Alcoholism, Hepatic Dysfunction, and Depression: How to Approach Management of this Patient?

PETER R. MARTIN, M.D.
PROFESSOR OF PSYCHIATRY & PHARMACOLOGY

Case Presentation

- CC: AB is a 45 y.o. divorced (thrice married) actor who presents with suicidal ideation
- HPI: Recently spiraled out of control due to drinking and has become quite focused on depression, hopelessness, and death
  - Repeated episodes of depression with SI
  - Repeated courses of fluoxetine beneficial, but d/c due to diminished sexual drive
  - Periods of energy and productivity; impatience with others is downfall
  - Highly active sexually, Hep C; interferon d/c due to severe depression
  - Smoking, suicidality with varenicline
- O/E Appears quite despondent, anxious, “cannot slow thoughts”, and wishes to die
  - No jaundice or hepatosplenomegaly
  - Elevated SGPT, GGT, +anti-HCV AB, normal PT, albumin, WBC, elevated MCV

Differential Diagnosis

- Alcohol use disorder
- Mood disorder
- Hepatic dysfunction
- Alcohol use disorder & Mood disorder
- Alcohol use disorder & Hepatic dysfunction
- Mood disorder & Hepatic dysfunction
- Alcohol use disorder, Mood disorder & Hepatic dysfunction

Major Depressive Episodes (MDE) Frequently Occur in Bipolar Disorder (BD)

- MDEs are generally more frequent and more distressing than hypomanic episodes
- Patients seek treatment for depression which is more easily diagnosed by physicians (SSRIs easily used)
- Bipolar features can be detected if looked for carefully, in 25-50% of patients diagnosed with MDD
- Among BD patients, 2/3 initially misdiagnosed MDD and consulted mean of 4 physicians before receiving definitive (correct) BD diagnosis
- BD patients are at increased risk for suicide, become treatment refractory, symptoms exacerbated with antidepressants, do well with mood stabilizers

DSM-IV-TR *vs* Bipolarity Specifiers (Angst et al, 2003)

- An episode of elevated mood
- An episode of irritable mood
- An episode of increased activity of no minimum duration (1 of 3 symptoms)
  - Unequivocal and observable change in functioning uncharacteristic of the person's usual behavior;
  - Marked impairment in social or occupational functioning observable by others; or
  - Requiring hospitalization or outpatient treatment

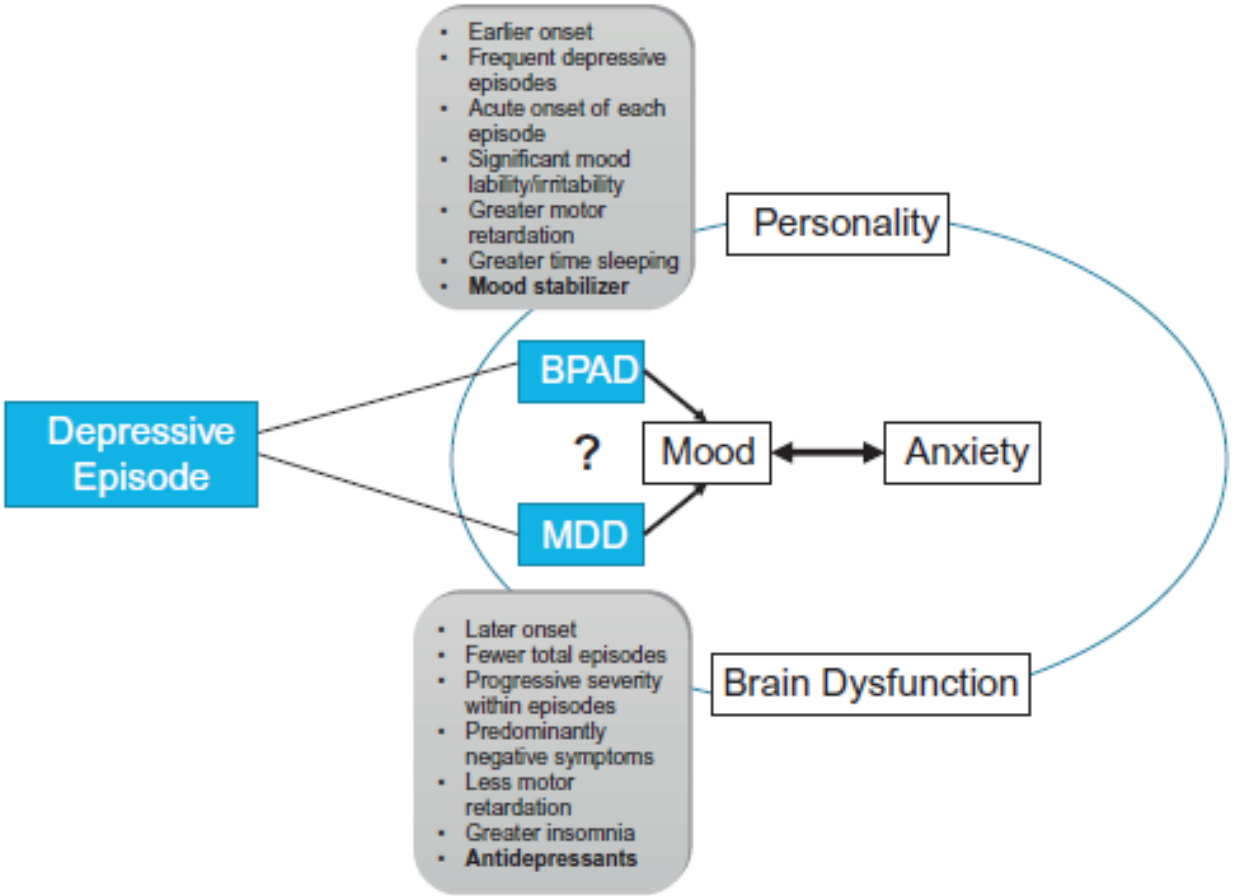
Angst et al, ARCH GEN PSYCHIATRY/VOL 68 (NO. 8), AUG 2011

What Mood Disorder is Associated with SUD

- Almost half of MDE patients (N=5098) presented core bipolarity symptoms (elevated mood, irritable mood, or increased activity) with **observable behavior changes**
- Associations with several potential items that can be reliably assessed in routine care settings as **indicators of bipolarity**, 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.

Angst et al, ARCH GEN PSYCHIATRY/VOL 68 (NO. 8), AUG 2011

Depressive Episodes in Substance Use Disorders Often Represent Underlying BPAD



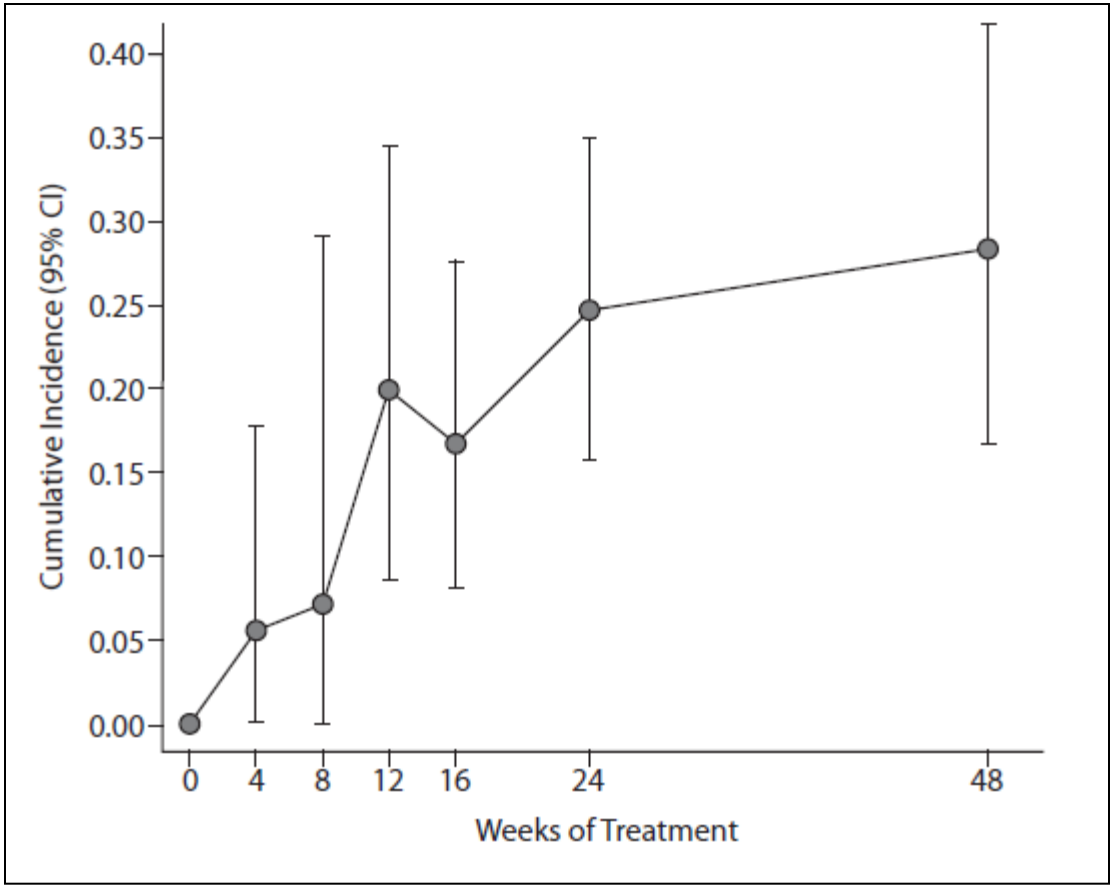
Rich and Martin, 2014

Other Psychiatric Diagnoses that Frequently Co-Occur with SUD

DIAGNOSIS	Lifetime Prevalence Rates 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

Cumulative Incidence of Depression with Interferon and Ribavirin Treatment



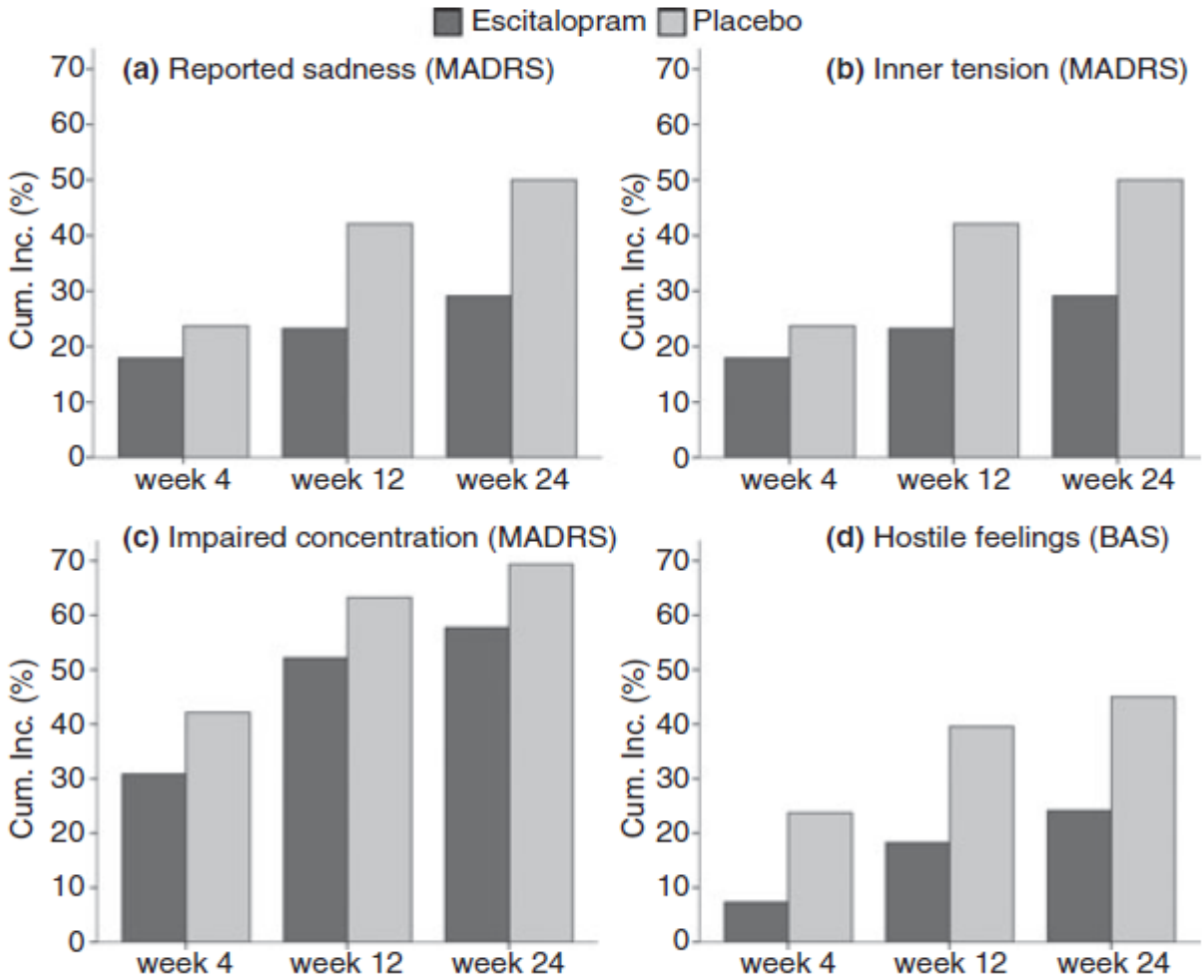
Udina et al, J Clinical Psychiatry 2012;73:1128

Risk Factors for Interferon-Induced Depression

- Incidence of depression during interferon-alpha and ribavirin treatment is substantial; 1 out of 4 patients with chronic hepatitis C who start antiviral treatment will develop an induced major depressive episode.
- Baseline levels of interleukin-6, female gender, history of depression or psychiatric disorder, subthreshold depressive symptoms, and low educational level are predictive variables of interferon-induced depression.
- Before starting antiviral treatment, clinicians should assess patients at risk of developing interferon-induced depression. During the treatment, a comprehensive assessment and management of depression must be performed.

Udina et al, J Clinical Psychiatry 2012;73:1128

RCT Escitalopram for Psychiatric Side-effects of HCV Treatment



R. J. de Knegt et al., 2011

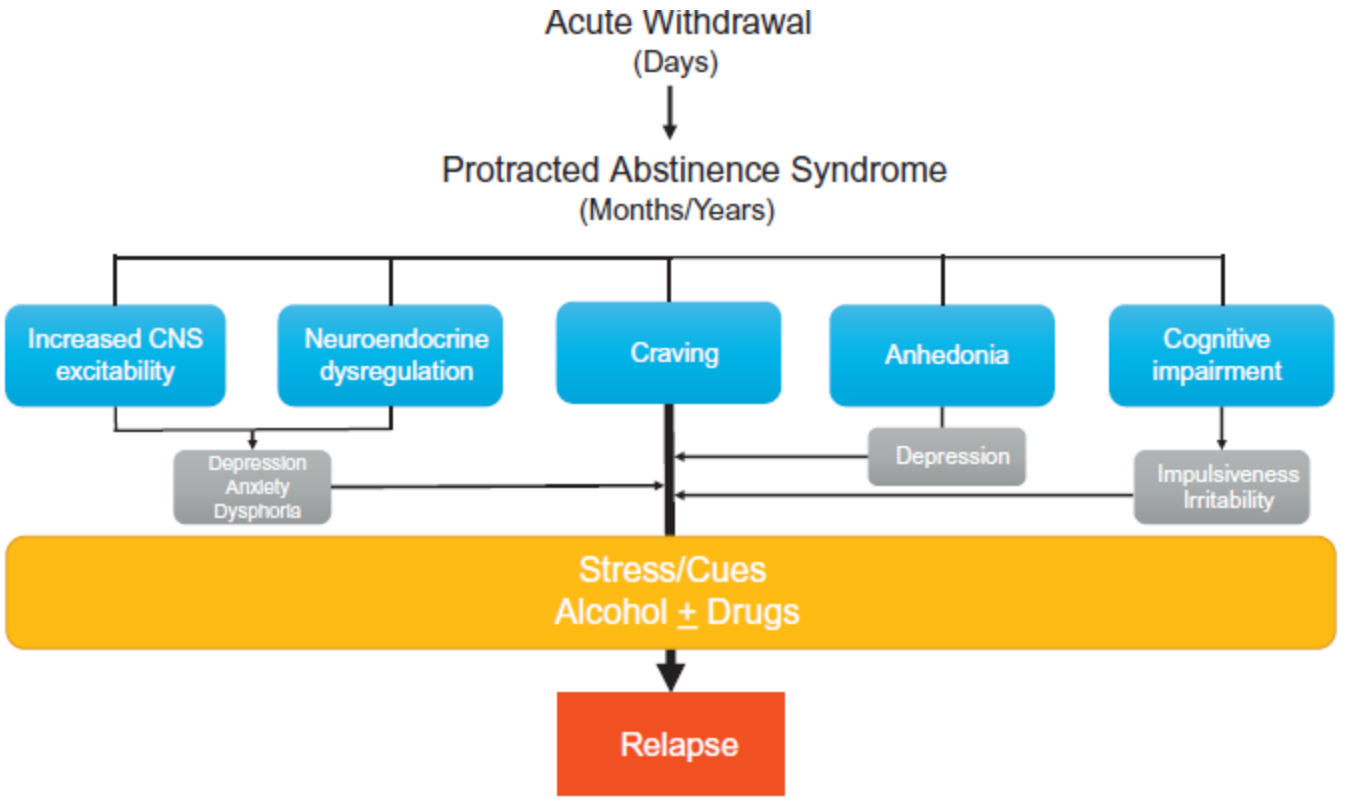
Treatment of Hepatitis C without Interferon

- Until a few years ago, there were only two drugs approved by the FDA for Hepatitis C treatment: Pegylated interferon (Peg-IFN) and Ribavirin (RBV)
- Protease inhibitors: Boceprevir (brand name VICTRELIS), Telaprevir (brand name INCIVEK) and Simeprevir (brand name OLYSIO)
- Polymerase inhibitors: Sofosbuvir (brand name SOVALDI)
- Direct acting anti-virals: Ledipasvir/sofosbuvir (brand name HARVONI)

Primary Psychiatric Disorder or Substance Use/Induced Disorder?

- Pharmacotherapy of a complicating psychiatric disorder is appropriate only if it is **independent** (primary), but not 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) or **failing to address the primary disorder** (substance dependence) may be detrimental
- Some medications may do more **harm** than good (e.g., SSRIs in patients with externalizing disorders)

Protracted Abstinence Syndrome Can Mimic or Exacerbate Primary Mood Symptoms



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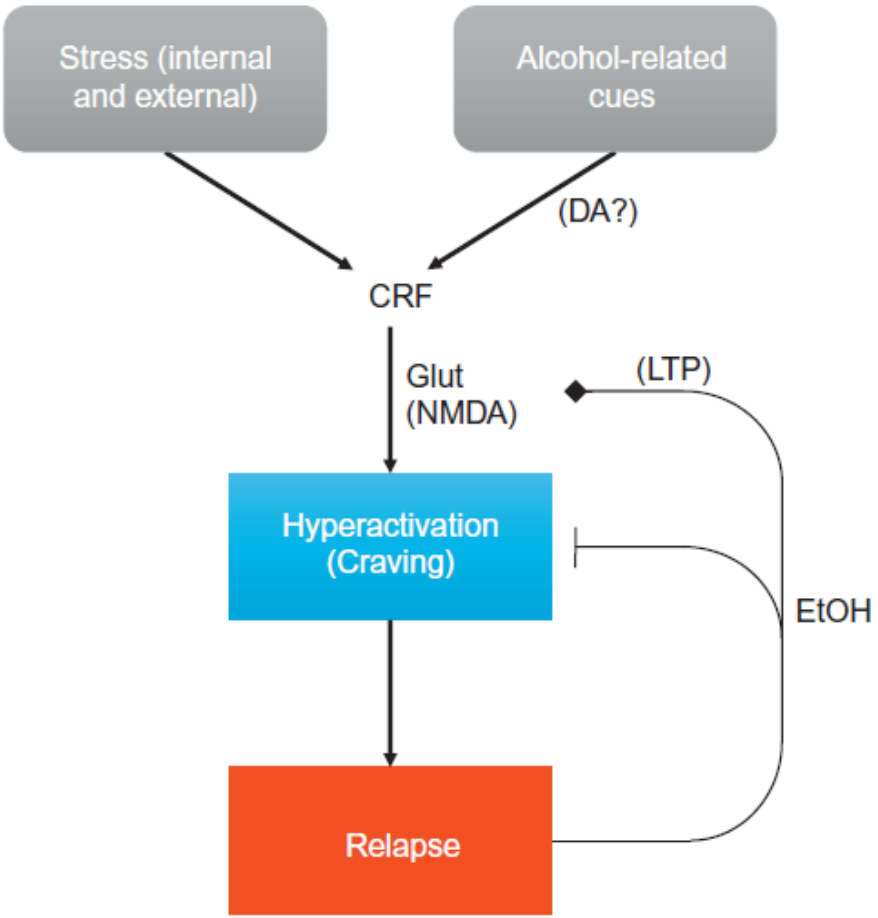
Relapse: Role of Extended Amygdala (esp. BNST to VTA)



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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

Medications Used in Treatment of Addiction

- 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

Mood Stabilizer Safety and Tolerability Concerns

Lithium	Valproate	Carbamazepine	Lamotrigine
Gastrointestinal	Gastrointestinal	Gastrointestinal	Gastrointestinal
Weight gain	Weight gain	Rash	Rash
Neurotoxicity	Tremor	Neurotoxicity	Headache
Renal toxicity	Hepatotoxicity	Hepatotoxicity	Dizziness
Thyroid toxicity	Thrombocytopenia	Thyroid changes	Pruritis
Hair Loss	Hair Loss	Blood dyscrasias	Dream abnormality
Cardiac toxicity	Pancreatitis	Cardiac toxicity	
Acne, Psoriasis	PCOS	Hyponatremia	
Teratogen	Teratogen	Teratogen	Teratogen
	Suicidality (?)	Suicidality (?)	Suicidality (?)

= boxed warning in prescribing information; (?) = recent alert

All Mood Stabilizers Have at Least One Boxed Warning

In: Ketter TA (ed). Advances in the Treatment of Bipolar Disorder. 2005.
Physician's Desk Reference. 2008.

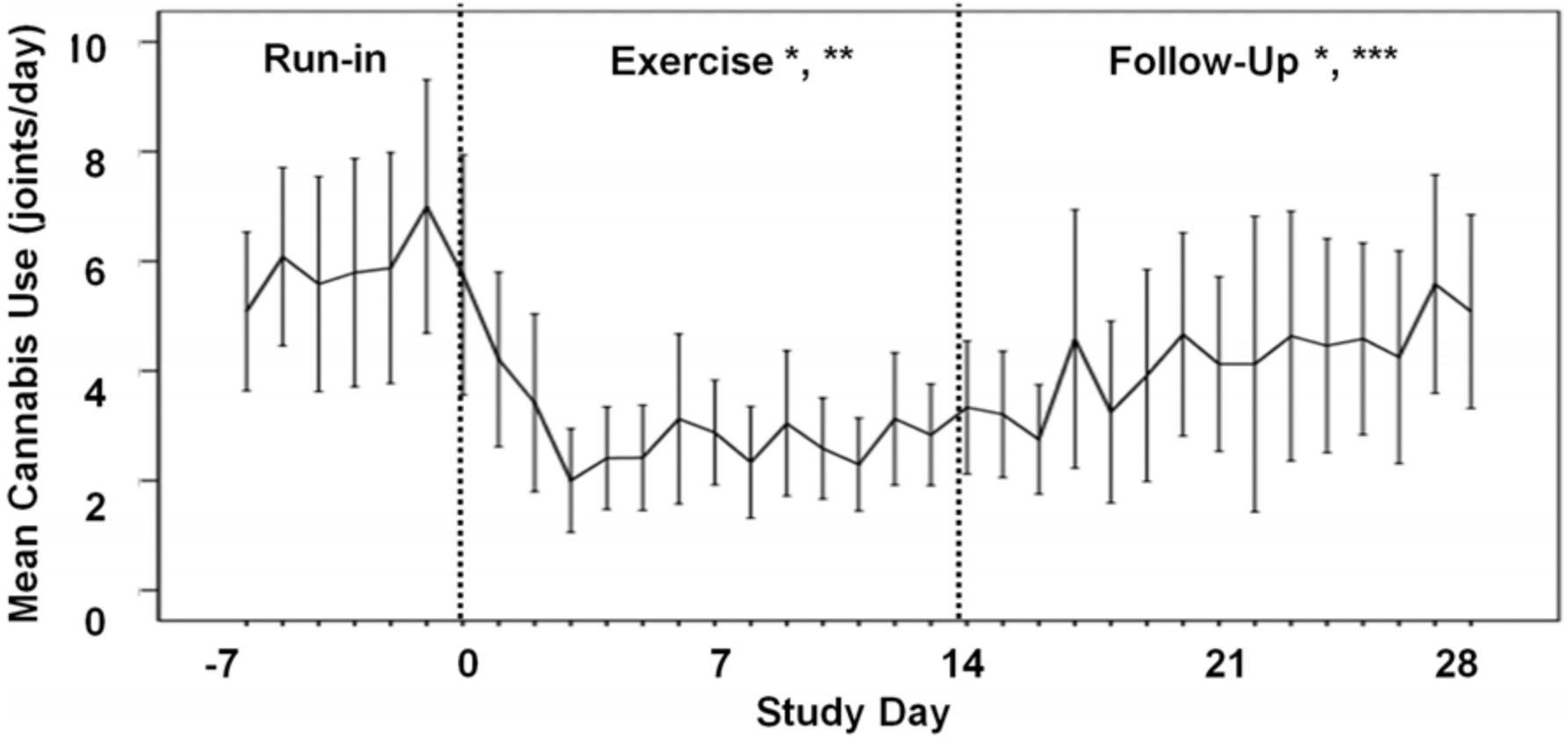
Summary of Adverse Events with the New AEDs

AED	Adverse Events	
	Serious	*Non-serious*
Gabapentin	None	Weight gain, peripheral edema, behavioral changes*
Lamotrigine	Rash, including Stevens Johnson syndrome and toxic epidermal necrolysis (increased risk for children, also more common with concomitant valproate/divalproex use and reduced with slow titration); hypersensitivity reactions, including risk of hepatic and renal failure, DIC, and arthritis	Tics* and insomnia
Levetiracetam	None	Irritability/behavior change
Oxcarbazepine	Hyponatremia (more common in elderly), rash	None
Tiagabine	Stupor or spike wave stupor	Weakness
Topiramate	Nephrolithiasis, open angle glaucoma, hypohidrosis*	Metabolic acidosis, weight loss, language dysfunction
Zonisamide	Rash, renal calculi, hypohidrosis*	Irritability, photosensitivity, weight loss

Non-pharmacologic modalities of substance abuse treatment

- Education
- 12-Step support program facilitation (eg, AA, NA, CA)
- Enhancement of coping strategies
- Relaxation training
- Family therapy
- Lifestyle change (avoiding drug use trigger situations)
- Psychotherapy (usually cognitive, relational, or supportive, in a group or individual setting)
- Vocational and physical rehabilitation
- Recreational therapy
- Sexual education
- Health and nutritional counseling
- Spiritual growth
- Aftercare

Effects of Exercise on Cannabis Use in Non-Treatment Seeking Individuals



Buchowski et al, PLoS ONE 6(3): e17465. doi:10.1371/journal.pone.0017465

Reduced Cannabis Craving Due to Exercise

Buchowski et al, PLoS ONE 6(3): e17465. doi:10.1371/journal.pone.0017465

Take Home Message

Martin et al., 2007