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Challenges & Opportunities For Comorbid Major Depressive Disorder (MDD) & Substance Use Disorder (SUD)

January 2020 MRC2.PSY.D.00071

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This program is paid for by
Otsuka Pharmaceutical Development &
Commercialization, Inc. and Lundbeck, LLC.

Speakers are paid consultants for Otsuka
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Objectives

- Describe the impact of drugs of abuse on MDD symptomatology
- Discuss how phases of recovery can impact MDD
- Identify considerations for treatment of comorbid SUD and MDD

Polling Question

In your clinical opinion, which of the following substances of abuse have most widely impacted your community and practice?

A. Opiates (heroin/prescription)
B. Cocaine or crack
C. Alcohol
D. Methamphetamine
E. Cannabis
F. Other

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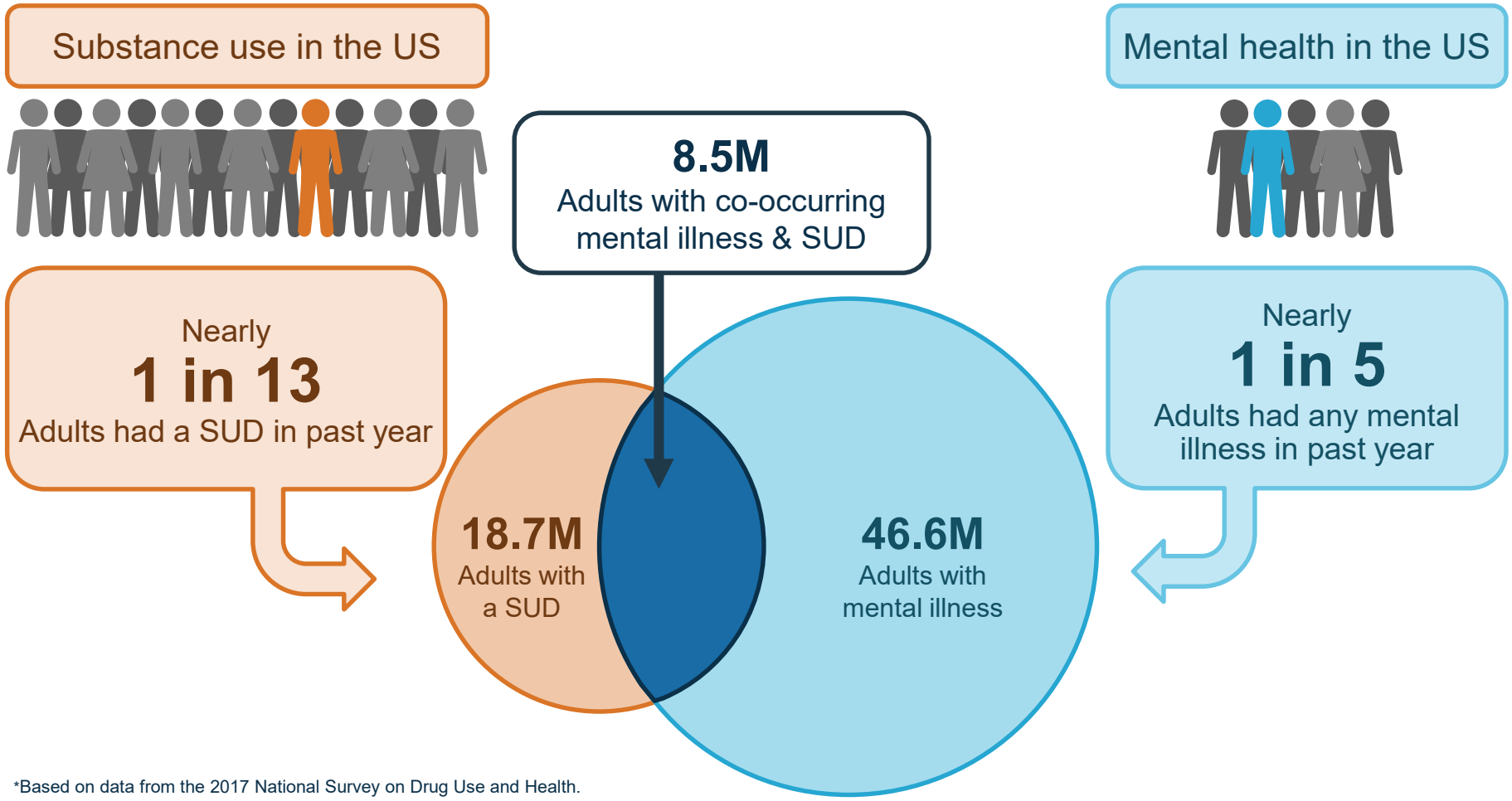
Statistics

Co-occurring Mental Illness & SUDs: Prevalence*



*Based on data from the 2017 National Survey on Drug Use and Health.
M, millions; SUD, substance use disorder; US, United States

1. Substance Abuse and Mental Health Services Administration. National Survey on Drug Use and Health 2017. https://www.samhsa.gov/data/report/2017-nsduh-annual-national-report. September 2018. Accessed March 14, 2019.

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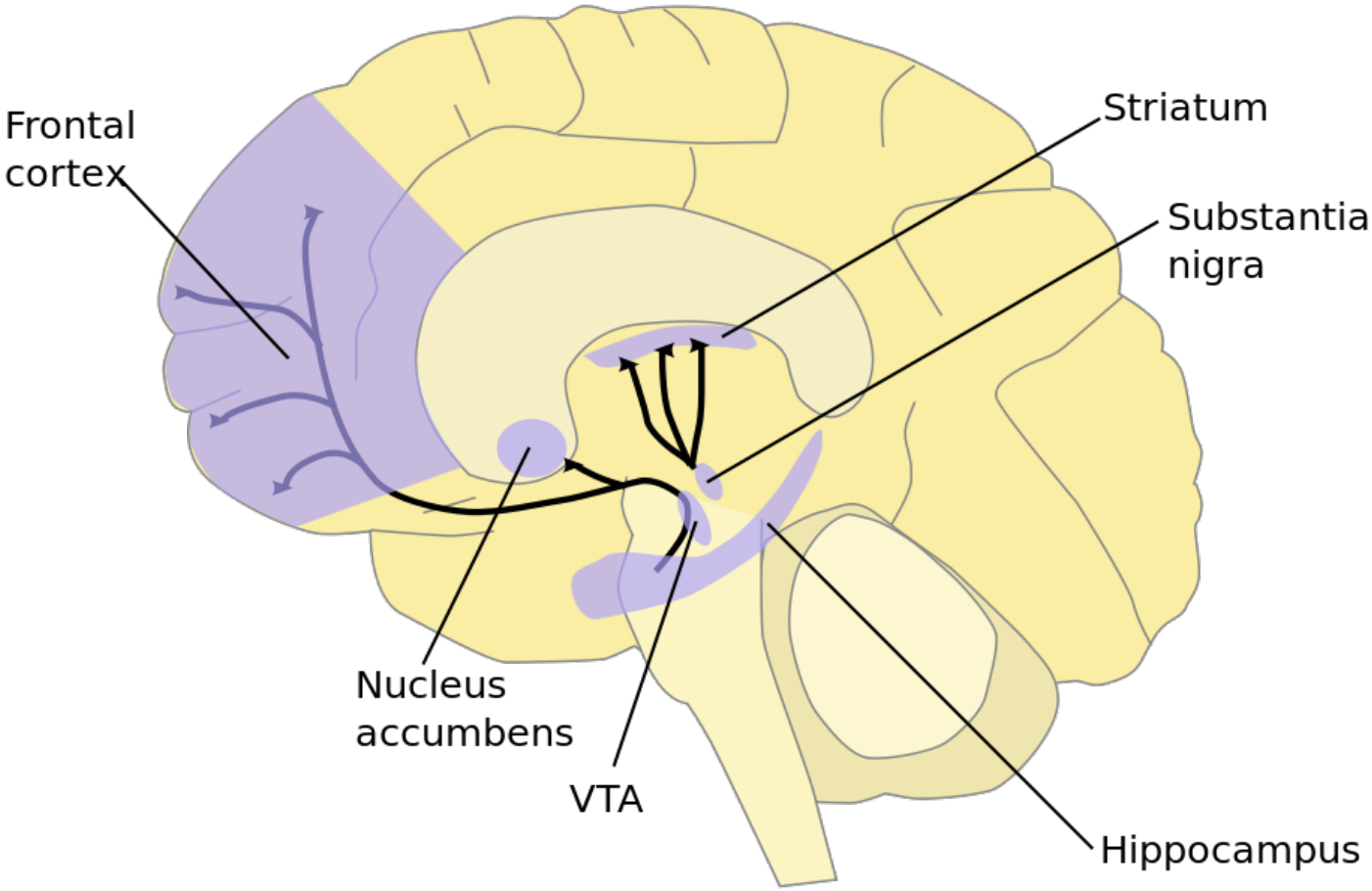
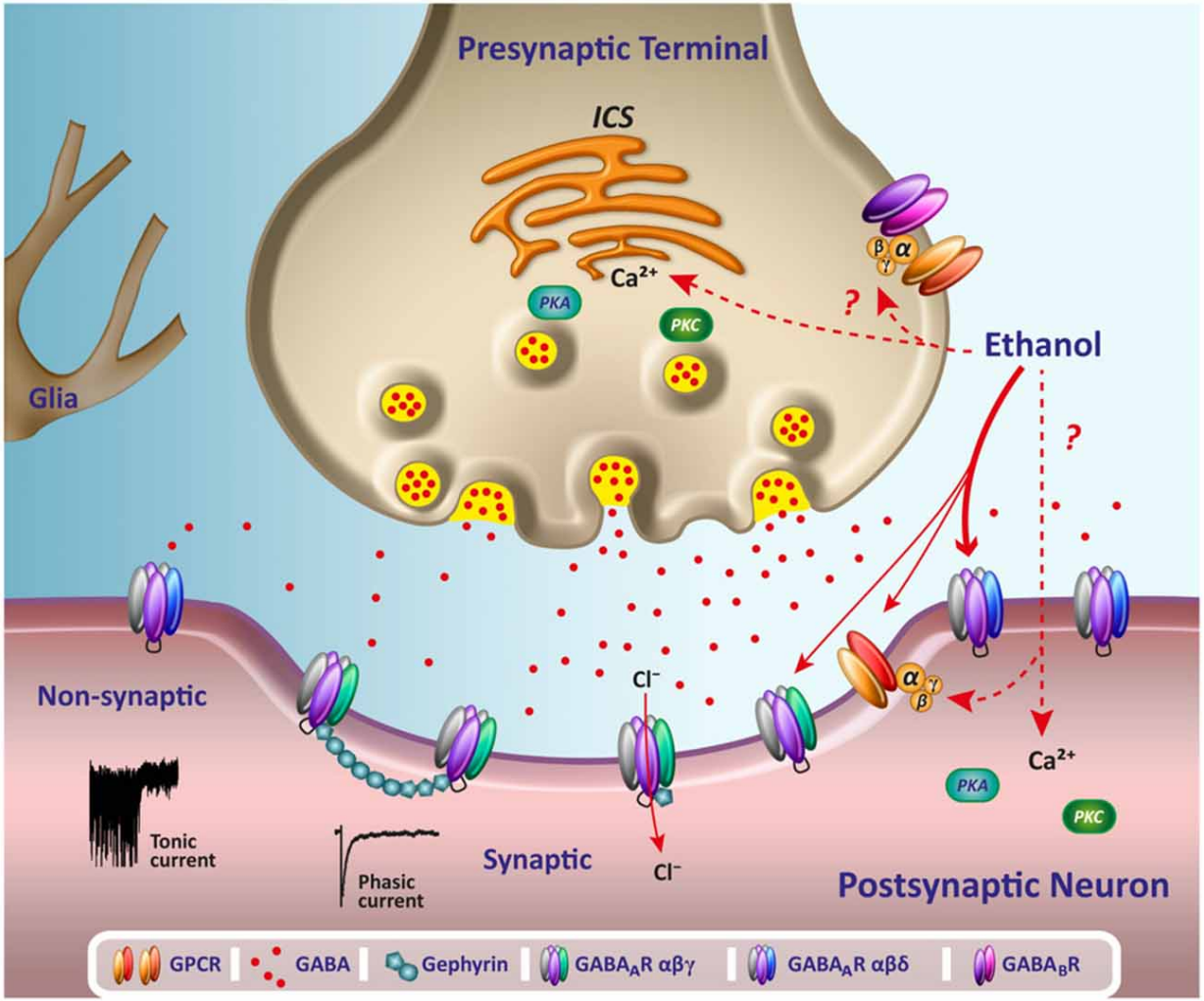
Impact of Drugs of Abuse on Neurobiological Pathways

Neurobiological Pathway Overlap for Substance Use Disorder (SUD)



https://upload.wikimedia.org/wikipedia/commons/d/de/Dopamine_pathways.svg

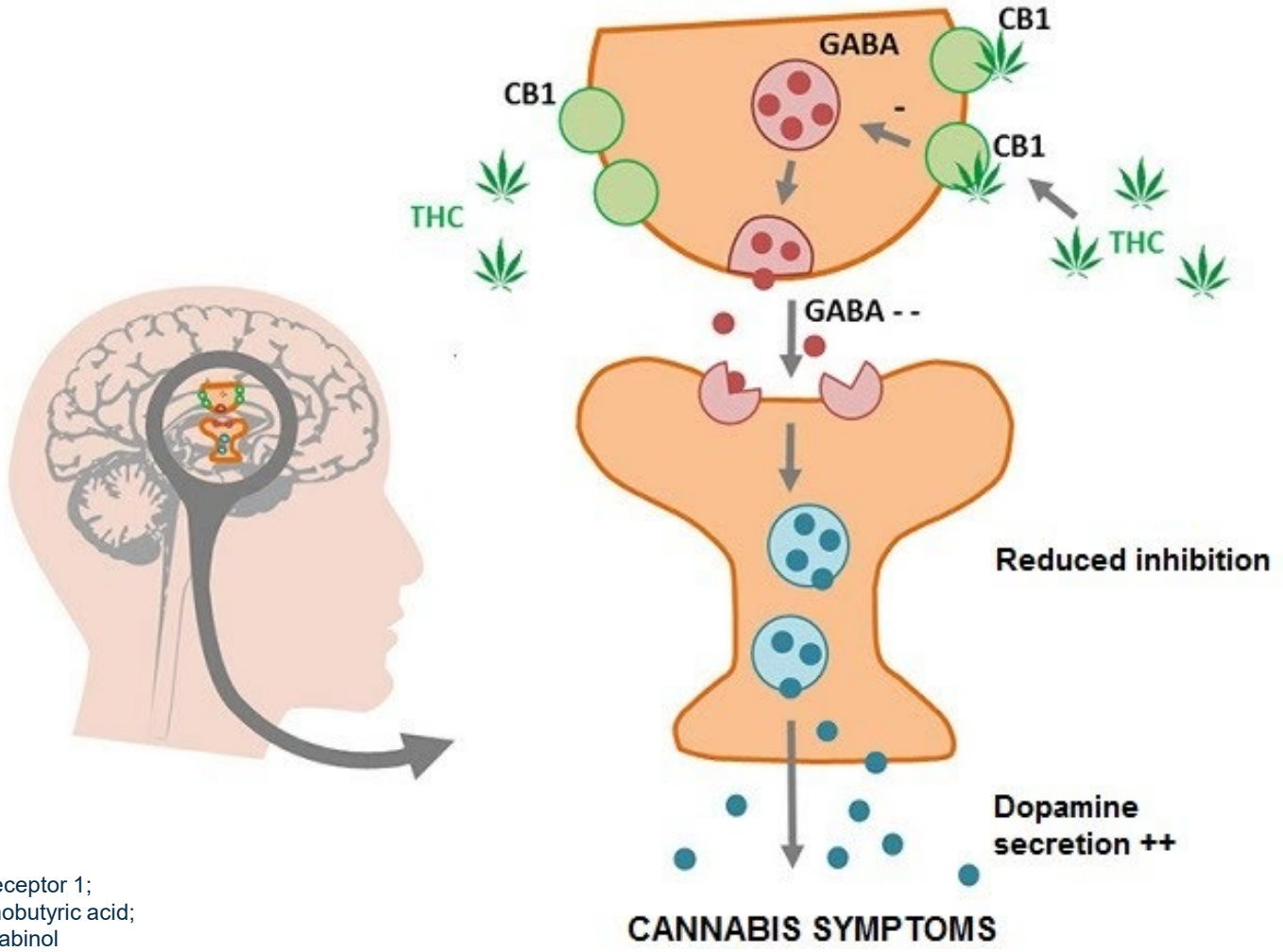
Alcohol Neurobiology



ICS= intracellular calcium stores; Ca^{2+}= calcium ions; Cl^- = chloride ions; PKA = protein kinase A; PKC = protein kinase C; GPCR = G-protein coupled receptor; GABA = gamma-aminobutyric acid; $GABA_AR$ = GABA A receptor and subtypes

Forestera et al *Front Cell Neuro* 2016. 10 (114): 1-17.

Cannabis Neurobiology



CB1 = Cannabinoid receptor 1;
GABA = gamma-aminobutyric acid;
THC= tetrahydrocannabinol

https://thealevelbiologist.co.uk/genetics-control-homestasis/the-nervous-system-and-the-identification-and-consequences-of-damage/ C

THC and CBD in Depression

The cannabis plant is composed of many chemical compounds, including THC and CBD[1]

5-HT1A, serotonin 1A; CB1, cannabinoid type 1; CBD, cannabidiol; CNS, central nervous system; THC, delta-9-tetrahydrocannabinol.

1. de Mello Schier AR et al. *CNS Neurol Disord Drug Targets*. 2014;13(6):953-60.
2. Zou S et al. *Int J Mol Sci*. 2018;19(3). doi: 10.3390/ijms19030833.

THC and CBD in Depression

The cannabis plant is composed of many chemical compounds, including THC and CBD[1]

THC

- Interacts with the endocannabinoid system to modulate mood[1]
- Binds with high affinity to CB1 receptors in the CNS[2]
- A major active chemical component of cannabis[1]
  - Can produce psychoactive and hallucinogenic effects[1]
- The therapeutic use of THC is limited[2]

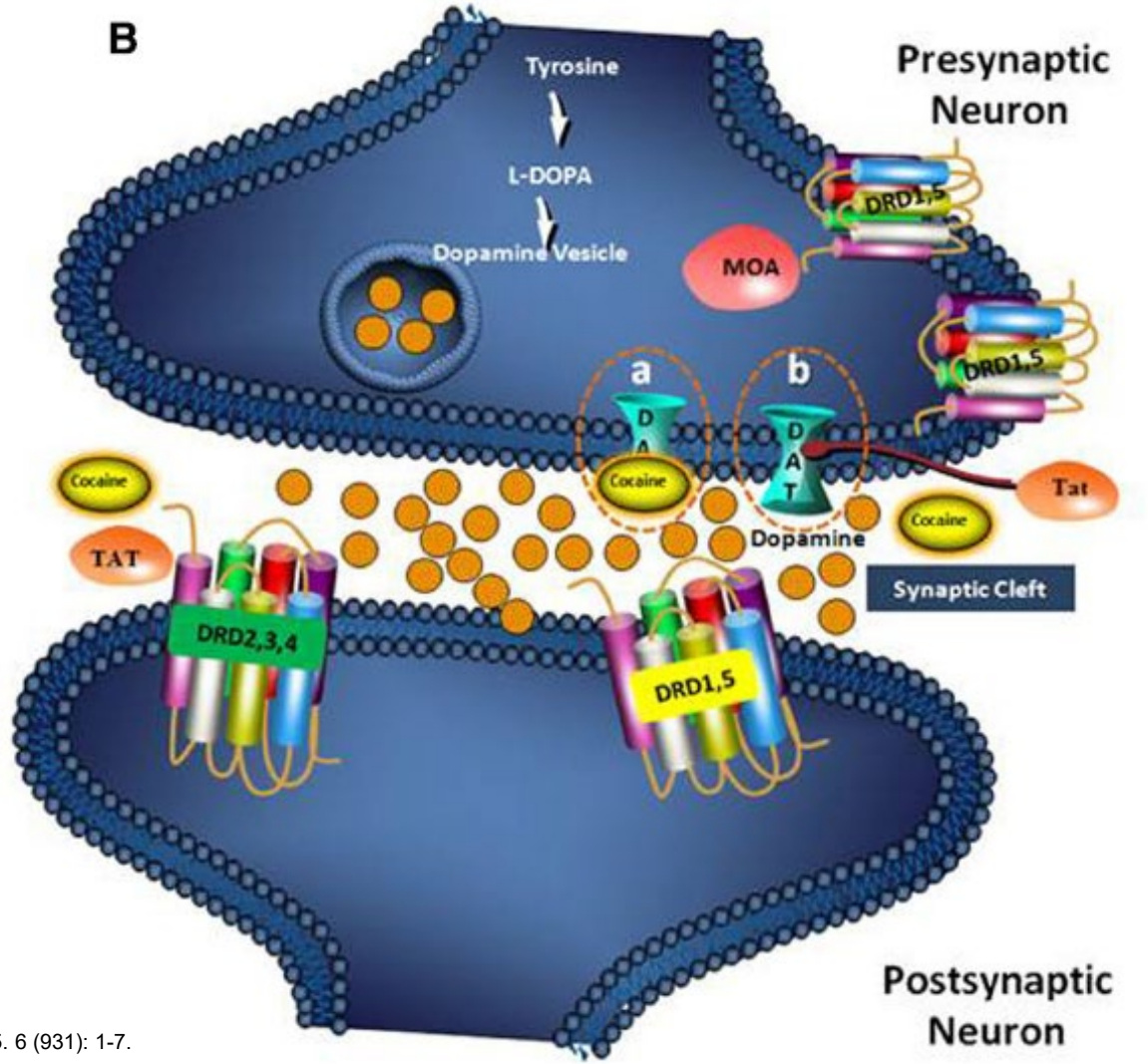
CBD

- Interacts with the endocannabinoid system and activates 5-HT1A receptors in the CNS[1,2]
- Binds with low affinity at CB1 receptors[2]
- Can produce anxiolytic and antidepressant therapeutic effects[1]
- CBD is non-hallucinogenic[1]
- The therapeutic use of CBD for depression is being explored[1]

5-HT1A, serotonin 1A; CB1, cannabinoid type 1; CBD, cannabidiol; CNS, central nervous system; THC, delta-9-tetrahydrocannabinol.

1. de Mello Schier AR et al. *CNS Neurol Disord Drug Targets*. 2014;13(6):953-60.
2. Zou S et al. *Int J Mol Sci*. 2018;19(3). doi: 10.3390/ijms19030833.

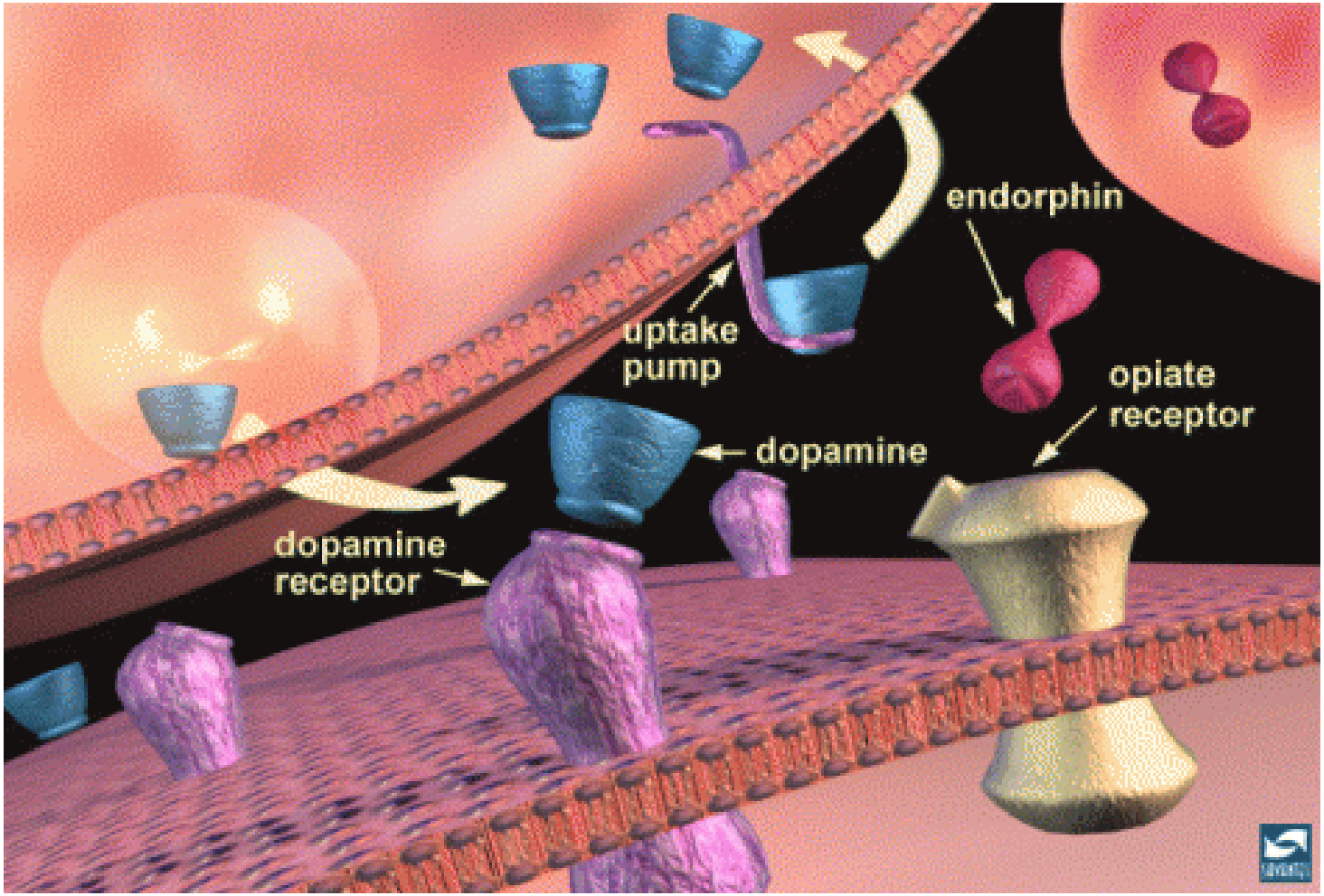
Cocaine Neurobiology



MOA = Monoamine Oxide;
DRD = Dopamine Receptor ;
DAT=Dopamine transporter;
Tat = tat protein

Dahal S et al *Frontiers Microbio* 2015. 6 (931): 1-7.

Opiate Neurobiological Pathways



http://addictionandgenetics.wikidot.com/the-science-behind-addiction

Impact of Drugs of Abuse on MDD Symptoms

Drug	Mechanism of Action	Impact on MDD Symptoms
Alcohol	• Increases DA receptor activation of the reward pathway in the NAc, leading to a decrease in DA levels with chronic use[1] • May increase the risk of MDD via reduced MTHFR production[2]	• Alcohol-use disorder increases the risk of MDD[2] • Alcoholism can be associated with social, psychological, and physical problems that may contribute to the development of depressive disorders[3]
Cannabis	• Cannabinoids interact with CB1 receptors in the eCB system and can influence emotional regulation and reward processing[4]	• Short-term use can reduce perceived symptoms of negative affect; however, continued use may exacerbate baseline symptoms of depression[5]
Cocaine	• Acts as a DA, NE, and 5-HT reuptake inhibitor and increases synaptic DA levels in the VTA-NAc reward pathway[6] • Changes in inflammatory gene expression may be associated with anhedonia in CUD[7]	• Acute ingestion is associated with temporary euphoria and hyperactivity[6] • Heavy use of stimulants like cocaine is associate with higher rates and severity of depressive symptoms, including anhedonia[8]
Opiates	• Act at mu, delta, and kappa receptors in the VTA-NAc reward pathway, and cessation of use may lead to low baseline receptor activity[9]	• Occasional use temporarily relieves MDD symptoms such as anxiety, pain, and insomnia[10] • Long-term use may increase the risk of incident, recurrent, and treatment-resistant depression[10]

5-HT, serotonin; CB1, cannabinoid type 1; CUD, cocaine use disorder; DA, dopamine; eCB, endocannabinoid; GABA, gamma-aminobutyric acid; MDD, major depressive disorder; MTHFR, methylenetetrahydrofolate reductase; NAc, nucleus accumbens; NE, norepinephrine; THC, delta-9-tetrahydrocannabinol; VTA, ventral tegmental area.

1. Hirth N et al. *Proc Natl Acad Sci U S A*. 2016;113:3024-9.
2. Boden JM and Fergusson DM. *Addiction*. 2011;106:906-14.
3. Trevisan LA et al. *Alcohol Health Res World*. 1998;22:61-6.
4. Lucatch AM et al. *Curr Addict Rep*. 2018;5:336-45.
5. Cuttler C et al. *J Affect Disord*. 2018;235:198-205.
6. Korpi ER et al. *Pharmacol Rev*. 2015;67:872-1004.
7. Fries GR et al. *PLOS ONE*. 2018;13:e0207231.
8. Leventhal AM et al. *Exp Clin Psychopharmacol*. 2010;18:562-9.
9. Semenkovich K et al. *Mo Med*. 2014;111:148-54.
10. Sullivan MD. *Clin J Pain*. 2018;34:878-84

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Treatment Challenges and Opportunities

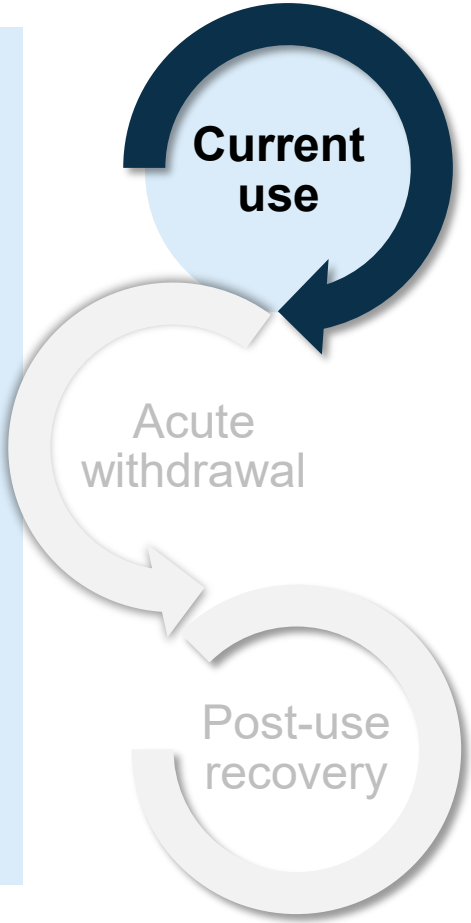
SUD Recovery and Impacts on Treatment for MDD

Alcohol
- May interact with treatment; a period of abstinence may be necessary before evaluating depression[1]

Cannabis
- Combined CBT and pharmacological interventions may be a promising approach to treat depression among occasional cannabis users[2]

Cocaine
- MAOIs are contraindicated in the presence of stimulants[3]

Opiates
- Certain antidepressants may increase the effects of opiates[3]



CBT, cognitive behavioral therapy; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; SUD, substance use disorder.

1. DeVido JJ and Weiss RJ. *Curr Psychiatry Rep*. 2012;14:610-8.
2. Bricker LB et al. *Depress Anxiety*. 2007;24:392-8.
3. Tirado-Munoz J et al. *Adicciones*. 2018;30:66-76.

SUD Recovery and Impacts on Treatment for MDD

Alcohol

- Treating medically complicated withdrawal may be prioritized until a patient is stable[1]
  - However, it has been suggested to treat SUD and MDD concurrently, even during acute episodes of either condition[2]

Cannabis

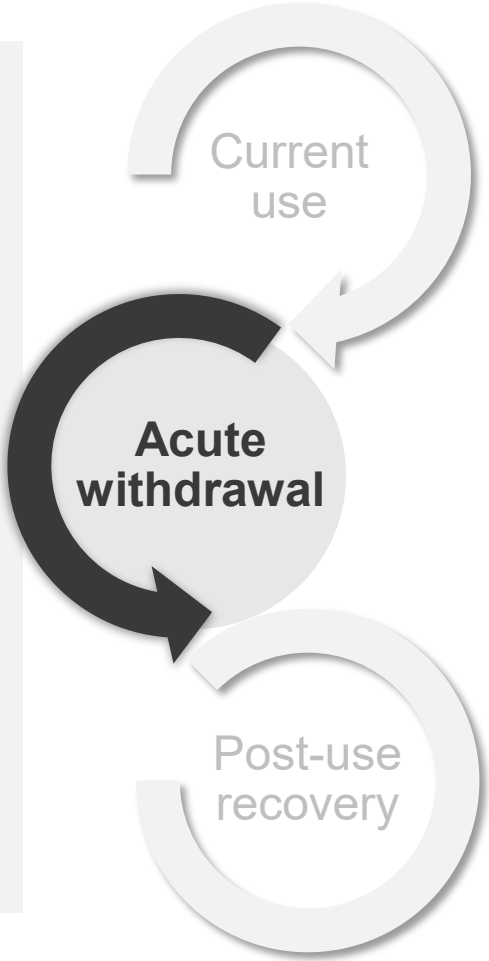
- In subjects with cannabis dependence and MDD, common withdrawal symptoms include depression, anxiety, craving, and irritability[3]

Cocaine

- Certain antidepressants have stimulant properties and are at risk for abuse[2]

Opiates

- Certain TCAs may induce delirium during opioid withdrawal[2]



MDD, major depressive disorder; SUD, substance use disorder; TCA, tricyclic antidepressant.

1. DeVido JJ and Weiss RJ. *Curr Psychiatry Rep*. 2012;14:610-8.
2. Tirado-Munoz J et al. *Adicciones*. 2018;30:66-76.
3. Cornelius JR et al. *Addict Behav.* 2008;33:1500-5.

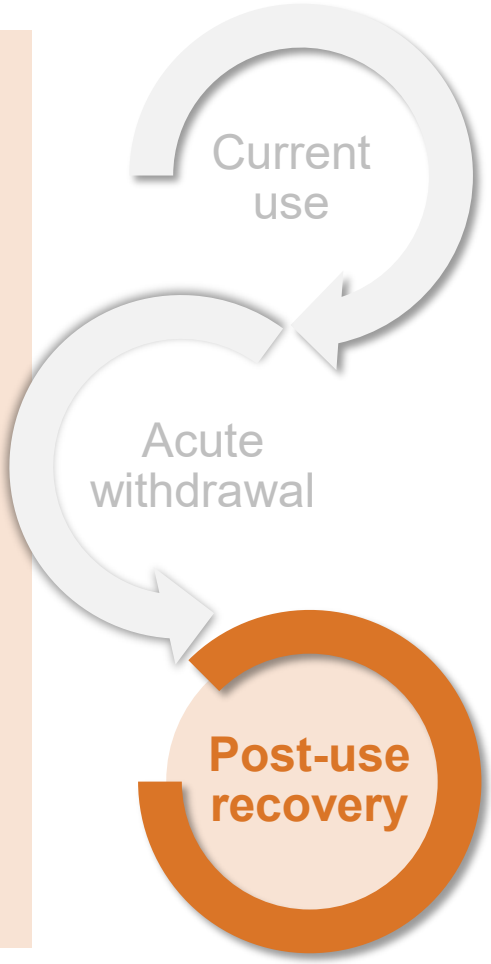
SUD Recovery and Impacts on Treatment for MDD

Alcohol
- If medication is not continued post-inpatient treatment, there can be a high risk of alcohol abuse relapse[1]

Cannabis
- Withdrawal symptoms have been associated with rapid relapse in subjects with cannabis dependence and MDD[2]

Cocaine
- Loss of control over cocaine cravings can lead to depression and anxiety[3]

Opiates
- In certain depressed subjects on maintenance medication for opioid dependence, SSRIs can significantly ameliorate depression and decrease drug use[4]



MDD, major depressive disorder; SSRI, serotonin selective reuptake inhibitors; SUD, substance use disorder.

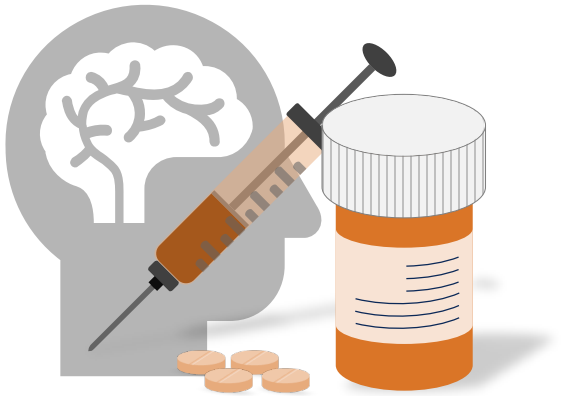
1. DeVido JJ and Weiss RJ. *Curr Psychiatry Rep*. 2012;14:610-8.
2. Cornelius JR et al. *Addict Behav* 2008;33:1500-5.
3. DiGirolamo GJ et al. *J Dual Diagn*.2017;13:298-304.
4. Quello BS et al. *Sci Pract Perspect.* 2005;3:13-21.

Treatment Considerations for Comorbid MDD and SUD

- MDD and SUD can be treated concurrently[1]
- Underlying causes of MDD (primary or induced) should be considered[1]
- Psychotherapy in addition to pharmacotherapy could be used[1]
- Pharmacological treatment options should consider an agent's efficacy, safety, interactions, and abuse potential[1]

The CANMAT evidence-based recommendations for the treatment of SUD and MDD[2]

- **For alcohol**: Antidepressant; add-on opioid antagonist (or alone); add-on opioid antagonist to SSRI
- **For cocaine**: SGA as an add-on or alone
- **For opiate**: TCA add-on to opioid agonist for withdrawal
- **For cannabis**: No recommendations



AUD, alcohol-use disorder; CANMAT, Canadian Network for Mood and Anxiety Treatments; MDD, major depressive disorder; SGA, second-generation antipsychotic; SSRI, selective serotonin reuptake inhibitor; SUD, substance-use disorder; TCA, tricyclic antidepressant.

1. Tirado-Munoz J et al. *Adicciones*. 2018;30(1):66-76.
2. Beaulieu S et al. *Ann Clin Psychiatry*. 2012;24(1):38-55.

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