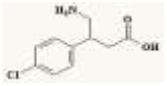
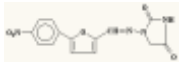
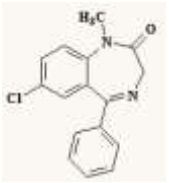
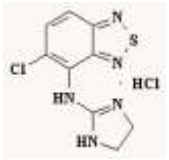
Skeletal Muscle Relaxants

Antispasticity Agents

Drug	**Structure**[22]	**Mechanism Of Action**	**Recommended Dosage** *Unless otherwise indicated, all dosages are PO*	**Adverse Effects & Therapeutic Issues**	**Pharmacokinetics**	**Drug Interactions**
Baclofen[1,2,12] (Lioresal®)		-Derivative of GABA -Inhibits polysynaptic and monosynaptic reflexes at the level of the spinal cord by hyperpolarization of afferent terminals -Additionally acts at supraspinal sites -Has general CNS depressant properties	5 mg TID x 3 days, then 10 mg TID x 3 days, then 15 mg TID x 3 days, then 20 mg TID x 3 days lowest dose compatible with an optimal response is recommended **Max Daily Dose** 80 mg	*Transient drowsiness, dizziness, weakness, fatigue, confusion, headache, insomnia, hypotension, nausea, constipation, urinary frequency* -Discontinue by slow taper -Withdrawal syndrome -hallucinations, seizures -May ↑ ALP and AST levels -Adjust dosage in patients with renal impairment -Poor tolerability in patients with stroke	**$T_{1/2}$ =** 2-4 hrs **Cmax** 600 ng/ml **Tmax** 1-2 hrs	-Caution with other CNS depressants and alcohol
Dantrolene[1,3,13] (Dantrium®)		-Dissociates the excitation-contraction coupling in skeletal muscle by disrupting calcium release from the sarcoplasmic reticulum -Does not appear to directly affect the CNS	25 mg daily x 7 days, then 25 mg TID x 7 days, then 50 mg TID x 7 days, then 100 mg TID thereafter	*Drowsiness, dizziness, weakness, general malaise, fatigue, diarrhea, constipation, dysphagia, abdominal cramps, nausea, vomiting, headache, visual disturbances, diplopia, alteration in taste, sialorrhea, tachycardia, phlebitis, confusion, pruritus* **Black Box Warning**: symptomatic fatal or nonfatal hepatitis -Contraindications: acute hepatitis, active cirrhosis -Discontinue if no benefit observed after 45 days	**$T_{1/2}$ =** 4.1-22.2 hrs **Cmax** 1,240 ng/ml **Tmax** 1-12 hrs	-Caution with other CNS depressants -CYP 3A4 Substrate -Potential for multiple drug interactions

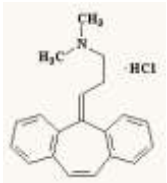
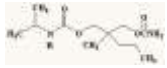
Antispasmodic/Antispasticity Agents

Drug	**Structure**[22]	**Mechanism Of Action**	**Recommended Dosage** *Unless otherwise indicated, all dosages are PO*	**Adverse Effects & Therapeutic Issues**	**Pharmacokinetics**	**Drug Interactions**
Diazepam*[1,4,14] (Valium®)		-Neuronal inhibition at the level of the spinal cord due to the binding of benzodiazepine receptors on postsynaptic GABA neurons	2-10 mg TID-QID	*Drowsiness, fatigue, muscle weakness, ataxia, confusion, depression, dysarthria, headache, slurred speech, tremor, vertigo, constipation, nausea, GI disturbances, blurred vision, diplopia, dizziness, hypotension, changes in salivation, neutropenia, jaundice* -Contraindications: patients with myasthenia gravis, severe respiratory deficiency, severe hepatic insufficiency, sleep apnea syndrome -Abuse potential -Avoid in elderly -Avoid in patients with renal or hepatic Impairment	**$T_{1/2}$ =** 20-50 hrs** **Cmax** 394 ng/ml **Tmax** 0.25-2.5 hrs	-Metabolized by CYP3A4 & CYP2C19 -Potential for multiple drug interactions
Tizanidine[1,5,15] (Zanaflex®)		-Centrally acting α_2-agonist -Causes presynaptic inhibition of motor neurons	**Initial Dose:** 4 mg may ↑ by 2-4 mg every 6-8 hours until relief **Max Daily Dose =** 36 mg	*Dry mouth, somnolence, asthenia, dizziness, UTI, infection, constipation, abnormal LFT's, vomiting, speech disorder, blurred vision, urinary frequency, flu syndrome, dyskinesia, nervousness, pharyngitis, rhinitis* -↑ LFT's -Hepatotoxicity (monitor at baseline, then at 1,3, and 6 months) -Limited data base for chronic use of single doses above 8 mg and multiple doses above 24 mg per day	**$T_{1/2}$ =** 1.5-2.5 hrs **Cmax (ng/ml)** ***Fasting:*** 2.29 (capsule), 2.20 (tablet) ***Fed:*** 1.91 (capsule), 2.86 (tablet) **Tmax** ***Fasting:*** 1 hr ***Fed:*** 3 hrs (capsule), 1 hr 25 mins (tablet)	-Contraindicated with CYP1A2 inhibitors ciprofloxacin and fluvoxamine -Caution with other CYP1A2 inhibitors -↓ levels with oral contraceptives -Caution with other CNS depressants & alcohol

***** *All benzodiazepines have muscle relaxant properties*

****** *The* $T_{1/2}$ *of the active metabolite, N-desmethyldiazepam, is up to 100 hrs*

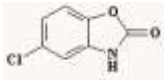
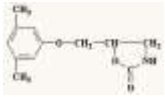
Antispasmodic Agents

Drug	**Structure**[22]	**Mechanism Of Action**	**Recommended Dosage** *Unless otherwise indicated, all dosages are PO*	**Adverse Effects & Therapeutic Issues**	**Pharmacokinetics**	**Drug Interactions**
Cyclobenzaprine[1,6,16] (Flexeril®)		-Chemical structure is similar to tertiary TCAs -Influences both gamma and alpha motor systems by reducing tonic somatic motor activity -Functions primarily at the brainstem level of the CNS rather than the spinal cord level	5 mg TID may ↑ to 10 mg TID	*Anticholinergic effects (drowsiness, urinary retention, dry mouth), fatigue, dizziness, palpitations, unpleasant taste, dyspepsia, nausea, asthenia, dizziness, headache, jaundice (rare), hepatitis (rare), tachycardia, arrhythmia* -Avoid in elderly -Avoid in patients with arrhythmias, cardiac conduction disturbances, heart block, heart failure, or recent MI -Avoid in patients with glaucoma -Avoid in patients with urinary retention -Treatment for periods longer than 2-3 Is not recommended	**$T_{1/2}$** = 18 hrs Elderly: 33 hrs Hepatic Impairment: 46 hrs **Cmax** (ng/ml)** Single Dose: 2.1 (2.5 mg), 4.3 (5 mg), 8.5 (10 mg) Multiple Dose: 7.1 (2.5 mg), 14.9 (5 mg), 25.9 (10 mg) **Tmax** 3.8-4 hrs	-Metabolized by CYP3A4, CYP1A2, & CYP2D6 -Caution advised with potential inhibitors -Do not use within 14 Days of MAOI -↑ seizure risk with tramadol
Carisoprodol[1,17] (Soma®)		-Centrally acting skeletal muscle relaxant -Appears to interrupt neuronal communication within the reticular formation and spinal cord -Metabolizes into meprobamate	250-350 mg TID-QID **Max Daily Dose** = 1400 mg	*Drowsiness, dizziness, headache, tachycardia, postural hypotension, facial flushing, vertigo, ataxia, tremor, agitation, irritability, syncope, insomnia, nausea, vomiting, epigastric discomfort, leukopenia, pancytopenia* -Not recommended in children < 12 yrs -Can cause psychological & physical dependence -Possible withdrawal with discontinuation -Excessive use, overdose, or withdrawal may precipitate seizures	**$T_{1/2}$ =** 2 hrs* **Cmax** 1,200-1,800 ng/ml **Tmax** 1.5-1.7 hrs	-Metabolized by CYP2C19 -Respiratory depression if used with benzodiazepines, barbiturates, or opioids

** The **$T_{1/2}$** of the metabolite, meprobamate, is approximately 10 hours*

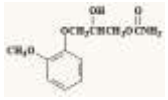
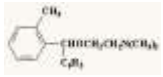
*** Multiple Dose: dosing every 8 hours for 7 consecutive days*

Antispasmodic Agents (continued)

Drug	Structure[22]	Mechanism Of Action	Recommended Dosage *Unless otherwise indicated, all dosages are PO*	Adverse Effects & Therapeutic Issues	Pharmacokinetics	Drug Interactions
Chlorzoxazone[1,7,8,9,18] (ParafonForteDSC®)		-Works primarily in the spinal cord and in the subcortical areas of the brain, inhibiting multi-synaptic reflex arcs involved in producing and maintaining skeletal muscle spasm of varied etiology	500-750 mg TID-QID	*Drowsiness, dizziness, lightheadedness, malaise, overstimulation, petechiae (rare), ecchymoses (rare), GI disturbances, angioneurotic edema (rare), allergic-type skin reactions (rare),* -May cause discoloration of urine -Avoid in patients with hepatic impairment	**$T_{1/2}$ =** 1.12 hrs **Cmax** 17,200-68,400 ng/ml **Tmax** 40-60 mins	-Respiratory depression if used with benzodiazepines, barbiturates, or opioids
Metaxalone[1,19] (Skelaxin®)		-Mechanism is unknown in humans, but presumed to be due to general depression of the CNS -No direct effect on the contractile mechanism of striated muscle, the motor endplate, or the nerve fiber	800 mg TID-QID	*Drowsiness, dizziness, headache, nervousness, nausea, vomiting, epigastric discomfort, rash, leukopenia, hemolytic anemia, jaundice* -Contraindications: patients with renal or hepatic failure or a history of anemia -Not recommended in children < 12 yrs -Taking with food may enhance general CNS depression; elderly people may be especially susceptible to this CNS effect	**$T_{1/2}$** = 8-9 hrs **Cmax* (ng/ml)** ***Fasting:*** 1,816 (young), 2,719 (middle-aged), 3,168 (elderly) ***Fed:*** 3,510 (young), 2,915 (middle-aged), 3,680 (elderly) **Tmax*** ***Fasting:*** 3.0 hrs (young), 3.0 hrs (middle-aged), 2.6 hrs (elderly) ***Fed:*** 4.9 hrs (young), 8.7 hrs (middle-aged), 6.5 hrs (elderly)	-Respiratory depression if used with benzodiazepines, barbiturates, or opioids

**Young= 25.6 ± 8.7 years; Middle-aged =39.3 ± 10.8 years; Elderly = 71.5 ± 5 years*

Antispasmodic Agents (continued)

Drug	Structure[22]	Mechanism Of Action	Recommended Dosage *Unless otherwise indicated, all dosages are PO*	Adverse Effects & Therapeutic Issues	Pharmacokinetics	Drug Interactions
Methocarbamol[1,10,20] (Robaxin®)		-Carbamate derivative of guaifenesin -Mechanism is not fully understood, but thought to be due to sedative properties -No direct effect on the contractile mechanism of striated muscle, the motor endplate, or the nerve fiber	1500 mg QID x 2-3 days, then 750 mg QID thereafter For severe conditions, 8 g/day may be given	*Angioneurotic edema, fever, headache, bradycardia, flushing, hypotension, syncope, thrombophlebitis, dyspepsia, jaundice, nausea, vomiting, leukopenia, amnesia, confusion, diplopia, dizziness, lightheadedness, drowsiness, insomnia, mild muscular incoordination, nystagmus, sedation, seizures, vertigo, blurred vision, conjunctivitis, nasal congestion, metallic taste, pruritus, rash, urticaria* -Do not use injection in patients with renal failure -May cause brown/black or green discoloration of urine -May exacerbate symptoms of myasthenia gravis	**$T_{1/2}$ =** 1-2 hrs **Cmax** 23,100 ng/ml **Tmax** 1.1 hrs	-Respiratory depression if used with benzodiazepines, barbiturates, or opioids
Orphenadrine[1,11,21] (Norflex®)		-Structurally similar to diphenhydramine, but orphenadrine possesses greater anticholinergic effects -Acts centrally at the brainstem -Mechanism of action is not presumed to be due to its analgesic and anticholinergic properties	100 mg BID combination products are given TID or QID	*Anticholinergic effects (drowsiness, urinary retention, dry mouth), tachycardia, palpitation, urinary hesitancy/retention, blurred vision, dilation of pupils, ↑ ocular tension, weakness, nausea, vomiting, headache, dizziness, constipation, drowsiness, pruritis, hallucinations, agitation, tremor, epigastric discomfort, urticaria (rare), confusion(rare)* -Contraindications: patients with glaucoma, pyloric or duodenal obstruction, stenosing peptic ulcers, prostatic hypertrophy or obstruction of the bladder neck, cardiospasm, myasthenia gravis -Avoid in elderly	**$T_{1/2}$ =** 25.8 hrs **Cmax** 82.8 ng/ml **Tmax** 3 hrs	-Respiratory depression if used with benzodiazepines, barbiturates, or opioids

Note: Not all brand names listed

Compiled by Michael J. Nolan, Pharm.D. Candidate, Class of 2012
Albany College of Pharmacy & Health Sciences

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