

## ANTI-ANXIETY AGENTS (non-SSRIs)

- A. FDA Approved Indications in Psychiatry (Documentation Required)  
(Note: The FDA approved indications for specific benzodiazepines vary considerably; e.g. only lorazepam is FDA-approved for both anxiety and insomnia (see Table 1))
1. Anxiety disorder
  2. Panic disorder (Alprazolam, alprazolam **XR** & clonazepam)
- B. Non-FDA approved indications commonly used in Psychiatry (Documentation Required)
1. All Anxiety Disorders
  2. Sleep Disorders
  3. Abnormal movements associated with medications
  4. Catatonia (may require high doses)
  5. Tourette's syndrome (Clonazepam)
  6. Delirium; delirium tremens
  7. Agitation
- C. Minimal Documentation (Documentation Required)
1. All standard outpatient & inpatient requirements
  2. For Outpatient: Document rationale when making any medication change.
  3. For Inpatient: Document rationale when making more than 3 changes in any 7-day period.
  4. CURES:

**Review of cures report is required prior to initiation of any controlled psychotropic medication, and again at intervals no longer than 4 months throughout treatment or whenever misuse of the medications suspected, including when it's used more frequently or at higher dose than prescribed without provider consultation.**

### **DOCUMENT YOUR OBSERVATION IN THE PROGRESS NOTE.**

5. NARCAN: (Assembly Bill No. 2760)
  1. When prescribing opioids, the prescriber shall offer a prescription for naloxone to a patient if:
    - The prescription daily dose is >90 morphine mg equivalents
    - An opioid is prescribed with a benzodiazepine
    - The patient has an increased risk of overdose
  2. When prescribing opioids, the prescriber shall provide education on overdose prevention and the use of naloxone to the following individuals:

- Patient
- One or more persons designated by the patient

[https://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill\\_id=201720180AB2760](https://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=201720180AB2760)

D. Maximum Dosage – see Medication Summary for MDD

E. Duration

F. Polypharmacy (Refer to Purpose Section for exceptions)

If using >1 anti-anxiety agent with the same mechanism of action (i.e. 2 benzodiazepines) clear documentation of rational including clinical response to monotherapy is required. For the purposes of this guideline, concurrent use of a benzodiazepine and a non-benzodiazepine hypnotic i.e. zolpidem, zaleplon and eszopiclone is considered polypharmacy, requiring the appropriate documentation of rational including clinical response to benzodiazepine is required.

G. Standard laboratory and examination requirements (Documentation Required)

1. For inpatient: Basic laboratory studies on admission
2. For outpatient: Not Applicable
3. Additional monitoring should be considered depending on the clinical situation and whenever there is a change in the patient's status.

H. Black Box Warning

#### Risks from Concomitant Opioid Use

Concomitant benzodiazepine use with opioids may result in profound sedation, respiratory depression, coma, and death; reserve concomitant use for patient with inadequate alternative treatment options. Limit to minimum required dosage and duration. Monitor patients for signs and symptoms of respiratory depression and sedation.

I. Warnings and Precautions (Documentation Required)

- For patients with substance use refer to Section P: medication guidelines for prescribing controlled psychotropic medications to patients with substance use.
- Psychological dependence is a risk with all benzodiazepines (Schedule IV). The risk may increase at higher doses and with longer term usage. This risk is further increased in patients with a history of alcohol or drug abuse. Periodic reassessment of drug usefulness for the individual patient must be done to avoid creating physiological abuse and dependence.
- Withdrawal reactions/symptoms, such as convulsions, psychosis, rebound anxiety, insomnia, hallucinations, behavioral disorders, tremor, abdominal and muscle

cramps, may occur following abrupt discontinuation. The more severe withdrawal symptoms generally occur for those patients receiving higher doses over an extended period of time. However, milder withdrawal symptoms, such as dysphoria and insomnia, have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic doses over several months. Therefore, to minimize discontinuation symptoms after extended exposure, gradual taper from benzodiazepine is recommended.

- Respiratory impairment, severe (with IV use)
- Caution if sleep apnea present
- Caution if CNS depression present
- Caution if alcohol use or drug abuse history present
- Caution if seizure hx present
- Caution if renal or hepatic impairment present
- Caution if elderly or debilitated patients
- Caution if depression present

J. [Drug-Drug Interactions – Refer to www.epocrates.com](http://www.epocrates.com) Concomitant treatment with other medications with anticholinergic properties (including Alcohol & Opioids: see Minimal documentation section regarding Narcan) may increase risk of CNS depression, psychomotor impairment (additive effects).

K. Adverse Effects: (See PI for each drug for a complete list of Adverse Effects)  
 Serious Adverse Effects:

- Respiratory depression & failure
- Apnea
- Dependence, abuse
- Seizures
- Suicidality
- Tachycardia
- Hypotension
- Syncope
- Blood dyscrasias
- Jaundice
- CNS stimulation, paradoxical
- Gangrene (intra-arterial)
- Cognitive deficits
- Behavioral changes

Common Adverse Effects:

- Sedation
- Dizziness

- Asthenia
- Ataxia
- Local injection site reaction
- Respiratory depression
- Hypoventilation (IV use)
- Hypotension
- Fatigue
- Amnesia
- Confusion
- Disinhibition
- Irritability
- Libido changes
- Menstrual irregularities
- Diplopia
- Dysarthria
- Constipation
- Incontinence
- Urinary retention
- Dystonia
- ALT, AST elevated

Attachments:

Table 1: FDA Approved Indication for Anti-Anxiety Agents

Table 2: Maximum Daily Dose

Table 3: Pregnancy and Nursing Mother Category

## References:

1. Epocrates
2. Micromedex
3. Physician's Package Inserts for Xanax, Klonopin, Tranxene, Ativan, and Ambien
4. Rudolph U, Knoflach F. Beyond classical benzodiazepines: Novel therapeutic potential of GABAA receptor subtypes. *Nat Rev Drug Discov.*; 10(9): 685-697. Doi:10.1038/nrd3502.
5. Morin A, Jarvis C, Lynch A. Therapeutic Options for Sleep-Maintenance and Sleep-Onset Insomnia. *Pharmacotherapy.* 2007;27(1): 89-110.
6. Estivill E and et. Al. Consensus on Drug Treatment, Definition and Diagnosis for Insomnia. *Clin Drug Invest.* 2003;23(6)
7. Pigeon W, Cribbet M. The pathophysiology of Insomnia, From Models to Molecules (and back). *Curr Opin Pulm Med.* 2012; 18(6);546-553.

## MOST COMMONLY USED ANTIANXIETY AGENTS

**FDA-Approved Indications**  
For SSRI, refer to Antidepressant Section

**Table 1:**

Agents	Brand	Ax. Disorder	PD	Insomnia	Alc. W/D	Sz. Disorder
Benzodiazepines						
Alprazolam	Xanax	X				
Alprazolam	<b>Xanax XR</b>		X			
Chlordiazepoxide	Librium	X			X	
Clonazepam	Klonopin		X, Children >6y.o.			X
Clorazepate	<b>Tranxene</b>	X			X	X
Diazepam	Valium	X			X	X
Lorazepam	Ativan	X		X		X (Status Epilepticus)
Oxazepam	Serax	X			X	
Non-Benzodiazepines						
Buspirone	Buspar	X				
Hydroxyzine <sup>1</sup>	Atarax/Vistaril	X				
Prochlorperazine	Compazine	X				
Meprobamate <sup>1</sup>		X				

<sup>1</sup>Only available as generic

**\*Lorazepam: The only BZD on this list FDA approved for Insomnia**

**\*Clonazepam: The only BZD on this list with FDA approved for children>6y.o.**

References: EPOCRATES, MICROMEDEX, Physician’s Package Insert

## MOST COMMONLY USED ANTI-ANXIETY AGENTS

### Maximum Daily Dose

For SSRI, refer to Antidepressant Section

Table 2:

Agents	Brand	Adult	Children & Adolescent
<b>Benzodiazepines</b>			
Alprazolam	Xanax	4 mg	non-FDA approved
Alprazolam	<b>Xanax XR</b>	6 mg	non-FDA approved
Chlordiazepoxide	Librium	100 mg	>6 y.o. 10-30mg/day in divided doses. Taper to DC gradually
Clonazepam	Klonopin	4 mg	non-FDA approved
Clorazepate	<b>Tranxene T-Tab</b>	60 mg	non-FDA approved
	<b>Tranxene SD</b>	90 mg	non-FDA approved
Diazepam	Valium	40 mg	0.12-0.8 mg/kg (6 mo-12 yo); 40 mg (>12 yo)
Lorazepam	Ativan	10 mg	non-FDA approved
Oxazepam	Serax	120 mg	non-FDA approved
<b>non-Benzodiazepines</b>			
Bupirone	Buspar	60 mg	non-FDA approved
Hydroxyzine <sup>1</sup>	Atarax/Vistaril	600 mg	2mg/kg (<6 yo); 100mg (6-12 yo)
Prochlorperazine	Compazine	20 mg	non-FDA approved
Meprobamate <sup>1</sup>		2400 mg	600 mg (6-12 yo)

<sup>1</sup>Only available as generic

References: EPOCRATES, MICROMEDEX

**Table 3: Pregnancy and Lactation Information**

Agents	Brand	Use During Pregnancy	Use In Nursing Mother
Benzodiazepines			
Alprazolam	Xanax; <b>Xanax XR</b>	Consider alternative during pregnancy; possible risk of teratogenicity based on conflicting human & risk of neonatal W/D SX based on limited human data, risk of floppy infant syndrome near term based on human data with other BZDs; risk of teratogenicity & fetal death based on animal data at doses of 50mg/kg	May use low doses short-term, monitor infant closely; no known risk of infant harm based on limited human data, possible risk of infant CNS depression based on limited human data with longer-acting BZDs; no human data available to assess effects on milk production
Chlordiazepoxide	Librium	Weigh risk/benefit during pregnancy; possible risk of teratogenicity based on conflicting human and animal data; risk of neonatal W/D SX & floppy infant syndrome near term based on limited human data	Use alternative or consider short-acting BZDs, no human data available to assess risk of infant harm or effects on milk production; possible risk of infant CNS depression based on limited human data based on limited human data with other BZDs
Clonazepam	Klonopin	Weigh risk/benefit; no known risk of teratogenicity based on limited human data & on animal data at 4-100x MRHD; risk of infant floppy synd. Based on limited human data; risks of neonatal W/D SX based on human data with other BZDs	Consider short-acting BZDs or monitor infant closely; possible risk of CNS depression based on limited human data & drug properties; no human data available to assess effects on milk production
Clorazepate	<b>Tranxene T-Tab;</b> <b>Tranxene SD</b>	weigh risk/benefit during pregnancy; inadequate human data available to assess risk; possible risk of teratogenicity based on conflicting human data w/ other benzodiazepines and risk of neonatal withdrawal sx and floppy infant syndrome near term based on human data w/ other benzodiazepines; no known risk of teratogenicity based on animal data	consider short-acting benzodiazepine or monitor infant closely while breastfeeding; possible risk of infant CNS depression based on limited human data and drug properties; no human data available to assess effects on milk production
Diazepam	Valium	weigh risk/benefit during pregnancy; possible risk of teratogenicity based on conflicting human data; risk of neonatal withdrawal sx and floppy infant syndrome near term based on human data; risk of teratogenicity based on animal data w/ PO form at 8x MRHD	consider short-acting benzodiazepine or monitor infant closely while breastfeeding; possible risk of infant CNS depression based on limited human data and drug properties; no human data available to assess effects on milk production
Lorazepam	Ativan	weigh risk/benefit in 3rd trimester if prolonged (>3h) or repeated admin. for sedation use, otherwise consider alternative during pregnancy; possible risk of teratogenicity based on conflicting human data and risk of floppy infant syndrome near term based on limited human data; risk of neonatal withdrawal sx based on human data w/ other benzodiazepines; possible risk of teratogenicity based on animal data and risk of embryo-fetal toxicity and death based on animal data w/ PO form at doses of 40 mg/kg; possible risk of adverse neurodevelopmental outcomes based on animal data w/ other sedatives	may use low doses short-term while breastfeeding, otherwise monitor infant closely; no known risk of infant harm based on limited human data, though possible risk of infant CNS depression based on limited human data w/ longer-acting benzodiazepines; no human data available to assess effects on milk production
Oxazepam	Serax	consider alternative during pregnancy; possible risk of teratogenicity based on conflicting human data and risk of neonatal withdrawal sx based on limited human data; risk of floppy infant syndrome near term based on human data w/ other benzodiazepines; no known risk of teratogenicity based on animal data at 100 mg/kg/day	may use low doses short-term while breastfeeding, otherwise monitor infant closely; no known risk of infant harm based on limited human data, though possible risk of infant CNS depression based on limited human data w/ longer-acting benzodiazepines; no human data available to assess effects on milk production
non-Benzodiazepines			
Buspirone	Buspar	may use during pregnancy; risk of teratogenicity not expected based on limited human data; no known risk of fetal harm based on animal data at 30x MRHD	caution advised while breastfeeding; no known risk of infant harm based on limited human data and drug properties; no human data available to assess effects on milk production
Hydroxyzine	Atarax/ Vistaril	caution advised during pregnancy; risk of fetal harm low based on limited human data	consider alternative while breastfeeding; possible risk of infant CNS depression based on limited human data; no human data available, though theoretical risk of decreased. milk production based on decreased. prolactin levels
Prochlorperazine	Compazine	caution advised in 3rd trimester; no known risk of teratogenicity based on human data, though risk of neonatal extrapyramidal and withdrawal sx in 3rd trimester based on human data w/ other antipsychotics	consider alternative, though may use short-term while breastfeeding; no human data available to assess risk of infant harm, though possible risk of infant CNS depression based on drug's mechanism of action; no human data available to assess effects