

Implications of the Co-occurrence of Substance Use and other Psychiatric Disorders



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“Drugs take you prisoner.”



A patient sketched this during his hospital stay...

Why do young people *say* they start taking drugs?



- To feel good
- To feel better
- To do better
- To feel (predictably) different
- Curiosity: “because others are doing it”



- However, the good feelings do not last and afterwards you feel **BAD**, those with whom you used are not there when you need them, you need drugs just to feel **NORMAL**, and using over and over again damages your **BRAIN** so eventually it may be difficult to **CHOOSE** to stop.

Major questions concerning substance use disorders



- Why, in the face of **widespread availability** of alcohol and drugs, do certain individuals develop a substance use disorder and others do not?
- Why does substance use disorder **continue inexorably** to death in spite of treatment in certain cases, whereas in others **abuse can decrease or stop** either spontaneously or with treatment?

Current best answers



- Substance use disorders are **heterogeneous**, either a **primary psychiatric disorder** in its own right, or the **final common pathway** for a variety of behavioral difficulties in diverse sociocultural contexts
- Pathogenesis of substance use disorder is currently conceptualized as multiple **simultaneous risk/protective factors** interacting over time:
 - the manifest **psychopathology** of the individual
 - the **psychopharmacologic actions** of alcohol within the **sociocultural context**

Initiation, Progression, and Complications of Substance Use Disorders

Antecedents/Sociocultural Context/Consequences
Use / Abuse / Compulsive Use

Psychopharmacologic Effects

Vulnerable Individual

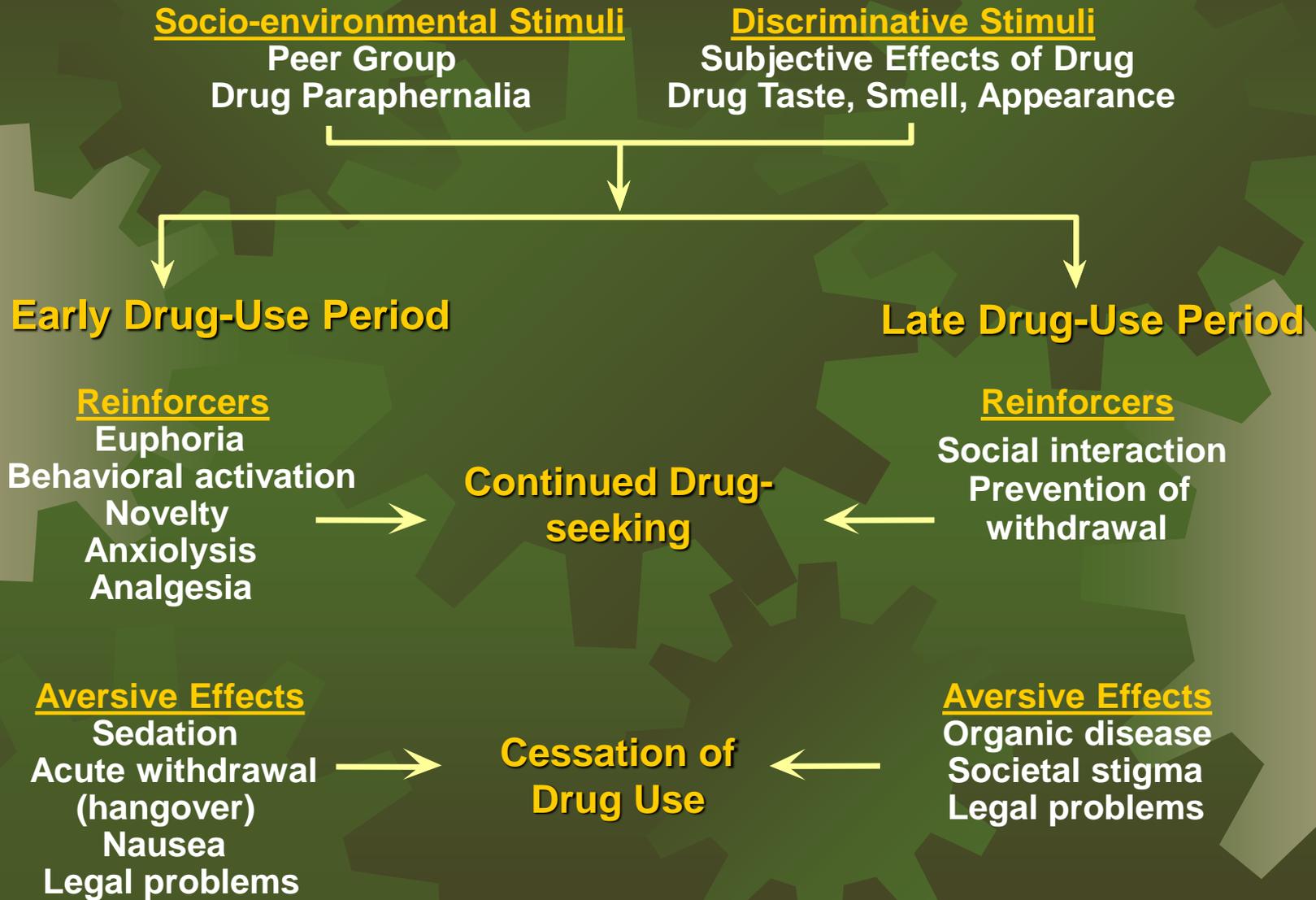
- Biological
- Psychological
- Social

Drug-seeking
Neuroadaptation
Dependence

Complications

- Social
- Neuropsychiatric
- Medical

Drug-Seeking: Basis of Addiction



Addiction and Learning



- Addiction relies on some of the **same neurobiological mechanisms** as learning (*eg.* tolerance, dependence, withdrawal)
- Cravings are **triggered** by memories, affective states, and situations associated with drug use
- Both declarative and non-declarative (more recalcitrant) memories are involved in relapse and must be diminished or modified in treatment using pharmacopsychosocial approaches

Brain changes can influence the clinical course of substance use disorder (SUD)



- Initially or eventually, SUD involves altered structure and function of the brain
- Brain circuitry involved in adaptive motivated behavior, stress responses, and survival are affected by chronic substance use
- These brain changes convey lifelong **vulnerability to relapse**, a powerful automatic behavioral (learned) action reflex
- SUD may also cause more overt **neurocognitive deficits**, e.g. problem solving, memory, visuospatial and motor disturbances

Long-term Effects of Drug Use



- **Anhedonia** results from ‘allostatic change’ in neural pathways (reduced numbers of dopamine receptors demonstrable by PET, changes in extended amygdala) that subserve reward and reinforcement
- Less sensitivity to dopamine results in **less pleasure from natural stimuli** and eventually only unnatural stimuli (drugs) can ‘tweak’ the brain’s pleasure systems
- **Drug/alcohol-induced brain injury** can indirectly affect memory and motivation systems and thereby alter reinforcement, e.g., alcohol amnestic disorder/dementia

Psychoactive Substances with Abuse Liability



- **CNS Depressants:** alcohol, *benzodiazepines** (Valium, Librium, Xanax, Halcion, Ativan, Klonopin, etc), *barbiturates* (seconol, butalbatol), *nonbarbiturate hypnosedatives* (qualudes, Placidyl, Ambien)
- **Stimulants:** *amphetamine*, *cocaine*, *methylphenidate* (Ritalin)
- **Cannabinoids:** *marijuana*, hashish, THC
- **Tobacco:** *nicotine*, cigarettes, etc.

*prescribed for medical indications

Psychoactive Substances with Abuse Liability



- **Opioids:** heroin, *morphine*, *methadone*, *codeine*, *hydromorphone* (Dilaudid), *Oxycodone/aspirin* (Percodan), *Pentazocine* (Talwin), *Meperidine* (Demerol), *meperidine/promethazine* (Mepergan), etc.
- **Hallucinogens:** LSD, *psylocybin*, *mescaline*, mushrooms
- **Anesthetics:** PCP, *ketamine*, *nitric oxide* (laughing gas)
- **Inhalants:** gasoline, glue, paint, paint thinners, spray paint, other volatile compounds

**prescribed for medical indications*

Substance-related Disorders (DSM-IV)



- **Substance use disorders**
 - Substance dependence
 - Substance abuse
- **Substance-induced disorders**
 - Intoxication
 - Withdrawal
 - Delirium
 - Persisting dementia
 - Persisting amnestic disorder
 - Psychotic disorder
 - Mood disorder
 - Anxiety disorder
 - Sexual dysfunction
 - Sleep disorder

DSM-5



- Substance use disorders
- Non-Substance related disorder
- Substance-induced disorders
 - Intoxication
 - Withdrawal
 - Delirium
 - Persisting dementia
 - Persisting amnesic disorder
 - Psychotic disorder
 - Mood disorder
 - Anxiety disorder
 - Sexual dysfunction
 - Sleep disorder

Essentials of clinical diagnosis of substance use disorders



- Clinical criteria must **avoid value judgments** and be **generalizable** across cultures and substances
- **Maladaptive use** leading to **significant impairment or distress** manifested by 2-3 (mild), 4-5 (moderate), or ≥ 6 (severe) symptoms from following clusters:
 - Loss of control
 - Salience to the behavioral repertoire
 - Neuroadaptation
- **Drug-seeking** underpins each the above symptom clusters and is the *sine qua non* of substance use disorder

Distinguishing primary from substance-induced psychopathology is purely clinical judgment



- Determine the history of **onset** of any psychopathology with respect to the age at which substance use was initiated
- Correlate clinical state with **duration of abstinence** at the time of assessment—persistent psychopathology after drug use has ceased suggests (but does not prove) a primary disorder
- **Dissociation of treatment responses** for psychopathology and substance use disorder

Other psychiatric diagnoses that frequently co-occur with SUD



Lifetime Prevalence Rates

DIAGNOSIS

ANY

ALCOHOL

DRUGS

SCHIZOPHRENIA

47 %

33.7

27.5

ANTISOCIAL

83.6

ANXIETY DIS.

23.7

17.9

11.9

Phobias

22.9

17.3

11.2

Panic

35.8

28.7

16.7

OCD

32.8

24

18.4

MOOD DISORDERS

32

Major Depression

27.2

16.5

18

Bipolar I Disorder

60.7

46.2

40.7

ECA Data. Regier et al. 1990

What might co-occurrence of psychiatric disorders *actually mean*?



- Substance use disorders (SUD, abuse/dependence) are highly prevalent **psychiatric disorders**
- Most SUD patients have co-occurring other psychiatric disorders (some equally prevalent), simply by chance as an **independent disorder** or as a **precursor or consequence** of alcohol/drug use
- Co-occurrence rates greater than expected by chance suggest behavioral and neurobiologic **synergism, shared mechanisms or even causality**
- Co-occurring disorders have a **bidirectional relationship** yielding a result more complex than the mere sum of the component disorders
 - **High rate of SUD in patients with BPAD** strongly suggests that AUD may play a significant role in the pathogenesis of BPAD or *vice versa*, or both are influenced by common factors
 - **Smaller odds ratios for MDD and anxiety disorders** indicate that, although these disorders have a higher prevalence among SUD than in the general population, the association may be of less relevance in explaining causality
 - Moreover, this lesser association may even be inflated, at least for MDD due to misdiagnosis

Only certain psychiatric disorders are robustly associated with drug and alcohol use disorders



Disorder	12-month prevalence	12-month prevalence in AUD	Odds ratio for AUD
Bipolar (affective) disorder	2.82%	30.97–43.6%	3.5
Major depressive disorder	7.06%	13.70%	1.8
Anxiety disorders	11.08%	17.05%	1.7
Personality disorders (Grant et al., 2004b)	14.8%	28.6%	2.6
Drug use disorders (Compton et al., 2007)	2.0%	33.05%	9.0

Source: (Grant et al., 2004a), except where otherwise noted.

What Mood Disorder is Associated with SUD?



- Almost half of MDE patients (N=5098) presented **core (observable) bipolarity symptoms**, e.g., elevated mood, irritable mood, or increased activity
- Several potential **indicators of bipolarity** that can be reliably assessed in routine care settings, e.g., FH of bipolar disorder, co-occurring SUD, or borderline personality disorders
- No significant comorbidity between pure MDD and SUD remained after removal of the bipolar-specifier group
- Suggests reported **association between MDD and SUD may be an artifact** as a result of the inclusion of patients with unidentified bipolar disorder.

Why this distinction is important?



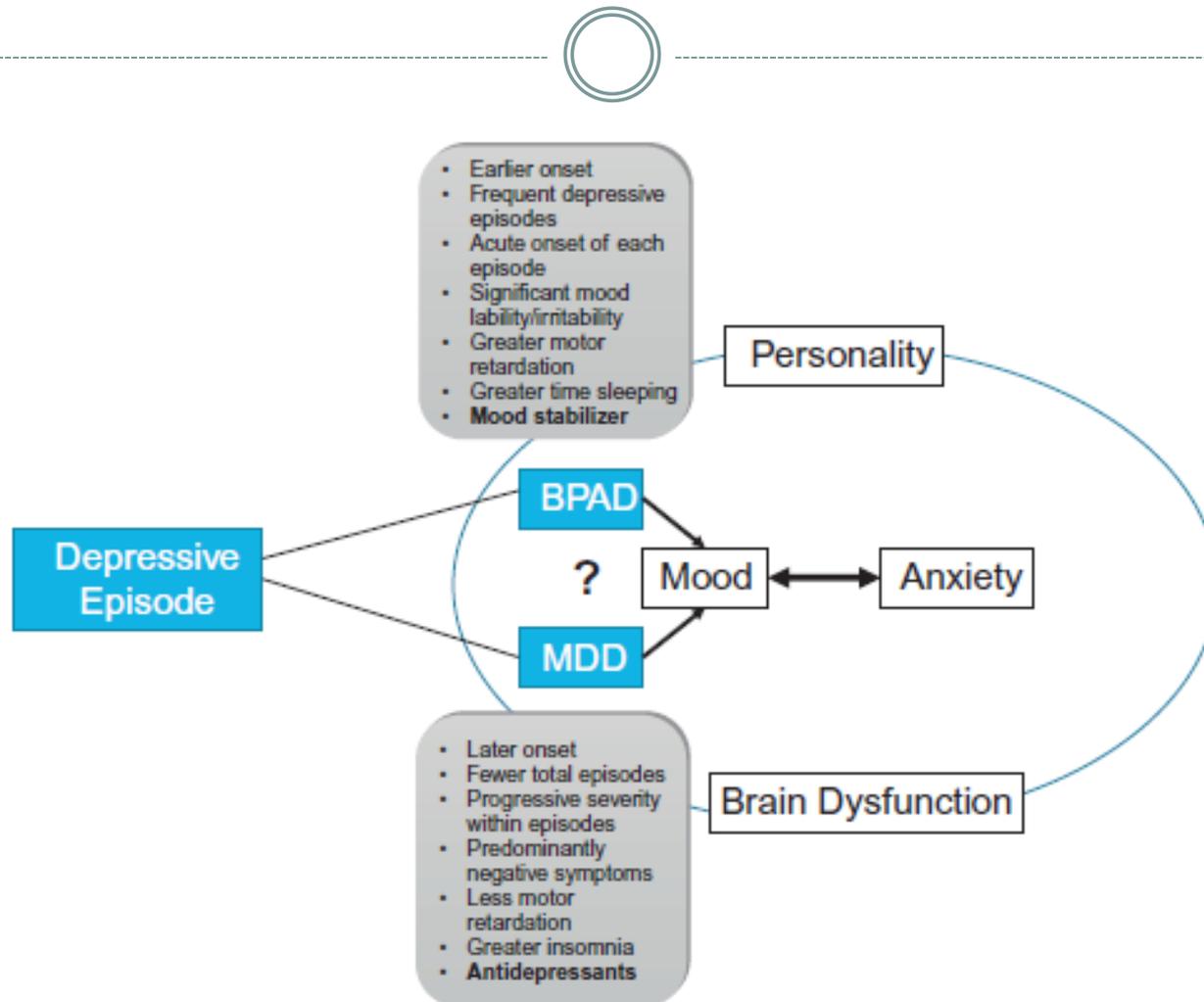
- One of the most important considerations in care for the SUD patient with a co-occurring other psychiatric disorder may be recognizing the **presence** and accurately characterizing a **comorbid condition** and understanding how it should modify **management**
- BD patients are at increased risk for **suicide**, become treatment **refractory**, their symptoms **exacerbated with antidepressants**—but they do well with **mood stabilizers**

Why is this distinction difficult to make?

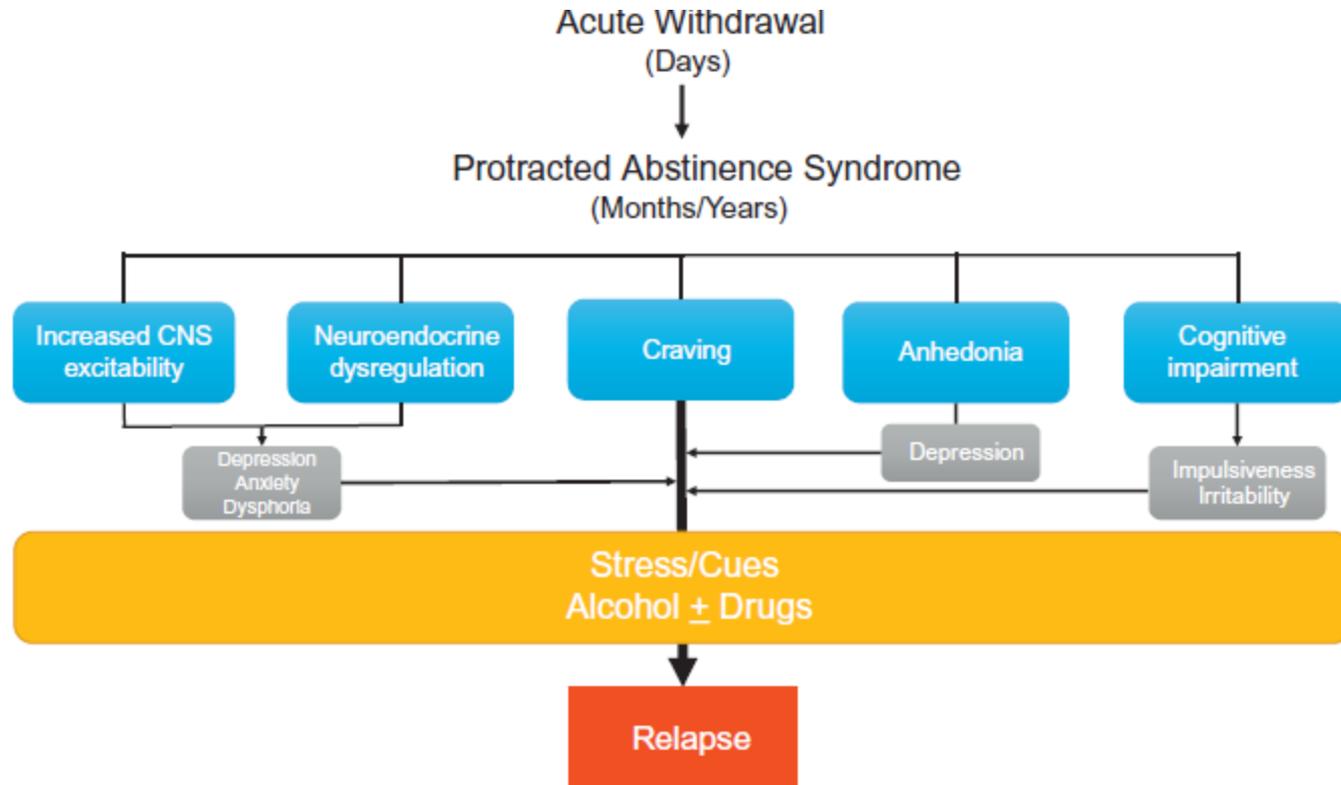


- It is exceedingly difficult to make a mood diagnosis in the midst of active substance use (Franken and Hendriks, 2001), especially in adolescent population, when both mood and drug disorders tend to begin almost at once (Judd and Akiskal, 2003; Duffy et al., 2012)
- The most common presentation for the patient with a mood disorder involves an episode of depression (Judd and Akiskal, 2003)
- Both the number and severity of depressive episodes in patients with bipolar symptoms have been associated with severity of substance abuse (Hoertel et al., 2012)

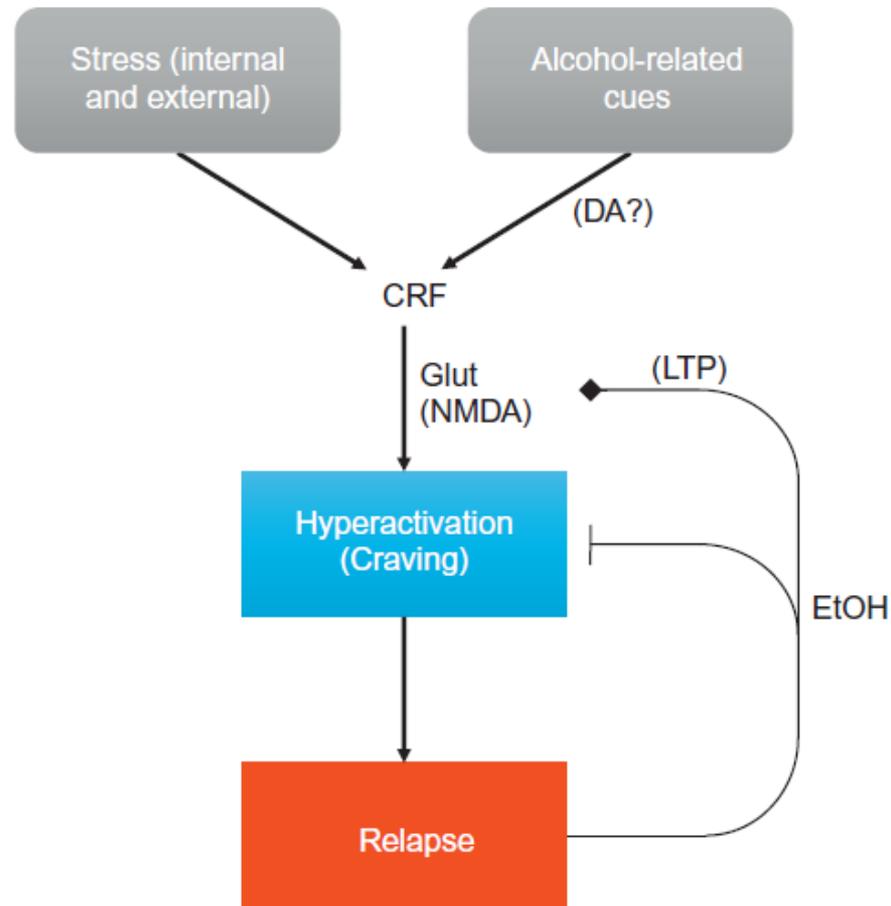
Depressive episodes in substance use disorder: BPAD or MDD?



Protracted abstinence syndrome can mimic or exacerbate primary mood symptoms



Relapse: Role of Extended Amygdala (especially BNST to VTA)



Diminish and Manage Relapse(s) in a Life-long Chronic Disorder



- Reduce states and stimuli which might reinstate active addiction:
 - Stress and related internal cues
 - Environmental cues
 - Re-exposure to drugs

Treatment: Primary psychiatric disorder or substance use/induced disorder?



- Pharmacotherapy of a complicating psychiatric disorder is most appropriate if it is **independent** (primary), but much less so if it is a consequence of a substance use disorder (secondary)
- Treating a co-existing psychiatric disorder using **medications with dependence liability** (e.g. benzodiazepines, methylphenidate, barbiturates, anticholinergics, cannabinoids, ketamine, buprenorphine or methadone) or **failing to address the primary issue** (substance use disorder) may be detrimental
- Some medications may do more **harm** than good (e.g., SSRIs in patients with externalizing disorders)

Personality traits and age of onset of AUD in the Cloninger typology



Personality trait	Type 1 Late onset Internalizing	Type 2 Early onset Externalizing	Proposed neurotransmitter
Novelty seeking	Low	High	Dopamine
Harm avoidance	High	Low	Serotonin
Reward dependence	High	Low	Norepinephrine

Source: Cloninger et al. (1993).

Medications typically used in SUD Treatment



- **Withdrawal**
 - diazepam, phenobarbital, clonidine/buprenorphine
- **Craving/Relapse**
 - disulfiram, naltrexone, acamprosate, topiramate, oxcarbazepine
 - methadone, buprenorphine, LAAM
 - bupropion, nicotine replacement, varenicline
- **Depression/Anxiety**
 - fluoxetine, sertraline, paroxetine, etc
- **Mood instability**
 - valproate, carbamazepine, oxcarbazepine, lithium, etc
- **Psychosis**
 - haloperidol, risperidone, olanzapine, etc

Anticonvulsant can have a spectrum of effects in SUD: withdrawal/mood stabilization/craving



- Topiramate (Na^+ , Ca^{++} channels; GABA, glutamate)
- Valproate (Na^+ and Ca^{++} channels; GABA)
- Carbamazepine/Oxcarbazepine (Na^+ channels)
- Gabapentin (Ca^{++} channels; GABA)
- Lamotrigine ($\text{Na}^+ \pm \text{Ca}^{++}$ channels)
- Levetiracetam (Ca^{++} channels; GABA)
- Zonisamide (Na^+ and Ca^{++} channels)
- Lithium (mood stabilizer/no anticonvulsant)

Co-occurring psychopathology influences the course of substance use disorders

