If someone is taking Suboxone, Subutex or methadone for drug rehab, can they take another controlled substance such as a benzo? I have been told that there is or will be a legislation that states if someone is on Suboxone they cannot be on any other controlled medications. I have also been informed that people that are taking Suboxone cannot take benzodiazepines due to interactions. As for the methadone, I have been told that an internal med/primary care provider cannot prescribe methadone for drug rehab but can prescribe methadone for pain control.

Methadone is a Federal Schedule II controlled substance approved by the Food and Drug Administration (FDA) for treatment of moderate to severe pain that is not responsive to non-narcotic analgesics as well as for detoxification and maintenance treatment of opioid dependence.[1] Methadone may be prescribed for treatment of pain by any clinician that is authorized to prescribe Schedule II controlled substances. Prescribing of methadone for treatment of opioid dependence is limited to prescribers affiliated with Opioid Treatment Programs that have been certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA).

Buprenorphine and buprenorphine/naloxone are Federal Schedule III controlled substances with an FDA-approved indication for treatment of opioid dependence.[2,3] As stated in the product labeling, prescribing of these products is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription. In July 2016, the Comprehensive Addiction and Recovery Act (CARA) was signed into law with the intent to expand access to addiction treatment services.[4] CARA includes a provision to allow Nurse Practitioners and Physician Assistants with appropriate training to prescribe buprenorphine for opioid addiction treatment.

There is currently no known legislation restricting the use of controlled substances such as benzodiazepines in patients receiving treatment for opioid dependence with either methadone, buprenorphine or buprenorphine/naloxone. However, there are strong warnings in the product labeling regarding the risk of respiratory depression, coma and death with concomitant use of benzodiazepines or other central nervous system depressants with either methadone or buprenorphine.[1-3] These warnings are based upon case reports of such incidents and the known pharmacokinetic and pharmacodynamic interactions associated with use of these agents in combination.[1-3, 5] As excerpted from the FDA labeling for buprenorphine products in Drug Interaction Section 7.3: *"Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine□induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists."*[2,3]

Related to these risks of harm, the FDA issued a safety announcement in August 2016 regarding the addition of boxed warnings to all labels for benzodiazepines and opioids, excerpted as follows:

"A U.S. Food and Drug Administration (FDA) review has found that the growing combined use of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths.[6] Opioids are used to treat pain and cough; benzodiazepines are used to treat anxiety, insomnia, and seizures. In an effort to decrease the use of opioids and benzodiazepines, or opioids and other CNS depressants, together, we are adding Boxed Warnings*, our strongest warnings, to the drug labeling of prescription opioid pain and prescription opioid cough medicines, and benzodiazepines."*

Based upon these warnings and known risks, individual pharmacy benefit plans may have restrictions in place to manage the concomitant utilization of these agents. Prescribing limitations and related drug interaction warnings in FDA labeling for methadone and buprenorphine products are summarized in the table below.

METHADONE & BUPRENORPHINE PRESCRIBING LIMITATIONS [1-3]			
Generic Names	**Methadone hydrochloride**	**Buprenorphine**	**Buprenorphine/naloxone**
Trade Names	**Dolophine®; Methadose®**	**Subutex®**	**Suboxone®**
Dosage Forms	5 mg and 10 mg oral tablet 40 mg tablet for oral suspension 10 mg/mL oral concentrate 10 mg/mL injectable solution	Sublingual tablet: 2 mg buprenorphine 8 mg buprenorphine	Sublingual film: 2 mg buprenorphine/0.5 mg naloxone 4 mg buprenorphine/1 mg naloxone 8 mg buprenorphine/2 mg naloxone 12 mg buprenorphine/3 mg naloxone
CS Schedule	C-II[a]	C-III[b]	C-III[b]
FDA-Approved Indications	1. Treatment of moderate to severe pain not responsive to non-narcotic analgesics 2. Detoxification treatment of opioid addiction (heroin or other morphine-like drugs) 3. Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services **See note on prescribing limitations.[c]**	Treatment of opioid dependence – preferred for induction and should be used as part of a complete treatment plan to include counseling and psychosocial support **Prescription use of this product is limited under the Drug Addiction Treatment Act.[d]**	Treatment of opioid dependence – preferred for maintenance and should be used as part of a complete treatment plan to include counseling and psychosocial support **Prescription use of this product is limited under the Drug Addiction Treatment Act.[d]**
Boxed Warnings	Yes – see full text below[e]	None	None
Selected Drug Interaction Warnings	Coadministration of methadone with inducers of CYP 3A4, 2B6, 2C19, and to a lesser extent 2C9 and 2D6, may result in decreased effects of methadone. Conversely, administration with CYP inhibitors may potentiate methadone's effects. **Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics or other CNS depressants (including alcohol) concomitantly with methadone may experience respiratory depression, hypotension, profound sedation, or coma.**	**Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the IV route in combination with benzodiazepines or other CNS depressants (including alcohol).** Consider dose reduction of CNS depressants, buprenorphine products, or both in situations of concomitant prescription. Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing. **Use caution in patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse.**	

CNS = central nervous system; CS = Controlled Substance; CYP = cytochrome P450; FDA = Food and Drug Administration; IV = intravenous

[a] Schedule II controlled substances have a high potential for abuse which may lead to severe psychological or physical dependence.

[b] Schedule III controlled substances have a potential for abuse less than substances in Schedules I or II and abuse may lead to moderate or low physical dependence or high psychological dependence.

Table legend continued on next page.

[c] METHADONE PRESCRIBING NOTE: Outpatient maintenance and outpatient detoxification treatment may be provided only by Opioid Treatment Programs (OTPs) certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA). This does not preclude the maintenance treatment of a patient with concurrent opioid addiction who is hospitalized for conditions other than opioid addiction and who requires temporary maintenance during the critical period of his/her stay, or of a patient whose enrollment has been verified in a program which has been certified for maintenance treatment with methadone.
[d] BUPRENORPHINE & BUPRENORPHINE/NALOXONE PRESCRIBING NOTE: Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.
[e] METHADONE BOXED WARNING:

Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. It is critical to understand the pharmacokinetics of methadone when converting patients from other opioids. Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

In addition, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone is considered and outweighs the risks.

Conditions For Distribution And Use Of Methadone Products For The Treatment Of Opioid Addiction

Code of Federal Regulations, Title 42, Sec 8

Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment.

Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

REFERENCES:

1. Methadone prescribing information. Boehringer Ingelheim for Roxane Laboratories. Revised October 2006.
2. Buprenorphine (Subutex®) prescribing information. Reckitt Benckiser Healthcare (UK) Ltd. Hull, UK. for Indivior Inc. Richmond, VA. Revised June 2016.
3. Buprenorphine/naloxone (Suboxone®) prescribing information. Monosol Rx, LLC. Warren, NJ for Indivior Inc. Richmond, VA. Revised June 2016.
4. Comprehensive Addiction and Recovery Act of 2016. Public law 114-198. https://www.gpo.gov/fdsys/pkg/PLAW-114publ198/html/PLAW-114publ198.htm
5. McCance-Katz EF, Sullivan L, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications. *Am J Addict*. 2010; 19(1):4-16.
6. Food and Drug Administration Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. August 31, 2016. http://www.fda.gov/Drugs/DrugSafety/ucm518473.htm