Low back pain: 70-80% at some time in their lives

- 1% temporarily disabled; 1% chronically disabled
- Majority show rapid improvement:
  - 40-50% recovery in 1 week
  - 50-85% recovery in 1 month
  - 90% recovery in 2 months

Frequent causes:

- Strain on muscles or supporting ligaments (heavy lifting, sports injury, poor posture)
- Protrusion (hernia) of disc
- Irritation of joints (facets) due to osteoarthritis

Lumbosacral spine:

- Vertebrae, discs, facets, nerve root
- Muscles & ligaments
  - Paravertebral muscles (transversospinalis) control vertebral position
  - Deep muscles of lower back provide support & mobility to spinal column
    → often source of LBP
  - Muscle nociceptors transmit pain → spinal cord sensory tract cells and interneurons → muscle tension → pain

Treatment:

- Non-pharmacological: bed rest, proper exercises, proper posture & support (resume normal activities asap)
- Drugs: analgesic agents / muscle relaxants (NSAIDs, ASA, APAP, codeine/morphine, **CNS muscle relaxants**)

CNS muscle relaxant acting on spinal motorneurons

Spinal motorneurons: subjected to descending facilitatory influences mediated by norepinephrine released from descending fibers that originate in pontine/medullary brain nuclei (ex// locus coeruleus)

→ muscle tension is maintained or enhanced

Cyclobenzaprine: decreases the activity of LC neurons → disfacilitation (decreases facilitator influence on motor neurons → decrease muscle tension and reduced pain)

- Structurally similar to tricyclic antidepressants
- Antmuscarinic SEs: sedation, confusion, dry mouth, dizziness
- Onset of action: 1 h; $t_{1/2}$: 18 h

CNS muscle relaxant acting on spinal interneurons

Spinal interneurons: receive input from nociceptors and excite spinal motorneurons (glutamate) = polysynaptic reflex → motorneurons project to neuromuscular junction → muscle tension

Orphenadrine, Methocarbamol, Chlorzoxazone

- MOA unclear: reported to decrease amplitude of polysynaptic reflexes by suppressing excitatory interneurons in spinal cord → less excitatory drive to motoneurons → muscle relaxation occurs
- SEs: dizziness, blurred vision, dyspepsia, metallic taste
- Onset of action: 30 min; $t_{1/2}$: 1-2 h

GABA (inhibitory) **actions in spinal cord:** $GABA_A$ opens chloride channel; $GABA_B$ opens potassium channel (GPCR)

GABA released from axo-axonic synapses:

1. GABA released from presynaptic terminal
2. Binds to $GABA_A$ receptor on primary afferent fiber
3. Chloride ion efflux
4. Terminal partially depolarized = primary afferent depolarization (PAD)
5. Amplitude of terminal depolarization from incoming impulse reduced → less calcium influx → lower NT release → REDUCED MUSCLE TONE

Post-synaptically on $GABA_{A/B}$ receptors: causes hyperpolarization of motoneurons via increased chloride ($GABA_A$) & potassium ($GABA_B$) efflux

Pre-synaptically on $GABA_B$ receptors:

- Reduces calcium influx → reduces releases of excitatory NT in brain & spinal cord
- Promotes potassium efflux → terminal less excitable
- Reduces pain by inhibiting release of substance P and glutamate in the spinal cord

CNS muscle relaxants acting through GABA:

Baclofen: GABA-B agonist

→ Acts post-synaptically: increased K+ efflux → hyperpolarizes motoneurons

→ Acts pre-synaptically: reduces NT release → motor outflow reduced → less muscle tension, spasticity, and pain

- Equally effective, but less sedating than BZDs
- Rapid onset of action orally; $t_{1/2}$: 3-4 h
  - Intrathecal for refractory spasticity
- High doses: excessive somnolence, respiratory depression & coma

Benzodiazepines (BDZ): Diazepam, Lorazepam

- Act on $GABA_A$ receptors (increase PAD)
  - Enhance action of synaptically released GABA → presynaptic inhibition of motoneurons is enhanced → muscle relaxation
- Post-synaptic inhibition via $GABA_A$ mediated receptors also enhanced

Alpha 2 adrenergic agonist (Tizanidine) action on spinal cord: congener of clonidine (CNS muscle relaxant; analgesic; manages migraine headaches)

- Exerts 1/15th amount of blood pressure lowering action of clonidine
- Enhances presynaptic inhibition (reduced NT from locus coerulus) → less muscular contraction
- Restores glycine-mediated inhibition due to specialized inhibitory interneurons that specifically inhibit motoneurons in spinal cord
- Inhibits activity of nociceptive neurons responding to painful inputs
- No effect on intrinsic properties of muscles
- $T_{1/2}$: 2.5 h
- Inhibits CYP1A2 (interacts w/ SSRIs, fluoroquinoles)
- SEs: drowsiness, hypotension, dizziness, dry mouth, asthenia, tingling in extremities

Spasticity: hypertonus, paralysis and exaggerated reflexes
→ spinal cord injury, stroke, cerebral palsy or multiple scleroris

- CNS muscle relaxants: baclofen and/or BZDs (enhance GABA-ergic inhibition)
- Periphery: dantrolene

Malignant Hyperthermia (MH): during general anesthesia using inhalation agents

- Due to abnormal ryanodine receptor (on SR) → buildup of Ca2+ in skeletal muscle → sustained muscular contraction
- Sx: muscular rigidity, tachycardia, ↑temp, CO_2 production, O_2 consumption, metabolic acidosis, rapid skeletal muscle deterioration

Dantrolene: binds to ryanodine receptor (agonist)

→ Inhibits Ca2+ ion release from sarcoplasmic stores → reduces excitation-contraction coupling in muscle cells → skeletal muscle relaxes

→ Doesn't directly affect spinal motoneurons

→ Doesn't affect action potential invasion during neuromuscular transmission at NMJ

- Uses: can "rescue" MH pts; managing spasticity
- SEs: NVD, headache, sedation, anxiety, cognitive impairment, speech & visual disturbances; hallucinations, seizures, respiratory difficulty
- Drug interactions: calcium channel blockers (CV failure); other CNS muscle relaxants (increased muscle weakness)