Management of Substance-Induced Psychosis, Depression, and Anxiety

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Disclosure

Speaker: Darren Holub, MD

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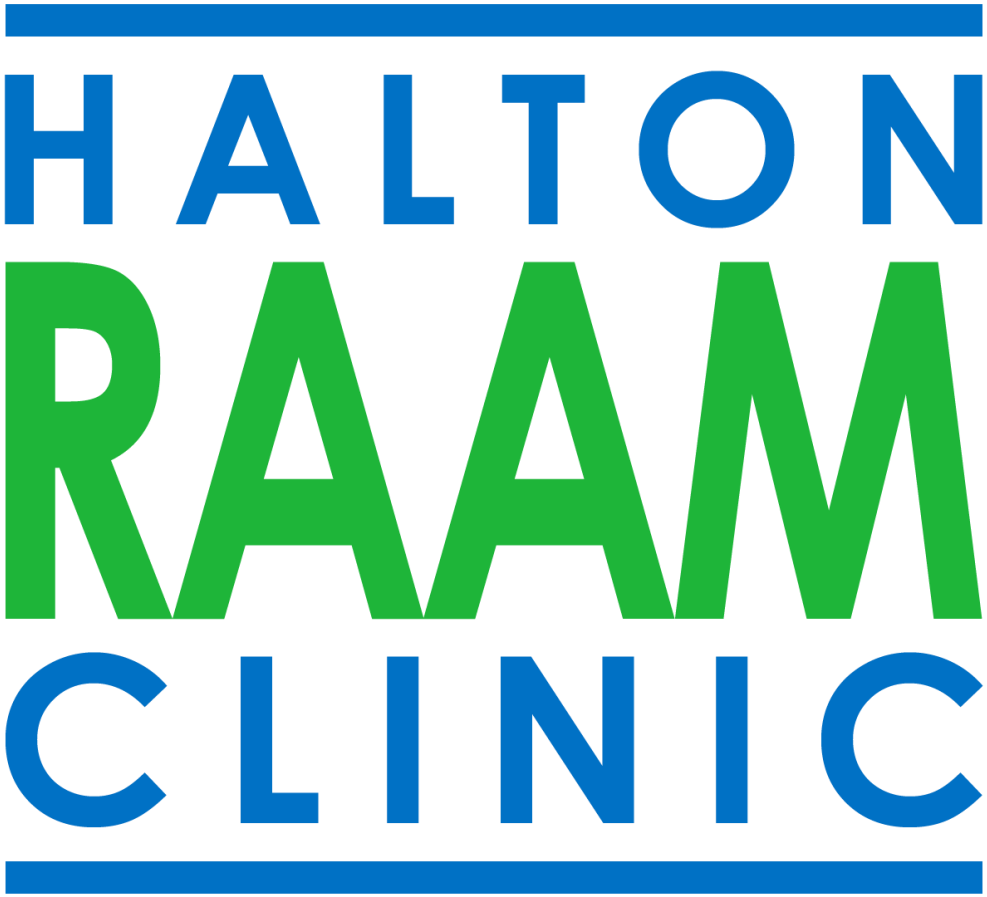

Oakville & Milton (January 2019)

Georgetown (April 2019)


DOVE
MEDICAL SERVICES

Previously Lead Psychiatrist – Concurrent Disorders Program
Presently Courtesy Staff, Department of Psychiatry

No formal affiliation with the Halton RAAM Clinic

Learning Objectives

By the end of this session, participants will be able to:

1. Understand principles in differentiating between substance-induced disorders and independent mental disorders;

2. Recognize diagnostic challenges and diagnostic approaches involved in clarifying these complex and frequently nebulous clinical presentations;

3. Identify therapeutic strategies (including pharmacological) which could be considered in the practical management of patients with select presentations.

DSM-5 Layout & Criteria

Substance-Related Disorders (DSM-5)

Divided into two groups:

1. Substance Use Disorders (9/10 Classes of Drugs):

Alcohol	**Opioids**
Caffeine	**Sedatives, hypnotics, or anxiolytics**
Cannabis	**Stimulants**
Hallucinogens (PCP & Other)	**Tobacco**
Inhalants	**Other (or unknown)**

2. Substance-Induced Disorders:

- Substance Intoxication and Withdrawal
- Substance/Medication-Induced Mental Disorders

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Substance-Induced Disorders (DSM-5)

Divided into two groups:

1. Substance Intoxication and Withdrawal

2. Substance/Medication-Induced Mental Disorders (9):

   - Psychotic Disorders
   - Bipolar Disorders
   - Depressive Disorders
   - Anxiety Disorders
   - Obsessive-Compulsive and Related Disorders
   - Sleep Disorders
   - Sexual Dysfunctions
   - Delirium
   - Neuro-Cognitive Disorders

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Substance-Related Disorders in DSM-5

TABLE 1 Diagnoses associated with substance class

	Psychotic disorders	Bipolar disorders	Depressive disorders	Anxiety disorders	Obsessive-compulsive and related disorders	Sleep disorders	Sexual dysfunctions	Delirium	Neurocognitive disorders	Substance use disorders	Substance intoxication	Substance withdrawal
Alcohol	I/W	I/W	I/W	I/W		I/W	I/W	I/W	I/W/P	X	X	X
Caffeine				I		I/W					X	X
Cannabis	I			I		I/W		I		X	X	X
Hallucinogens												
Phencyclidine	I	I	I	I				I		X	X	
Other hallucinogens	I*	I	I	I				I		X	X	
Inhalants	I		I	I				I	I/P	X	X	
Opioids			I/W	W		I/W	I/W	I/W		X	X	X
Sedatives, hypnotics, or anxiolytics	I/W	I/W	I/W	W		I/W	I/W	I/W	I/W/P	X	X	X
Stimulants**	I	I/W	I/W	I/W	I/W	I/W	I	I		X	X	X
Tobacco						W				X		X
Other (or unknown)	I/W	I/W	I/W	I/W	I/W	I/W	I/W	I/W	I/W/P	X	X	X

Note. X = The category is recognized in DSM-5.
I = The specifier "with onset during intoxication" may be noted for the category.
W = The specifier "with onset during withdrawal" may be noted for the category.
I/W = Either "with onset during intoxication" or "with onset during withdrawal" may be noted for the category.
P = The disorder is persisting.
*Also hallucinogen persisting perception disorder (flashbacks).
**Includes amphetamine-type substances, cocaine, and other or unspecified stimulants.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013. Page 482.

Substance-Related Disorders in DSM-5

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Alcohol	I/W	I/W	I/W	I/W		I/W	I/W	I/W	I/W/P	X	X	X
Caffeine				I		I/W					X	X
Cannabis	I			I		I/W		I		X	X	X
Hallucinogens												
Phencyclidine	I	I	I	I				I		X	X	
Other hallucinogens	I*	I	I	I				I		X	X	
Inhalants	I		I	I				I	I/P	X	X	
Opioids			I/W	W		I/W	I/W	I/W		X	X	X
Sedatives, hypnotics, or anxiolytics	I/W	I/W	I/W	W		I/W	I/W	I/W	I/W/P	X	X	X
Stimulants**	I	I/W	I/W	I/W	I/W	I/W	I	I		X	X	X
Tobacco						W				X		X
Other (or unknown)	I/W	I/W	I/W	I/W	I/W	I/W	I/W	I/W	I/W/P	X	X	X

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Substance-Induced Disorders (DSM-5)

General Criteria:

A. Clinically-significant symptomatic presentation.
- **Psychotic Disorder:**
  - Delusions and/or Hallucinations
- **Depressive Disorder:**
  - Predominates the clinical picture
  - Depressed mood,
    or markedly diminished pleasure/interest in all, or almost all, activities
- **Anxiety Disorder:**
  - Panic attacks or anxiety predominate the clinical picture

B. Evidence from the history of both:
1. Symptoms develop during, or soon after, substance exposure.
2. Substance is capable of producing symptoms in A.

Substance-Induced Disorders (DSM-5)

General Criteria:

C. Not an independent mental disorder. Evidence of an independent mental disorder *could* include:

- Symptoms **precede** the onset of substance use
- Symptoms **persist** for a substantial period of time (*e.g. about 1 month*) after cessation of acute withdrawal or intoxication
- Other evidence suggesting an independent disorder (e.g. **history of recurrent non-substance-related episodes**)

D. Not exclusively during a delirium.

E. Clinically significant distress or impairment.

Diagnostic Challenges

Challenges in Making a Diagnosis?

C. Not an independent mental disorder. Evidence of an independent mental disorder *could* include:

- Symptoms **precede** the onset of substance use
- Symptoms **persist** for a substantial period of time (*e.g. about 1 month*) after cessation of acute withdrawal or intoxication
- Other evidence suggesting an independent disorder (e.g. **history of recurrent non-substance-related episodes**)

Interactive Activity:

Briefly, with some people around you, discuss some of the real-world challenges associated with making a “clear-cut” mental health diagnosis in our patient population, or cases that don’t fit in the box, despite the guidance provided by DSM-5.

Contributors to Diagnostic Challenges

1. Difficulties or bias with recall, timelines.
2. Lack of collateral information.
3. Absence of previous documentation.
4. Distortions or denial.
5. Unclear if patient is still using substances or not.
6. Secondary gain including financial compensation, legal issues, avoidance of responsibilities, etc.
7. Malingering.
8. Stigma of addiction > mental health diagnoses.

Contributors to Diagnostic Challenges

9. Symptom duration >1 month with certain substances.
10. Subacute (aka post-acute or protracted) withdrawal syndromes (e.g. alcohol, BZDs, stimulants) are not yet described in DSM-5.
11. Behavioural checklist of DSM vs. a phenomenological description of the Disease of Addiction itself (ASAM/CSAM Definition of Addiction).
12. Adjustment factors – consequences, stressors, losses.
13. Inherent poor inter-rater reliability for many diagnoses.

Diagnostic Nihilism?

Article

DSM-5 Field Trials in the United States and Canada, Part II: Test-Retest Reliability of Selected Categorical Diagnoses

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Diana E. Clarke, Ph.D., M.Sc.

Helena C. Kraemer, Ph.D.

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Emily A. Kuhl, Ph.D.

David J. Kupfer, M.D.

Objective: The DSM-5 Field Trials were designed to obtain precise (standard error <0.1) estimates of the intraclass kappa as a measure of the degree to which two clinicians could independently agree on the presence or absence of selected DSM-5 diagnoses when the same patient was interviewed on separate occasions, in clinical settings, and evaluated with usual clinical interview methods.

Method: Eleven academic centers in the United States and Canada were selected, and each was assigned several target diagnoses frequently treated in that setting. Consecutive patients visiting a site during the study were screened and stratified on the basis of DSM-IV diagnoses or symptomatic presentations. Patients were randomly assigned to two clinicians for a diagnostic interview; clinicians were blind to any previous diagnosis. All data were entered directly via an Internet-based software system to a secure central server. Detailed research design and statistical methods are presented in an accompanying article.

Results: There were a total of 15 adult and eight child/adolescent diagnoses for which adequate sample sizes were obtained to report adequately precise estimates of the intraclass kappa. Overall, five diagnoses were in the very good range (kappa=0.60–0.79), nine in the good range (kappa=0.40–0.59), six in the questionable range (kappa=0.20–0.39), and three in the unacceptable range (kappa values <0.20). Eight diagnoses had insufficient sample sizes to generate precise kappa estimates at any site.

Conclusions: Most diagnoses adequately tested had good to very good reliability with these representative clinical populations assessed with usual clinical interview methods. Some diagnoses that were revised to encompass a broader spectrum of symptom expression or had a more dimensional approach tested in the good to very good range.

(Am J Psychiatry 2013; 170:59–70)

Diagnostic Nihilism?

Results: There were a total of 15 adult and eight child/adolescent diagnoses for which adequate sample sizes were obtained to report adequately precise estimates of the intraclass kappa. Overall, **five diagnoses were in the very good range** (kappa=0.60–0.79), **nine in the good range** (kappa=0.40–0.59), **six in the questionable range** (kappa=0.20–0.39), and **three in the unacceptable range** (kappa values <0.20). Eight diagnoses had insufficient sample sizes to generate precise kappa estimates at any site.

DSM-5 Diagnosis	Kappa Coefficient	Interpretation
PTSD	0.67	Very good
Schizophrenia	0.46	Good
Alcohol use disorder	0.40	Good
Major depressive disorder	0.28	Questionable
Generalized anxiety disorder	0.20	Questionable
Mixed anxiety-depressive disorder	-0.004	Unacceptable

Regier DA et al. Am J Psychiatry 2013; 170: 59-70.

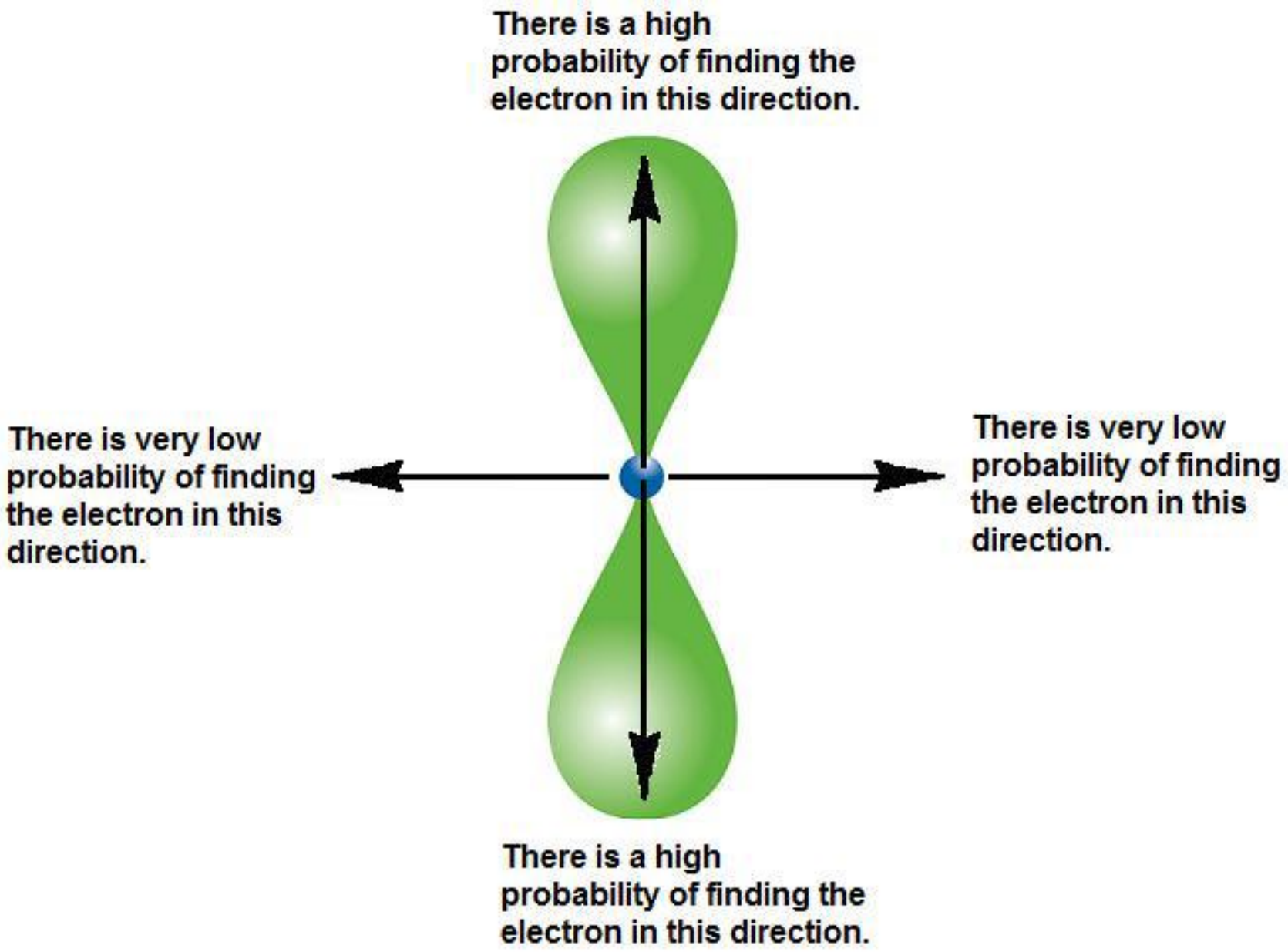
Diagnostic Nihilism?

"Psychiatrists have a hard time agreeing on who does and does not have major depressive disorder: the field trials for DSM-5 demonstrated an intraclass kappa of 0.28. This represents a value of 'minimal agreement', and means that highly trained specialist psychiatrists under study conditions were only able to agree that a patient has depression between 4 and 15% of the time."

Lieblich SM et al. BJPsych Open (2015) 1, e5-e7.

$$1 + 1 = 2$$


1 + 1 ≈ 2?



https://upload.wikimedia.org/wikipedia/commons/b/bd/P_orbital_electron_density.png

Diagnostic Approaches & Strategies

Interactive Activity:

Briefly, with some people around you, discuss some practical, real-world strategies to assist in making an accurate diagnosis in our patient population, despite the inherent challenges in doing so.

Strategies to Assist in Diagnosis

1. Careful history, including childhood history.
2. Timelines of use and symptoms, periods of abstinence.
3. Analysis of response to prior treatments.
4. Longitudinal approach.
5. Obtain collateral information.
6. Clarify family history.
7. Locate prior documentation (e.g. family, physicians, medical records, ConnectingOntario ClinicalViewer).
8. Urine drug testing (POCT, GCMS).
9. Use of a breathalyzer.

Strategies to Assist in Diagnosis

10. Understand the phenomenology of Addiction
    - ASAM/CSAM Definition of Addiction
    - “Addiction is Addiction” by Dr. Raju Hajela
11. Psychoeducation and de-stigmatization.
12. Understanding that a range of negative emotions (including guilt, shame, sadness, fear, anger) related to the consequences of Addiction is common.
13. Understanding persisting and subacute (post-acute/protracted) withdrawal syndromes.
14. Recognizing the challenges including poor inter-rater reliability for many diagnoses.
15. Collaboration with ‘addiction-informed’ psychiatry.
16. Acceptance-based strategies (e.g. of uncertainty).

Practical Management Approaches for Select Clinical Presentations

(Substance-Induced & Concurrent Disorders)

Select Clinical Presentations

1. Alcohol Use Disorder + Depressive Symptoms
2. Substance Use Disorders + Anxiety / PTSD
3. Methamphetamine-Induced Psychotic Disorder

General Treatment Principles

- Aside from emergency situations (e.g. suicidality, toxic psychosis), the classic approach has been to treat the addiction first (i.e. abstain), and observe what happens to the psychiatric symptoms
- Not always easy, based on the patient's stage of change (if simple, it probably wasn't addiction)
- Integrated treatment of concurrent disorders is the optimal approach
- Importance of psychosocial supports for addiction (not always desired) & MH supports if available too
- Psychoeducation & motivational enhancement therapy can go a long way
- Set realistic expectations

1. Alcohol Use Disorder (AUD) & Depressive Symptoms

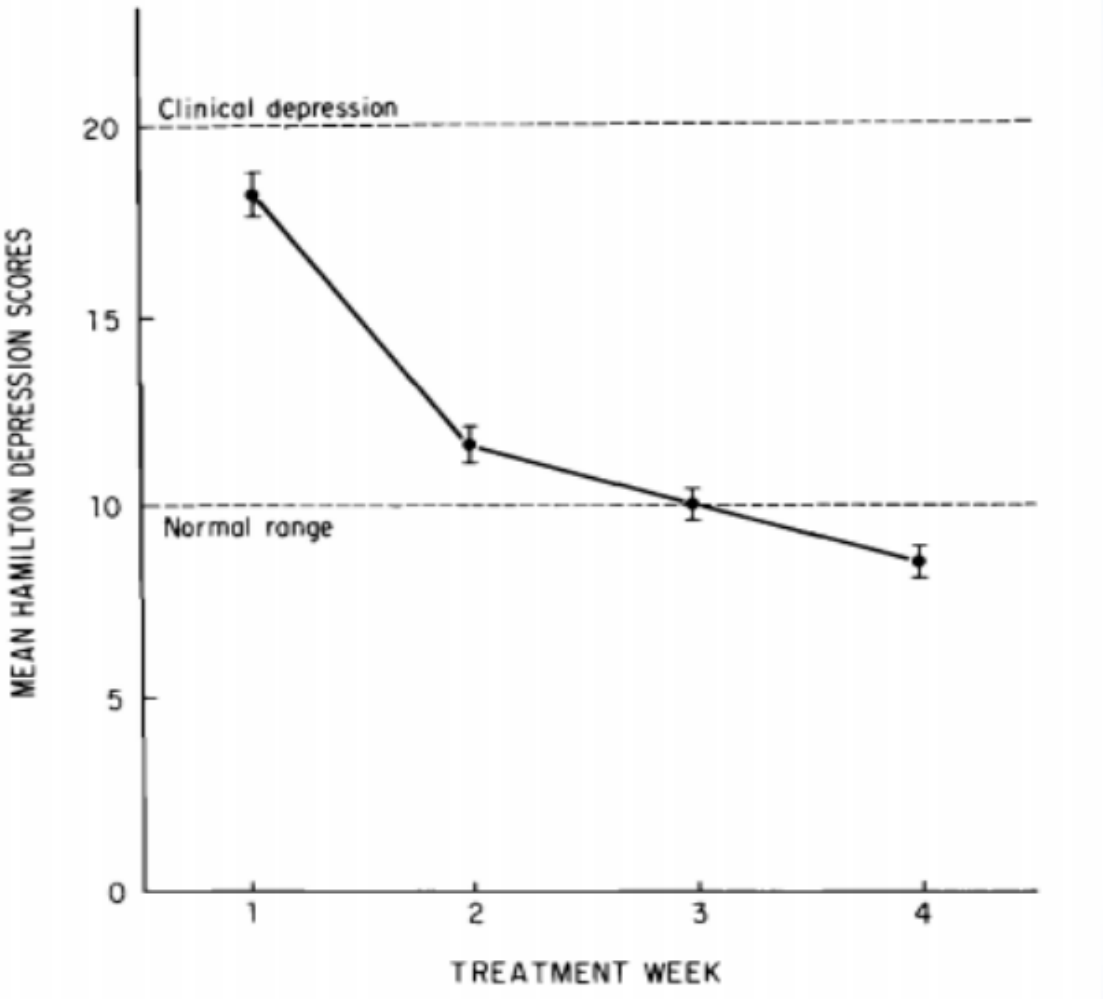
AUD & Depressive Symptoms

- Brown & Schuckit (1988) studied 191 males with AUD (no pre-existing major psychiatric diagnoses) throughout a 4-week residential treatment program
- At intake, 42% had clinically significant depressive symptoms (HAM-D ≥ 20)
- By week 4, only 6% remained clinically depressed
- Depressive sxs abated quickly with the largest reduction by week 2
- Study suggested that antidepressant medication should be deferred until after 4 weeks of abstinence.

Brown SA & Schuckit MA. J Stud Alcohol. 1988 Sep;49(5):412-7.

AUD & Depressive Symptoms

FIGURE 1. Hamilton depression scores of male primary alcoholics during four weeks of hospitalization.



Brown SA & Schuckit MA. J Stud Alcohol. 1988 Sep;49(5):412-7.

AUD & Depressive Symptoms

- Kahler et al (2002) examined Substance-Induced Depressive Disorder (SIDD) & independent MDD in 166 treatment-seeking AUD patients with elevated depressive symptoms
- 122 met DSM-IV criteria for MDD
- Of these 122 subjects:
  - 61.6% had “pure” SIDD
  - 15.2% had independent MDD
  - 23.2% had a diagnosis of SIDD with a history of independent MDD
- Important point: MDD syndrome with a history of independent MDD could still be SIDD

Kahler CW et al. J Stud Alcohol. 2002 May;63(3):363-71.

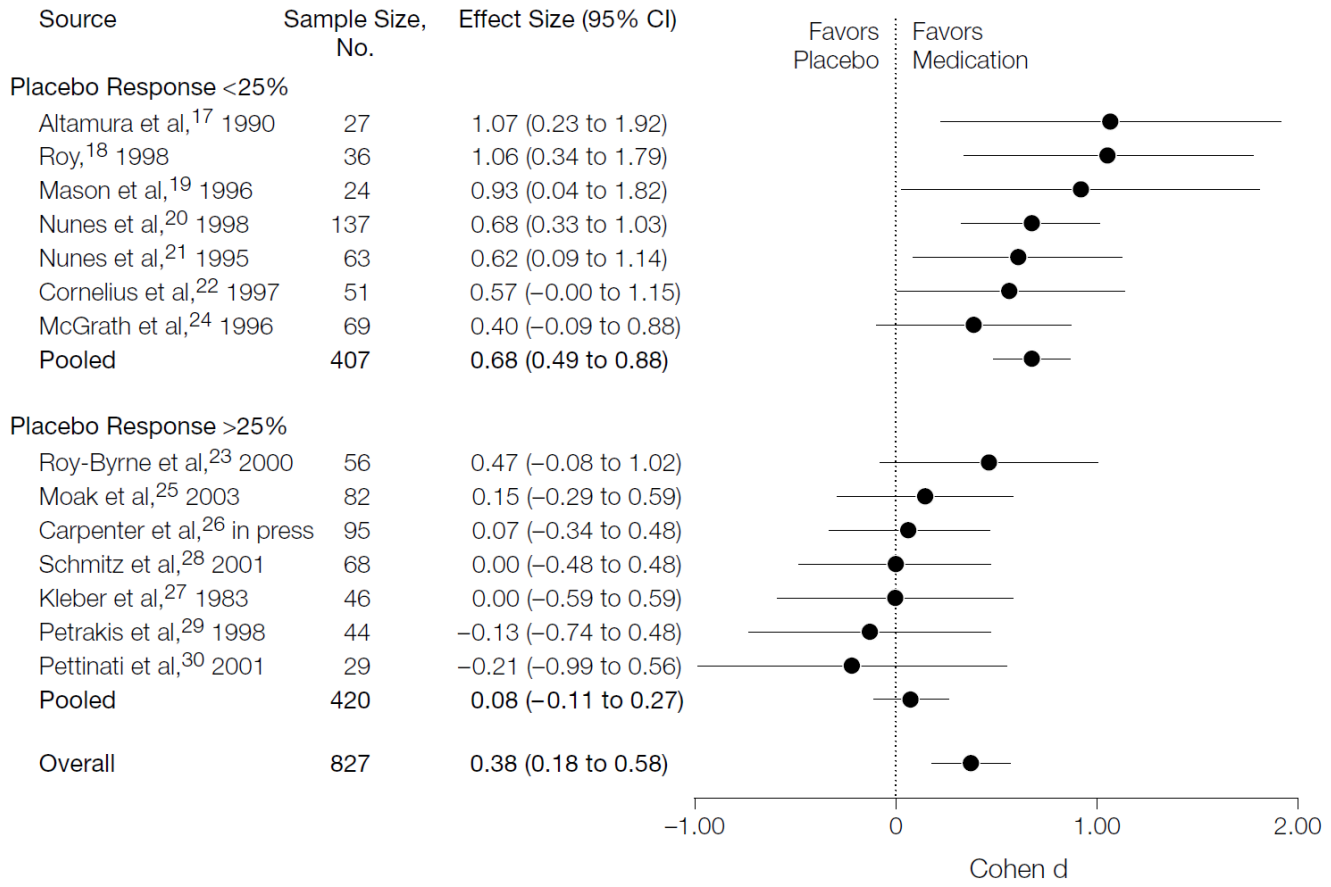
AUD & Depressive Symptoms

- Nunes & Levin (2004) conducted a meta-analysis of 14 studies
- Patients with any SUD plus an independent unipolar depressive disorder
- Found that antidepressant (AD) medication exerted a modest beneficial effect for patients with combined depressive and SUDs
- ADs not a stand-alone treatment, and concurrent therapy targeted at addiction is indicated
- Care should be exercised in making the diagnosis (observe depression to persist in brief abstinence, or by screening out SIDD)

Nunes EV & Levin FR. JAMA. 2004 Apr;291(15):1887-96.

AUD & Depressive Symptoms

Figure 1. Effect of Antidepressant Medication on Outcome of Depression (Hamilton Depression Scale)

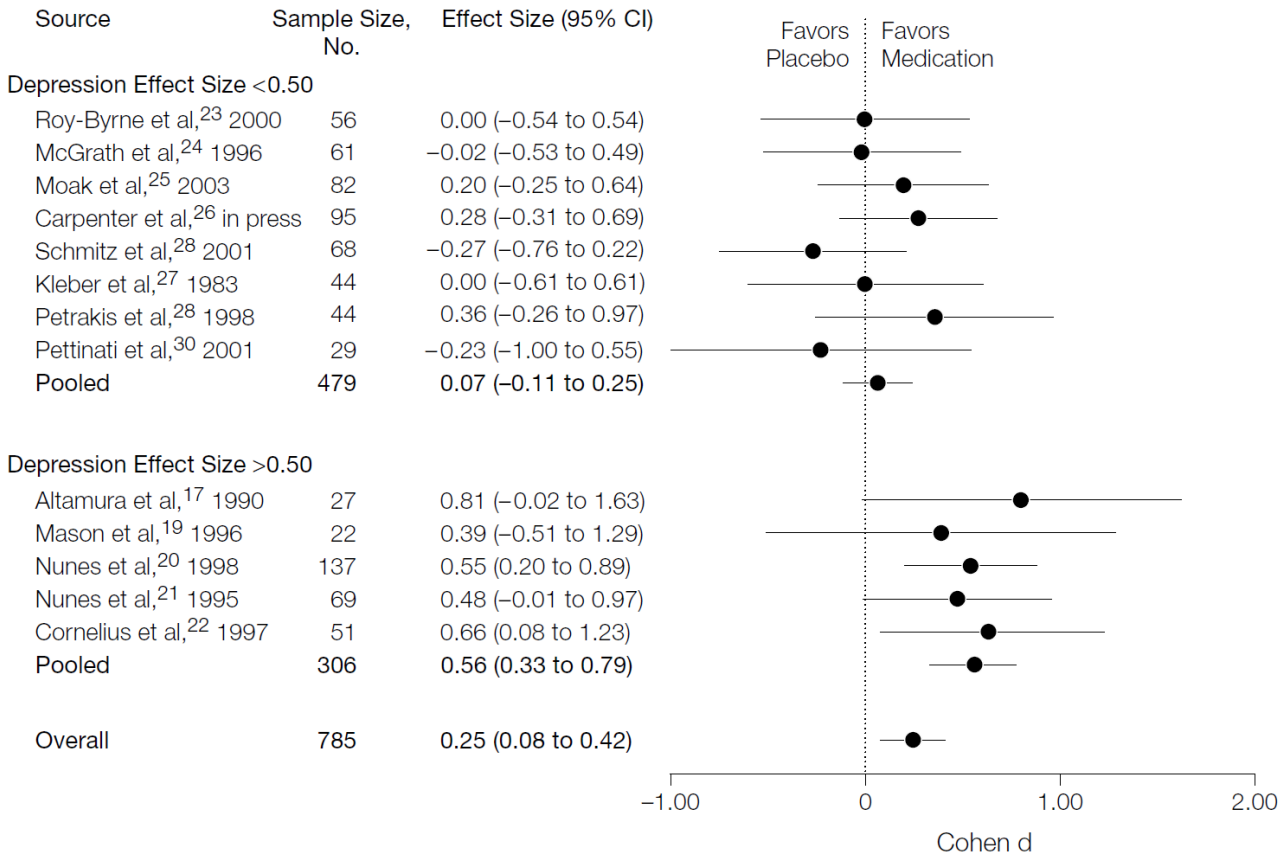


Effect sizes are Cohen d, error bars represent the 95% confidence intervals (CIs). Studies are stratified into groups with low (<25%) vs high (>25%) categories of placebo response, measured as the percentage decrease in the Hamilton Depression Scale between baseline and end-of-study in the placebo group.

Nunes EV & Levin FR. JAMA. 2004 Apr;291(15):1887-96.

AUD & Depressive Symptoms

Figure 2. Effect of Antidepressant Medication on Outcome of Substance Use*



Effect sizes are Cohen d on outcomes reflecting quantity of substance use (mainly by self-report). Error bars represent the 95% confidence intervals (CIs). Studies are stratified into 2 groups based on the size of the effect of medication on depression outcome (Cohen d for the Hamilton Depression Scale) effect size lower than 0.50 (low); and effect size greater than 0.50 (high). The study by Roy[18] did not have the data necessary for analysis for this figure.

Nunes EV & Levin FR. JAMA. 2004 Apr;291(15):1887-96.

AUD & Depressive Symptoms

A Double Blind, Placebo-Controlled Trial that Combines Sertraline and Naltrexone for Treating Co-Occurring Depression and Alcohol Dependence

- 170 patients with AUD and a depressive disorder
- Sertraline 200 mg/d, naltrexone 100 mg/d, combined, or placebo
- Combined treatment was superior to either sertraline or naltrexone alone, regarding both drinking and mood outcomes

Pettinati HM et al. Am J Psychiatry. 2010 June;167(6):668-675.

AUD & Depressive Symptoms

AUD Typology (Babor, 1992)

Domain	Type A (Lower Risk)	Type B (Higher Risk)
Age of Onset	**Later onset (> 25 yo)**	**Early onset (≤ 25 yo)**
Heritability	Low	High
Severity	Low	High
Chronicity, Consequences	Low	High
Psychopathology	Low	High
Depressive Symptoms	Low	High

Babor TF et al. Arch Gen Psychiatry. 1992 Aug;49(8):599-608.

AUD & Depressive Symptoms

In patients not selected for depression, can AUD Subtype affect drinking response to SSRI treatment?

- Fluoxetine treatment seems to reduce the beneficial effects of CBT in type B alcoholics.
  - Kranzler HR et al. Alcohol Clin Exp Res. 1996;20(9):1534-41.

- Sertraline treatment for alcohol dependence: interactive effects of medication and alcoholic subtype.
  - Pettinati HM et al. Alcohol Clin Exp Res. 2000;24(7):1041-9.

- Efficacy of fluvoxamine in preventing relapse in alcohol dependence: a one-year, double-blind, placebo-controlled multicentre study with analysis by typology.
  - Chick J et al. Drug Alcohol Depend. 2004;74(1)61-70.

AUD & Depressive Symptoms

Findings from AUD subtype studies:

- Fluoxetine (Kranzler 1996):
  - Type A – no effect
  - Type B – poorer drinking-related outcomes than placebo
  - “In the absence of a comorbid mood or anxiety disorder, fluoxetine should not be used to maintain abstinence or reduce drinking in type B subjects.”
- Sertraline (Pettinati 2000):
  - Type A subjects had less drinking days and longer abstinence
  - Type B subjects did not
- Fluvoxamine (Chick 2004):
  - Abstinence and relapse both worse in treatment vs placebo
  - Type B did worse than Type A
  - “Impulsivity in early-onset patients may be accentuated by serotonin enhancement.”


Let´s talk
about it!

AUD & Depressive Symptoms

American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder (2018):

"APA recommends that antidepressant medications not be used for treatment of alcohol use disorder unless there is evidence of a co-occurring disorder for which an antidepressant is an indicated treatment."

AUD & Depressive Symptoms

Choice of Antidepressant?

- Meta-analysis showed more favourable results for TCAs, however older trials and concerns of adverse effects (cardiac/prolonged QTc, seizures, overdose risk)
- High placebo response rates often seen in SSRI trials, studies with lower placebo response more likely to show SSRIs as effective
- Limited data regarding SNRIs, mirtazapine
- Bupropion – lowers seizure threshold, increased risk with alcohol use and particularly with alcohol withdrawal
- SSRIs may be a reasonable first choice due to safety profile and tolerability if an independent depressive disorder is present; however monitor drinking as always, with particular vigilance in Type B patients

2. Substance Use Disorders
&
Anxiety / PTSD

SUDs & Anxiety / PTSD

Anxiety/nervousness is a common symptom seen across a variety of substances in intoxication and/or withdrawal:

- Alcohol (withdrawal)
- Caffeine (intoxication)
- Cannabis (intoxication and withdrawal)
- Hallucinogens (intoxication)
- Opioids (not in DSM criteria but often seen in withdrawal)
- Sedative/Hypnotic/Anxiolytics (withdrawal)
- Stimulants (intoxication)
- Tobacco (withdrawal)

The “dysfunctional emotional state” of addiction, and associated stress (maintenance, negative consequences) can also contribute to perceived heightened anxiety.

SUDs & Anxiety / PTSD

Select Anxiety Disorders in DSM-5:

- Specific Phobia
- Social Anxiety Disorder
- Panic Disorder
- Agoraphobia
- Generalized Anxiety Disorder
- Substance-Induced Anxiety Disorder

Trauma- and Stressor-Related Disorders (DSM-5):

- Posttraumatic Stress Disorder (PTSD)
- Note: there is no diagnosis of 'Substance-Induced Trauma- and Stressor-Related Disorder' in DSM-5

SUDs & Anxiety / PTSD

Making The Diagnosis:

Which of these diagnoses would be more easily identifiable as primary disorders despite an active SUD?

- Specific Phobia
- Social Anxiety Disorder
- Panic Disorder
- Agoraphobia
- Generalized Anxiety Disorder
- Substance-Induced Anxiety Disorder
- Posttraumatic Stress Disorder (PTSD)

SUDs & Anxiety / PTSD

Making The Diagnosis:

Which of these diagnoses would be more easily identifiable as primary disorders despite an active SUD?

- **Specific Phobia**
- **Social Anxiety Disorder**
- Panic Disorder
- **Agoraphobia**
- Generalized Anxiety Disorder
- Substance-Induced Anxiety Disorder
- **Posttraumatic Stress Disorder (PTSD)**

SUDs & Anxiety / PTSD

Making The Diagnosis:

These conditions, due to their unique phenomenology, are less easily confused with a possible Substance-Induced Anxiety Disorder though a careful history (including childhood hx):

- **Specific Phobia**
- **Social Anxiety Disorder**
- **Agoraphobia**
- **Posttraumatic Stress Disorder (PTSD)**

Psychosocial treatments (often CBT or Exposure Therapy), +/- evidence-based medications, are options. Integrated treatment with SUD treatments leads to better outcomes.

SUDs & Anxiety / PTSD

Making The Diagnosis: Panic Disorder

- DSM-5 criteria for Panic Disorder states that the disturbance cannot be attributable to the direct physiological effects of a substance
- "Intoxication with CNS stimulants (e.g. cocaine, amphetamines, caffeine) or cannabis, and w/d from CNS depressants (e.g. alcohol, barbiturates) can precipitate a panic attack" → not counted towards the diagnosis
- "If panic attacks continue to occur… e.g. long after the effects of intoxication or w/d have ended… a diagnosis of panic disorder should be considered"
- Detailed history to determine if the patient had panic attacks prior to excessive substance use → if so, a panic disorder diagnosis can be considered in addition to the SUD

SUDs & Anxiety / PTSD

Making The Diagnosis: Generalized Anxiety Disorder (GAD)

- DSM-5 criteria for GAD states that the disturbance cannot be attributable to the direct physiological effects of a substance
- As noted, anxiety symptoms are common among many substances, either in intoxication or in withdrawal
- Similar to MDD vs SIDD, look for evidence of GAD which:
  - Precedes the development of an SUD
  - Is present in periods of abstinence
  - Persists despite a significant period of abstinence
- The GAD diagnosis is known to have questionable inter-rater reliability based on DSM-5 field trials and the presence of an active SUD will complicate this further

Alcohol Use Disorder
&
Anxiety

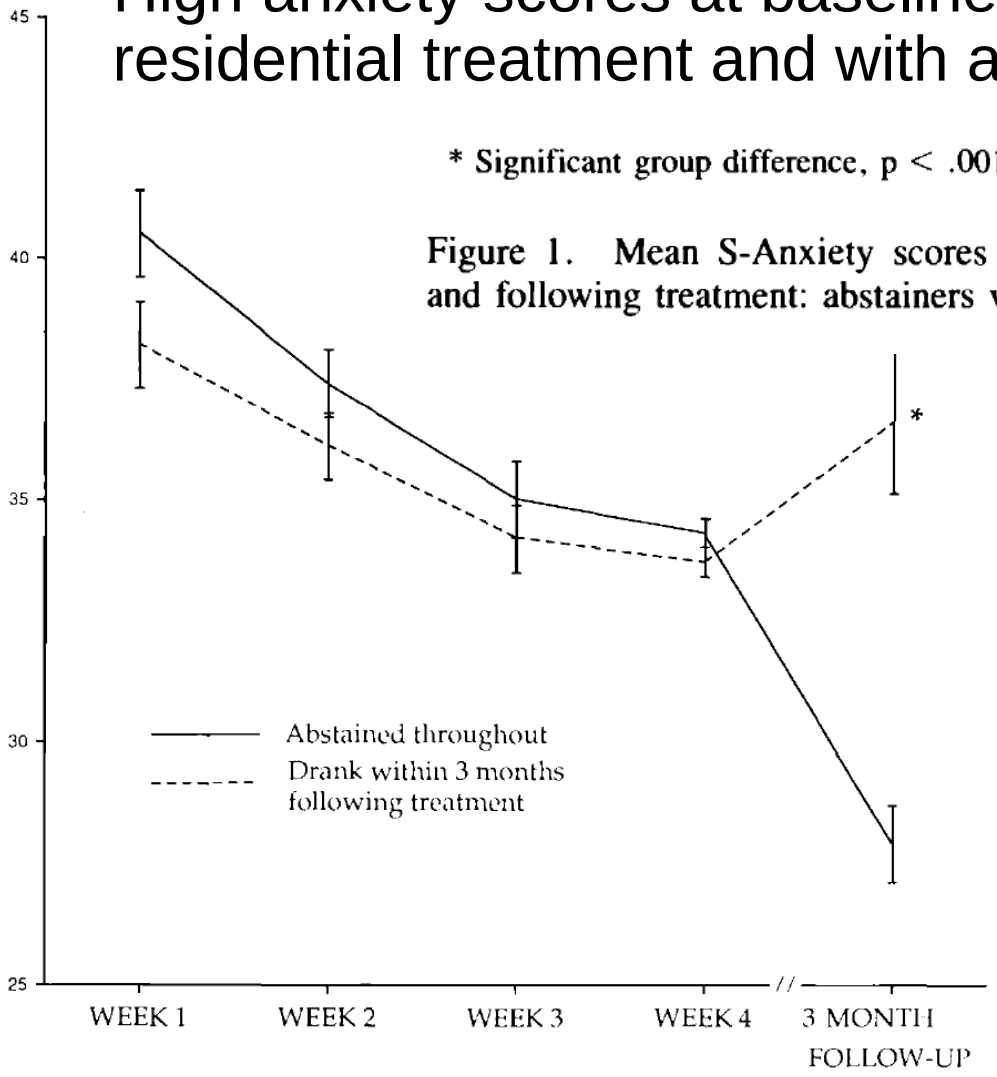
Alcohol Use Disorder & Anxiety

- Anxiety symptoms are very common in AUD patients
- Panic attacks experienced by 80% of men in withdrawal
- 50-67% of AUD subjects scored high on anxiety measures which resembled symptoms of GAD and Social Anxiety Disorder
- High comorbidity reported previously likely reflects a combination of primary anxiety disorders (rate equal to or slightly higher than the general population), along with temporary, but often severe, substance-induced anxiety symptoms

Alcohol dependence and anxiety disorders: what is the relationship? Shuckit MA & Hesselbrock V. Am J Psychiatry. 1994 Dec;151(12):1723-34.

Alcohol Use Disorder & Anxiety

- High anxiety scores at baseline, which decreased through residential treatment and with abstinence post discharge.



Changes in anxiety among abstinent male alcoholics. Brown SA et al. J Stud Alcohol. 1991 Jan;52(1):55-61.

Alcohol Use Disorder & Anxiety

Alcohol Use Disorder with Anxiety: Gabapentin

- Blocks alpha 2 delta subunit of voltage-gated calcium channels (VGCC) on presynaptic sites, indirectly modulating GABA neurotransmission
- Gabapentin is approved as adjunctive therapy for the management of epilepsy (anticonvulsant)
- Used off-label for neuropathic/chronic pain
- Evidence for off-label use in the treatment of anxiety disorders and alcohol use disorder
- Potential for misuse or recreational use (e.g. euphoria combined with opioids, alcohol, BZDs); or to mitigate withdrawal symptoms (Smith et al, Addiction 2016)

Alcohol Use Disorder & Anxiety

Katzman *et al. BMC Psychiatry* 2014, **14**(Suppl 1):S1
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BMC Psychiatry

REVIEW Open Access

Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders

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Gabapentin:

- 2nd line for Social Anxiety Disorder; 3rd line for Panic Disorder
- 3rd line adjunctive for PTSD; (pregabalin 1st line for GAD)
- Dose range 300-3600 mg/day divided TID

Katzman et al. BMC Psychiatry 2014, 14(Suppl 1):S1

Alcohol Use Disorder & Anxiety

Alcohol Use Disorder: Gabapentin monotherapy

- DB-RCT, 150 patients with AUD
- Compared gabapentin (300 mg TID, 600 mg TID) & placebo
- Gabapentin, particularly the 1800 mg dose, was effective in treating AUD and relapse-related symptoms of insomnia, dysphoria, and cravings
- Well tolerated

Mason BJ et al. JAMA Intern Med. 2014 Jan;174(1):70-7.

Alcohol Use Disorder & Anxiety

Alcohol Use Disorder: Gabapentin monotherapy

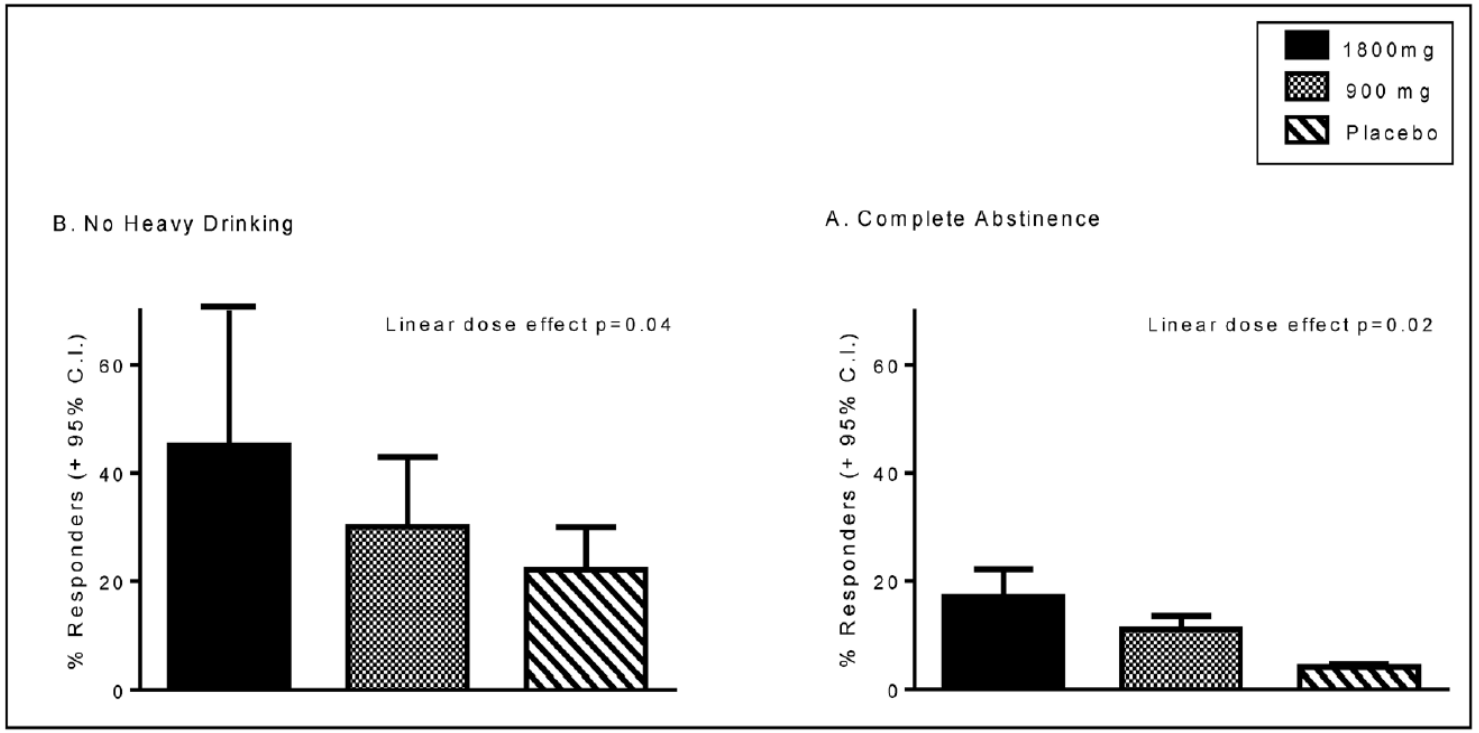


Figure 2.
Gabapentin effects on rates of no heavy drinking and complete abstinence during the 12-week study in the intention-to-treat population (N = 150).

Mason BJ et al. JAMA Intern Med. 2014 Jan;174(1):70-7.

Alcohol Use Disorder & Anxiety

Gabapentin + Naltrexone combination for the treatment of AUD:

- 150 patients with AUD
- 3 Groups:
  - Naltrexone 50 mg
  - Naltrexone 50 mg with Gabapentin 1200 mg
  - Double placebo
- NTX + GAB > NTX alone or PBO with:
  - Longer interval to heavy drinking
  - Fewer heavy drinking days
  - Fewer drinks per drinking day

Anton RE et al. Am J Psychiatry. 2011 Jul;168(7):709-17.

Alcohol Use Disorder & Anxiety

Alcohol Use Disorder with Anxiety: Gabapentin

- Off-label medications for AUD, if generic, may never be Health Canada approved
- Acamprosate back order
- ? Role in alcohol withdrawal and benzodiazepine tapering

3. Methamphetamine-Induced Psychotic Disorder

Schizophrenia Spectrum and Other Psychotic Disorders (DSM-5)

Key Features among Psychotic Disorders:

- Delusions
- Hallucinations
- Disorganized thinking / speech
- Grossly disorganized behavoiour, or abnormal motor behaviour (including catatonia)
- Negative symptoms (diminished emotional expression, avolition, alogia, anhedonia, associality)

Schizophrenia Spectrum and Other Psychotic Disorders (DSM-5)

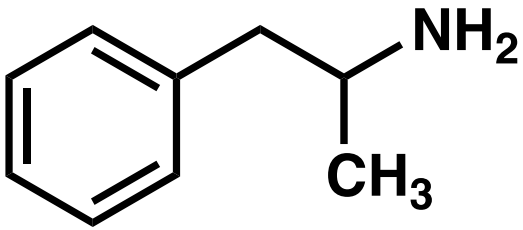
Primary Psychotic Disorders (all not attributable to the effects of a substance):

- Delusional Disorder
- Brief Psychotic Disorder
- Schizophreniform Disorder
- Schizophrenia
- Schizoaffective Disorder

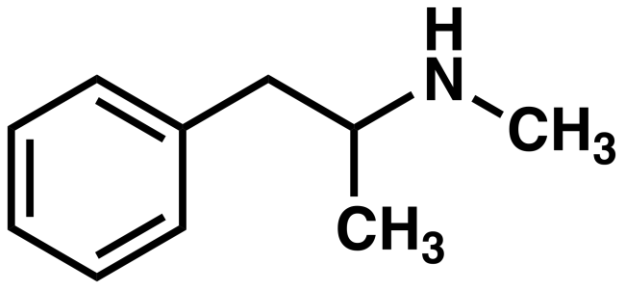
Versus

- Substance-Induced Psychotic Disorder

Amphetamines

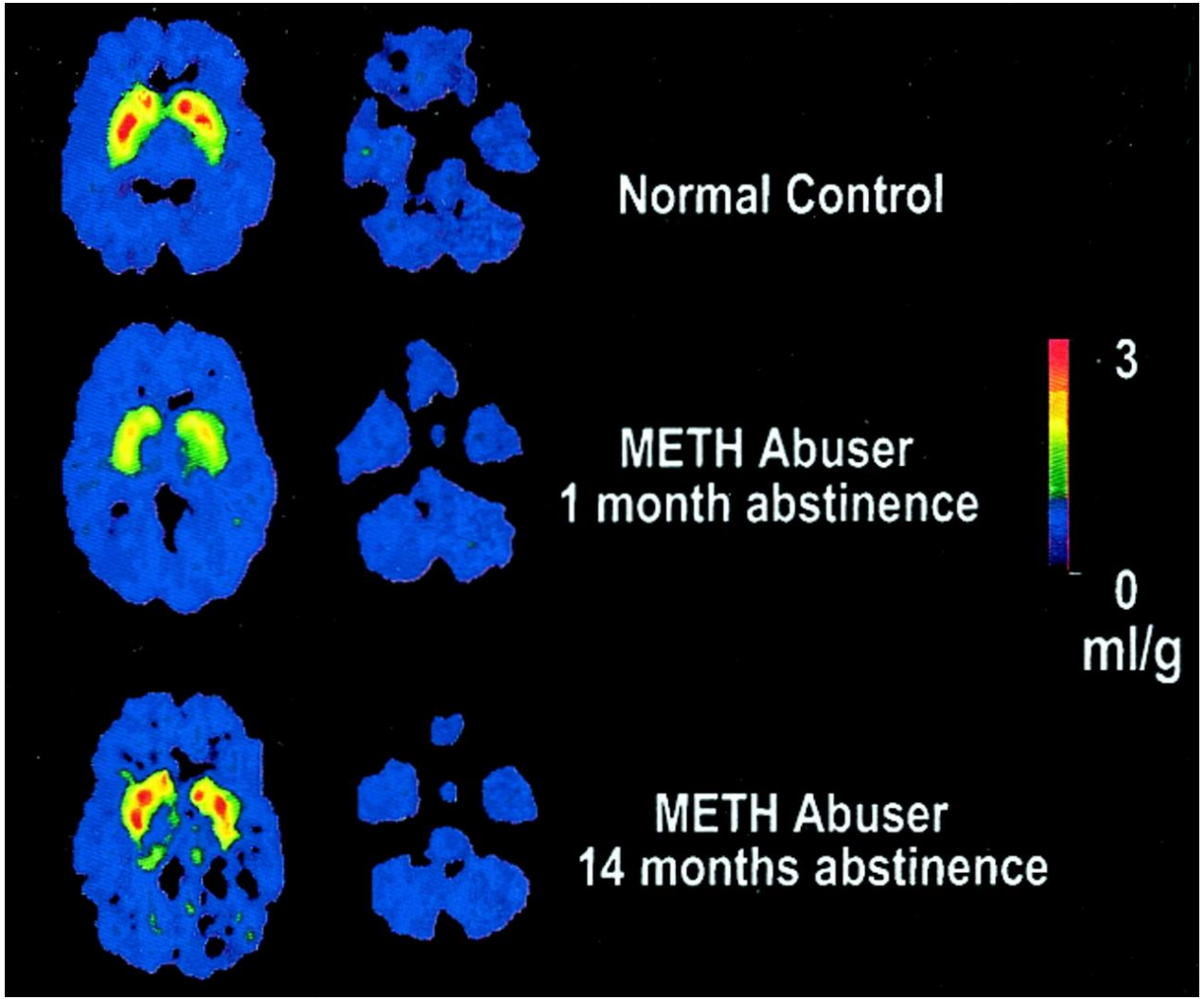


Amphetamine



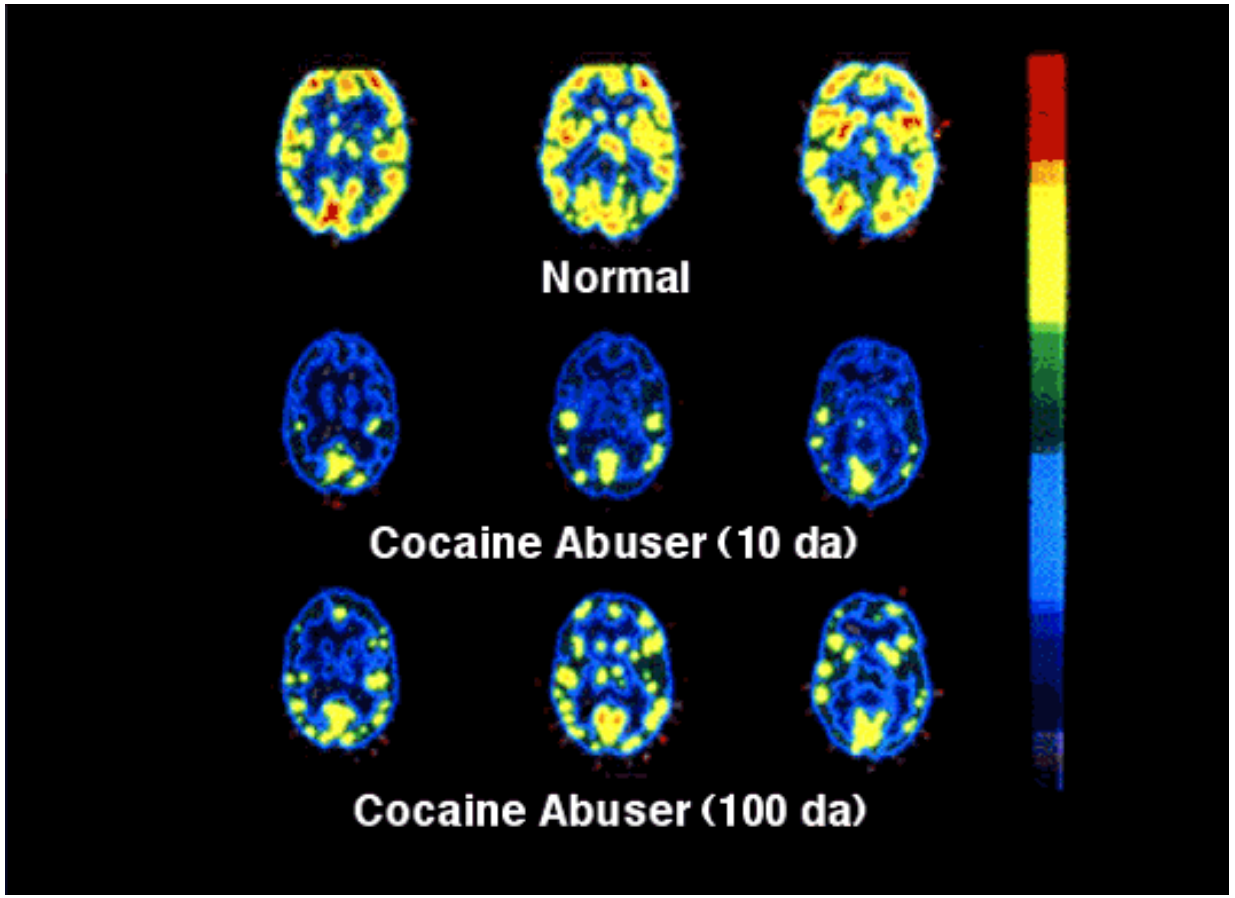
Methamphetamine (MA)

Brain images of DAT availability in a control and methamphetamine abuser (with abstinence) - Striatum (L), Cerebellum (R)



Volkow ND et al. J. Neurosci. 2001;21:9414-9418

Long-term frontal brain metabolic changes in cocaine abusers. Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism.



Volkow ND et al, Synapse 14:169-177, 1993.

Methamphetamine and Psychosis

MA-Induced Psychosis: Symptomatology

- Psychotic symptoms & syndromes are common in MA users, seen in up to 40%
- Mostly transient (e.g. often within a week), but in a subset psychosis can persist and recur – may be difficult to distinguish from a primary psychotic disorder
- Prominent psychotic symptoms include:
  - Auditory, visual, & tactile hallucinations
  - Paranoid/persecutory delusions
  - Ideas of reference
  - Often associated with hostility/violent behaviour
- Negative symptoms were mostly absent (< 20%)
- 25% of participants across the studies experienced persistent psychotic symptoms (> 1 month duration)

Glasner-Edwards S & Mooney LJ. CNS Drugs. 2014 Dec;28(12):1115-26.

Voce et al. Subst Use Misuse. 2019;54(4):549-559.

Methamphetamine and Psychosis

A systematic review of risk factors for methamphetamine-associated psychosis.

- The most consistent correlates of psychotic symptoms were:
  - Increased frequency of MA use
  - Severity of MA dependence
- Inconsistent evidence for other/sociodemographic factors

Arunogiri S et al. Aust N Z J Psychiatry. 2018 Jun;52(6):514-529.

Methamphetamine and Psychosis

Risk factors for MA Psychosis:

- Increased frequency of MA use
- Severity of MA dependence (if Dx MAUD is met: psychosis 3x more likely)
- Personal history of schizophrenia, schizoaffective disorder, and schizotypal personality
- Polydrug use
- Affective disorders
- Antisocial personality disorder
- Family psychiatric history
- Smoking shorter latency to onset versus injection use
- Sleep deprivation

Arunogiri S et al. Aust N Z J Psychiatry. 2018 Jun;52(6):514-529.
Glasner-Edwards S & Mooney LJ. CNS Drugs. 2014 Dec;28(12):1115-26.

Methamphetamine and Psychosis

Progression to a Primary Psychotic Disorder:

- Varying estimates, between 30-38% of patients with a previous amphetamine or methamphetamine-induced psychotic disorder, proceeded to be diagnosed with a primary psychotic disorder (often schizophrenia) due to persisting psychosis

Kittirattanapaiboon P et al. Drug Alcohol Rev. 2010 Jul;29(4):456-61.

Niemi-Pynttäri JA et al. J Clin Psychiatry. 2013 Jan;74(1):e94-9.

Methamphetamine and Psychosis

Behavioural interventions in the ER/acute setting (psychotic, agitated, intoxicated):

- Calm reassurance
- “Talk down” the individual in a quiet environment
- Minimize stimulation
- Physical restraints generally delayed and used as a last resort

Glasner-Edwards S & Mooney LJ. CNS Drugs. 2014 Dec;28(12):1115-26.

Methamphetamine and Psychosis

Pharmacological interventions in the ER/acute setting (psychotic, agitated, possibly requiring chemical restraint):

- Short-term anxiolytics (i.e. benzodiazepines) to target anxiety, agitation, and insomnia
  - e.g. lorazepam 1-2 mg po/sl/im q45 min, max 6-8 mg/24h
- May be combined with antipsychotics to reduce severe symptoms of agitated psychosis
  - e.g. olanzapine ODT (orally disintegrating tablet) 5-10 mg BID prn
  - e.g. haloperidol 5 mg po/IM
- Avoid the concomitant IM use of olanzapine and IM benzodiazepines due to concerns of fatalities

Glasner-Edwards S & Mooney LJ. CNS Drugs. 2014 Dec;28(12):1115-26.

Methamphetamine and Psychosis

Pharmacological treatment of MA-induced psychotic symptoms:

- Limited published trial data to date
- Olanzapine vs. haloperidol (Leelahanaj 2005):
  - Both efficacious in the treatment of amphetamine psychosis
  - Olanzapine superior in safety and tolerability with less EPS
- Quetiapine vs. haloperidol (Verachai 2014):
  - Both efficacious in treating methamphetamine psychosis
  - Quetiapine and haloperidol comparable in therapeutic effects and tolerability
- No placebo - which would have been useful to compare

Leelahanaj T et al. J Med Assoc Thai. 2005 Nov;88 Suppl 3:S43-52.

Verachai V et al. Psychopharmacology (Berl). 2014 Aug;231(16):3099-108.

Methamphetamine and Psychosis

Pharmacological treatment of MA-induced psychotic symptoms:

- Risperidone vs. aripiprazole (Farnia 2014):
  - Both efficacious in the treatment of amphetamine psychosis
  - Risperidone better for +ve sxs, aripiprazole better for -ve sxs
- Risperidone vs. aripiprazole (Wang 2016):
  - Aripiprazole 5-15 mg, risperidone 2-6 mg
  - Both efficacious in treating methamphetamine psychosis
  - Risperidone superior regarding cravings and retention
- Risperidone vs. haloperidol (Samiei 2016):
  - Both similarly beneficial for MA-psychosis
- No placebo again – would be useful to compare

Farnia V. Am J Drug Alcohol Abuse. 2014 Jan;40(1):10-5.

Wang G et al. J Subst Abuse Treat. 2016 Mar;62:84-8.

Samiei M. Iran J Psychiatry Behav Sci. 2016 Sep 4;10(3):e7988.

Methamphetamine and Psychosis

Pharmacological treatment of MA-induced psychotic symptoms:

Typical daily dose ranges from our inpatient unit:

- Olanzapine 5-20 mg daily
- Quetiapine 100-200 mg daily
- Haloperidol 5-10 mg daily
- Loxapine 25-100 mg (divided doses)

Methamphetamine and Psychosis

Longitudinal Management:

- Data unclear regarding duration of treatment of antipsychotic medication, and how/when to trial a taper off medication (generally individualized, ? ”harm reduction” role for continuing medication in active use)
- Abstinence from MA is clearly advised
- Psychosocial treatment for MA use disorder (counseling, mutual support groups, contingency management)
- Emerging evidence for medications for MAUD (bupropion, mirtazapine, naltrexone, methylphenidate, d-amphetamine, topiramate)
- Identify & treat comorbid psychiatric disorders (psychosocial and/or pharmacotherapy)

Glasner-Edwards S & Mooney LJ. CNS Drugs. 2014 Dec;28(12):1115-26.


Bon Appetit

Questions?

Thank-you