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APPROACHES TO CANNABIS USE DISORDER MEDICATION-ASSISTED TREATMENT GUIDELINE

SCOPE: This Approach to Cannabis Use Disorder Medication-Assisted Treatment (CUD MAT) Guideline is intended to offer prescribing assistance for providers, clients, and the interested general public to increase the effectiveness and utilization of CUD MAT in the ambulatory care setting. It is not intended to be comprehensive in scope. These recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual client

INTRODUCTION: Cannabis is derived from plants in the Cannabaceae family that include the species *Cannabis sativa* and *Cannabis indica*. The main active chemical is called delta-9 tetrahydro-cannabinol (THC) and the potency ranges between products. Marijuana is a common form of cannabis and is made from the dried flowers of the cannabis plant. Cannabis is the most commonly used illicit drug in the United States. While cannabis continues to be illegal at the federal level, 10 states have legalized recreational use in adults over 21 years of age, and 33 states have legalized medical cannabis. In general, studies indicate that people do not perceive cannabis use as risky. In the 2017 National Survey on Drug Use and Health (NSDUH), approximately one third of people indicated they perceived that weekly cannabis use as risk for great harm. This is significantly fewer people than in previous surveys.

In fact, cannabis is associated with multiple medical conditions. Smoking cannabis can irritate lungs and lead to breathing problems. Chronic use can lead to a syndrome with cycles of severe vomiting called cannabinoid hyperemesis syndrome. There are multiple psychiatric symptoms that can occur including hallucinations, paranoia, anxiety, and depression. In people already prone to these symptoms due to a mental illness, they may be worsened with cannabis use.

Cannabis use can have long-term effects on brain development in adolescents. Cannabis use in adolescents is associated with declines in attention and memory. While cannabis cessation is associated with some improvements, research is currently being conducted to understand whether these changes are permanent, and the duration of effect.

Cannabis use disorder (CUD) occurs when recurrent use of cannabis leads to significant impairment. The NSDUH survey in 2017 indicated that approximately 4.1 million people 12 years of age or older had a CUD. This represents 1.5% of the population 12 years of age or older. For comparison, alcohol use disorder affects 5.3%, pain reliever use disorder effects 0.6%, and stimulant use disorder affects 0.2% of the population. The number of people with a CUD has stayed relatively constant in between 2010 and 2017.

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A range of interventions should be considered for all people with CUD including assessment of withdrawal, management of detoxification, and long-term strategies to reduce the medical and psychosocial harms of CUD. In addition, any co-occurring conditions that jeopardize a person's treatment success should be addressed.

ASSESSMENT AND INTERVENTION PLANNING: As with any substance with abuse potential, the DSM-5 details diagnostic criteria for CUD (specifiers: in early remission, in sustained remission, in a controlled environment, mild, moderate, severe) in addition to cannabis intoxication (specifier: with perceptual disturbances), cannabis withdrawal, other cannabis-induced disorders, and unspecified cannabis-related disorder. To meet criteria for CUD, patients must exhibit at least 2 out of 11 DSM-5 criteria over a 12-month period leading to clinically significant impairment and/or distress. Examples of these criteria include: using cannabis in larger amounts over a longer period of time than intended, use in hazardous situations, cravings for cannabis, and experiencing tolerance and/or withdrawal, among others. The severity of the use disorder is based on the number of criteria met with mild use disorder associated with 2-3, moderate use disorder associated with 4-5, and severe use disorder associated with 6 or more criteria met. There is strong evidence that frequency of cannabis use as well as younger age of first use are associated with higher severity CUD.

Several tools varying in length have been developed to assist in screening, assessing, and monitoring CUD. For example, the Cannabis Abuse Screening Test (CAST, appendix IV) is a 5-item, 15-point screen that has been validated for use in adolescents and young adults. The Cannabis Use Problems Identification Test (CUPIT©) is a 16-item, 82-point instrument validated for use in adolescents and adults.

There are associations between mental health problems contributing to cannabis use as well as cannabis use contributing to mental health problems. Therefore, it may be useful for specialty mental health evaluation anytime along the course of treatment for a patient with CUD. Active use and active withdrawal complicate evaluation and/or treatment of underlying primary mental health diagnoses. Currently, more work is needed to develop evidence based approaches to the pharmacological management of individuals with comorbid CUD and other mental health diagnoses.

WITHDRAWAL AND MANAGEMENT: After heavy or prolonged cannabis use, cessation can lead to clinically significant impairment or distress due to a withdrawal syndrome that can include:
1. Irritability, anger, or aggression
2. Nervousness or anxiety
3. Sleep difficulty (e.g. insomnia, disturbing dreams)
4. Decreased appetite or weight loss
5. Restlessness
6. Depressed mood
7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache

Individual withdrawal symptoms have their own time course but generally withdrawal symptoms begin a day or two after abstinence and can last about two weeks. Not surprisingly, higher levels of dependence are associated with higher levels of withdrawal after cannabis cessation. In one study, angry outbursts and trouble sleeping were associated with the most distress for cannabis dependent users experiencing withdrawal. The Cannabis Withdrawal Scale (CWS, appendix V) is a 19-item measure that has been validated for use in both clinical and research settings to assess the severity of cannabis withdrawal. Higher withdrawal severity is correlated with a higher degree of functional impairment in normal daily activities as well as the propensity for relapse to cannabis use.

While withdrawal symptoms contribute to functional impairment and propensity for relapse during the withdrawal period, the role of pharmacological management of withdrawal symptoms is not clear. Generally low quality studies have shown some benefit on cannabis withdrawal sleep difficulties for gabapentin, lofexidine, mirtazapine, quetiapine, or zolpidem but it is the consensus that the need for further, higher quality studies exists (Refer to Community Behavioral Health Services guidelines for prescribing information). THC replacement strategies have demonstrated some positive effects on craving and withdrawal symptoms but should still be considered experimental and their recommendation is considered outside the standard of practice for our system.

CUD OFF-LABEL PHARMACOTHERAPY: Clinical trials have not shown consistent evidence of efficacy for any medication in the treatment of CUD; no medication is approved for this indication by the US Food and Drug Administration. N-acetylcysteine (NAC) and gabapentin have yielded the most favorable results in clinical trials in reducing cannabis use. Trials with other medications have shown mixed or negative findings, including antidepressants, anxiolytics, and anticonvulsants.

GABAPENTIN: Gabapentin is a GABAergic agent that binds to receptors with GABA-like activity modulating release of excitatory neurotransmitters. The exact mechanism to aid in treatment of CUD is not known. In one clinical trial, gabapentin in addition to psychosocial intervention led to short-term reduction in cannabis use compared to placebo. See Appendix II for dosing recommendations and client considerations.

Side effects: Common side effects include dizziness, drowsiness, ataxia, nausea, vomiting, and tremor.

Drug interactions: There are no clinically meaningful drug interactions with gabapentin. Side effects may be enhanced when combined with other CNS depressant medications and substances.

N-ACETYLCYSTEINE (NAC): NAC is an N-acetyl prodrug of the naturally occurring amino acid cysteine. It is an agent typically used for acetaminophen overdose or as a mucolytic in its IV form, but has been tested orally in the treatment of CUD. NAC is available over-the-counter as a dietary supplement. There have been two phase II randomized controlled trials that have produced different results, with one trial showing reduced cannabis use in conjunction with contingency management, and the other no difference between NAC and placebo. See Appendix II for dosing recommendations and client considerations.

Side effects: When given orally, side effects can include chest tightness, hypotension, urticaria, nausea, vomiting, and bronchospasm. When used in trials, NAC was well tolerated.

Drug interactions: There are no clinically meaningful drug interactions with N-acetylcysteine.

DURATION OF TREATMENT WITH CUD PHARMACOTHERAPY: Published clinical trials evaluated efficacy of gabapentin for 12 weeks and efficacy of NAC for 8 weeks. Long term and discontinuation trials have not been performed, therefore the optimal duration of CUD MAT has not been established.

CO-OCCURING DISORDERS:

Substance Use Disorders: Gabapentin has been implicated increasingly as a potential substance of abuse, with rates of abuse in individuals with substance use disorders estimated in the range of 15 to 22%. The risk is increased when combined with CNS depressants such as opioids. Gabapentin has been studied as treatment of other substances of abuse including cocaine and methamphetamine, and has failed to consistently show efficacy in decreasing use.

NAC has been investigated as a treatment of other substances of abuse in addition to cannabis. Studies have looked at NAC in the treatment of cocaine, nicotine and methamphetamine abuse with the most of the data showing limited efficacy on most study primary outcome results.

Schizophrenia: NAC has been investigated as an adjunct treatment of schizophrenia and there is some evidence that it may be effective in reducing the negative and general symptoms of schizophrenia. One study found that taking NAC in doses of 1000 mg twice daily improved symptoms when compared with placebo.

Obsessive-Compulsive and Anxiety Disorders: Gabapentin was shown in one OCD study to improve symptoms initially but failed to show sustained improvement for the duration of the eight-week study. There is some evidence supporting the use of gabapentin in combined treatment with an antidepressant for the symptoms of posttraumatic stress disorder (PTSD).

NAC has been investigated in the treatment of OCD and the results are mixed. Some studies have found benefit while others have not. Doses have been tried in the 2400 to 3000 mg/day range. Two areas that may show some promise are for treating the symptom of excoriation and NAC as an adjunct with citalopram in the treatment of children and adolescents with OCD.

Mood Disorders: Gabapentin has been used and investigated as both primary and adjunctive treatment of bipolar disorder, however, placebo controlled studies have not supported that efficacy in the treatment of bipolar disorder. There are few studies and weak evidence for the role gabapentin in the treatment of depressive disorders.

NAC has been investigated in the treatment of Bipolar and Depressive Disorders with mixed results. NAC is often studied as an adjunctive treatment with more traditional mood disorder medications and while some studies have indicated and meta-analysis have shown NAC to be promising other studies have found no significant impact on depressive or manic symptoms.

Chronic Pain: Gabapentin has been used for the treatment of chronic pain.

SPECIAL POPULATIONS:

Pregnancy: While limited data does not support an increased risk of preterm delivery, low birth weight, or congenital anomalies in pregnant women who smoke cannabis, the American College of Obstetricians and Gynecologists (ACOG), the American Academy of Pediatrics (AAP), and the Academy of Breastfeeding Medicine advise avoiding cannabis use during pregnancy due to concerns for the neurodevelopmental impact on the fetus. Chemical products from cannabis use are transferred across the placenta.

Gabapentin crosses the placenta and adverse effects have been observed in animal reproduction studies, however pregnancy registry outcome data following maternal use of gabapentin during pregnancy is limited. Folic acid supplementation is recommended prior to and during pregnancy in women using gabapentin.

With NAC use, adverse events have not been observed in animal reproduction studies. Based on limited reports using NAC to treat acetaminophen overdose in pregnant women, NAC has been shown to cross the placenta.

Lactation: Cannabis is transferred into breast milk and may be present up to 6 days after maternal use.

Gabapentin is present in breast milk. The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. The potential risks of exposure for the infant include drowsiness, inadequate weight gain, and delay in developmental milestones.

It is not known if NAC is excreted in breast milk and the decision to continue or discontinue breast-feeding during therapy should consider the risk of infant exposure, the benefits of breast-feeding to the infant, and benefits of treatment to the mother.

Adolescents: NAC was found in one review to show some clinical usefulness in the treatment of CUD in young people.

Hepatic Impairment: Both gabapentin and NAC can be safely used in hepatic impairment, no dosage adjustments necessary.

Renal impairment: Gabapentin requires dose reduction for clients with creatinine clearance less than 60ml/min. NAC does not require dosage adjustment. See appendix II for recommendations.

BEHAVIORAL THERAPIES:

A 2016 Cochrane review looked at the efficacy of various psychosocial interventions for the treatment of CUD in the outpatient setting. The selection included 23 randomized controlled studies involving 4045 participants from the United States, Australia, Switzerland, Canada, Brazil, and Ireland. While the generalizability of the findings were limited due to the homogeneous nature of the treatment seekers in each locality and other study limitations, psychosocial intervention, in comparison with minimal treatment controls, reduced the frequency of use and severity of dependence in the short-term.

The strongest evidence of efficacy for the use of psychosocial interventions was for cognitive-behavioral therapy (CBT), motivational enhancement therapy (MET), and their combination, provided in more than four sessions delivered over a period of four to six months. Contingency management (CM) interventions were found to contribute to improvements in CUD when combined with CBT or MET + CBT. MET may be particularly useful when working with individuals with lower motivation to change their cannabis use who are just beginning treatment.

Cognitive-Behavioral Therapy (CBT): CBT is a structured behavioral therapy that emphasizes the identification and management of thoughts, behaviors, and the external triggers that lead to the undesired or problematic behavior. The clinician engages the client into learning coping and problem-solving skills that promote the replacement of an undesired behavior with one that is desired.

Motivational Enhancement Therapy (MET): MET, also frequently called motivational interviewing, is a directive, client-centered approach that emphasizes the importance of self-efficacy and positive change with the goal of building and maintaining motivation through non-judgmental and empathic interviewing and active listening. Clinicians provide personalized feedback and education related to patterns of behaviors and thinking.

Contingency Management (CM): CM, a behavioral intervention, utilizes behavioral reinforcement techniques to encourage and promote specific behaviors. Frequently, individuals are provided with voucher incentives when target behaviors are expressed. In the treatment of CUD, the specific behaviors may include consistent treatment attendance or cannabis-negative urine toxicology results.

We recommend the use of structured behavioral and motivational enhancing therapies as an adjunct to psychopharmacological interventions. The intervention utilized will be based on client preference and actual treatment availability.

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APPENDIX I: LOCAL RESOURCES & INFORMATION:

Program name	Overview
Treatment Access Program (TAP) 1380 Howard St, 1st Floor San Francisco, CA 94103 Phone: (415) 503 – 4730 Hours of Operation: Mon – Fri: 8:00AM – 5:00PM *Accepts walk-in. New intakes until 2:00pm.*	The centralized site within SFDPH BHS that provides substance use disorders screening, assessment, level of care recommendations, and placement authorization for SUD residential treatment. Provide referrals to other SUD programs and provider consultation.
Free Cannabis Use Cessation Groups	
Marijuana Anonymous "Friends Of Bud Group" 4301 Geary Blvd. San Francisco, CA Hours: Tuesday 7:30-8:45pm "On A Mission" 2872 Folsom St. San Francisco, CA Hours: Saturday 11:00-12:00	A 12-step help program for men and women.
12-Step Programs (NA, AA, Al-Anon, etc) Various dates, time and locations	A fellowship or society of men and women for whom drugs had become a major problem and who meet regularly to help each other stay clean. Narcotics Anonymous (NA): http://sfna.org/ Alcoholics Anonymous (AA): http://www.aasf.org/
Free Phone and Online Programs	
Cannabis Hotline 855-978-2989	Free, confidential cannabis helplines to help those battling with their addiction. A cannabis hotline focuses specifically on that drug as well as co-existing addictions or conditions.
Resources for Providers	
Marijuana Lit: A Fact-Based Toolkit for Prevention https://attcnetwork.org/centers/network-coordinating-office/marijuana-lit-infographics	In today's climate messages abound regarding cannabis use, its harm, and legalization, making it difficult to determine fact from fiction. The ATTC Network Coordinating Office presents a user-friendly package with straightforward, accurate information and resources to help substance use disorder providers in their work.

Resources for Patients & Families	
California DPH: Let's Talk Cannabis https://www.cdph.ca.gov/Programs/DO/letstalkcannabis/Pages/LetsTalkCannabis.aspx	The California Department of Public Health provides facts and resources regarding cannabis and how it affects our bodies, minds and health.
NIDA: Cannabis Facts for Teens https://www.drugabuse.gov/sites/default/files/teens_brochure_2013.pdf	Patient brochure directed at providing information, FAQs, and resources for adolescents/young adults regarding cannabis use.
[CANNABIS] DECODED https://www.smchealth.org/cannabis	[Cannabis] Decoded is a San Mateo County initiative to educate youth and young adults about the facts on cannabis use.
Truth (or nah?!) SF https://www.truthornahsf.org/	A resource for youth and adolescents to have safe and accurate information for answering their questions about cannabis consumption.

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APPENDIX II: CUD MEDICATION ASSISTED TREATMENT PHARMACOTHERAPY

Product	Dosage	Common Side Effects	Availability	Counseling Points	Advantages	Disadvantages
Off-label Agents						
Gabapentin 100mg, 300mg, 400mg capsules 600mg, 800mg tablets 250mg/5ml oral solution	Take 300mg once or twice daily, may increase up to 1200mg TID Dosing adjustment is necessary for clients with renal impairment: >30-50ml/min: 200 to 700mg BID >15-29ml/min: 200 to 700mg daily 15ml/min: 100 to 300mg daily <15ml/min: reduce daily dose in proportion to CrCl based on dose for CrCl of 15 ml/min	Dizziness, drowsiness, ataxia, peripheral edema, abnormal gait, confusion, weight gain, nausea, diarrhea, xerostomia, tremor, nystagmus.	Prescription Only Relative Cost: $	• Start medication at bedtime as it can cause drowsiness and dizziness • Avoid driving and doing other tasks or actions that call for you to be alert until you see how this drug affects you	• May be beneficial in clients with co-morbid anxiety, or neuropathic pain • Relatively inexpensive	• Dose adjustments for renal impairment • Requires dose titration • Up to TID dosing
N-acetylcysteine IV: 200mg/ml 500mg, 2500mg effervescent tablets OTC: 600mg capsules	CUD studied dose: 1200mg BID	Upper respiratory infection, vivid dreams, insomnia, hypotension, nausea, vomiting, urticarial, rash.	Oral: OTC IV: prescription only Relative Cost: $	• Mix effervescent tablets with water, do not swallow the tablets whole. Drink within 2 hours of mixing	• Relatively well tolerated • Minimal drug interactions or monitoring required	• Oral tablets OTC only • Studies have shown mixed efficacy results

APPENDIX III: CANNABIS TERMS

Alcohol Extraction: A process in which cannabis is placed in alcohol to extract the THC from the plant. The plant soaks in alcohol, is boiled, and what remains is oil containing around 90% of the THC from the plant.

Bhang: Bhang is frequently used as a synonym for marijuana flowers, though the word itself originally refers to a cannabis-infused beverage produced in the Indian subcontinent.

Blunt: A method of smoking cannabis which consists of hollowing out a cigar, filling it with cannabis, and rerolling it.

Bong: A filtration device generally used for smoking **cannabis**, tobacco, or other herbal substances

Bowl: The part of an instrument where one packs the cannabis. Alternatively, bowl can be used to refer to the pipe, or it can be used as a crude unit of measurement.

Bubbler: A bubbler is a cross between a pipe and a bong and is an instrument used to smoke cannabis.

Dab: A highly concentrated cannabis extract. The precise definition of "dabs" varies by location, but it is widely regarded as a more potent way to consume cannabis.

Earwax: This cannabis product is made by whipping oils extracted from hash.

Edibles: Baked goods or candy that have been infused with cannabis and can be consumed orally.

Hookah: The hookah is a traditional Indian smoking device that has a centralized bowl with many tubes protruding from it.

Joint: The joint is a cannabis version of the cigarette. They are almost always rolled up by hand using rolling papers.

Oil: Oil is extracted through alcohol, CO_2, or any other solvent extraction process and is often considered the most potent form of cannabis due to its high THC content. Oil can be consumed through dabbing, oral consumption, vaporization, or smoking.

Vaporizer: An alternative to smoking and burning cannabis, a vaporizer activates the ingredients in the plant with enough heat for the user to inhale. Vaporizers provides a way to use cannabis while reducing carcinogens from the burning of the plant.

APPENDIX IV: CANNABIS USE DISORDER MEDICATION ASSIST

CANNABIS ABUSE SCREENING TEST

In the last 12 months, have you smoked cannabis?
Yes □   No □

In the last 12 months…	Never	Rarely	From time to time	Fairly often	Very often
Have you smoked cannabis before midday?	□ 0	□ 1	□ 2	□ 3	□ 4
Have you smoked cannabis when you were alone?	□ 0	□ 1	□ 2	□ 3	□ 4
Have you had memory problems when you smoked cannabis?	□ 0	□ 1	□ 2	□ 3	□ 4
Have friends or members of your family told you that you ought to reduce your cannabis use?	□ 0	□ 1	□ 2	□ 3	□ 4
Have you tried to reduce or stop your cannabis use without succeeding?	□ 0	□ 1	□ 2	□ 3	□ 4
Have you had problems because of your use of cannabis (argument, fight, accident, bad result at school, etc)? Which ones?	□ 0	□ 1	□ 2	□ 3	□ 4

To calculate a score, the responses are coded on a scale of 0 to 4. The total score obtained (which can range from 0 to 24) indicates if the questioned users are at risk. A score of less than 3 indicates no addiction risk. A score of 3 or less than 7 indicates low addiction risk, and a score of 7 or above indicates high addiction risk.

SCORE	

APPENDIX V: The Cannabis Withdrawal Scale

Instructions: This version of the CWS asks about symptoms experienced over the last 24 hours, and can be administered by an interviewer OR by self-report.

The following statements describe how you have felt over the last 24 hours. Please **circle the number** that most closely represents your personal experiences for each statement. For each statement, please rate its negative impact on normal daily activities on the same scale (0 = Not at all to 10 = Extremely), writing the number in the right-hand column.

		Not at all Extremely					Moderately						Negative Impact on daily activity (0 – 10)
1	The only thing I could think about was smoking some cannabis	0	1	2	3	4	5	6	7	8	9	10	
2	I had a headache	0	1	2	3	4	5	6	7	8	9	10	
3	I had no appetite	0	1	2	3	4	5	6	7	8	9	10	
4	I felt nauseous (like vomiting)	0	1	2	3	4	5	6	7	8	9	10	
5	I felt nervous	0	1	2	3	4	5	6	7	8	9	10	
6	I had some angry outbursts	0	1	2	3	4	5	6	7	8	9	10	
7	I had mood swings	0	1	2	3	4	5	6	7	8	9	10	
8	I felt depressed	0	1	2	3	4	5	6	7	8	9	10	
9	I was easily irritated	0	1	2	3	4	5	6	7	8	9	10	
10	I had been imagining being stoned	0	1	2	3	4	5	6	7	8	9	10	
11	I felt restless	0	1	2	3	4	5	6	7	8	9	10	
12	I woke up early	0	1	2	3	4	5	6	7	8	9	10	
13	I had a stomach ache	0	1	2	3	4	5	6	7	8	9	10	
14	I had nightmares and/or strange dreams	0	1	2	3	4	5	6	7	8	9	10	
15	Life seemed like an uphill struggle	0	1	2	3	4	5	6	7	8	9	10	
16	I woke up sweating at night	0	1	2	3	4	5	6	7	8	9	10	
17	I had trouble getting to sleep at night	0	1	2	3	4	5	6	7	8	9	10	
18	I felt physically tense	0	1	2	3	4	5	6	7	8	9	10	
19	I had hot flashes	0	1	2	3	4	5	6	7	8	9	10	