Guidelines for Prescribing Controlled Psychotropic Medications to Patients with Substance Use

Purpose:

The following guideline was developed to provide physicians a framework for prescribing controlled psychotropic medications to patients with active or previous substance use. It is intended to improve patient safety and outcomes. Therefore, this guideline applies to all patients who either currently use, or have histories of substance use, whether or not a substance use disorder has been diagnosed. Once a disorder is diagnosed, it should be listed in the diagnosis throughout treatment, including the remission status.

The recommendations in this guideline are based on:

- American Psychiatric Association Practice Guidelines for Treatment of Substance Use Disorder, the California Medical Board, American Society of Addiction Medicine, and an extensive literature review including Drug Abuse Warning Network Data (DAWN report).
- Discussion with child/adolescent psychiatrists for Consideration of factors unique to this patient population.
- Direct input and approval from the county psychiatrists, Medical Director, County of Santa Clara Behavioral Health Services and the contract agency medical directors.
- Direct input from providers at Substance Use Treatment Services and Alexian Homeless Health Plan.

BACKGROUND

According to the Controlled Substances Act, all scheduled controlled drugs CI thru CV are considered to have varying potential to cause physical and psychological dependency with Schedule I drugs having the highest potential and having no accepted medical use, making their distribution a federal offense. At the federal level, marijuana remains classified as a Schedule I substance and its distribution is considered a federal offense. Therefore, the prescriptions for medical marijuana are considered invalid and such prescriptions are considered to be recommendation\(^1\). In California, passage of Prop 64 on 11/09/2016, recreational marijuana for persons aged 21 years or older and allowed growing marijuana for personal use.

All controlled drugs in schedule I thru V as well as alcohol can cause psychiatric adverse effects. The safety profile of all controlled drugs and alcohol can in turn complicate the diagnosis and the treatment course of mental illness and make it nearly impossible to assess the safety and efficacy of psychotropics prescribed by providers. As a result, the substance use or alcohol use complicates the assessment and treatment of the underlying psychiatric condition. Therefore, when the controlled drugs are prescribed by another provider and noted to cause adverse psychiatric effects (including addiction); it is incumbent on the psychiatrist to coordinate the care with those provider(s) (see attachment 1 for more details).
Process Flow for patients receiving Controlled Medications from outside Providers
(Flow Diagram 1)

Controlled Drugs Schedule I-V Including Marijuana

Prescribed Controlled Drug Schedule II-V plus Medical Marijuana

+ Adverse Psychiatric Effects

- Adverse Psychiatric Effects

Coordinate care with other providers

Monitor for Adverse psychiatric effects at each appointment

Document the adverse psychiatric effects & the coordination of care

Document absence of adverse psychiatric effects & monitor at each f/u appointment

Recommendations & restrictions in the guideline apply ONLY if you are considering to prescribe controlled RX.
General Considerations

I. When prescribing controlled medications, a higher level of caution is applied to patients with active or histories of substance use and patients on Medication Assisted Treatment with Methadone/Buprenorphine.

II. Higher levels of restrictions are applied for patients actively using, compared to those in levels of remission.

III. Different strategies are applied to patients currently on controlled medications compared to new starts.

IV. “Controlled Drugs” refer to DEA Scheduled I-V including cannabinoids.

V. Substance-induced symptoms should initially be treated with non-controlled medications.

VI. Schedule II medications are not refillable and cannot be dispensed in partial amounts. Separate RXs may be written with the fill date specified.

VII. Although caffeine and nicotine are addictive substances; for the purposes of this guideline, they are Excluded. Nonetheless, smoking cessation should be routinely pursued and documented.

VIII. Document psychoeducation specifying risks for each controlled medication and combining specific agents; as well as the potential for worsening underlying mental disorder(s).

IX. Providers should limit prescribing any combination of opioid analgesics with benzodiazepines to when Alternative treatment regimens have been attempted with suboptimal response. If these medicines are prescribed together, limit the dosage and duration of each drug to the minimum possible while achieving the desired clinical effect. **Document psychoeducation regarding risk and benefit of such combinations and the availability of Nasal Naloxone.**

(http://www.fda.gov/Drugs/DrugSafety/ucm518473.htm)

X. For the purpose of this guideline, an adequate trial consists of treatment for a minimum of 4-8 weeks duration, at the maximum tolerable dose. When describing treatment response, use terms such as: no response, minimal/partial response. Intolerance should be documented using terms such mild, moderate, and severe and explain the timing of side effects in relation to initiation and administration time.

XI. Urine toxicology screens should include THC and measures of alcohol consumption i.e. GGT (Gamma-glutamyl transferase). Currently, THC and certain benzodiazepines need to be specified in the lab order. Order urine toxicology screen at baseline and randomly as index of suspicion rises. Toxicology screens should be considered for all patients with or without substance use history to ascertain medication adherence, diversion and to screen for other reported or unreported substances.

XII. Diversion of medication should be considered when urine toxicology screens are negative while controlled medications have been prescribed (Consider half-life and frequency of medication prescribed). When this occurs, the following is recommended: (Note: There may be a delay of 1-2 weeks before recent dispensing data appears on the CURES report).

A. Perform a thorough review of medication adherence by confirming the directions and timing
of the medications, compared to appointments, pharmacy dispensing data, and the timing of the toxicology screen.

B. Prescribe smaller quantities of the medications, order random toxicology screens, and schedule more frequent follow up appointments prior to refills.

XIII. Refused or missed urine toxicology screens should be deemed as positive results; therefore, patient considered to be actively using. (Patient should be informed of this agreement prior to requesting screens and the discussion documented).

XIV. When limiting RX supply, indicate "no early refills" on the PRESCRIPTION.

XV. Many of the symptoms of ADHD in adults such as: restlessness, distractibility, concentration difficulty and organizational problems also occur in other conditions i.e., Depression, Anxiety and Bipolar Disorder. Treatment for these conditions must be initiated prior to prescribing medications for possible underlying ADHD.

XVI. When initially diagnosing ADHD in adults, screening tools such as Adult Self-Reported Rating Scale (ASRS) should not be deemed as diagnostic. DSM-V requires symptoms to have been present before age 12 and functional impairments (e.g., current employment and/or academic performance).

Therefore, to diagnose ADHD in adults, additional information must be obtained such as:

A. Neuropsychiatric testing or obtaining collateral information from family to confirm the early onset of symptoms. If prior neuropsychiatric testing is reported, the results must be confirmed. If results are unavailable, testing must be repeated.

B. Patients must have a Negative toxicology screen including Cannabis and must agree to random testing.

C. Following a confirmed diagnosis of ADHD in adults, treatment for patients with substance use history may begin with two adequate trials with non-controlled FDA approved agents.

D. Reported prior failed trials must be confirmed via EMR, CURES report or the pharmacy records. If unable to confirm prior adequate trials, restart two non-controlled trials.

XVII. In the context of Patient Centered Care, when transferring adult patients who are on controlled medications:

A. For patients with diagnoses of substance use disorder who are on controlled medications, The transferring provider should inform the receiving provider of the rationale for current regime. Communication must be documented in the patient’s EMR.

B. Prior to continuing the controlled medications, the receiving provider must discuss and document the following:
1. Explanation of the risks of addiction (psychological and physiologic dependence).

2. Potentially dangerous Interactions with other substances/alcohol and medications with the potential to cause sedation, falls, MVA, respiratory depression, and death.

3. Cognitive effects worsening with age and duration of therapy.

4. In general, the current regimen should ideally be maintained unless there is an acute risk.

5. For patients receiving high doses or long duration of treatment with controlled medications, balancing safety and patient centered care requires developing a plan for gradual adjustment.

XVIII. When deviating from the guidelines, consultation with a second provider is needed. The consultation must be documented.

XVIII. Document referral to a substance abuse program (i.e., Gateway, Outpatient Groups).

XX. Review of CURES report is required prior to initiation of any controlled medication, and again at intervals no longer than every 6 months throughout treatment or whenever misuse of the medications suspected, including when it is used more frequently or at higher dose than prescribed without MD consultation.

XXI. Benzodiazepines play a significant role in the short-term treatment of anxiety and sleep disorders. However, caution is advised for long-term treatment with these agents (i.e., >3m duration)

XXII. When prescribing for longer periods, document the risk-benefit analysis related to patient’s age, medical and psychiatric comorbidities, current mental status, substance use recency, observations on CURES report and potential drug-drug interactions.

General Considerations for slow taper from BZDs

Ideally tapering off a patient from long term benzodiazepine use should be done in a monitored setting where patients vitals can be closely monitored. However, if tapering is attempted in the outpatient setting, more frequent appointments and monitoring of vitals is recommended. The following strategies may be considered is a slow taper process and changes need to be made as clinically indicated:

1. Reduce the dose of the BZD by 25% each week. If withdrawal symptoms are reported, then the dose should be increased to the previous dose and taper schedule slowed.

2. Use of Adjunctive treatments to help mitigate potential withdrawal symptoms. Anticonvulsant Gabapentin may be considered for high-dosage withdrawal. Studies have shown that adjunctive medications such as Carbamazepine, Imipramine, divalproex, and trazodone can mitigate
some the withdrawal discomfort. Use of antidepressants, such as duloxetine or amitriptyline may help patients with chronic pain. https://www.aafp.org/afp/20171101:p606.html

3. Another method described by Dr. Ashton involves converting the short and intermediate acting BZDs such as Alprazolam, Clonazepam and Lorazepam to the long-acting Diazepam and then do a slow taper of Diazepam. The various slow withdrawal schedules may need to be adapted to each clinical scenario and dependent on withdrawal symptoms and side effects during the taper process. Below is the general overview of the process:

A. Convert the total daily dose of Alprazolam, Clonazepam and Lorazepam to a long-acting BZD such as Diazepam and then slowly taper off the Diazepam using the following conversion:

B. Alprazolam and Clonazepam 0.5mg approximately equals to 10mg of Diazepam and Lorazepam 1-2mg approximately equals to 10mg of Diazepam.

C. In general, every 1-2 weeks, ½ of each dose is converted to Diazepam starting with the HS dose and then the Diazepam is decreased every 1-2 weeks by 1mg starting with the a.m. dose.

Example: Patient is on Lorazepam 1mg tid which approximately equals to a daily Diazepam dose of 30mg.

Stages 1-7 are weekly. Stages 8 to the end may be q1-2 weeks. Continue reducing the Diazepam by 1mg every 1-2 weeks.

<table>
<thead>
<tr>
<th>Morning</th>
<th>Midday/Afternoon</th>
<th>Evening/Night</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam 1mg</td>
<td>Lorazepam 1mg</td>
<td>Lorazepam 1mg</td>
</tr>
<tr>
<td>Stage 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam 0.5mg</td>
<td>Lorazepam 0.5mg</td>
<td>Lorazepam 1mg</td>
</tr>
<tr>
<td>Stage 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam 0.5mg</td>
<td>Lorazepam 0.5mg</td>
<td>Lorazepam 0.5mg + Diazepam 5mg</td>
</tr>
<tr>
<td>Stage 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam 0.5mg</td>
<td>Lorazepam 0.5mg</td>
<td>Lorazepam 0.5mg + Diazepam 5mg</td>
</tr>
<tr>
<td>Stage 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam 0.5mg</td>
<td>Lorazepam 0.5mg</td>
<td>Stop Lorazepam, Diazepam 10mg</td>
</tr>
<tr>
<td>Stage 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stop Lorazepam, Diazepam 10mg</td>
<td>Lorazepam 0.5mg + Diazepam 5mg</td>
<td>Diazepam 10mg</td>
</tr>
<tr>
<td>Stage 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam 10mg</td>
<td>Stop Lorazepam, Diazepam 10mg</td>
<td>Diazepam 10mg</td>
</tr>
<tr>
<td>Stage 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam 10mg</td>
<td>Diazepam 8mg</td>
<td>Diazepam 10mg</td>
</tr>
<tr>
<td>Stage 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam 8mg</td>
<td>Diazepam 8mg</td>
<td>Diazepam 10mg</td>
</tr>
<tr>
<td>Stage 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam 8mg</td>
<td>Diazepam 6mg</td>
<td>Diazepam 10mg</td>
</tr>
<tr>
<td>Stage 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam 6mg</td>
<td>Diazepam 6mg</td>
<td>Diazepam 10mg</td>
</tr>
<tr>
<td>Stage 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam 6mg</td>
<td>Diazepam 4mg</td>
<td>Diazepam 10mg</td>
</tr>
<tr>
<td>Stage 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam 6mg</td>
<td>Diazepam 2mg</td>
<td>Diazepam 10mg</td>
</tr>
<tr>
<td>Stage 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam 6mg</td>
<td>Stop Diazepam</td>
<td>Diazepam 10mg</td>
</tr>
<tr>
<td>Stage 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam 5mg</td>
<td>--</td>
<td>Diazepam 10mg</td>
</tr>
<tr>
<td>Stage 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam 4mg</td>
<td>--</td>
<td>Diazepam 10mg</td>
</tr>
</tbody>
</table>
Stage 16 | Diazepam 3mg |  Diazepam 10mg
Stage 17 | Diazepam 2mg |  Diazepam 10mg
Stage 18 | Diazepam 1mg |  Diazepam 10mg
Stage 19 | Stop Diazepam |  Diazepam 10mg

For more details and the conversion schedule from other BDZs to Diazepam, see the following link:

https://benzo.org.uk/manual/bzsched.htm

*Below are other references related to dosage equivalency between BZDs.
https://psychopharmacopeia.com/bzd_dose_convert.php

https://clincalc.com/Benzodiazepine/

** Specific Considerations:

The decision to discontinue the Controlled psychotropics in patients who are actively using substances, but also are experiencing active psychiatric symptoms requires careful consideration and a thorough risk-benefit analysis. The documentation should include:

1. The rational for discontinuing treatment despite the active symptoms. Further detail is needed when patients are experiencing active psychotic symptoms, or symptoms suggestive of dangerousness (SI/HI).

2. Attempts to engage the patient in substance treatment, including medical treatments for substance use (alcohol, opioids, etc.).

3. Psychoeducation performed related to interactions between substance use and mental illness and psychotropics.

4. Failure of motivational interviewing techniques.

5. How patient should proceed if subsequently follows MD’s recommendation to discontinue substances, and restart treatment.

6. For the purposes of these guidelines, Active Substance Use is defined as use during the last 30 days.

7. For patients, whose last use was >1 year, one month supply of a controlled substance with up to two refills may be provided if the requirements in Flow Diagram 3 are met.

SPECIAL CONSIDERATION RELATED TO CONCOMMITANT USE OF MAT WITH METHADONE/BUPRENORPHINE AND BDZS

I. The combination of CNS depressants/BDZs with Methadone or Buprenorphine is considered unsafe in patients with active or history of substance use due to increased risk for respiratory depression, overdose, and death*. Therefore, a higher level of caution and monitoring is
required. It should be noted that this combination is not contraindicated by FDA or the manufacturers.

II. To ensure patient safety, close collaboration with other providers is necessary to discuss appropriate course of treatment including:

- Taper/cross taper of BZDs
- Non-BZD alternatives to treat patients’ target symptoms.
- In cases where consultation has occurred and providers are unable to identify an appropriate treatment plan, second opinion with a SUTS provider is required.

Consequently, providers should obtain a signed release of information prior to initiating MAT in combination with BZDs.

*Note that individuals without h/o substance use are still at risk when combining opioids with benzodiazepines.*

III. Patients with opioid dependency who are receiving BZDs may be offered either MAT under the following conditions or may continue BZDs if the conditions in bullet point V below are met.

IV. If MAT is not selected, long-term benzodiazepines may be continued under the following conditions:

1. Specific medical or psychiatric contraindications to the treatment have been ruled out (i.e. hepatic/renal impairment, drug-disease, drug-drug and drug-food interactions; fall risks based on medical status) and documented

2. The patient agrees to engage in behavioral therapy/interventions (i.e. CBT, progressive muscle relaxation, deep breathing exercise, meditation, yoga, exercise, etc.) and agrees that if does not comply, benzodiazepine taper will be considered.

V. If benzodiazepines are required in patients who are currently on or being considered for Methadone/Buprenorphine, the following must be documented:

1. The specific trials of non-controlled alternatives for the diagnoses listed.
   - The trials must be of at least 4-6 weeks duration

2. If the patient reports intolerance to the non-controlled alternatives, the specific strategies utilized to address the intolerance (i.e., changing of dose, timing of dose, attempts to take with food, addressing other medication combinations that may have caused side effects and whether the combination is current)

VI. Shorter acting BZDs (e.g., alprazolam), and non-BZD hypnotics (“Z drugs”) should generally be avoided in this population.

VII. BZD received from acute settings (i.e., ED, EPS or inpatient) SHOULD BE discontinued/tapered as clinically indicated, while initiating treatment with non-controlled alternative medications.
Specific Considerations for patients with active substance use or history of, and/or on Opioid pain killers and either are currently on controlled RX or being considered for them: (Flow Diagram 2)

Active Substance Use (<30Days) +/- Opioid Analgesic (Verified by Tox screen)

New Start on Cont. RX

One Week supply + 1 Refill may be prescribed provided each of the following is documented:

1. An "adequate trial" with at least two FDA-approved non-controlled agents & tx. response.
2. Documentation of tx. Failure must include adherence, specific nature of side effects experienced and tx efficacy.
3. Risk vs. benefit analysis of utilizing controlled RX in context of substance use.
4. Must produce a negative tox screen including cannabis (except for prescribed RX) prior to starting controlled RX. f/u Tox. screen including Cannabis prior to each appointment.
5. In cases where controlled RX is needed prior to obtaining a tox screen, quantity must be limited to one week supply + no refills and neg. tox screen required before any further controlled RX can be provided.
6. Status of substance use at each f/u appointment (must elaborate beyond “pt. denies”, including objective measures, collateral, etc.).
7. Consideration of role of substances when symptom exacerbation occurs.
8. No additional refills on controlled RX until patient is seen by the Provider.

Currently on Cont. Rxs/Transferred

No Response for the Primary Diagnosis:

Partial Response for the Primary Diagnosis:

Cross Titrate

One Week supply + 2 Refill may be prescribed provided each of the following is documented:

1. Prior to dosage escalation, an “adequate trial" with at least two non-controlled agents and tx response.
2. Documentation of tx. Failure must include: adherence, specific nature of side effects experienced and tx efficacy.
3. Risk vs. benefit of utilizing controlled medication in context of substance use.
4. Must produce a negative tox screen including cannabis (except for prescribed RX) prior to dosage escalation. f/u random Tox. screen including Cannabis x2 within 6 months.
5. Status of substance use at each f/u appointment (must elaborate beyond “pt. denies”, including objective measures, collateral, etc.).
7. No additional refills on controlled RX until patient is seen by the Provider.

*Note: Must determine & consider type, quantity and recency of Opioid RX prescribed*
Flow Diagram 3

A. + h/o abuse/dependence (no use between 1-12 months)

- Pt. already on cont. RX/ transferred

- Up to 1 week supply with up to 1 refill may be provided if each of the following is documented:
  1. An "adequate trial" with at least two FDA-Approved non-controlled agent & tx. Response.
  2. Documentation of tx. Failure must include adherence, specific nature of side effects experienced and tx efficacy.
  3. Risk vs. benefit of utilizing controlled medication in context of substance use.
  4. Must produce a negative tox. screen including cannabis (except for prescribed RX) prior to starting a controlled RX. F/u random tox. Screen including cannabis x2 within 6 months.
  5. Status of substance use at each f/u appointment (must elaborate beyond "pt denies", include objective measures, collateral, etc.).
  6. Consideration of role of substances when symptom exacerbation occur.
  7. No additional refills on controlled medication until patient is seen by the provider.

- No Response For The Primary DX:

- At Least Partial Response For a Primary DX:

B. – h/o abuse and/or dependence

- No restrictions

- II. No active substance use +/- Opioid Analgesic (Verified by Tox screen)

- Cross titrate

- Up to 2 weeks supply with 2 refills may be provided if each of the following is documented:
  1. Prior to dosage escalation, An "adequate trial" with at least two preferably FDA-approved non-controlled agents & tx. Response.
  2. Documentation of tx. Failure must include adherence, specific nature of side effects experienced and tx efficacy.
  3. Risk vs. benefit of utilizing controlled medication in context of substance use.
  4. Must produce a negative toxicology screen including cannabis (except prescribed RX) prior to dosage escalation. F/u random tox. Screen including cannabis x2 within 6 months.
  5. Status of substance use at each f/u appointment (must elaborate beyond "pt denies", including objective measures, collateral, etc.).
  6. Consideration of role of substances when symptom exacerbation occur.
  7. No additional refills on controlled medication until patient is seen by the provider.

*Note: Must determine & consider type, quantity and recency of Opioid RX prescribed*
Medical-Legal Issues Related to Marijuana:

Marijuana is the most commonly used illicit drug on earth. The most frequently used substances among American adolescents are tobacco, alcohol, and marijuana. Marijuana dependence is the most common type of drug dependence in many parts of the world (including the U. S., Canada, and Australia) after tobacco and alcohol. It is estimated that 9% of people who try marijuana become dependent. Those who begin using the drug in their teens have approximately a one in six risk of developing marijuana dependence. Many marijuana users who try to quit experience, withdrawal symptoms that include irritability, anxiety, insomnia, appetite disturbance and depression.

The term “medical Marijuana” is generally used to refer to the whole unprocessed marijuana plant or its crude extracts, which are not recognized or approved as medicine by the U.S. Food and Drug Administration. On November 5, 1996; 56% of California voters approved Proposition 215. The law removes state-level criminal penalties on the use, possession, and cultivation of cannabis by patients who possess a "written or oral recommendation" from their physician that he/she "would benefit from medical cannabis. Senate Bill 420: Medical Marijuana Program Act (MMP) was intended to clarify Proposition 215. It states: to be eligible for a medical cannabis card a patient must be diagnosed by the attending physician to have a serious medical condition and that the medicinal use of cannabis is appropriate. A “serious medical condition” is defined to include:

1. Acquire immune deficiency syndrome (AIDS)
2. Anorexia
3. Arthritis
4. Cachexia
5. Cancer
6. Chronic pain
7. Glaucoma
8. Migraine
9. Persistent muscle spasms, including, but not limited t spasms associated with Multiple sclerosis
10. Seizures, including but not limited to seizures associated with epilepsy
11. Severe nausea
12. Any other chronic or persistent medical symptom that either:
   A. Substantially limits the ability of the person to conduct one or more major life activities as defined in the Americans and Disabilities Act of 1990 (Public Law 101-336).
   B. If not alleviated, may cause serious harm to patient’s safety or physical or mental health.

The California Medical Association and American Psychiatric Association suggest that the above list of serious medical conditions is broad and, in most cases, not supported by solid clinical research. Many medical uses for marijuana have been proposed. Those indications with the most evidence include:

1. Severe nausea/vomiting associated with cancer chemotherapy
2. Cachexia associated with AIDs or cancer
3. Spasticity secondary to neurological diseases such as multiple sclerosis
4. Pain management, especially neuropathic pain
5. Rheumatoid arthritis
The Institute of Medicine concluded that there is therapeutic potential for some of the cannabinoids found in marijuana but that the smoked marijuana is an unacceptable delivery system with harmful health effects. There are many other concerns including but not limited to: efficacy, safety, potency, purity, and composition. Approving medications by ballot initiatives and state legislative actions sets a dangerous precedent for public health. Medical marijuana bypasses the century-old, scientifically based drug approval procedure and carefully regulated distribution of medication through licensed pharmacies. APA, AMA and ASAM have considered the medical marijuana movement and oppose it and highlight the need for scientifically done studies to determine safety and efficacy of marijuana.

Regardless of marijuana’s legal status, non-specific strains of Cannabis containing THC (the psychoactive component) have acute and chronic side effects that can impact multiple organ systems. Side effects of THC include but not limited to: dependency, abuse, seizure, depression, hallucinations, paranoia, anxiety, sedation, dizziness, ataxia, asthenia, amnesia and a number of cardiopulmonary side effects including orthostatic hypotension (CSAM-ASAM: Adverse Effects of Marijuana (for healthcare professionals 2011). Withdrawal symptoms can occur if discontinued abruptly and they can mimic the symptoms of underlying mental illness such as: anxiety, insomnia and depression. In addition, THC may have an additive effect when given with psychotropics with the potential for increased CNS depression, psychomotor impairment and orthostatic hypotension. The side effect profile of THC along with its potential for drug-drug interactions makes it quite challenging to diagnose and treat co-morbid conditions such as psychosis, anxiety and depression. The combination of alcohol and marijuana produces levels of impairment greater than their independent sum, and this too has been demonstrated among experienced users with high levels of tolerance (Bramness, Khiabani et al.; Liguori, Gatto et al. 2002).

**Marijuana and anxiety/depression/psychotic disorders:**

Marijuana is well known to cause fluctuations in mood and anxiety, but the extent to which these fluctuations persist beyond the period of marijuana use is unclear (de Graaf, Radovanovic et al). Although many recreational users say that smoking marijuana calms them down, for others it has the opposite effect. In fact, the most commonly reported side effects of smoking marijuana are intense anxiety and panic attacks. Studies report that about 20% to 30% of recreational users experience such problems after smoking marijuana. The people most vulnerable are those who have never used marijuana before. Dose of THC also matters. At low doses, THC can be sedating. At higher doses, however, this substance can induce intense episodes of anxiety (Human Psychopharmacology (Oct. 2009): Vol. 24, No. 7, PP. 515-23; Cannabis and Anxiety: A Critical Review of the Evidence,” Cripta Ja, et al. At low and moderate doses, consistent with ordinary marijuana smoking, the THC leads to an increase in sympathetic and a reduction in parasympathetic activity (P. Korantzopoulos, et al).

Heavy marijuana use has been shown to increase the association with anxiety and depression and weekly or more frequent cannabinoid use in teenagers predicts an approximately twofold increase in risk for later depression and anxiety (Degenhardt, Hall et al. 2001; Patton, Coffey et al. 2001). In addition to causing psychosis, marijuana may also contribute to the development of lifelong psychotic disorders such as schizophrenia (Degenhardt, Hall et al. 2003). Marijuana exacerbates psychotic symptoms and worsens outcomes in patients already diagnosed with schizophrenia or other psychotic disorders. Several large observational studies also strongly suggest that using marijuana particularly in the early teenage years can increase the risk of developing psychosis. An often-cited study of more than 50,000 young Swedish soldiers, for example, found that those who had smoked marijuana at least once were more than twice as likely to develop schizophrenia as those who had not smoked marijuana. The heaviest users (who said they had used the drug more than 50 times) were six times as likely to develop schizophrenia as the nonsmokers (P. Korantzopoulos, et al.).
Alcohol Use:

Alcohol consumption accounts for a significant health burden and is common among groups that report high rates of prescription drug abuse. When taken with Opioid Pain Relievers (OPRs) or Benzodiazepines, alcohol increases central nervous system depression and the risk for overdose. The Food and Drug Administration (FDA) and CDC analyzed 2010 data for drug abuse-related ED visits in the United States and drug-related deaths that involved OPRs and alcohol or benzodiazepines and alcohol in 13 states. The analysis showed alcohol was involved in 18.5% of OPR and 27.2% of benzodiazepine drug abuse-related ED visits and 22.1% of OPR and 21.4% of benzodiazepine drug-related deaths (CDC MMWR 10/10/14). These findings indicate that alcohol can significantly contribute to negative outcomes when taken with OPR and benzodiazepines. The data also highlights the need for caution, increased vigilance and monitoring when prescribing controlled drugs in patients who consume alcohol.

From the pharmacokinetic perspective, the process of ethanol oxidation involves at least three distinct enzymatic pathways. The most significant pathway, responsible for the bulk of ethanol metabolism involves alcohol dehydrogenase available in high concentrations in hepatocytes. The second major pathway for ethanol metabolism involves cytochrome P450 CYP2E1 enzyme. Chronic low level alcohol consumption can lead to hepatic CYP2E1 induction. The hepatic Induction of CYP2E1 enzymes can result in increased metabolism of drugs metabolized by CYP2E1 and thereby reduce their efficacy. With the exception of Ezopiclone, CYP2E1 does not play a major role in metabolism of many currently marketed psychotropics. Therefore, the major concerns related to combination of alcohol with psychotropics seem to involve pharmacodynamics and interactions at the level of neurotransmitter systems.

***Alcohol interacts with a number of neurotransmitters. Glutamate is an excitatory neurotransmitter and alcohol inhibits the NMDA which is a type of glutamate receptor (NMDA: N-Methyl-D-Aspartate). Alcohol inhibits the glutamate receptor and thereby reduces its excitatory effect. This in part explains the blackouts and the effects on learning and memory. GABA is the main inhibitory neurotransmitter and alcohol acts as an agonist at GABA-A receptor similar to Benzodiazepines (The Pharmacology of alcohol: Robo’s guide to understanding booze Drugs-forum). As a result; alcohol taken in combination with benzodiazepines can have an additive effect and increase the risk of: drowsiness, dizziness, psychomotor retardation, increased risk of falls, increased CNS depression, increased risk of coma and death. Alcohol, particularly when consumed in excess can reduce the seizure threshold and when taken in combination with stimulants may increase the risk of seizure. Abuse of benzodiazepine is almost exclusively among subjects who also abuse alcohol, doubtless due to the fact that the two drugs show cross-dependence. The clinical practice of avoiding use of benzodiazepines (or other sedative-hypnotics) in known alcoholics is sound and should avoid many potential problems. For the purpose of this guideline, any alcohol use is considered to be inappropriate and therefore the prescribing of controlled medications would be subjected to recommendations and restrictions of this guideline.

References:

2. BZD dosage equivalency calculator, https://clicncalc.com/Benzodiazepine/
6. file:///D:/fda%20safety%20bulletine%20BDZs%20+%20Opioids%208-31-16.html
9. California Society of Addiction Medicine’s Position on Medical Marijuana: Summer2010
14. Physicians and Medical Marijuana; American Journal of Psychiatry 169:6, June 2012
19. [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6353a2.htm?s_cid=mm6353a2_w Vital Signs: Alcohol Poisoning Deaths – United States, 2010-2012](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6353a2.htm?s_cid=mm6353a2_w)
21. [http://www.cdc.gov/mmwr/pdf/wk/mm6340.pdf Alcohol Involvement in Opioid Pain Reliever and Benzodiazepine](http://www.cdc.gov/mmwr/pdf/wk/mm6340.pdf)

Drug Abuse–Related Emergency Department Visits and Drug-Related Deaths — United States, 2010

- Medical Marijuana. The Medical Board of California (Department of Consumer Affairs), [http://www.mbc.ca.gov/medical_marijuana.html](http://www.mbc.ca.gov/medical_marijuana.html)
- Guidelines for Prescribing Controlled Substances for Pain. The Medical Board of California (Department of Consumer Affairs), [http://www.mbc.ca.gov/medical_marijuana.html](http://www.mbc.ca.gov/medical_marijuana.html)
- Vistaril Package Insert
- Attention-Deficit-Hyperactivity Disorder An Update Abstract and Introduction.mht
- ADHD-and-Comorbid-Substance-Use-Disorder-Psych Times 2010.pdf
- Paul Lichtenstein, Ph.D. and et. Al, Medication for Attention Deficit-Hyperactivity Disorder and Criminality, NEJM,367:21, 2006-2014
- Adolescent Drug Use- NIDA overview2011.pdf
- APA Substance Use guidelines 2006-quick reference.pdf
- APA Tx Substance Abuse guidelines 2006.pdf
- Benzos and stimulants for substance disorders- Current Psych Online 5-11.pdf
• Beyond Abuse and Exposure-Framing Impact of Prescription Medication Sharing Abstract and Introduction.mht
• Biederman ADHD and Substance Use.pdf
• psychostimulantusecocainedependence.pdf
• RCT of osmotic release methylphenidate with CBT in adolescents with ADHD and SUD.pdf
• Richard Lawrence Merkle Jr. and Ajay Kuchibhatla, Expert Opinion: Safety of stimulant treatment in attention deficit hyperactivity disorder part I.pdf
• www.samhsa.gov. Quick Guide For Clinicians: Treatment For Stimulant Use Disorders, DHHS Publication No. (SMA)01-3598
• Lilly Hechtman, M.D., Gabrielle Weiss, M.D, and Terrye Perlman, M.S., young adult outcome of hyperactive children who received long-term stimulant treatment, J. of Am. Academy of Child Psych, 23, 3:261-269, 1984