# *Therapeutic Reviews*

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## *Benzodiazepines* AHFS 28:24.08

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Benzodiazepines are useful in the management of various symptoms encountered in palliative care. Tolerance and dependence are unlikely to be a problem when used for ≤4 weeks. However, other undesirable effects include drowsiness, falls, and memory and cognitive impairment. Thus, appropriate caution and monitoring is required, particularly for those at greater risk, e.g., the elderly and frail patients.

**Indications:** Authorized indications vary between products; consult the manufacturers' PIs for details; they include insomnia; anxiety and panic disorder; seizures; myoclonus; skeletal muscle spasm; alcohol withdrawal. Off-label indications include: †drug-induced movement disorders; †restless legs syndrome; †acute psychotic agitation; †terminal agitation; †neuropathic pain; †nausea and vomiting; †intractable pruritus; †intractable hiccup.

**Contraindications:** Unless in the imminently dying: acute severe pulmonary insufficiency, untreated sleep apnea syndrome, severe liver disease, myasthenia gravis. Also see individual PIs.

### Pharmacology

GABA is the major inhibitory neurotransmitter of the nervous system. Several drug classes enhance its action (GABAmimetics):

- $GABA_A$ modulators: benzodiazepines, non-benzodiazepine hypnotics ('Z' drugs, e.g., zopiclone), barbiturates, some general anesthetics (e.g., propofol), alcohol
- $GABA_B$ agonists: baclofen
- inhibitors of GABA transaminase (e.g., vigabatrin) or re-uptake (e.g., tiagibine).[1]

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The $GABA_A$ receptor is a chloride channel formed by 5 subunits comprising varying subtypes (Fig. 1) $GABA_A$ modulators bind to sites distinct from GABA itself (allosteric modulation), increasing the receptor's affinity for GABA (benzodiazepines) or prolonging channel opening (barbiturates).[2] The α subunit of the $GABA_A$ receptor, of which there are six subtypes, is the predominant determinant of benzodiazepine affinity and function (Table 1). In an attempt to improve efficacy and/or tolerability, more selective α-modulators are under investigation, e.g., α2-selective non-sedating anxiolytics.[3]

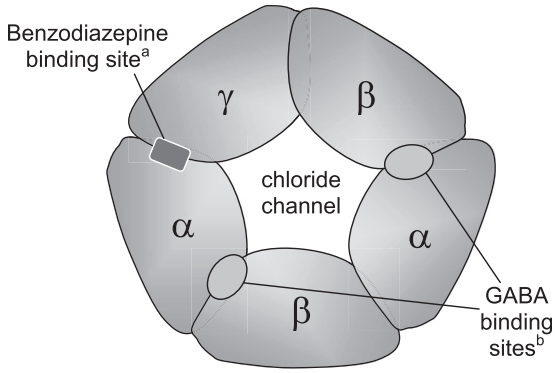


Fig. 1. Structure of the $GABA_A$ receptor.
a. the binding sites for barbiturates, ethanol, neurosteroids and other allosteric modulators are less well characterized
b. the central chloride channel is opened by the concurrent binding of 2 GABA molecules.

*Table 1*
**$GABA_A$ α-subunit Subtypes and Relative Activity of Selected GABAmimetics[3-8]**

| Alpha Subunit Subtype<br>Function | 1<br>Sleep<br>Anti-epilepsis[b] | 2<br>Anxiolysis<br>Anti-epilepsis[b] | 3<br>Anti-epilepsis[b] | 4[a]<br>Anti-epilepsis[b] | 5<br>Amnesia | 6[a] |
|---|---|---|---|---|---|---|
| Clonazepam | ++ | ++ | ++ | − | | − |
| Diazepam | ++ | ++ | ++ | − | ++ | − |
| Flunitrazepam | ++ | ++ | ++ | − | ++ | − |
| Midazolam | ++ | | ++ | − | ++ | − |
| Zaleplon[c] | ++ | ++/+ | ++/+ | | ++/+ | |
| Zolpidem[c] | ++ | ++/+ | ++/+ | − | − | − |
| Zopiclone | ++ | ++ | −/+[c] | − | + | − |
| Pentobarbital | ++ | ++ | ++ | ++ | ++ | |
| Ethanol[d] | + | + | + | ++ | + | |

Activity: ++ high, + low, − negligible or none; blank = no data.
[a]Benzodiazepines do not bind to α4- and α6-subunits, or to receptors lacking α and γ subunits (benzodiazepine-insensitive $GABA_A$ receptors).
[b]Relative importance of subunits varies with different seizure models.
[c]α Subunit affinity varies with different β and γ subunit configurations. Prior to cloning, $GABA_A$ classifications encompassed more than one subunit configuration which may account for earlier conflicting affinity data.
[d]Tonic α4(δ) mediated inhibition predominates at lower doses whereas synaptic (α 1, 2 and 3) effects are responsible for severe intoxication. Ethanol also enhances release of GABA and GABAmimetic neurosteroids.

The sedative effects of benzodiazepines (and Z-drugs) probably result from the inhibition of the wakefulness-promoting system.[9,10] Their anxiolytic effects result from α2-$GABA_A$ receptor agonism in the "fear circuits" which are co-ordinated by the amygdala.[11]

Although GABA *antagonists* might be expected to improve wakefulness or memory, the use of non-selective $GABA_A$ antagonists is precluded by anxiogenic and pro-seizure properties. However, the memory-enhancing properties of α5-selective inverse agonists are being investigated. Endogenous ligands for the benzodiazepine binding site include peptide and neurosteroid molecules, but their physiological function is not yet understood.