Anxiety and SUDs

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Disclosures

"Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose."

Epidemiology

- Lifetime prevalence of any anxiety disorder is thought to be 14.6%
- Lifetime prevalence of generalized anxiety disorder is estimated to be 2.8%
  - Primary care settings have *twice* the rate reported
- Lifetime prevalence of AUD with an anxiety disorder is estimated at around 30.3%
- Anxiety disorders with specific SUDs:
  - Opioids: 36.3%
  - Cannabis: 15.1%
  - Cocaine: 5.4%
  - Amphetamine: 4.8%
  - Hallucinogen: 3.7%
  - Sedatives: 2.6%

"I can't sleep. I think I'll get up and solve all my problems."

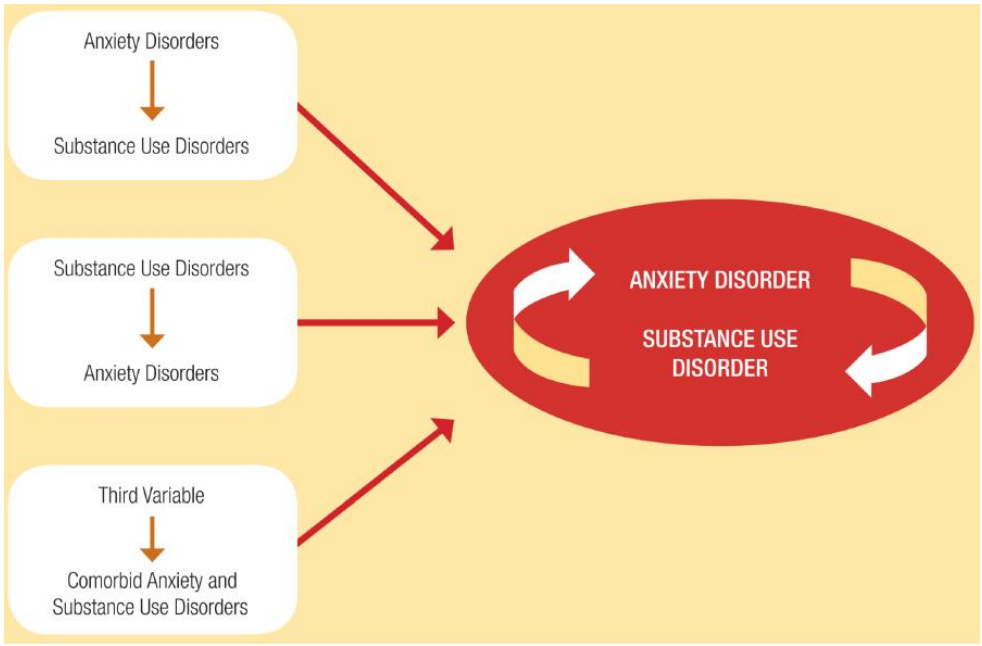
Grant B, et al. *Arch Gen Psychiatry* 2004; 61:807-16.
Conway KP, et al. *J Clin Psychiatry* 2006; 67:247-257.
Bakken K, et al. *BMC Psychiatry* 2007; 7:29.

Brief Descriptions of Major Anxiety Disorders

Disorder	Description
Panic Disorder	Episodes of intense fear and anxiety in the absence of real danger associated with both physical and cognitive symptoms such as rapid heartbeat, shortness of breath, shaking, chest pain, nausea, fear of dying or going 'crazy,' derealization, or depersonalization. They can occur in the context of any anxiety disorder, mood disorders, substance-induced disorders, and from some general medical problems. Characterized by recurrent unexpected panic attacks followed by persistent worry and concern about additional attacks.
Agoraphobia	Described as anxiety about being in places or situations from which escape may be difficult or help is unavailable, leading to avoidant behavior or marked distress.
Social phobia	Characterized by persistent and intense fear of social or performance situations with the fear of embarrassment or humiliation. Anxiety symptoms can be similar to those of a panic attack and may result in a situational bound panic attack. Feared situations are usually avoided or endured with great distress or anxiety.
Generalized anxiety disorder	Characterized by constant and undue worry and anxiety for 6 months or longer, causing significant impairment in functioning or distress.
Obsessive-compulsive disorder	Characterized by recurrent excessive obsessions and compulsions that either are time consuming or cause significant impairment or distress.
PTSD	Direct or witnessing traumatic event. The disturbance causes clinically significant distress or impairment in the individual's social interactions, capacity to work or other important areas of functioning. It is not the physiological result of another medical condition, medication, drugs or alcohol.

Diagnostic Dilemma

- DSM criteria indicate:
  - Anxiety disorder is primary if it is not due to the effects of alcohol or drugs.
  - Anxiety disorder symptoms should have been present prior to the patient's substance problem and/or should persist during abstinent periods.
  - All other occurrences of anxiety disorder symptoms, according to DSM, are likely "substance induced."



Smith JPS & Book SW, *Psychiatr Times* 2008; 25(10): 19-23

DSM Criteria

Independent Anxiety Disorder

- Anxiety symptoms preceded the onset of substance use
- Anxiety symptoms persist for a substantial period of time after cessation of acute withdrawal and severe intoxication
- Anxiety symptoms substantially in excess of what would be expected given the type or amount of the substance used or the duration of use
- Other evidence of an independent anxiety disorder

Substance-Induced Anxiety Disorder

- Prominent and persistent disturbance in anxiety
- Anxiety symptoms develop during substance intoxication or withdrawal
- Anxiety symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome
- Sufficiently severe to warrant independent clinical attention
- Not better accounted for by an independent anxiety disorder

Screening for Anxiety

- Why?
  - Prevalence data of bidirectional relationship
  - Clinical consideration of substance induced or withdrawal related symptoms overlapping with anxiety
  - *Under-recognized and under-treated*

- What?
  - GAD-7
  - Four-Dimensional Symptoms Questionnaire (4DSQ)
  - Primary Care PTSD Screen (PC-PTSD)
  - Mini-International Neuropsychiatry Interview (MINI)

Anxiety Screening Questions from the MINI

Panic disorder	Have you, on more than once occasion, had spells or attacks when you suddenly felt anxious, frightened, uncomfortable, or uneasy, even in situations where most people would not feel that way? Did the spells surge to a peak, within 10 min of starting?
Agoraphobia	Do you feel anxious or uneasy in places or situations where you might have a panic attack or panic like symptoms or where help might not be available or escape might be difficult: like being in a crowd, standing in a line when you are away from home or alone at home, or when crossing a bridge or traveling in a bus, train, or car?
Social phobia	In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations
Generalized anxiety disorder	Have you worried excessively or have been anxious about several things over the past 6 months?
Obsessions	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing?
Compulsions	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively; counting or checking things over and over; repeating, collecting, or arranging things; or other superstitious rituals?

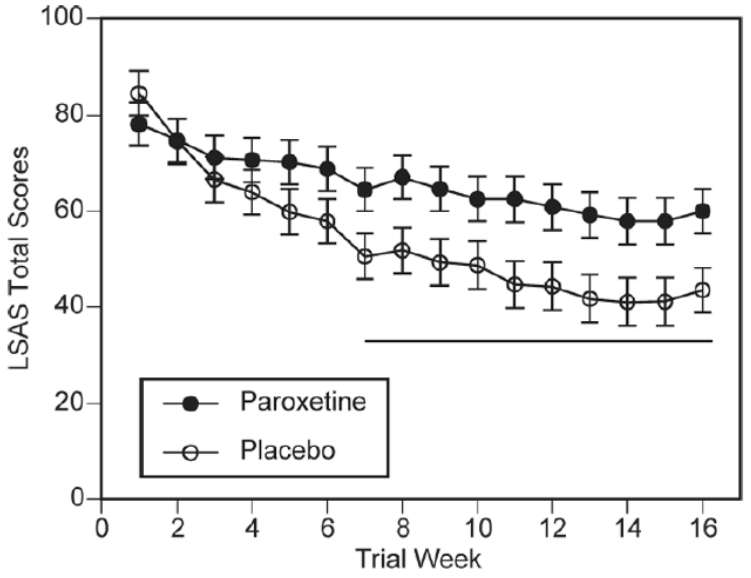
Management of Anxiety and SUD

- **Serotonin Reuptake Inhibitors (SSRIs):**
  - Fluoxetine, paroxetine, sertraline, citalopram, escitalopram
- **Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs):**
  - Venlafaxine, duloxetine, desvenlafaxine, levomilnacipran*
- **Tricyclics (TCAs)**
  - E.g., nortriptyline, amitriptyline, imipramine, clomipramine
- **Miscellaneous Agents**
  - Mirtazapine
  - Vilazodone* and vortioxetine*
  - Trazodone
  - Buspirone
  - Hydroxyzine
  - Dopamine antagonists (i.e., quetiapine, olanzapine)
  - Prazosin, clonidine, tizanidine
- **Benzodiazepines**
  - Lorazepam
  - Clonazepam
  - Diazepam
  - Chlordiazepoxide

* Brand name only

Management of Anxiety and AUD

- Paroxetine for social anxiety with co-occurring AUD
  - Looked at in two studies
  - Improved SoAD as compared with placebo
  - Alcohol quantity and frequency not affected
  - ? Decrease in alcohol reliance for social settings



Book SW, et al. *J Anxiety Disord* 2008; 22(2): 310-318

Management of Anxiety and AUD

- **Sertraline, PTSD, and AUD – Brady K. et al, 2005**

METHODS:

- A total of 94 individuals with current alcohol dependence and PTSD were randomly assigned to receive sertraline (150 mg/day) or placebo for 12 weeks. Post hoc cluster analysis of baseline characteristics was used to define subgroups of participants.

RESULTS:

- There was a significant decrease in alcohol use during the trial in both the sertraline and the placebo groups. Cluster analysis revealed significant medication group by cluster interactions for alcohol-related outcomes. Sertraline-treated participants with less severe alcohol dependence and early-onset PTSD had significantly fewer drinks per drinking day ($p < 0.001$). For participants with more severe alcohol dependence and later onset PTSD, the placebo group had significantly greater decreases in drinks per drinking day ($p < 0.01$) and average number of drinks consumed per day ($p < 0.05$).

CONCLUSIONS:

- There may be subtypes of alcohol-dependent individuals who respond differently to serotonin reuptake inhibitor treatment. Further investigation of differential responders may lead to improvements in the pharmacological treatment of co-occurring alcohol dependence and PTSD.

Brady et al. *Alcohol Clin Exp Res* 2005; 29(3): 395-401

Management of Anxiety and AUD

- SSRIs/buspirone

Author	Condition	Design/Duration	Sample/doses	Results
Thomas et al.	Social Anxiety	RCT/16 weeks	N=42/40-60mg/day paroxetine	Paroxetine reduced social anxiety and alcohol consumption (self-medication)
Book et al.	Social Anxiety	RCT/16 weeks	N=42/40-60mg/day paroxetine	Paroxetine reduced social anxiety
Brady et al.	PTSD	RCT/12 weeks	N=94/150mg/day sertraline	See previous slide
Labbate et al.	PTSD	RCT/12 weeks	N=93/50mg/day sertraline	Anxiety or mood comorbidity did not decrease treatment response in those with comorbid PTSD and an AUD
Kranzler et al.	Generalized anxiety	RCT/12 weeks	N=61/max. dose of 60mg/day buspirone *GAD and AUD patients received weekly relapse prevention psychotherapy	Buspirone therapy associated with > retention in treatment, reduced anxiety, slower return to heavy alcohol consumption, and fewer drinking days during f/u period
Tollerfson et al.	Social Anxiety	RCT/24 weeks	N=51/60mg/day buspirone	Buspirone superior to placebo as an anxiolytic

Management of Anxiety and AUD

- Quetiapine/pregabalin/naltrexone

Author	Condition	Design/Duration	Sample/doses	Results
Monnelly et al.	PTSD	Retrospective controlled/12 months	N=50/25-200mg/night quetiapine	Average abstinence duration was significantly longer. Hospitalization was shortened in the quetiapine group; the difference was statistically significant
Martinotti et al.	AUD and anxiety	RCT/pregabalin/naltrexone /16 weeks	N=71/150-450mg/day pregabalin; 50mg/day naltrexone	Pregabalin resulted in greater improvement in specific symptoms in anxiety, hostility, and psychosis and duration of abstinence from alcohol. Pregabalin also led to better outcome in patients reporting a comorbid psychiatric disorder. Seemed as effective as naltrexone for AUD.
Petrakis et al.	Anxiety	RCT/12 weeks	N=254/50mg/day naltrexone; 250mg/day disulfiram	High rate of abstinence across groups. Those with active medications had more consecutive weeks of abstinence and less craving than those treated with placebo but no group differences in other alcohol use measurements. No benefit of combination.
Petrakis et al.	PTSD	RCT/12 weeks	N=254/50mg/day naltrexone; 250mg/day disulfiram	Those with PTSD had better alcohol outcomes with active medications than they did on placebo; overall psychiatric symptoms of PTSD improved. Group with only disulfiram reported fewer PTSD

Management of Anxiety and SUD

Selecting an antidepressant

- **Generic SSRIs, SNRIs, are reasonable first line agents**
- **No evidence for superiority of one agent or class for 'usual' outpatient depression or anxiety**

Clinical considerations

- **Prior good response/tolerability** → re-try same agent
- **Depression with anxiety and/or irritability** → SSRI
- **Severe depression and/or chronic pain** → SNRI
- **Prominent weight loss, insomnia** → mirtazapine
- **Problems with antidepressant sexual dysfunction** → mirtazapine
- **Prior intermittent missed doses** → fluoxetine

Management of Anxiety and SUD

The following agents are relatively less favorable first line agents when concerns exist about:

- **Cytochrome P450 2D6 inhibition of metabolism of co-prescribed substrates (e.g., codeine, tamoxifen, TCAs, propranolol):**
  X→ fluoxetine, paroxetine, duloxetine
- **Weight gain:** X→ mirtazapine, paroxetine
- **Drowsiness:** X→ mirtazapine, paroxetine, trazodone
- **Hypotension:** X→ trazodone
- **Hypertension:** X→ SNRIs
- **Seizures:** X→ bupropion
- **QTc prolongation**: X→ citalopram, escitalopram
- **Abrupt discontinuation-emergent reactions:** X→ paroxetine, SNRIs

Management of Anxiety and SUD

Dopamine antagonists

Second generation medications:

- Quetiapine
  - Initiated at a dose of 50 to 100 mg once daily or in two divided doses
  - The usual target dose is 50-200mg taken at bedtime or in two divided doses
  - Common side effects include headache, dry mouth, constipation, weight gain, sedation, dizziness, and orthostatic hypotension

- Olanzapine
  - Initiated at dose of 2.5-5mg once daily or in divided doses
  - Usual target dose is 5-10mg once daily or in divided doses
  - Common side effects include dry mouth, constipation, weight gain, sedation

Management of Anxiety and SUD

Benzodiazepines

Management of Anxiety and SUD

- Disulfiram and lorazepam – Bogenschutz MP, et al. 2016
  - Open label trial to explore effects of co-administration of lorazepam and disulfiram to alcohol dependent patients with anxiety disorder symptoms
  - Methods:
    - 41 patients with DSM-IV alcohol dependence who met criteria for anxiety disorder with or without co-occurring major depression
    - Lorazepam 0.5mg three times daily
    - Disulfiram at starting dose of 500mg three times weekly
    - Received 16 weeks of monitored pharmacotherapy with manualized medical management
  - Results:
    - Significant increase in percent abstinent days during treatment and at 24 week follow up
    - Large reduction in anxiety, depression, and craving observed
    - Adherence to treatment decreased steadily with time (85.4% at 4 weeks and 36.6% at 16 weeks)
    - Duration of adherence with disulfiram strongly predicted abstinence at 16 weeks

Bogenschutz MP, et al. *Am J Drug Alcohol Abuse*. 2016; 42(5): 490-499.

Management of Anxiety and SUD

Possible

- Careful selection of patients and close monitoring, abstinence was possible (Adinoff, 1992)
- Harvard/Brown Anxiety Disorder Research Program study, no significant differences in dose or frequency of BZD use among those with and without AUD. 12 year f/u did not find significant risk in comparing groups (Mueller et al, 1996; Mueller et al, 2005)
- Studies showing risks of BZD misuse in those with SUD was based on skewed data (Maletzy & Klotter, 1976))
- Studies suggesting that those with AUD and SUD are at high risk of BZD misuse is inconclusive (Ciraulo et al, 1988))
- Prolonged BZD use decreased morbidity in chronic conditions (Schatzberg, 1990)
- Other treatments are often ineffective (Lader, 1990)

Avoid

- Association with increased unintentional overdoses, especially with comorbid OUDs
- Those with personal and family history of SUDs may be more susceptible to the addictive effects of BZDs and at greater risk of misusing medications (Ciraulo et al, 1996; Ciraulo et al, 1997)
- BZD misuse is common among those with SUDs particularly among those with more severe SUDs, multiple SUDs, and greater psychiatric severity (Busto et al, 1996; Ross et al, 1993)
- Physiologic tolerance and dependence occurs with every long-term BZD use and these risks are compounded in those with SUD (Hamlin, 1989)
- Long-term BZD use may cause structural brain changes (Piesiur-Strehlow et al, 1986))
- Guilt and failure to spend enough time with patients are the main reasons physicians prescribe BZDs (Bendtsen et al, 1999)

Management of Anxiety and SUD

Guidelines

- Before initiating BZDs, perform a thorough medical history, including personal and family history of substance use disorder and a thorough assessment of physical health, with special attention to hepatic, renal and pulmonary disease.
- Utilize PMPs for all patients
- The use of benzodiazepines with opioids at least doubles the risk of respiratory arrest and death and should be avoided
  - The U.S. Food and Drug Administration now requires black boxed warnings – the FDA's strongest warning – for concurrent use of prescription opioids and benzodiazepines
  - In the rare instance that patients require both an opioid prescription and a benzodiazepine prescription, they should be counseled about the risk of respiratory arrest and death and co-prescribed naloxone
- If BZDs are prescribed to patients with history of substance use disorder or active substance use disorder, prescribing should be associated with careful patient monitoring that includes documentation of treatment benefit and assessment for potential harm, including regular urine drug screens

Guidelines

- Providers should understand how to interpret the results of urine drug screens and have an established process for responding to abnormal results
- When initiating benzodiazepine treatment, the prescriber should discuss and document the risks and potential benefits associated with treatment (including education about the risk of developing dependence and/or tolerance) and the intended duration of treatment
- When initiating BZD treatment to provide symptom relief in the early phase of treatment of depression or an anxiety disorder, educate the patient about evidence-based, non-pharmacological treatments available for that disorder and to facilitate appropriate referrals, e.g., for cognitive behavioral therapy (CBT); or to simultaneously initiate the intended first-line treatment, e.g., SSRIs or SNRIs
- BZDs may worsen some conditions, including hypoxia associated with asthma, COPD, CHF, CFS, depression, impulse control disorders, PTSD
- There is no data to support use of BZDs for insomnia
- Chronic BZD treatment should be reassessed at least biannually to monitor effectiveness and potential for misuse
- Sample patient – provider agreement forms: https://www.drugabuse.gov/sites/default/files/files/SamplePatientAgreementForms.pdf

Management of Anxiety and SUD

General aspects of pharmacological treatment:

- Discuss anticipated balance of risks and benefits of medications prior to starting
- Consider an SSRI/SNRI for first line treatment
- Remain familiar with other options for other classes of medications as many patients may not respond or may be intolerant of SSRI/SNRI treatment
- Benzodiazepines may not be fully off the table for a select population, ***but*** use should be very time limited, controlled, and there is ***no*** evidence to support its chronic use in those with comorbid PTSD
- Don't forget to always ask about craving and/or treat independently

Alcohol and Specific Anxiety Disorders

GAD

- Little evidence-based research to direct treatment decisions for individuals with GAD and AUD
  - Buspirone has been studied with mixed results
  - SSRI/SNRI's have been studied in uncomplicated GAD and pose little risk in those with SUD
  - Bupropion should be avoided or used cautiously in those with history of or at risk for seizures
  - Topiramate has been shown to reduce anxiety, alcohol craving, and relapse in early studies
  - Pregabalin and gabapentin have demonstrated some efficacy for GAD and emerging data in comorbid AUD and GAD

SoAD

- Those with SoAD may need treatment targeting social anxiety before being able to benefit from group interventions; individual therapy may be better tolerated, and a period of sobriety and skills training may be important before increasing exposure to social situations
- Few studies examining treatment in comorbid populations
  - CBT plus optional fluvoxamine versus treatment as usual
  - Two smaller placebo-controlled trials of paroxetine in AUD and SoAD have shown significant improvement in social anxiety with paroxetine treatment but no differences in alcohol use in either study

PD

- SSRIs fluoxetine, sertraline, paroxetine, and fluvoxamine have demonstrated effectiveness in clinical trials and are the best choice for those with co-occurring PD and AUD

Opioids and Anxiety

- Among individuals with OUDs, lifetime prevalence of any anxiety disorder was 36.3% (61% in those with opioid dependence)
  - SoAD: 13%
  - PD with AG: 5%
  - PD without AG: 14%
  - GAD: 11%
- No clinical trials of treatment for co-occurring anxiety disorders have been conducted
  - General treatment principles apply with emphasis on a comprehensive treatment plan to address opioid use, anxiety, other comorbid SUDs, and chronic pain

Stimulants and Anxiety

- Reported lifetime anxiety disorder with those with methamphetamine use disorder is approximately 39%
- Reported lifetime anxiety disorder with those with cocaine use disorder is approximately 31%
- Paucity of research focused on treatment of co-occurring stimulant use and anxiety disorders
  - Carbamazepine and clonazepam showed some promise in those with cocaine induced PD
  - Use of AEDs in this population warrants further studies

Management of Anxiety and SUD

- Behavioral approaches
  - Cognitive-behavioral therapy
    - Impressive efficacy of CBT for all major anxiety disorders, including OCD
    - Psychoeducation, cognitive techniques, exposure to feared stimuli, and relapse prevention
    - Utilize active CBT components of self-efficacy, behavioral choice, and control within the context of the 1st step of AA – 'Came to believe I was powerless over alcohol and my life had become unmanageable'
      - Show patients how they can make consistent behavioral choices each day that can improve symptoms of both anxiety and SUDs
      - Can also adapt CBT protocols to meet needs of populations (e.g., designing exposures for socially anxious patients to speak up at 12 step meetings rather than encouraging to go out with high risk acquaintances)

Weiss RD, *J Subst Abuse Treat* 2004; 27:307-312.
Schmitz J et al. *Addict Disord Treat* 2002; 1:17-24.

Management of Anxiety and SUD

- Behavioral approaches
  - Concurrent Treatment of PTSD and SUDs Using Prolonged Exposure (COPE)
    - Methods:
      - 22 treatment seeking women with PTSD and AUD
      - Received COPE (manualized form of CBT with exposure to address PTSD and SUD) for 12 90-minute sessions delivered weekly PLUS offered standard treatment for AUD (psychosocial treatment for AUD, outpatient counseling, MI, relapse prevention, and biofeedback)
    - Results:
      - No adverse events
      - Treatment attendance and completion were higher than in previous studies
      - All efficacy-related outcomes (PTSD, depression, alcohol use, craving, and dependence severity were significantly reduced)

Persson A, et al. *J Addict Med*. 2017; 11(2):119-125

Summary

- Intervention should contain evidence-based treatment modalities for anxiety, namely pharmacotherapy and namely, CBT
- Likely that typical addiction treatment has some effect on both anxiety symptoms and perhaps mild anxiety disorders.
  - Little evidence to suggest that clinically significant anxiety disorders are successfully treated by SUD treatment alone
- What personnel in addiction-treatment setting can deliver specialized evidence-based anxiety disorder treatment?
  - Not enough psychologists
  - Not enough psychiatrists
  - Fraction of community-based addiction treatment outpatient facilities have onsite prescribers
- Education for patients to understand relationship between SUD and anxiety symptoms and role that substances play in maintaining and potentially exacerbating their anxiety disorders