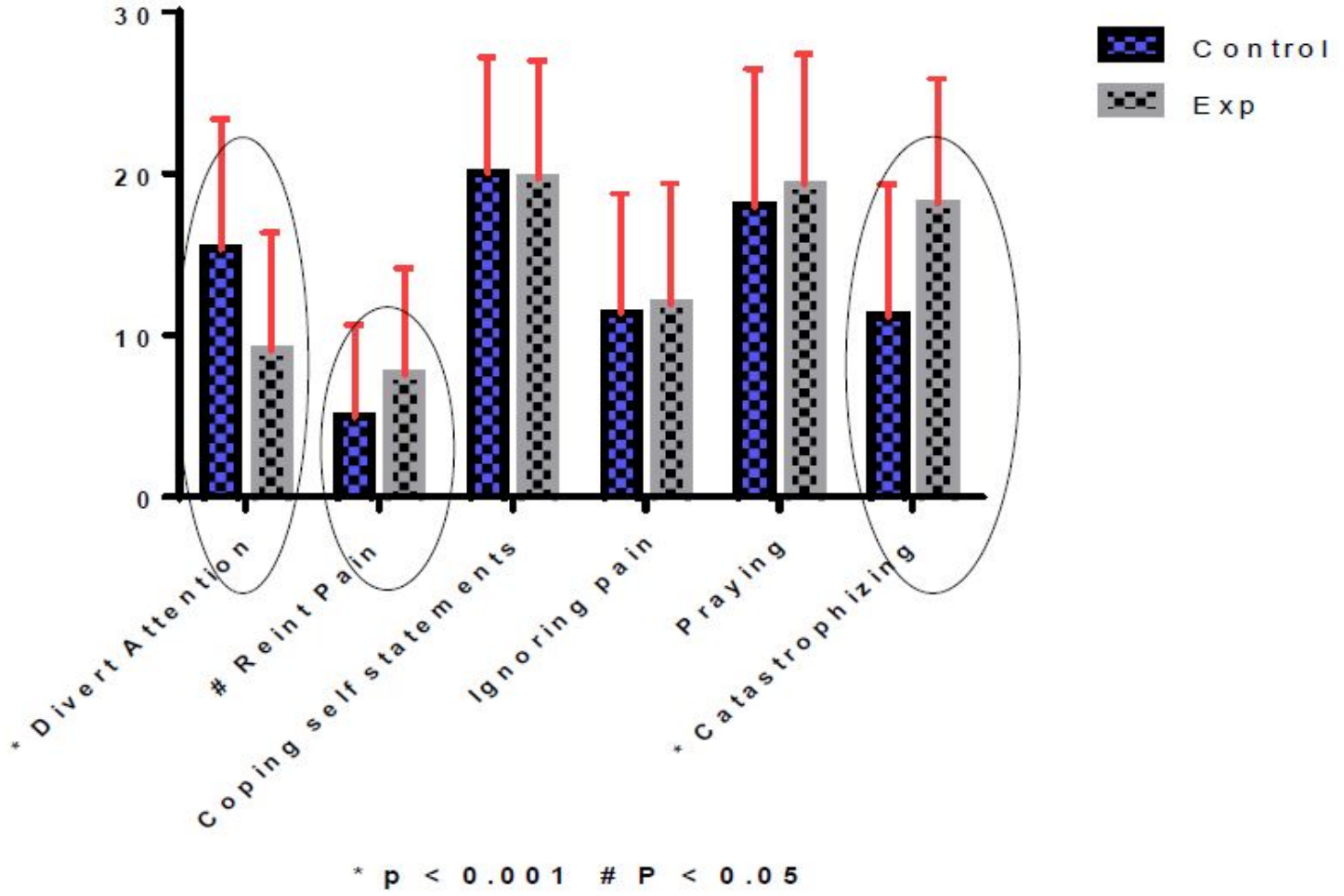
Cognitive Behavioral Therapy

- CBT focuses on maladaptive thought patterns (catastrophizing) and behaviors (kinesiophobia) that occur frequently in patients with CNCP
- The objective of CBT is to guide the patient in recognizing and reconceptualizing his/her personal view of pain, identifying their role in the process of healing and promoting the patient being proactive rather than passive, and competent rather than incompetent
- CBT include specific skill acquisition (relaxation therapy, stress management, cognitive restructuring) followed by skill consolidation and rehearsal, and relapse training (Turk, Flor, 2006)

CBT cont'd

- **CBT has been found to be efficacious for a number of chronic pain disorders including:**
  - Arthritis (Keefe & Caldwell, 1997)
  - Sickle Cell disease (Chen et al, 2004)
  - Chronic low back pain (Lamb et al, 2010; Glombiewski et al, 2010)
  - TMJ (Turner et al, 2006)
  - Lupus (Greco et al, 2004)
  - Pain in breast cancer patients (Tatrow et al, 2006)

Coping Strategies Questionnaire



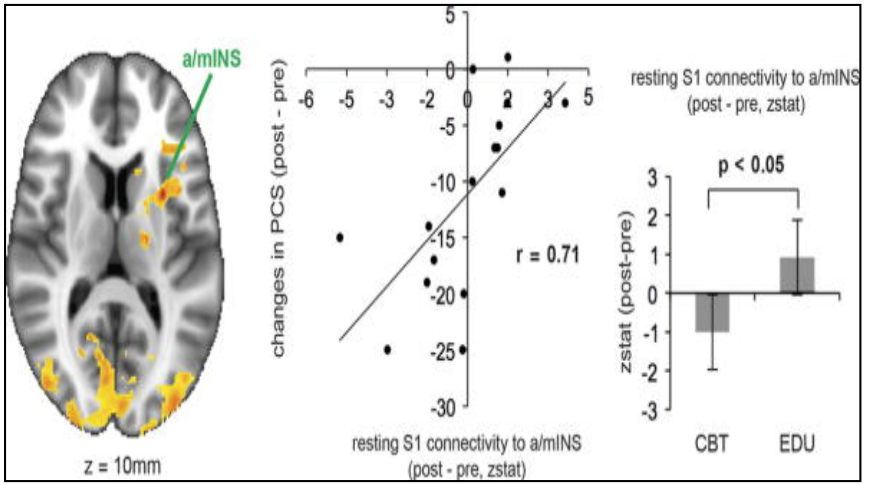
Cheatle et al Clinical and genetic characteristics of opioid addiction in patients with chronic pain
1R01DA032776-01 NIH/NIDA

Biological Substrates of CBT on Pain

- **16 high catastrophizing patients with fibromyalgia were randomized into a group that received a 4 week course of CBT or a control group that received only fibromyalgia education material.**
- **Resting state fMRI evaluated functional connectivity between key pain processing brain regions at baseline and post-treatment.**

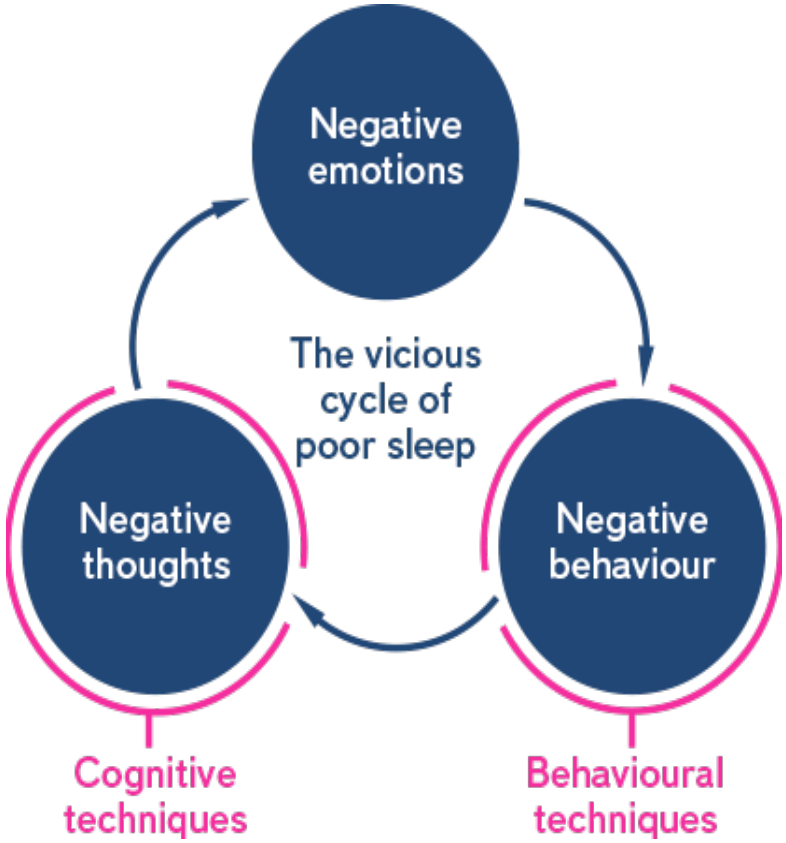
Lazaridou, A., et al., *Effects of Cognitive-Behavioral Therapy (CBT) on Brain Connectivity Supporting Catastrophizing in Fibromyalgia.* Clin J Pain, 2017. **33**(3): p. 215-221.

- **Results revealed that catastrophizing correlated with increased resting state functional connectivity between S1 and anterior insula.**
- **The CBT group demonstrated a larger reduction in both pain and catastrophizing as compared to the control group at the 6-month follow-up and reduced resting state connectivity between S1 and anterior/medial insula at post-treatment and these changes were associated with concurrent treatment-related reduction in catastrophizing.**
- ***The authors concluded that CBT via reducing catastrophizing helps normalize pain-related brain responses***



Cognitive Behavioral Therapy for Insomnia

- **CBT-I has been demonstrated to be equally effective or even superior to pharmacotherapy in patients with chronic primary insomnia.**



CBT-I cont'd

- **CBT-I consists of:**
  - Psychoeducation about sleep and insomnia
  - Stimulus control
  - Sleep restriction
  - Sleep hygiene
  - Relaxation training
  - Cognitive restructuring

Research Article

The Durability of Cognitive Behavioral Therapy for Insomnia in Patients with Chronic Pain

Carla R. Jungquist,[1,2] Yolande Tra,[3] Michael T. Smith,[4] Wilfred R. Pigeon,[2,5] Sara Matteson-Rusby,[2] Yinglin Xia,[6] and Michael L. Perlis[7]

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[7] *Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104, USA*

- **This was a parallel-group, randomized, single blind trial of CBT-I with a contact/measurement control condition**
- **Twenty-eight subjects with chronic neck and back pain were randomized into the 2 groups.**
- **Results revealed that patients who received CBT-I had significantly improved sleep and these patients maintained a statistically and clinically improved total sleep time even 6 months after treatment ended, despite the persistence of moderate to severe pain**

Sleep Disord. 2012;2012:679648.

Behaviour Research and Therapy 50 (2012) 814–821

Contents lists available at SciVerse ScienceDirect

Behaviour Research and Therapy

journal homepage: www.elsevier.com/locate/brat

Shorter communication

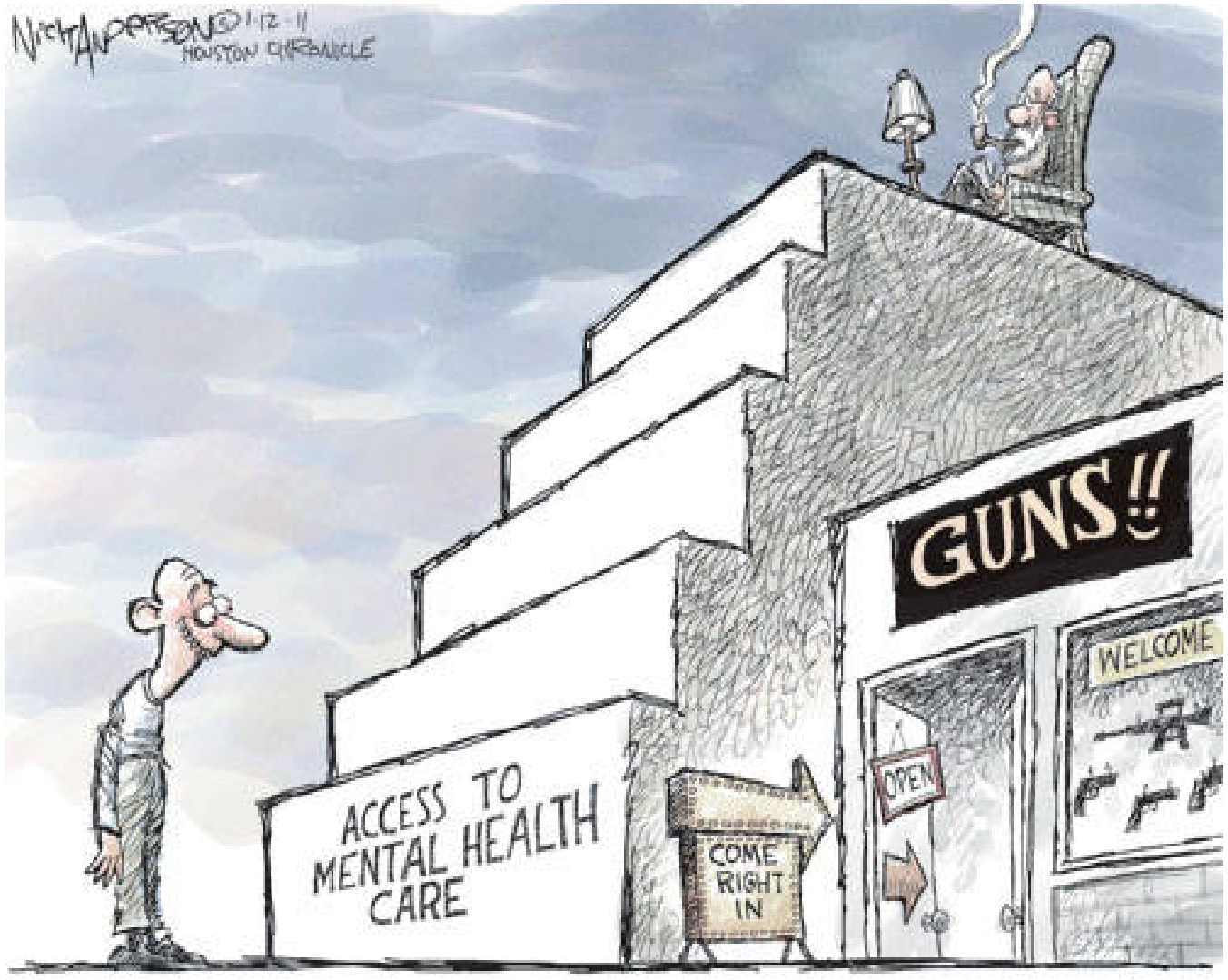
Hybrid cognitive-behaviour therapy for individuals with insomnia and chronic pain: A pilot randomised controlled trial

Nicole K.Y. Tang [a,b,*,1], Claire E. Goodchild [b], Paul M. Salkovskis [c]

[a] Arthritis Research UK Primary Care Centre, Primary Care Sciences, Keele University, UK
[b] Department of Psychology, Institute of Psychiatry, King's College London, UK
[c] Department of Psychology, University of Bath, UK

- **An RCT design comparing a Hybrid CBT P-I to a monitoring control group**
- **Compared to symptom monitoring, *the hybrid intervention was associated with greater improvement in sleep at post-treatment*. Although pain intensity did not change, the *Hybrid group reported greater reductions in pain interference, fatigue and depression than the Monitoring Group*. Changes associated with the hybrid intervention were clinically significant and durable at 1- and 6-month follow-ups.**

Access Issues

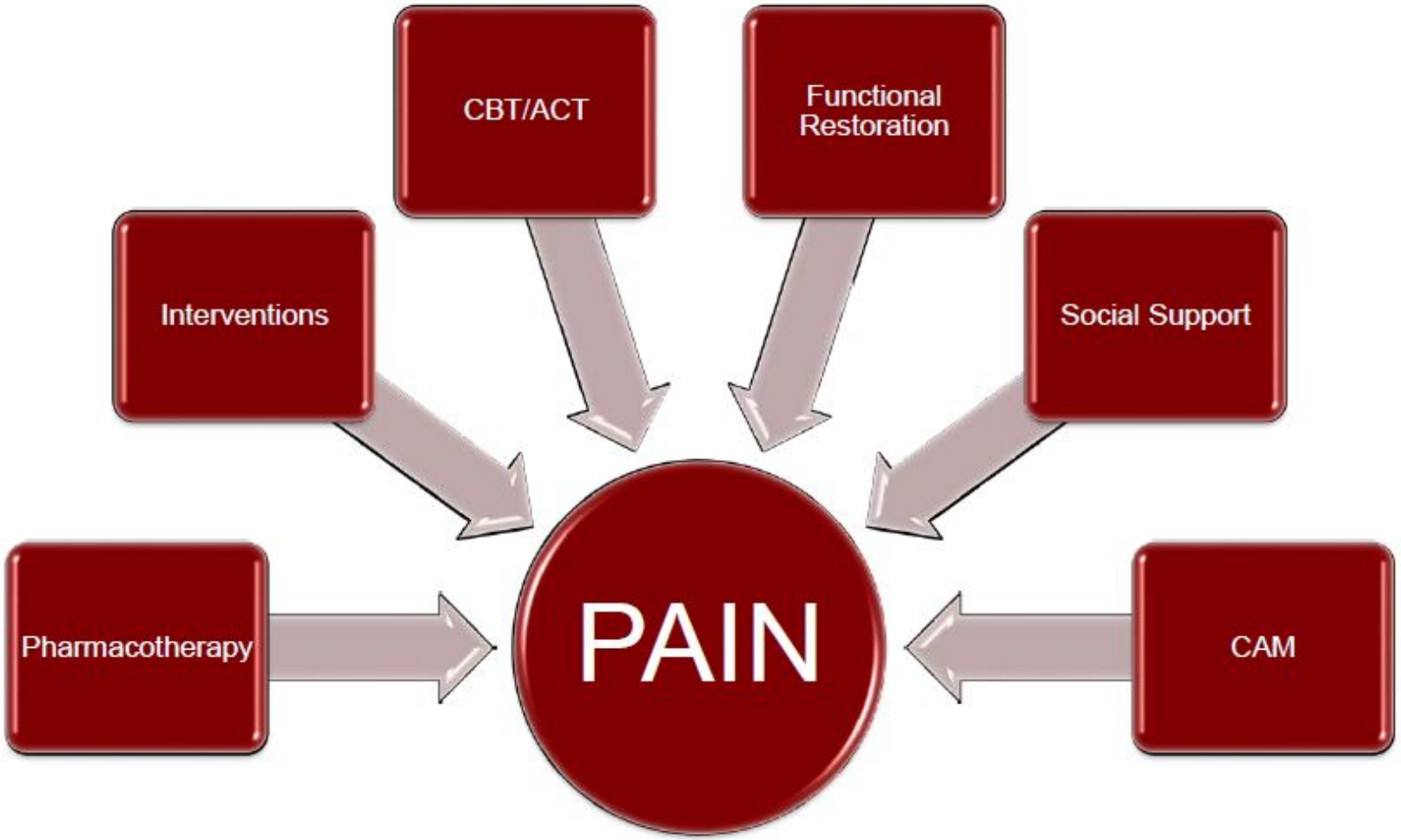


Interventions

- **Office-based interventions**
  - Training non-BH staff on CBT etc
  - Antidepressant therapy/pain self-management program

    Kroenke et al 2009
- **E-health**
  - Computer-assisted CBT
  - Telemedicine
  - Smartphone Apps

Multimodal Approach



Future Directions

- Develop and test novel delivery systems for CBT/CAM and other non-pharmacologic interventions
- Healthcare economics research to support improved access to interdisciplinary pain care, behavioral health and SUD treatment
- Pharmacogenomics research supporting decision making for non-opioid pharmacotherapeutics (precision medicine)
- Research on biological substrates of non-pharmacologic interventions
- Investigate phenotypic and genotypic characteristics of suicidal ideation and behavior in patients with pain and pain and SUD

Acknowledgements

- **Grant 1RO1DA032776-01 from the National Institute on Drug Abuse, National Institutes of Health**
- **University of Pennsylvania**
  - Charles P. O'Brien, MD, PhD
  - Wade Berrettini, MD, PhD
  - Kelly Farraday, BA, MSOD
  - Aaron Pinkett, BS
- **University of Washington**
  - Dennis C. Turk, PhD
  - Dana Divens
  - Ann Bradshaw
- **Lifetree Clinical Research Salt Lake City**
  - Lynn Webster, MD
- **Harvard University**
  - Mohammed Issa, MD
  - Robert Jamison, PhD

THANK YOU !!

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