Depression and Anxiety in Patients with Addiction

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Disclosure Information

Richard N Rosenthal, MA, MD

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Session Learning Objectives

At the end of the session, you will be able to:

- Describe approaches to distinguish between substance-induced and independent disorders, and the relevance to pharmacotherapeutic treatment of SUD and co-occurring mood and anxiety disorders.
- Explain the differential impact of substance use disorders on recovery from mood and anxiety disorders and vice-versa.
- Implement differential therapeutics based on current evidence, and consideration of presented co-occurring disorders principles where specific evidence is lacking.

General Rules in Assessment

- Given the high population comorbidity rates (higher in clinical samples) and adverse impact on recovery from SUD, patients presenting for addiction treatment should have a psychiatric assessment.
- Consistent with primary care good practice, SUD patients should at least have mood and anxiety disorder screens such as PHQ-2 or GAD-7.
- Conversely, all patients presenting for psychiatric treatment of mood and anxiety disorders should have an SUD assessment as SUD are part of DSM-5 and have adverse impact on recovery of other mental disorders.
- If feasible, get permission to get collateral information from patient's significant others.
  - They typically know patient's problems with substances, and potentially mental disorder symptoms, but are usually not present at visit.

Differential Diagnosis of Mood and Anxiety Symptoms

- How do symptoms change with abstinence? - a clue to etiology (r/o substance-induced disorders)
- Depressive symptoms may decrease in once abstinence is established[1, 2]
- Similar findings with anxiety symptoms:
  - Anxiety prominent during alcohol withdrawal[3]
  - Anxiety level declines as a function of the duration of abstinence from alcohol[4, 5]

[1]Dorus W et al. Alcohol Clin Exp Res. 1987(Aprl);11(2):150-154; [2]Brown SA. Am J Psychiatry. 1995(Jan);152(1):45-52; [3]George DT et al. Acta Psychiatr Scand. 1990(Feb);81(2):97-107; [4]Schuckit MA et al. J Stud Alcohol. 1990(Jan);51(1):34-41; [5]Brown SA et al. J Stud Alcohol. 1991(Jan);52(1):55-61

Epidemiology-Based Recommendations

- When evaluating SUD patients, higher severity SUD, female gender, drug- compared to alcohol use disorders, earlier-onset (<25 y/o) and higher social deviance (e.g., criminal justice, homelessness) increased risk for co-occurring other mental disorders (COD). (A)
- If an individual is diagnosed with COD, the clinician should anticipate another COD in that individual, since disorders tend to cluster. (A)
- Smoking tobacco should be routinely screened for in treatment-seeking patients and when identified, its presence should alert the clinician of increased risk of a COD. (A)

[6]Rosenthal RN, Nunes EV, LeFauve C. Am J Addictions 21:97-103, 2012

Depressive Disorders and SUD

Risk of Mood Disorder with Comorbid AUD Relative to No AUD (N=43,093)

	Odds Ratio
Any Mood Disorder	4.1
Major Depression	3.7
Dysthymia	2.8

Prevalence of Substance-Induced Mood or Anxiety Disorders < 1%

[7]Grant BF, et al. Arch Gen Psychiatry. 2004;61:807-816.

Depression and Alcohol Dependence: Meta-analysis of 14 Antidepressant RCTs

Key depression treatment findings:[8]

- Depression diagnosis after at least a week of abstinence is associated with greater antidepressant effect
- Adequate doses for at least 6 weeks of antidepressants is effective for acute treatment of co-occurring depressive disorder
  - small to medium effect size (.38) is like that of a meta-analysis of depression trials in non-AUD patients (.43)
- Type and severity of depression not associated with outcome
- Treating depression reduces quantity of used alcohol but does not sustain abstinence
- Alcohol-specific therapy is needed in patients with co-occurring AUD

[8]Nunes EV, Levin FR. *JAMA*. 2004;291:1887-1896.

Meta-analysis of Antidepressant Trials in AUD Patients with and without Depression

Key depression treatment findings in AUD + depression (9 RCTs):

- Overall effect of SSRI treatment was not significant
- Effect of other antidepressants (TCA, Nefazodone) was significant (p=0.01; OR 4.15)

Key AUD treatment findings, AUD alone (8 RCTs):

- Overall effect of antidepressants on AUD was not significant for SSRI's or other antidepressants

Key AUD treatment findings in AUD with depression (9 RCTs):

- Overall effect was not significant for either SSRI or other antidepressants (e.g., TCA)

[9]Torrens M et al., *Drug Alc Dep* 2005;78:1-22

Cochrane Systematic Review: Antidepressants for Co-occurring Depression and AUD

- RCTs[10] included mostly sertraline; also, amitriptyline, citalopram, desipramine, doxepin, escitalopram, fluoxetine, fluvoxamine, imipramine, mirtazepine, paroxetine, venlafaxine, (nefazodone)
- RCTs of antidepressants compared to placebo demonstrated:
  - higher number abstinent (RR 1.69, 95% CI 1.18 to 2.43)
  - lower number of drinks per drinking days (Mean Difference -1.21, 95% CI -1.91 to -0.51)
  - rate of abstinent days, NS

[10]Agabio R et al. Cochrane Database Syst Rev. 2018. DOI:10.1002/14651858.CD008581.pub2

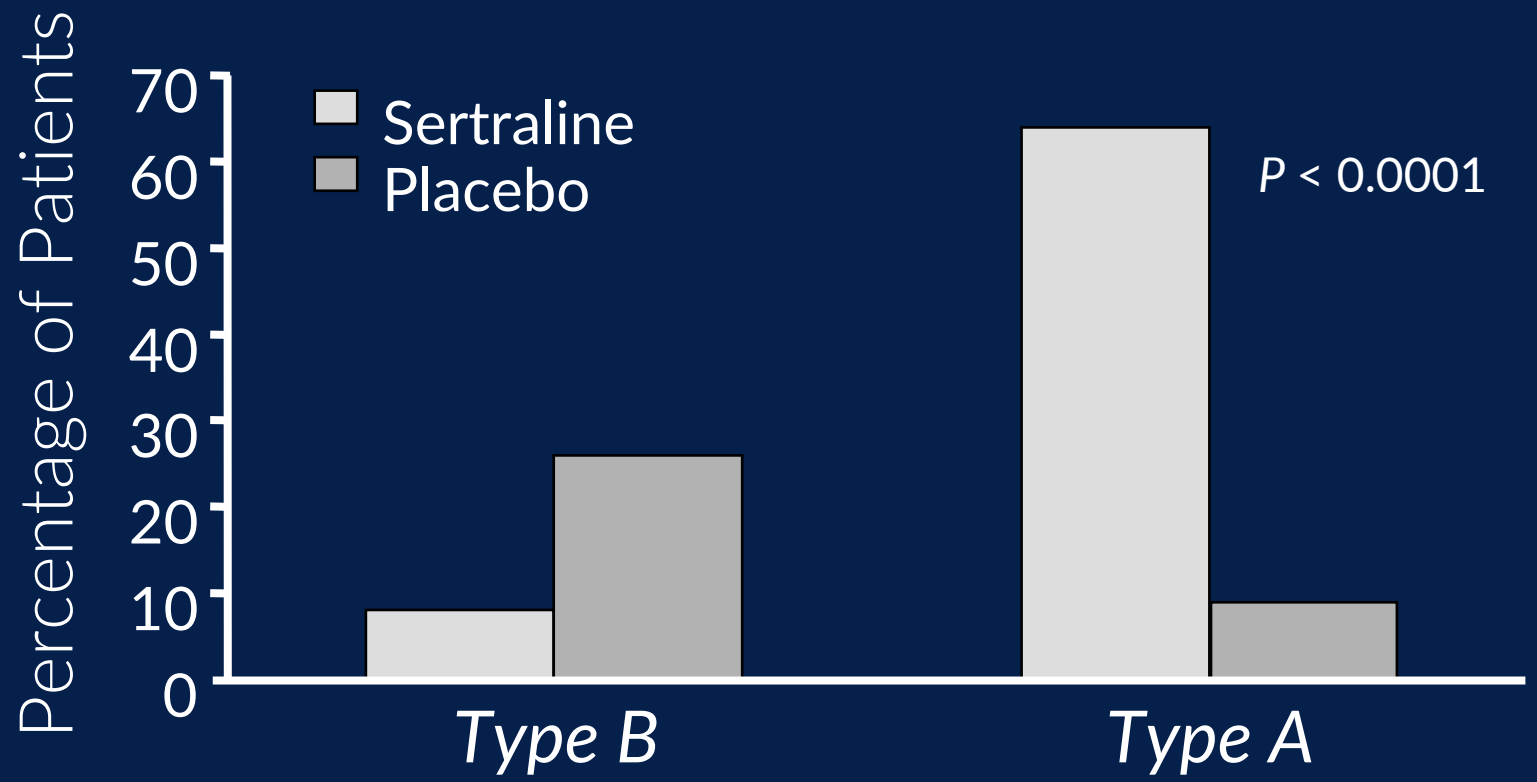
Differential Response: Types A & B

Typology-based response of AUD to SSRI medications:

- Patients with high-risk/severity, early-onset AUD (Type B) have poorer drinking-related outcomes compared to placebo after Fluoxetine[11] or Sertraline[12]
- In the absence of a comorbid mood or anxiety disorder, later-onset Type A (AUD onset > 25 y/o) may do better with SSRI.
- Open trial comparing fluoxetine to placebo in depressed adolescents with SUD resulted in worse urine toxicology outcomes in the active medication group[13]

[11]Kranzler et al., Alcohol Clin Exp Res. 1996 Dec;20(9):1534-41. [12]Pettinati HM et al., Alcohol Clin Exp Res. 2000;24:1041. [13]Riggs PD et al., J Child Adolesc Psychopharmacol. 1997;7(2):87-95.

Percentage of Non-Depressed Patients with AUD Completely Abstinent



[12]Pettinati et al. *Alcohol Clin Exp Res.* 2000;24:1041.

Summary of Pharmacotherapy Research Findings on Depression in AUD

- Depression in AUD
  - can be reliably diagnosed if DSM criteria are met after at least 1 week of abstinence
  - responds to antidepressant medication
- Response is independent of chronology of onset of each disorder (i.e., primary vs. secondary, not substance induced)
- Failure to treat associated with unchanged depressive severity, drinking relapse, and negative bio-psycho-social consequences
- Controlled trials do not support antidepressant use alone for AUD without comorbid disorders where antidepressants are indicated

Treatment of Depression in Alcohol Use Disorder

- SSRI's and TCA both efficacious
- First Line: SSRI/SNRI for safety/tolerability compared to TCA
- Secondary depression (i.e., after AUD onset) responds to treatment
- Don't withhold depression treatment from AUD patients in stable recovery based on an assumption the depression is an effect of protracted intoxication or withdrawal[14]
- Antidepressants may improve drinking outcome among AUD patients with diagnosed depression, but not among patients without diagnosed depression, with or without depressive symptoms.

[14]Hasin DS, Grant BF. *Arch Gen Psychiatry*. 2002;59:794-800.

Treatment of Depression in Opioid Use Disorder

- Almost all data from studies of methadone- maintained OUD patients
- Little study in outpatient drug free, naltrexone maintained, buprenorphine maintained
- No study of depression in OUD prescription opioids
- Little study of outpatient psychiatric patients with mild OUD

Imipramine Trial: Results

- 6-week Imipramine RCT in methadone patients with depression
- N=137 enrolled, 84 completers, Many dropouts due to side effects
- Positive effect on depression and craving
- 50% reduced self-reported other drug use in >1 day/week at baseline, mediated by mood improvement

	IMI	*Placebo*	*P*
Global response	57%	7%	.001
Depression response	67%	26%	.001
HAM-D	8.0	13.6	.001
Craving (days/week)	2.7	4.5	.01
Sustained abstinence	14%	2%	ns

[15]Nunes EV et al. Arch Gen Psychiatry. 1998(Feb);55(2):153-160

RCT's of SSRIs for Depression in Opioid Use Disorder

- Fluoxetine N=50, 40 [16,17]
  - No effect on mood
  - High placebo response rate
- Sertraline N=95[18]
  - No effect on mood or substance use
  - Poor compliance with sertraline (low blood levels)
  - Nefazodone, an SNRI (withdrawn in 2003) , was effective in some non-responders, →*suggests trial of duloxetine or venlafaxine*
  - Anhedonia and insomnia remained prominent symptoms
    - Sedating medication may be preferable

[16]Petrakis I et al. Drug Alcohol Depend. 1998(May 1);50(3):221-226; [17]Dean AJ et al. J Affect Disord. 2002(Oct);72(1):85-90 [18]Nunes EV et al. Psychiatr Clin North Am. 1996;19(2):311-327

Antidepressants in Methadone-treated Patients with Depression and OUD

- Small-sample (N=317 patients, 4 RCTs) meta-analysis:[19]
  - Response rates between antidepressant and placebo therapy were NS for major depression/dysthymia patients with OUD treated with methadone (risk ratio for response, 1.182; 95% CI: 0.822-1.700; P = 0.366).

[19]Pedrelli P. et al., J Clin Psychopharmacol. 2011 Oct;31(5):582-6.

Treatment of Depression in Opioid Use Disorder

- SSRIs are still first line choice because of safety and good tolerability
  - However, unclear efficacy
  - TCAs have efficacy, but also toxicity, AE's
  - Consider other meds with sedating properties (e.g., mirtazapine [Remeron], trazodone [Desyrel])
- Opioid agonists alone may prolong the QT interval, increasing risk of fatal arrhythmias
- TCAs, which can also produce cardiac conduction delays, may exacerbate this risk when combined with opioids
  - Extra clinical scrutiny is warranted for treating depression with antidepressants in patients on opioid maintenance therapy (e.g., methadone, buprenorphine).

Bipolar Disorder and SUD

Risk of Mood Disorder with Comorbid AUD Relative to No AUD (N=43,093)

	Odds Ratio
Any Mood Disorder	4.1
Major Depression	3.7
Dysthymia	2.8
Mania	**5.7**
Hypomania	**5.2**

NOTE: Prevalence of Substance-Induced Mood or Anxiety Disorders were < 1% in the general population-clearly higher in treatment-seeking individuals

[20]Grant BF, et al. Arch Gen Psychiatry. 2004;61:807-816.

Bipolar Disorder and Comorbid AUD: Treatment

- Lithium[21]
  - not effective for AUD
- Anticonvulsants (e.g., carbamazepine, topiramate, gabapentin, divalproex sodium)[21]
  - efficacy in AUD
- Valproate[22]
  - significantly decreased drinking and earlier remission of manic symptoms relative to placebo in lithium-treated patients

[21]Frye MA , Salloum IM *Bipolar Disorders*. 2006;8:677-685.
[22]Salloum IM, et al. *Arch Gen Psychiatry*. 2005;62:37-45.

Bipolar Disorder and AUD

- 24-week RCT of divalproex vs. placebo, N=59 BD-I patients with AUD1
- All patients received lithium and psychosocial treatment
- Divalproex group
  - Lower proportion of heavy drinking days (p=0.02)
  - Fewer drinks per heavy drinking day (p=0.055)
  - Prolonged time to sustained heavy drinking (p=0.048)

[22]Salloum IM, et al. *Arch Gen Psychiatry*. 2005;62:37-45.

Bipolar Disorder and AUD

- Few RCTs of medication for BPD and AUD
- No reason to suspect that medications effective for AUD are not also effective for AUD in Bipolar Disorder patients:
  - Topiramate (not FDA-approved)
  - Naltrexone (oral and long-acting)
  - Disulfiram
  - Acamprosate
- **Common sense suggests using AUD-specific medication until the evidence base suggests otherwise.**

[23]Singh JB, Zarate Jr CA, *Bipolar Disorders* 2006;8:696-709.

What is Sensible in Bipolar Disorder?

- Use evidence-based treatments for SUD, considering risks
  - Opioid Use Disorder:
    - Methadone maintenance
    - Buprenorphine
  - Alcohol Use Disorder:
    - Naltrexone (ReVia)
    - Naltrexone (Vivitrol)
    - ? Disulfiram (Antabuse)
    - Topiramate
    - Acamprosate (Campral)
- Anticonvulsants for mood stabilization;
  - Divalproex added for reduction in heavy drinking
- Atypical antipsychotic agents for treatment of psychosis

[23]Singh JB, Zarate Jr CA, *Bipolar Disorders* 2006;8:696-709.

Anxiety Disorders and SUD

Co-Occurring SUD and Anxiety Disorders: Bidirectional Complexity

- Anxiety disorders may be earlier-onset risk factor for SUD development
- Anxiety disorders modify the presentation and outcome of SUD treatment
- SUDs modify presentation and outcome of treatment for anxiety disorders.
- Anxiety symptoms also emerge during chronic intoxication and withdrawal.
- Substance-related anxiety symptoms abate over time frequently related to substance elimination half-life.
- What increases probability of independent anxiety disorder?
  - Family History+
  - Symptoms develop (1° disorder) before substance use onset
  - With abstinence, continued anxiety symptoms compared to a decreasing trajectory

Treatment of Co-Occurring SUD and Anxiety Disorders : General Considerations

- Medications are typically those in use for treating anxiety disorders with provisos for management of SUD, given abuse liability
  - Start with lowest-risk medications such as SSRI or SNRI, explain that effects may take several weeks
  - Be wary of BZDs, if used in early-phase treatment when waiting for other meds to exert effects, brief co-prescription of limited amounts, close monitoring.
  - Move to chronic treatment only if prior stepped treatment strategies have failed.
  - In chronic situations use less potent, less lipophilic, slower onset (less cocktail effect), less reinforcing BZD's such as chlordiazepoxide or oxazepam, rather than lorazepam or clonazepam, and *especially not triazolobenzodiazepines*, *e.g.*, *alprazolam which has higher risk for rebound anxiety*[24]

[24]Griffin CE et al. Ochsner J. 2013;13(2):214-23.

Treatment of Co-Occurring SUD and Anxiety Disorders : General Considerations

- Overall, SSRIs and SNRIs are first-line for anxiety disorders for safety, tolerability and effectiveness[25]
- Venlafaxine: FDA indications for Generalized Anxiety, Panic, and Social Anxiety Disorder, SNRI have lower risk of prolonged QTc than Tricyclics[26]
- Pregabalin has good RCT support for GAD, approved in Great Britain; is a controlled substance in US due to increased addiction liability, so not 1st line in SUD[25]
- Gabapentin is anxiolytic[27], not a controlled substance and though some risk for non-medical use, especially in OUD[28], modest support for Social Anxiety Disorder[29] and is also used off label for GAD, PD[30]
- TCA and MAOI are 3rd and 4th line due to side-effects, and increased risks both alone and in context of substance use, e.g., MAOI and Cocaine are not a good match!

[25]Ravindran LN et al., J Clin Psychiatry 2010;71:839–854. [26]Rochester MP et al., Ther Adv Drug Saf. 2018 Jun;9(6):297-308. [27] Hong JSW, et al., Mol Psychiatry. 2022 Mar;27(3):1339-1349. [28] Greenblatt HK et al., Clin Pharmacol Drug Dev. 2018 Mar;7(3):228-232. [29] Pande AC, et al. J Clin Psychopharmacol 1999;19:341–348. [30] Garakani A, et al., Front Psychiatry. 2020 Dec 23;11:595584.

Treatment of Co-Occurring SUD and Anxiety Disorders : General Considerations

- Cognitive Behavior Therapy (CBT) demonstrates efficacy for most anxiety disorders and is compatible with effective CBT approaches for SUD[31,32]
  - For example, cognitive behavioral therapy tools such as activity scheduling, relaxation training, and cognitive restructuring can help address both anxiety and SUD symptoms[33]
- Psychotherapy should also focus on medication acceptance and adherence, given the preponderance of stigmatizing messaging in parts of the recovery community and internalized stigma for patients

[31]McHugh RK, et al. Psychiatr Clin North Am 2010;33:511–525. [32]Otte C. Dialogues Clin Neurosci 2011;13:413–421. [33]Satre DD et al., J Addict Med. 2020 Dec;14(6):e293-e296

Medications with Anxiolytic Properties

Medications	*Potential benefits*	*Concerns / Common side effects*
SSRI (e.g., paroxetine, sertraline)[33, 34] SNRI (e.g., duloxetine, venlafaxine)[34]	Reduced anxiety-Strong safety profiles, may have benefit in Type A	May not impact alcohol use, Sexual side effects
Buspirone, $5HT_{1a}$ partial agonist[33]	Reduced anxiety, Longer acting effect, Fewer drinking days, delayed relapse to heavy drinking @ higher target dose (60mg) [35]	Headache, Drowsiness. May take weeks to observe expected effects
Gabapentin (off label) [36]	Reduced anxiety, improved sleep, Reduced alcohol craving, Quick acting	Dizziness, Drowsiness

[33]Satre DD et al., J Addict Med. 2020 Dec;14(6):e293-e296. [34]Reinhold JA et al., Expert Opin Pharmacother. 2011;12(16):2457–67. [35]Kranzler HR et al. Arch Gen Psychiatry. 1994(Sept);51(9):720-731 [36]Mason BJ et al. JAMA Intern Med 2014;174(1):70–77.

Medications with Anxiolytic Properties

Medications	*Potential benefits*	*Concerns / Common side effects*
Atypical antipsychotic agents (off label) [37] (e.g., quetiapine, ziprasidone also risperidone, aripiprazole, or olanzapine)	Reduces anxiety symptoms of GAD, quetiapine 50 -150mg , may need higher doses in post-acute withdrawal states	Sedation , fatigue (50% not tolerated). Long-term risks (e.g., TD). Weight gain, metabolic dysregulation w/ olanzapine, Dose-related sudden cardiac death risk. [38]
Hydroxyzine 25-50mg – antihistamine, mild 5-HT_2 antagonism[33]	Reduced anxiety, improved sleep, Quick acting	Dizziness, Drowsiness, Dry mouth

[33]Satre DD et al., J Addict Med. 2020 Dec;14(6):e293-e296. [37]Hershenberg R, et al., CNS Drugs 2014 Jun;28(6):519-33. [38]Ray WA et al., N Engl J Med. 2009;360(3):225–35.

Generalized Anxiety Disorder and SUD

- 50% with lifetime GAD have SUD (90% is AUD): increased psychopathology, disability and use of drugs/alcohol to relieve anxiety[39]
- GAD is the anxiety disorder most likely to use alcohol to self-medicate[40]
- Anxiety symptoms overlap with acute stimulant intoxication and withdrawal from alcohol, opioids, sedative/hypnotics
  - Best diagnosis in post-detoxification or longer abstinent state, often impractical, so careful history taking as to timing of GAD symptoms relative to the SUD
- 20-40% relapse 6-12 months after meds d/c , so ≈1/3 may need chronic Tx[41]
- Escitalopram, paroxetine (SSRIs), duloxetine, venlafaxine XR, (SNRIs) , buspirone and alprazolam are FDA approved for GAD.42 Escitalopram & duloxetine may have largest effect sizes[43]
- 1st SSRI → 2nd SSRI or duloxetine, or alternately: buspirone, hydroxyzine, or venlafaxine → 3rd quetiapine or risperidone, or valproate[42]

[39] Alegría AA, et al. J Clin Psychiatry. 2010 Sep;71(9):1187-95 [40] Robinson J, et al. J Anxiety Disord 2009;23:38–45. [41]McKeehan MB, et al. Alcohol Treat Q 2002;20:45–59. [42] Abejuela HR et al. Harv Rev Psychiatry. 2016 ;24(4):243-56. [43] He H, et al. J Psychiatr Res. 2019;118:21–30.

Panic Disorder and SUD

- Lifetime risk of Panic Disorder(PD) is increased 4x in AUD[44]
- Diagnosis is best made in abstinent state, often impractical, so careful history taking as to onset and timing of panic symptoms relative to the SUD, taking into consideration of pharmacologic effects of substance intoxication or withdrawal
  - Panic attacks can occur in acute withdrawal from alcohol that remits with abstinence[44]
  - People with panic attacks may self-medicate with alcohol and develop an AUD[45]
- Clinical trials of fluoxetine, sertraline, paroxetine, citalopram, escitalopram and fluvoxamine have demonstrated effectiveness for individuals with co-occurring PD and SUD[46,47]
- As venlafaxine has also demonstrated efficacy in PD, SNRIs as well as SSRIs can be used for PD in the context of SUD[48]

- [44] Schuckit M, et al. Addiction 1997;92:1289–1304. [45] Cosci F, et al. J Clin Psychiatry 2007;68:874–880 [46]Kushner MG, et al. Alcohol Clin Exp Res 2005;29:1432–1443. [47]Roy-Byrne PP et al., Lancet. 2006 Sep 16;368(9540):1023-32. [48] Pollack MH, et al., Depress Anxiety. 2007;24(1):1-14.

Social Anxiety Disorder (SAD) and SUD

- In those with SAD, 48% lifetime prevalence of AUD, a risk 2.3 times that of those without lifetime SAD, and increases risk for lifetime SUD by 2.5[49]
- Developmentally, SAD symptoms typically precede onset of SUD[50]
- Fear of performance and fear of social situations are not substance-related effects, making diagnosis less complicated, so look for it, because:
  - Social anxiety reduces engagement in recovery activities- sharing in therapy groups, AA attendance, finding a sponsor[51]
- RCTs of paroxetine in SAD/AUD demonstrated efficacy for SAD only[52,53]
- Gabapentin has also demonstrated promise in case reports and in a double-blind RCT for SAD[29]

[49] Grant BF, et al., J Clin Psychiatry. 2005 Nov;66(11):1351-61 [50] Carrigan M, et al., Addict Behav 2003;28:269-284. [51] Book SW, et al. Addict Behav 2009;34:474–476. [52]Book SW, et al. J Anxiety Disord 2008;22:310-318. [53] Randall CL, et al. Depress Anxiety 2001;14:255–262. [29] Pande AC, et al. J Clin Psychopharmacol 1999;19:341–348.

Promising Directions?

Ketamine for Mood, Anxiety, and SUD?

- Systematic reviews and meta-analyses of RCTs of ketamine, an N-methyl-d-aspartate (NMDA) glutaminergic receptor antagonist, demonstrate rapid but transient (days-to-weeks) effects in severe depression (FDA-approved) and suicidal ideation, and some evidence for social and general anxiety disorders, attributable to glutamate neuromodulation, increased prefrontal synaptic remodeling, neural plasticity and altered functional connectivity.[54,55]
- Also less robust, but positive and short-lived effects for SUD, e.g., reduced cravings, decreased self-administration of illicit drugs, and higher abstinence rates in 14 studies in AUD, OUD and cocaine use disorder[55]

[54]Iqbal MN et al., Focus (Am Psychiatr Publ). 2019 Apr;17(2):88-97. [55]Walsh Z et al., BJPsych Open. 2021 Dec 23;8(1):e19.

Ketamine for Mood, Anxiety, and SUD?

- Ketamine 0.4-0.5 mg/kg infused intravenously over 40–60 min. is most common with superior dose control and bioavailability, but oral, intramuscular, sublingual and intranasal (e.g., esketamine or racemic ketamine) administration have advantages for typical need for repeated dosing and patient comfort. Higher dose ranges (0.71-2mg/kg) have been used in SUD studies with IV infusions
- CBT may enhance and prolong antidepressant effects[56], but psychotherapy is not in the FDA indication
- No published RCT as of yet for treating both mood or anxiety disorder, and SUD

[56]Wilkinson S. et al., Psychother Psychosom 2017; 86(3): 162–7.

Final Takeaways

- Mood disorders can be reliably diagnosed and should be treated with evidence-based medications that take the co-occurring SUD(s) into account
- Specific cognitive behavioral therapy approaches with evidence of efficacy have been developed for each of the anxiety disorders and are typically confluent with similar approaches to SUD recovery.
- Most co-occurring anxiety disorders should be treated with the medications that are evidence-based to treat them in the absence of SUD.
- Although effective for short-term anxiety relief, benzodiazepines should generally be avoided as they have high liability for non-medical use among patients with SUD
- Look for opportunities to use medications that may have some clinical impact on more than one disorder (e.g., gabapentin in AUD and GAD)

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