PainWeek

Bridges to Babylon: Assessing & Managing Comorbidities in Chronic Pain Patients

Martin D. Cheatle, PhD
Associate Professor of Psychiatry
Director, Pain and Chemical Dependency Program
Center for Studies of Addiction

Disclosure

- MDC has no conflict of interest related to the topic of this presentation
- This presentation does not contain off-label or investigational use of drugs or products

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Learning Objectives

- Describe the common comorbidities associated with chronic pain
- Explain the risk/benefit of antidepressants and benzodiazepines in patients with chronic pain
- Identify non-pharmacologic interventions for treatment of comorbidities in patients with pain

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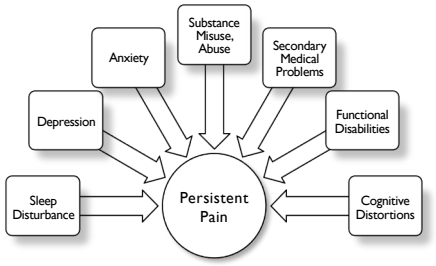

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Chronic Pain Comorbidites

- Mood disorders
- Anxiety disorders
- PTSD
- Sleep disorders
- Personality disorders
- Secondary medical conditions

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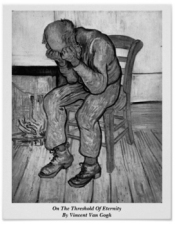
Pain, Mood, and Anxiety Disorders



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Pain 106 (2003) 127–133

PAIN

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]

[a]Department of Psychology, University of Manitoba, Winnipeg, Man., Canada
[b]Department of Psychiatry, PZ-430 PsycHealth Centre, University of Manitoba, 771 Bannatyne Avenue, Winnipeg, Man., Canada R3E 3N4

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- 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

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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.

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Pain, SUD, and Suicidal Ideation

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

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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

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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.

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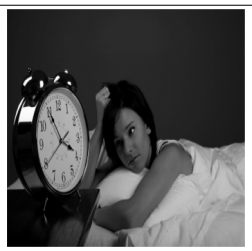
Pain and Sleep Disorders



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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

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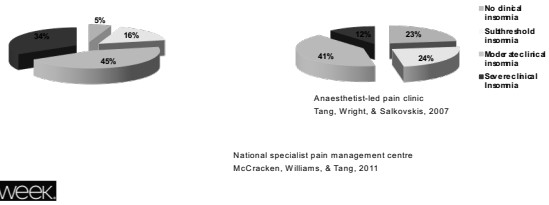
Pain-Insomnia Co-Occurrence



Anaesthetist-led pain clinic
Tang, Wright, & Salkovskis, 2007

National specialist pain management centre
McCracken, Williams, & Tang, 2011

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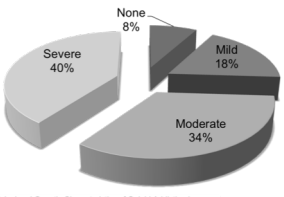
% Population Sleep Disturbance (n= 620)



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

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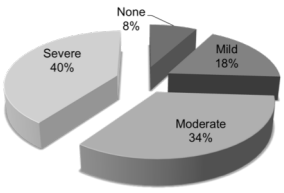

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Untreated or Undertreated Insomnia

Patients with chronic pain and sleep disturbance report:

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




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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

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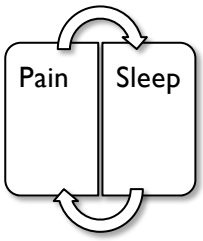
Pain and Sleep Are Bidirectional



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Pain and Sleep Are Bidirectional

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Pain and Sleep: Mechanisms of Action

- Reduced pain tolerance
- Proinflammatory process
- Increased anxiety/lower mood

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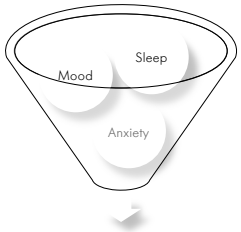
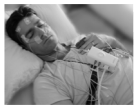
Opioid Sparing



Increased pain/opioid use/misuse

Assessment of Mood, Anxiety, and Sleep



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Mental Health Screening

- BDI-II
- BDI-FS
- Zung Self-Rating Depression Scale
- CES-D
- PHQ-9/PHQ-2
- BAI#
- GAD-7#
- HAS#
- HADS*
- POMS*
- PHQ-4*

- # Anxiety Scales *Anxiety/Depression Scales

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PHQ-4

Over the past few weeks have you been bothered by these problems?	Not at all	Several days	More days than not	Nearly every day
Feeling nervous, anxious, or on edge	0	1	2	3
Not being able to stop or control worrying	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Little interest or pleasure in doing things	0	1	2	3

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GAD-7

Generalised Anxiety Disorder Scale (GAD-7)

Over the **last two weeks** how often have you been bothered by any of the following problems?
For each question, select the option that best describes the amount of time you felt that way.

In last 2 weeks...	Not at all	Several days	More than half the days	Nearly every day
	0	1	2	3
1. Feeling nervous, anxious or on edge	○	○	○	○
2. Not being able to stop worrying	○	○	○	○
3. Worrying too much about different things	○	○	○	○
4. Having trouble relaxing	○	○	○	○
5. Being so restless it is hard to sit still	○	○	○	○
6. Becoming easily annoyed or irritable	○	○	○	○
7. Feeling afraid as if something awful might happen	○	○	○	○

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Sleep Assessment

- Sleep scales
- Sleep logs
- Actigraphy

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Sleep Assessment Scales

Questionnaire	Time frame	# of items
Sleep quality		
Pittsburg Sleep Quality Index	Past month	19
Sleep Questionnaire	Indefinite	59
Sleep Disturbance Questionnaire	Indefinite	12
SF-B	Past 2 weeks	12
Sleep onset		
Nocturnal Sleep Onset Scale	Past 2 weeks	2
General		
Steelman Insomnia Symptom Questionnaire	Past week	13
Athens Insomnia Scale	Past month	8
Pittsburgh Insomnia Rating Scale	Past week	65
Leeds Sleep Evaluation Questionnaire	Indefinite	10

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Pittsburgh Sleep Quality Index

- PSQI consists of 19 individual items used to generate seven composite scores:
  - Subjective sleep quality
  - Sleep latency
  - Sleep duration
  - Habitual sleep efficiency
  - Sleep disturbances
  - Use of sleeping medication
  - Daytime dysfunction
  - 5 to 10 minutes to administer and score
  - Global score can be used to identify presence of sleep disorder

Backhaus J, Junqhanns S, et al. Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. J Psychosom Res. 2002 Sep;53(3):737-40.

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Sleep Logs

SLEEP DIARY	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1. What time did you go to bed (lights off)?							
2. Approx how long did it take you to fall asleep?							
3. How many times did you awaken during the night?							
4. Approx how long were you awake each time?	1. 2. 3. 4.	1. 2. 3. 4.	1. 2. 3. 4.	1. 2. 3. 4.	1. 2. 3. 4.	1. 2. 3. 4.	1. 2. 3. 4.
5. What time did you wake in the morning?							
6. What time did you get out of bed?							
7. Approximately how many hours did you sleep?							
8. What medications did you take last night?							
9. Rate the quality of last night's sleep: (1 = excellent, 5 = poor)	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
10. Avoided naps? (Y/N)							
11. Exercised? (Y/N), When?							
12. Avoided stimulants? (Y/N)							
13. Relaxed before bed? (Y/N), How long?							

Cognitive appraisal/comments:	Please complete in the spaces provided below…
1. ________ (date)	
2. ________ (date)	
3. ________ (date)	
4. ________ (date)	
5. ________ (date)	
6. ________ (date)	
7. ________ (date)	

Actigraphy

CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN SLEEP MEDICINE

Wrist Actigraphy

Jennifer L. Martin, PhD; and Alex D. Hakim, MD

To record sleep, actigraph devices are worn on the wrist and record movements that can be used to estimate sleep parameters with specialized algorithms in computer software programs. With the recent establishment of a Current Procedural Terminology code for wrist actigraphy, this technology is being used increasingly in clinical settings as actigraphy has the advantage of providing objective information on sleep habits in the patient's natural sleep environment. Actigraphy has been well validated for the estimation of nighttime sleep parameters across age groups, but the validity of the estimation of sleep-onset latency and daytime sleeping is limited. Clinical guidelines and research suggest that wrist actigraphy is particularly useful in the documentation of sleep patterns prior to a multiple sleep latency test, in the evaluation of circadian rhythm sleep disorders, to evaluate treatment outcomes, and as an adjunct to home monitoring of sleep-disordered breathing. Actigraphy has also been well studied in the evaluation of sleep in the context of depression and dementia. Although actigraphy should not be viewed as a substitute for clinical interviews, sleep diaries, or overnight polysomnography when indicated, it can provide useful information about sleep in the natural sleep environment and/or when extended monitoring is clinically indicated. ***CHEST 2011; 139(6):1514–1527***

Abbreviations: AASM = American Academy of Sleep Medicine; MSLT = multiple sleep latency test; OSA = obstructive sleep apnea; PSG = polysomnography; SL = sleep latency; SOL = sleep-onset latency; TST = total sleep time; WASO = wake after sleep onset

Risk Assessment for Sleep Disordered Breathing

- History and physical examination
  - Assess neck circumference
  - Evaluate throat and nose for restricted airway
- Obtain a urine drug test to detect nonprescribed benzodiazepines or other CNS depressants
- Administer EPWORTH Sleepiness Scale
- If patient is candidate for opioid therapy, consider a polysomnogram
  - Portable at home
  - In a sleep lab

Cheatle, M.D., Webster, L.R. Opioid therapy and sleep disorders: Risks and mitigation strategies. Pain Medicine 16 Suppl 1: S 22-26, 2015.

THE EPWORTH SLEEPINESS SCALE
(To assess risk of Obstructive Sleep Apnea)

Use the following scale to choose the most appropriate number for each situation:-

0 = would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	
Total	

Score:
0-10 Normal range
10-12 Borderline
12-24 Abnormal

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Treatment Approaches

- Pharmacologic
- CBT/ACT

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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

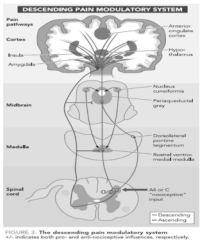

FIGURE 3. The descending pain modulatory system. +/- indicates both pro- and anti-nociceptive influences, respectively.

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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[7], Hanke Marcus[1], 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 amygdala, hippocampus, and brainstem in healthy volunteers compared to FM patients
- Evidence that there is a dysfunction of the descending pain modulatory network

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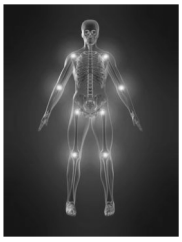
- Fibromyalgia patients endogenous opioid activity may be elevated at baseline (i.e. already working at full levels and thus can't increase with new pain stimuli)
  - CSF of FM patients show higher enkephalins compared to controls
  - High Baseline occupancy of opioid receptors in FM patients who have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



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Antidepressant Selection and Dosing

Priority	Drug	Class	Indications and Precautions	Initial Dose	Possible Increases
1	Venlafaxine	SNRI	Avoid if CV disease, ABN ECG, poorly-controlled HTN	75	150, 225
2	Fluoxetine	SSRI	SSRI of choice	20	30, 40
2	Sertraline	SSRI	SSRI of choice in patients with CV disease	50	100, 150
3	Citalopram	SSRI	Use if failed with first SSRI	20	30, 40
4	Bupropion	Other	Use if obese, have unacceptable weight gain with other agent, or if sexual AEs reported	200	300, 400
4	Mirtazapine	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

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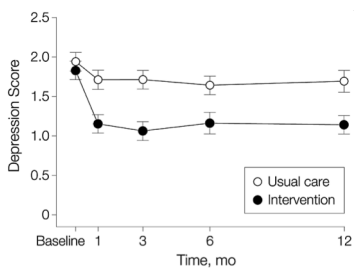
Kroenke K et al JAMA 2009;301 (20):2099-110

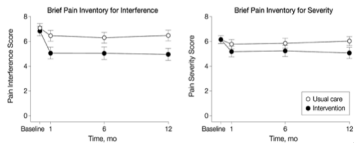
Mean 20-Item Hopkins Symptom Checklist Depression Scores



Kroenke, K. et al. JAMA 2009;301:2099-2110.

painweek JAMA

Mean Brief Pain Inventory Scores for Pain Interference and Pain Severity



Kroenke, K. et al. JAMA 2009;301:2099-2110.

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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

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

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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 Zagar [k], Piotr M. Czerski [l], Borut Jerman [k,m], Henriette N. Buttenschøn [n], Thomas G. Schulze [o], Astrid Zobel [p], Anne Farmer [a], Katherine J. Aitchison [a], 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,ad,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.

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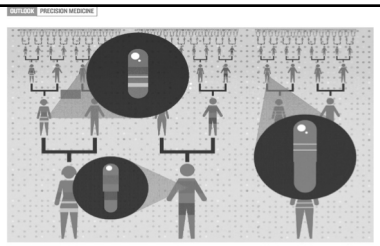

OUTLOOK PRECISION MEDICINE

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.

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Evidence-Based Guidelines: Overview

- There are no clinically significant differences in efficacy, effectiveness, or quality of life among SSRIs, SNRIs, SSNRIs, or other second-generation antidepressants for the treatment of MDD
- There are minor differences only in the incidence and severity of AEs, and mixed evidence of an increased risk of suicide with therapy
- Mirtazapine has a faster onset of action; all were the same at 4 weeks
- 38% of patients did not achieve a treatment response following 6-12 weeks of therapy with the first agent; 54% did not achieve remission

Ann Intern Med 2008; 149: 725-733

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Anxiety Disorders

- Anxiety disorders are the most commonly diagnosed psychiatric disorders and are highly co-occurring in patients with chronic pain
- Anxiety at times can be so severe that individuals can experience overwhelming fear, avoidance behavior and cognitive distortions that perpetuate anxiety symptoms such that they can not fully engage in other efficacious therapies (for example CBT, PT)
- SSRIs and other first-line antidepressant medication treatments may mitigate these maladaptive behaviors and thoughts related to the underlying anxiety disorder, but achieving a therapeutic response can take up to four to six weeks, and oftentimes up to twelve weeks, at a therapeutic dose to evaluate for treatment response
- A time-limited prescription of either a prn or standing dosing of benzodiazepines may be warranted
- Cheatle, M.D., Shmuts, R. Benzodiazepine and opioid use in patients with chronic pain: balancing risk and benefit. Pain Medicine, 16(2): 219-221, 2015.

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- In waiting for efficacy of these medications the patient would continue to suffer psychiatrically, which in turn will most likely worsen the perception of pain and affect the patient's functionality and quality of life.
- It is in these cases a time-limited prescription of either an as needed or standing dosing of benzodiazepines may be warranted.
- When and if the antidepressant becomes effective in treating the anxiety symptoms, the benzodiazepine can be easily discontinued if used on an as needed basis or tapered if taken as a standing regimen without any major adverse events or risks.
- Psychiatrists often call this method of treatment a "benzodiazepine bridge."
- Cheatle, M.D., Shmuts, R. Benzodiazepine and opioid use in patients with chronic pain: balancing risk and benefit. Pain Medicine, 16(2): 219-221, 2015.

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Non-Benzodiazepines

- While benzodiazepines can be very effective in certain cases there are other medications with anxiolytic qualities with low abuse potential and reduced risk for unintentional overdoses when combined with opioids.
- Buspirone is a medication like the SSRIs can require several weeks to achieve a therapeutic response, but it is generally well tolerated and used often for adjunctive treatment for anxiety, depression, and sometimes sexual dysfunction (especially in women).
- Mirtazapine, a central alpha-2 agonist, is another antidepressant medication that could be used as monotherapy or adjunctively for depression and anxiety
- Hydroxyzine, despite the anticholinergic and antihistamine side effect profile, is another medication that could help abort panic and improve sleep.

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Pharmacologic Approaches to Sleep Disorders

- Benzodiazepine and receptor agonists (BzRAS)
- Non-benzodiazepine receptor agonists
- Melatonin receptor agonists
- Sedative antidepressants
- Atypical antipsychotic medications
- Antiepileptic drugs

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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.

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Benzodiazepines

- FDA approved benzodiazepines for insomnia include temazepam, triazolam, estazolam, quazepam, and flurazepam.
- Lorazepam, alprazolam, and clonazepam, which are typically used as anxiolytics, are also used off-label for sleep.
- For patients with chronic pain, short-term benzodiazepines may be useful in muscle tension, anxiety, and neuropathic pain, as well as sleep.
- One study found that with long-term use (> 1 year), pain patients using benzodiazepines had no improvement in sleep.

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- 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).
- Long-term use of benzodiazepines may lead to a depressive symptomatology with cognitive and psychomotor slowing.
- Abruptly discontinuing benzodiazepines may lead to rebound insomnia and there is always a concern of tolerance and dependence, especially in patients with a history of sedative or alcohol abuse.
- Given these multiple safety concerns, benzodiazepines have fallen out of favor as a class of drugs for use in sleep disorders.

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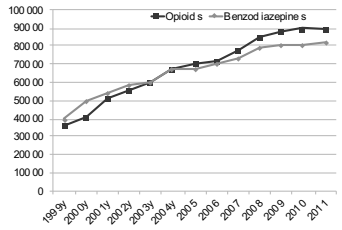
Drug Misuse and Abuse



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

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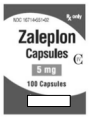
Non-Benzodiazepine Receptor Agonists (NBzRAS)

- Non-benzodiazepine receptor agonists, including Zolpidem, Zaleplon, and 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.



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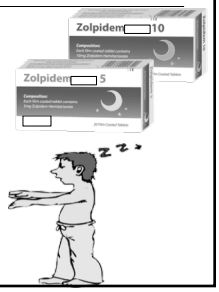
- Zolpidem has become the most prescribed drug for insomnia and, as compared to benzodiazepines, in a double blind placebo controlled study it has shown to remain effective for 8 months of nightly use with no evidence of tolerance or rebound.
- Safety trials have demonstrated that there are side effects consisting of sleep eating, sleep walking, and sleep driving.



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Antidepressants

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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:
  - Insomnia
  - Any associated depression that negatively influences pain perception
  - 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.

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TCAs

- At standard doses, all tricyclics have shown equal efficacy in treating neuropathic pain; however, they are not all equal in promoting sleep.
- Desipramine and imipramine are less sedating and may disrupt sleep.
- Amitriptyline, nortriptyline, Trimipramine and doxepin, on the other hand, may decrease sleep latency, increase sleep efficiency and increase total sleep time.

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Trazodone

- Trazodone is an antagonistic of serotonin type II, histamine and alpha 1 adrenergic receptors and weakly inhibits serotonin reuptake.
- Trazodone exerts most of its hypnotic effects at low doses and works as an antidepressant at higher doses.
- There is some evidence for adjunctive effect when used with pregabalin for pain patients.

Trazodone

PainWeek

Mirtazapine

- Mirtazapine is an antidepressant with sedating qualities due to antagonism of type I histaminergic and serotonin type II receptors.
- At doses 15-30 mg it improves sleep latency, total sleep time and sleep efficiency, and decreases frequency of awakenings. It has also been shown to improve sleep, appetite and mood in cancer patients.

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Melatonin Receptor Agonists

- Melatonin receptor agonists include the natural ligand, melatonin, as well as non-melatonin drugs (ramelteon and agalomantine).
- Melatonin has been shown to induce sleep by attenuating the wake-promoting impulses in the hippocampus.
- Melatonin is available over the counter and is not FDA approved.
- In 2005 the FDA approved ramelteon, which is a melatonin receptor agonist, for the treatment of sleep initiation insomnia.

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Antipsychotics

- Two of the newer, atypical antipsychotic medications, quetiapine and olanzapine, have been used off-label for treatment of insomnia.
- Self-reported outcomes and polysomnographic data suggests efficacy in increased total sleep time, slow wave restorative sleep, and decreasing sleep latency.
- At low doses, quetiapine primarily has antihistiminergic properties and is weakly pro-serotonergic .
- It has been known to decrease anxiety and serve as an adjunctive to antidepressant medication.
- These medications may cause significant weight gain and cardiac conduction abnormalities, such as prolonged QT interval, and a low risk of movement disorders, such as tardive dyskinesia.

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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.

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Over the Counter Medications

- Most of the OTC aids contain first generation antihistamines (diphenhydramine and doxylamine).
- Patients may quickly develop tolerance to these agents.
- There are no controlled studies demonstrating efficacy for >3 weeks in treatment with insomnia.
- Antihistamines may cause next-day sedation and impaired cognitive function and should be used with caution in the elderly.

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Clinical Considerations

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PAIN® 154 (2013) 345–349

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Topical review

Suicidality associated with antiepileptic drugs: Implications for the treatment of neuropathic pain and fibromyalgia

Anthony Pereira [a], Michael J. Gitlin [b], Robert A. Gross [c], Kelly Posner [d], Robert H. Dworkin [a,c,*]

[a] Department of Anesthesiology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA
[b] Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA
[c] Department of Neurology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA
[d] Department of Psychiatry, Columbia University, and New York State Psychiatric Institute, New York, NY, USA

- Results were conflicting and inconsistent regarding increased risk of suicide with Rx of AEDs possibly due to variability in research designs, controls, comparison groups and sample size and measures of SI/SB.
- Authors concluded that in spite of the limitations, the literature reviewed suggests that the risk of suicidality should be assessed in patients with neuropathic pain, fibromyalgia or other pain conditions being considered for AED therapy

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PAIN® 155 (2014) 2471–2475
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www.elsevier.com/locate/pain
Topical review

Suicidal ideation and behavior associated with antidepressant medications: Implications for the treatment of chronic pain

Anthony Pereira [a], Yeates Conwell [b], Michael J. Gitlin [c], Robert H. Dworkin [a,*]
[a] Department of Anesthesiology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA
[b] Department of Psychiatry, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA
[c] Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

- The FDA expanded warnings of increased risk of SI/SB for all antidepressants
- In the studies reviewed there were no differences between antidepressants and risk of SI/SB
- Results of studies reviewed were inconsistent and conflicting due to methodological limitations and variability between studies
- Authors concluded that assessment of risk for SI/SB should be standard practice in pain population especially patients initiating antidepressant therapy and in patients between the ages of 18-25.

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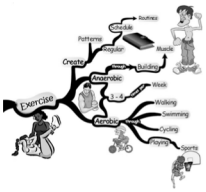
Exercise, Pain, and Opioid Sparing

- Exercise not only can enhance the release of endogenous opioids (endorphins) thus reducing the use of prescription opioids, but can also reduce the mortality and morbidity related to major health conditions.
- Recent data from randomized studies suggest that aerobic exercise also significantly improves function and quality of life in patients with chronic low back pain.
- Exercise has proven to be a potent anxiolytic as it both blunts the body's response to cortisol and increases brain serotonin levels; epidemiological studies have shown that exercise both prevents anxiety disorders and effectively treats them



Heldt, S.A., et al., Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. Mol Psychiatry, 2007. 12(7): p. 656-70.
Wipfli, B.M., C.D. Rethorst, and D.M. Landers, The anxiolytic effects of exercise: a meta-analysis of randomized trials and dose-response analysis. J Sport Exerc Psychol, 2008. 30(4): p. 392-410.

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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)

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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)

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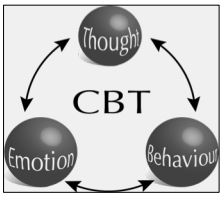
CBT (cont'd)



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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.

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CBT-I (cont'd)

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

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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]

[1] *School of Nursing, University at Buffalo, Wende Hall 304, Buffalo, NY 14214, USA*
[2] *Sleep & Neurophysiology Research Lab, University of Rochester Medical Center, Rochester, NY 14642, USA*
[3] *Maryland Poison Center, School of Pharmacy, University of Maryland Baltimore, Baltimore, MD 21201, USA*
[4] *Department of Psychiatry and Behavioral Sciences, John Hopkins University, Baltimore, MD 21287, USA*
[5] *VA Center of Excellence for Suicide Prevention, Washington, DC 20420, USA*
[6] *Department of Biostatistics and Computational Biology, University of Rochester School of Medicine, Rochester, NY 14642, USA*
[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.

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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.

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Conclusions

- Mood, anxiety, and sleep disorders are common comorbidities to chronic pain
- Each condition separately can cause additional suffering and impact QOL and in combination can be devastating to the individual with chronic pain
- Only a comprehensive approach to assessment, monitoring and treatment will effectively manage these conditions
- Access to efficacious therapeutics needs to be addressed and non-traditional delivery systems further developed.

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THANK YOU !!

- Martin D. Cheatle, PhD
- cheatle@pennmedicine.upenn.edu

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