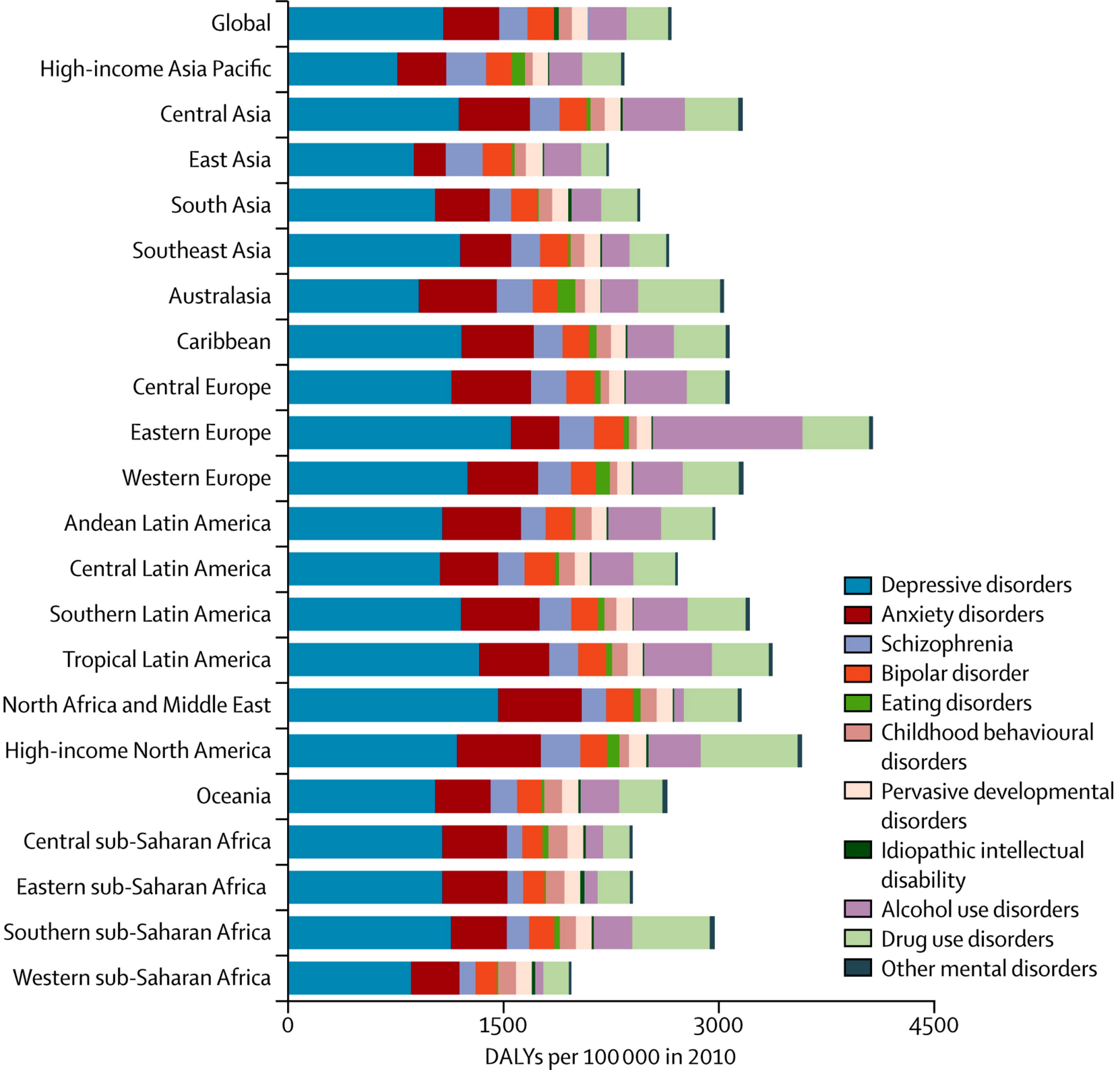
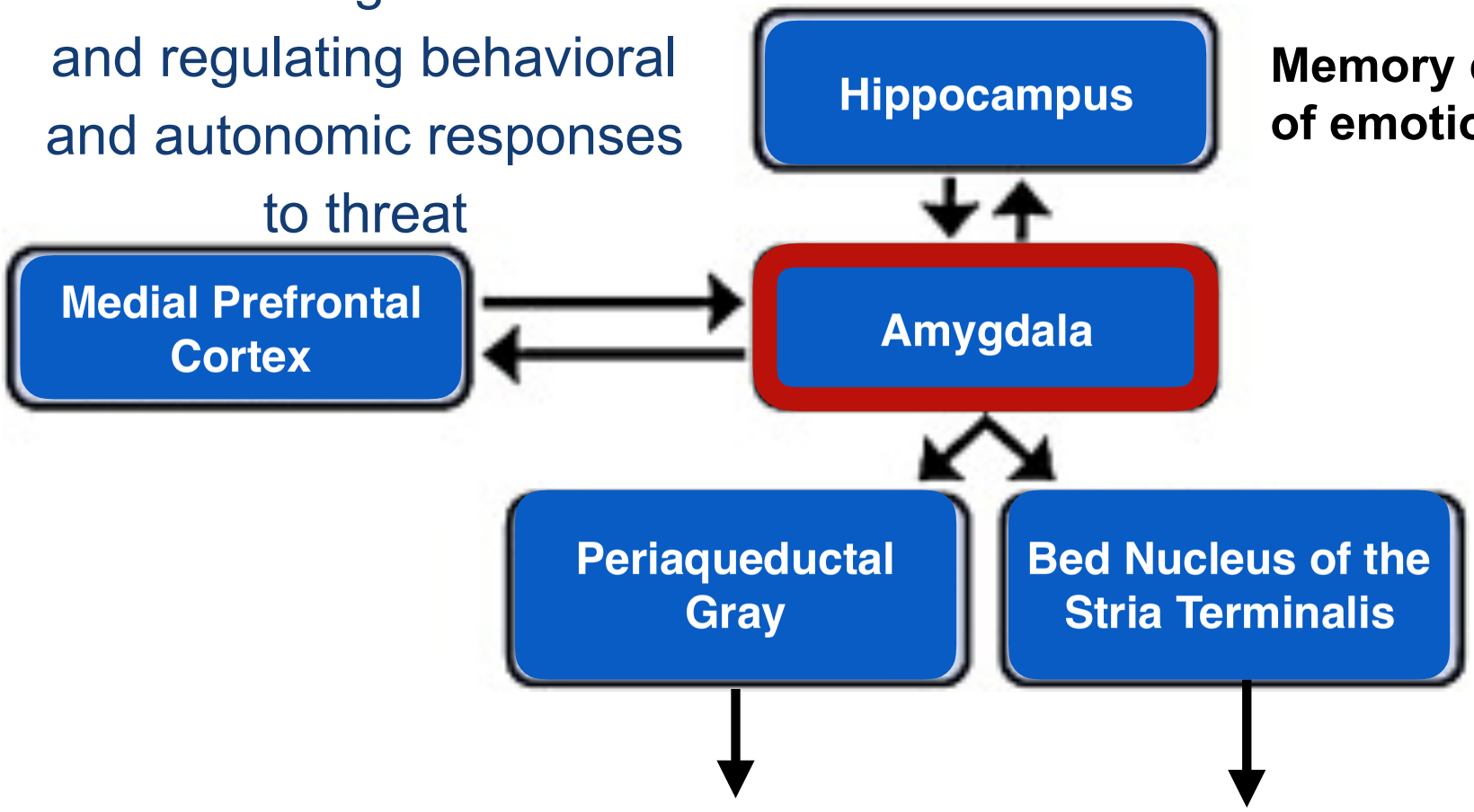

Global
High-income Asia Pacific
Central Asia
East Asia
South Asia
Southeast Asia
Australasia
Caribbean
Central Europe
Eastern Europe
Western Europe
Andean Latin America
Central Latin America
Southern Latin America
Tropical Latin America
North Africa and Middle East
High-income North America
Oceania
Central sub-Saharan Africa
Eastern sub-Saharan Africa
Southern sub-Saharan Africa
Western sub-Saharan Africa
0
1500
3000
4500
DALYs per 100 000 in 2010
Depressive disorders
Anxiety disorders
Schizophrenia
Bipolar disorder
Eating disorders
Childhood behavioural disorders
Pervasive developmental disorders
Idiopathic intellectual disability
Alcohol use disorders
Drug use disorders
Other mental disorders

Neural systems involved in detecting threats and regulating behavioral and autonomic responses to threat



Memory consolidation of emotional events

Autonomic, somatic signs of anxiety

stereotyped defensive reactions to threat (immobility and panic)

autonomic and motor responses to threat (tachicardia, sweating)

Autonomic, somatic signs of fear

unconditioned (innate) anxiety responses

conditioned (learnt) anxiety responses

ANXIETY

Anxiety is an adaptive response that enables the individual to recognize danger and deal with an unknown vague internal or external threat

Normal anxiety is an advantageous response to a threatening situation that accompanies many aspects of life

Pathological anxiety is an inappropriate response to an internal or external stimulus

Anxiety disorders are characterized by feelings of anxiety and fear and inappropiately severe and prolonged anticipation of negative event.
Symptoms can range from mild to severe.
It is more a chronic than an episodic disorder.

Anxiety Disorders

- Generalized anxiety disorder (GAD): general symptoms of motor tension, autonomic hyperactivity, etc. for at least one month
- Phobic anxiety:
  - Simple phobias (Agoraphobia, fear of animals, etc.)
  - Social phobias
- Panic disorders: Characterized by acute attacks of fear as compared to the chronic presentation of GAD
- Obsessive-compulsive behaviors (OCB): repetitive ideas (obsession: a persistent idea, image or desire) and behaviors (compulsion: a strong impulse to perform an act, especially one that is irrational or contrary to one's will)
- Post-traumatic stress disorders (PTSD)

GENERALIZED ANXIETY DISORDER

First-line therapy	Second-line therapy
• **SSRI** (citalopram, paroxetine) **SNRI** (venlafaxine) with good risk/ benefit ratio, efficacy and tolerability • Note: slow onset of activity and early discontinuation has high risk of relapse (treatment for one year, gradual discontinuation)	• **benzodiazepines** (early onset of action but adverse effects), TCA (poor safety and tolerability) • **partial 5-HT1A receptor agonist** (buspirone) for comorbidity with alcohol dependence and add-on SSRI therapy • **Inhibitors of VDCC** (Gabapentin and pregabalin) • **atypical antipsychotic drug** (quetiapine) in refractory patients

OBSESSIVE-COMPULSIVE DISORDER

• **SSRI** (fluoxetine, paroxetine, sertraline)	• **glutamate- modulating agents**: topiramate, riluzole (inhibition of glutamate release), memantine (blocker) and cycloserine (partial agonist) • **5-HT 3 receptor antagonist** (ondansedron)

PANIC DISORDER

First-line therapy	Second-line therapy
• **SSRI** (fluoxetine, paroxetine, sertraline)	• **MAOI** (dietary restriction), **benzodiazepines** (alprazolam) • **Anticonvulsants** (valproate) • • Novel target: adenosine receptors

POST-TRAUMATIC DISORDER

• **SSRI**	• **MAOI** (dietary restriction) • **Anticonvulsants** (lamotrigine BUT available data are limited) • From animal studies: prevention (beta- blockers, hydrocortisone I.v.)

SOCIAL DISORDER

• **SSRI**	• MAOI (dietary restriction), RIMA (moclobemide) • clonazepan (add-on therapy)

GABA-A receptors

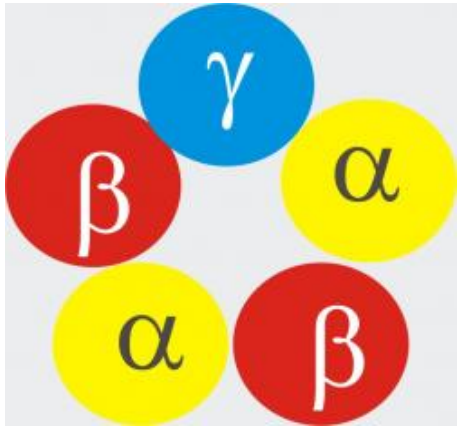
The GABAA-R are members of the Cys-loop pentameric LGIC superfamily, including nicotinic Ach receptors, inhibitory glycine receptors, and ionotropic 5-HT3 receptors

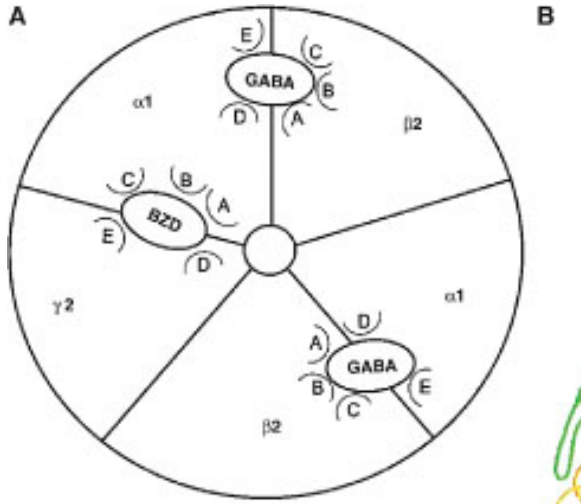
19 different $GABA_A$ receptor subunits have been identified in mammals:

α (1–6), β (1–3), γ (1–3), δ, ε, ρ (1–3), θ and π

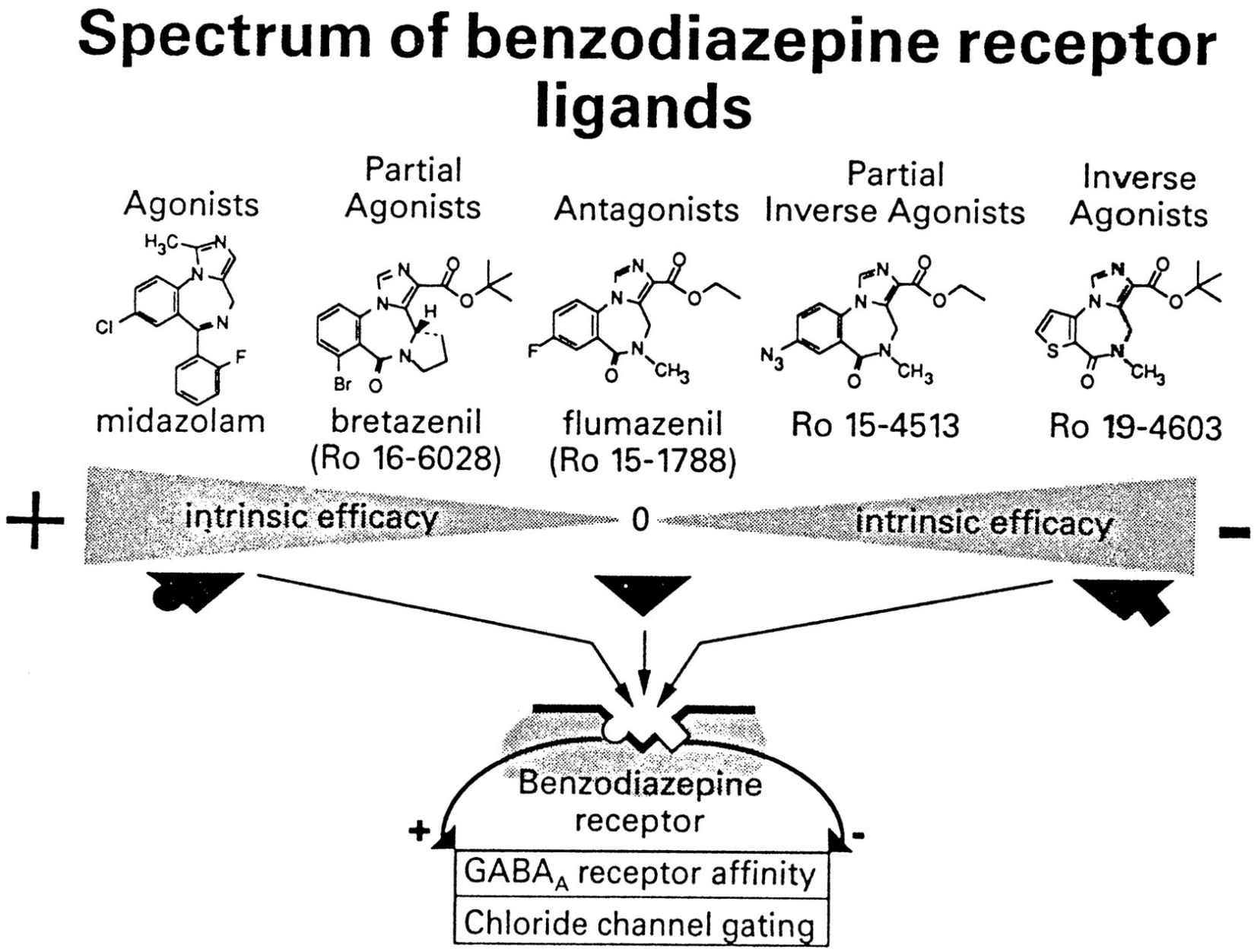
The majority of the native receptors are composed of α, β and γ subunits with at least one of 3 general compositions subunit in a 2:2:1 stoichiometry :

2α2β1γ
2α1β2γ
1α2β2γ

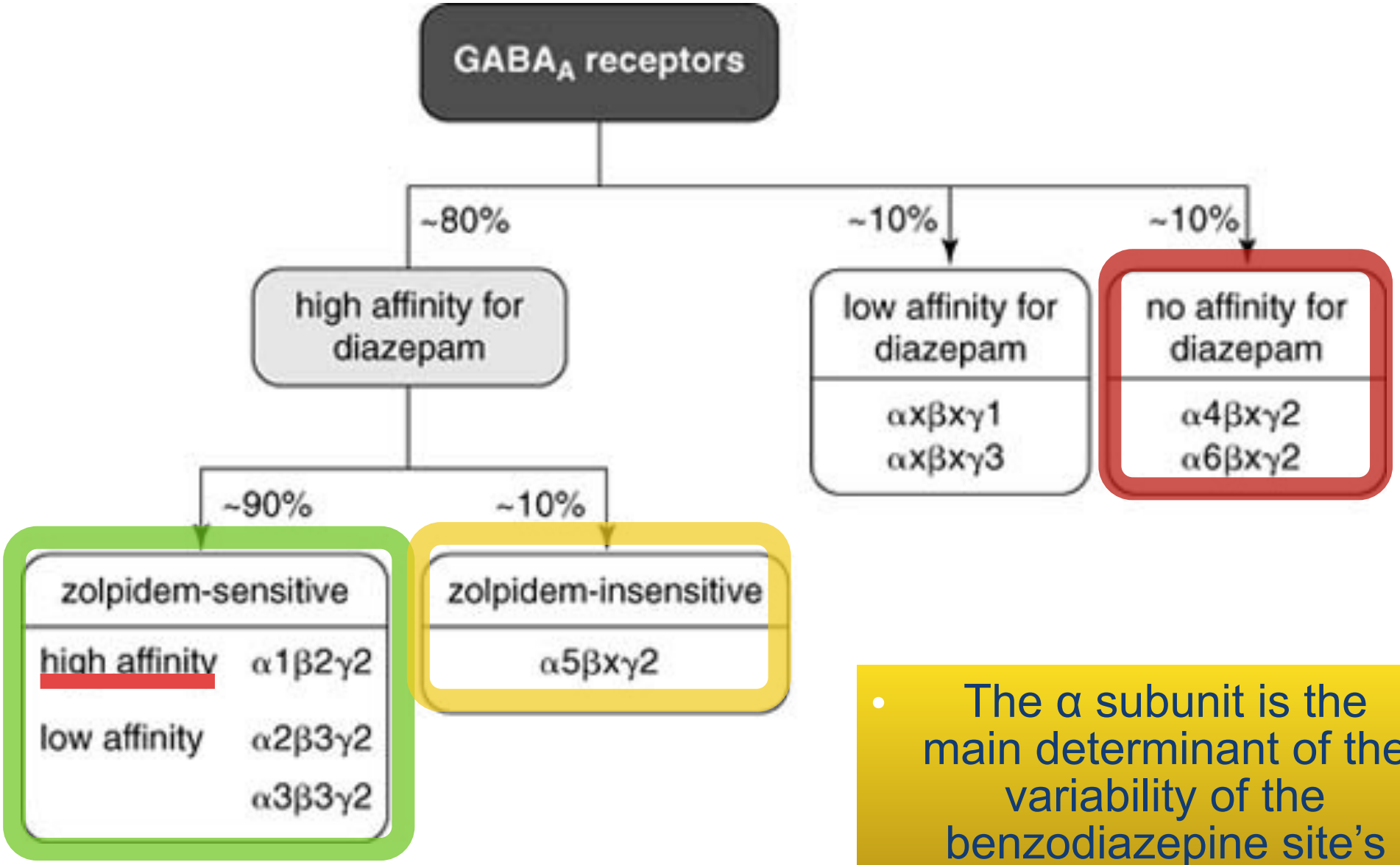




The benzodiazepine binding site

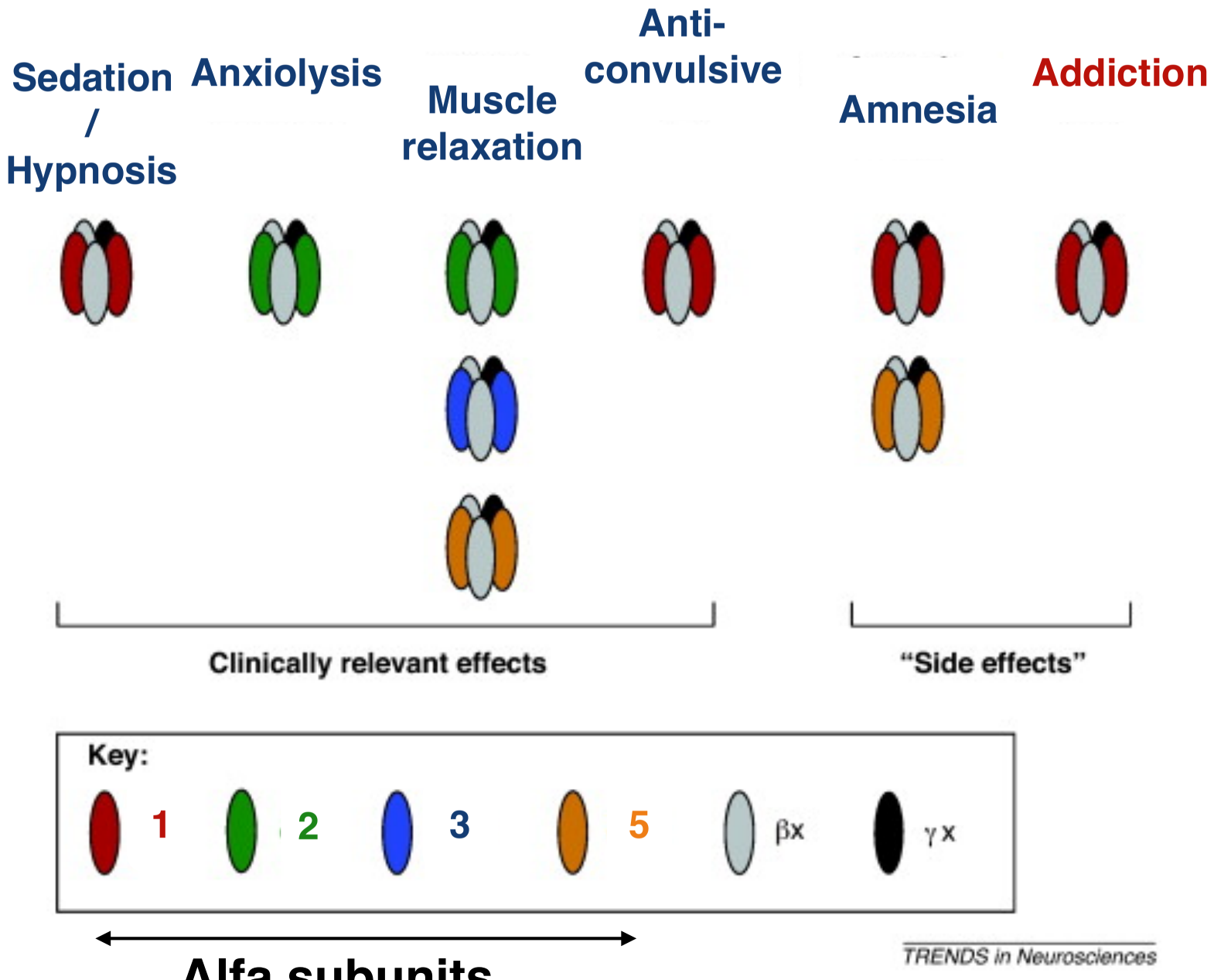


The benzodiazepine binding site



- The α subunit is the main determinant of the variability of the benzodiazepine site's
- **affinity** and **efficacy**

BDZs Functions associated with different α subunits

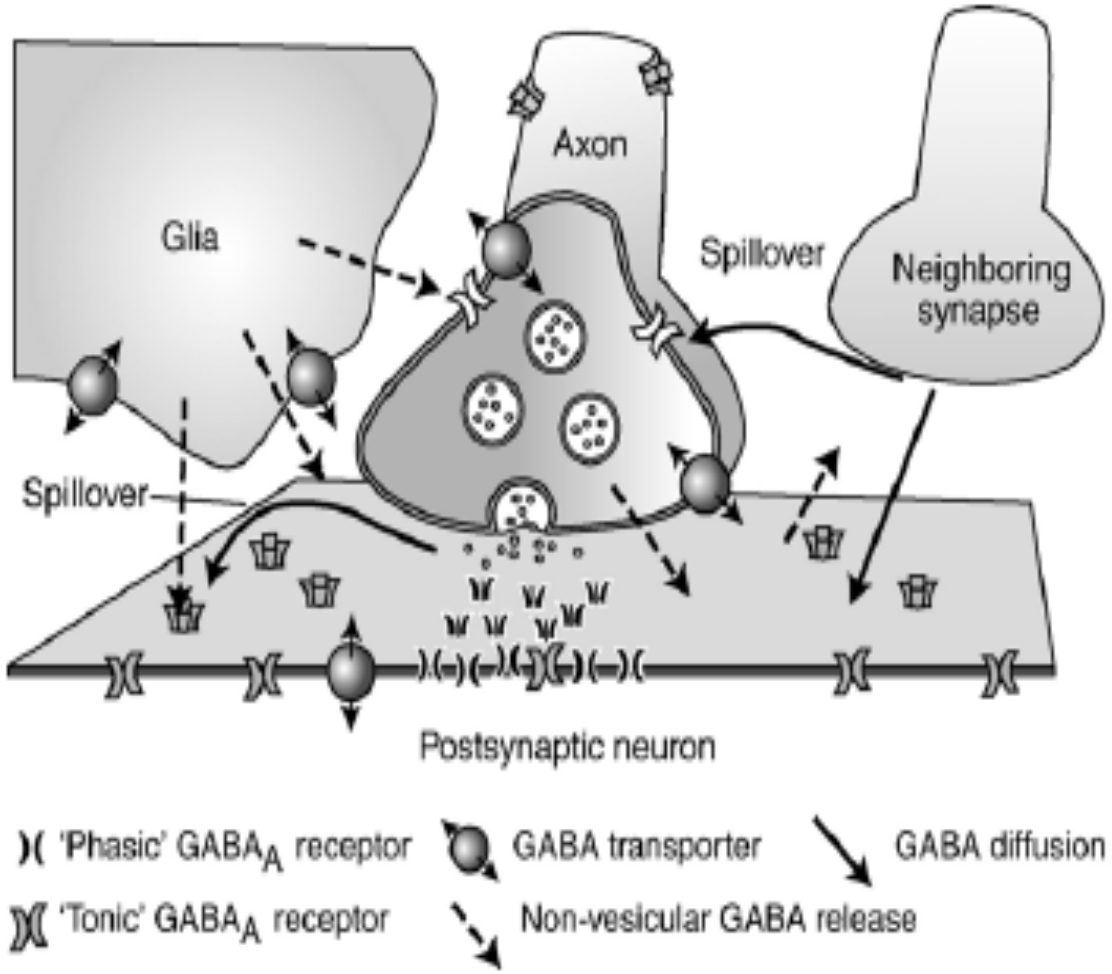


GABA-ergic synaptic and extrasynaptic neurotransmission

Phasic inhibition is mediated by release of GABA into the synaptic cleft with rapid desensitization of postsynaptic receptors

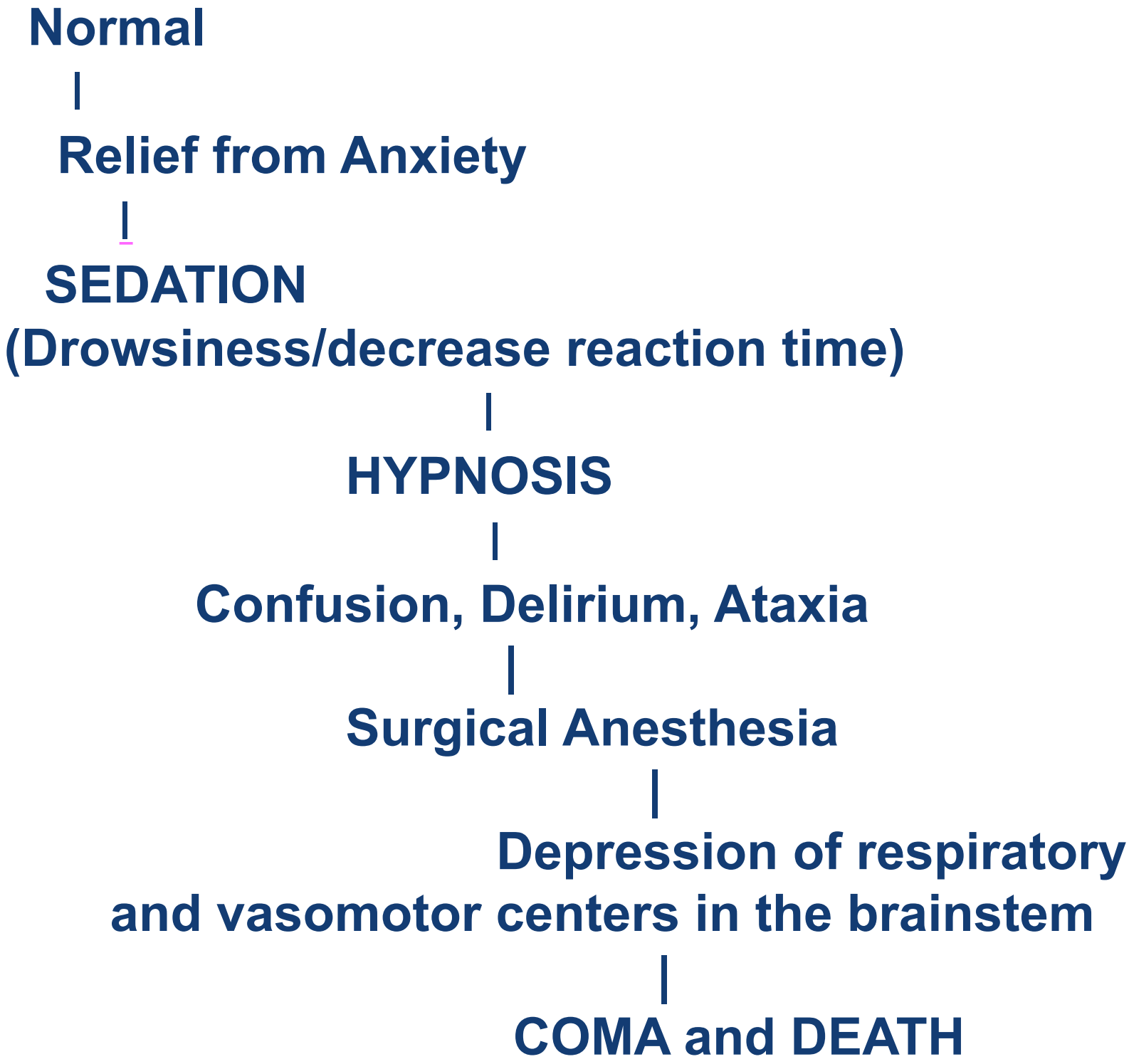
Tonic inhibition is mediated by GABA spillover from the synapse or nonvesicular pathways

The nondesensitizing currents modulate the electrical potential of pre- and postsynaptic membranes



Properties of BDZs

Wanted effects	Unwanted effects
Anxiolysis	Tolerance and dependence
Sedation/hypnosis	Sedation
Amnesia	Cognitive impairment
Muscle relaxation	Ataxia
Seizure protection	


Normal
Relief from Anxiety
SEDATION
(Drowsiness/decrease reaction time)
HYPNOSIS
Confusion, Delirium, Ataxia
Surgical Anesthesia
Depression of respiratory
and vasomotor centers in the brainstem
COMA and DEATH

What Are BDZs for?

Hypnotic
Midazolam

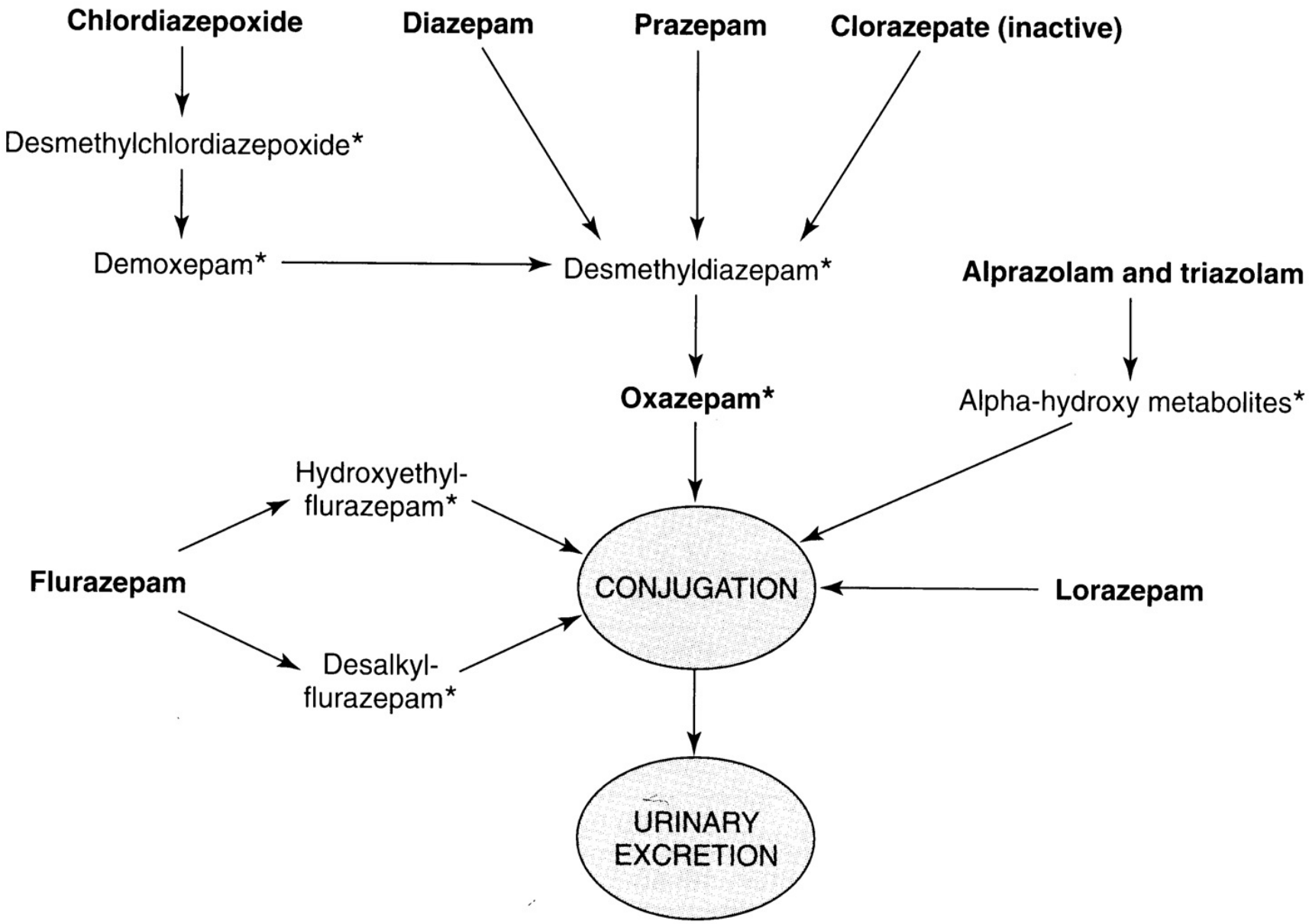
Anxiolytic
Alprazolam (Xanax), Nitrazepam, Fluorazepam

Hypnotic - Anxiolytic
Lorazepam, Oxazepam, Temazepam

Anxiolytic - Muscle relaxant
Diazepam (Valium), Chlordiazepoxide (Librium)

Anticonvulsant - Anxiolytic
Diazepam, Clonazepam (mania)

Biotransformation of BZDs



	Elimination half-time (h)	Clearance (ml/kg/min)	Vd (L/kg)	Plasma protein binding %
Midazolam	1.7-2.6	5.8-9.0	1.1-1.7	96
Diazepam	20-50	0.2-0.5	0.7-1.7	98
Lorazepam	11-22	0.8-1.8	0.8-1.3	90
Flumazenil	0.7-1.3	13-17	0.9-1.1	40

Side Effects of Benzodiazepines

BDZs have a wide margin of safety if used for short periods

Long-term use (> 2 weeks) increases risk for adverse effects:

- Misuse, abuse, dependence
- Motor impairment (reaction time)
- Cognitive impairment (sedation, amnesia)

Pharmacodinamic drug interactions with other CNS depressants (alcohol, other anxiolytic drugs, OTC antihistaminic and anticholinergic drugs)

Pharmacokinetic drug interactions with SSRI's and oral contraceptives (decrease metabolism of BDZs)

Withdrawal syndrome

Side Effects of Benzodiazepines

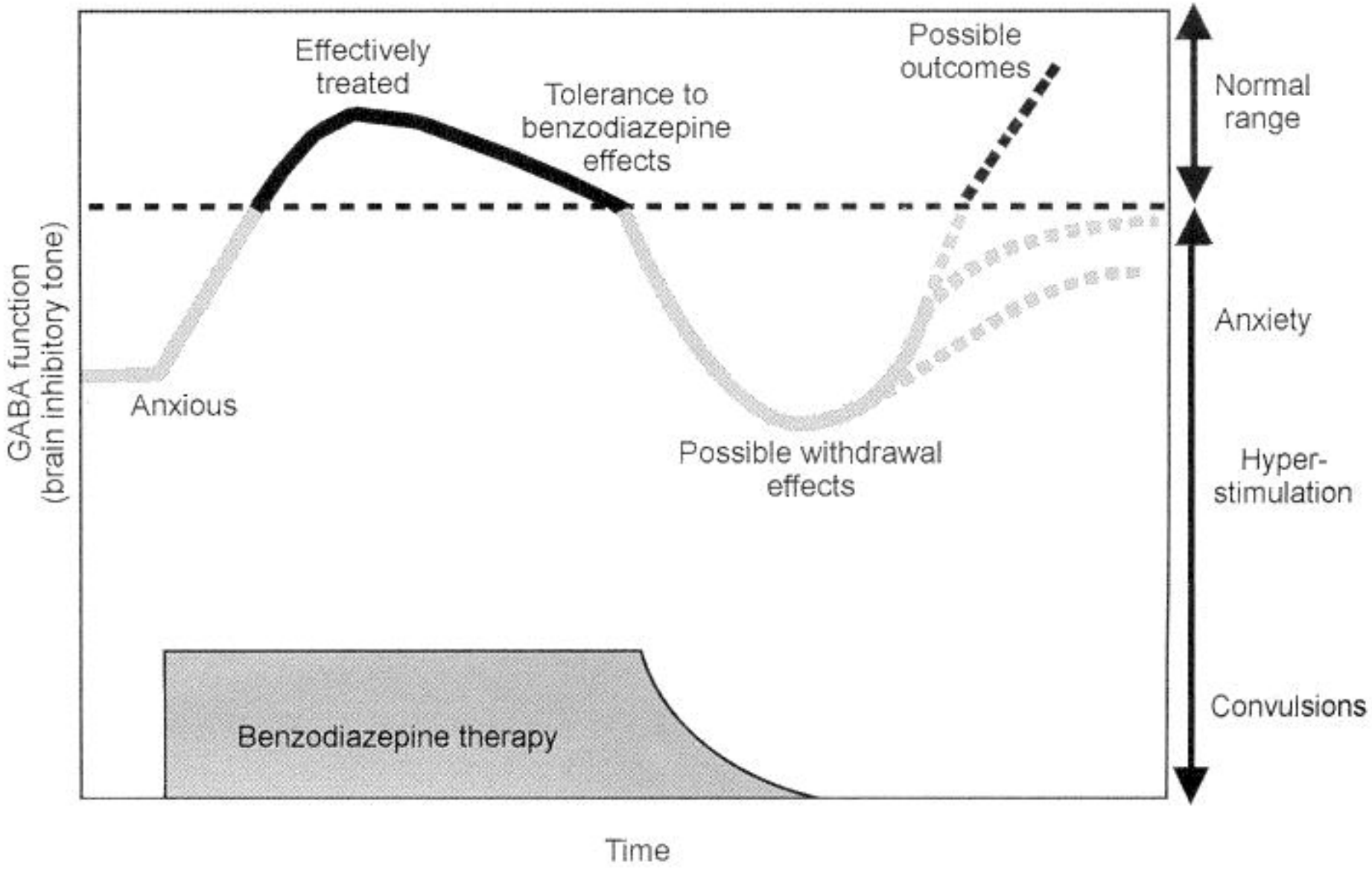
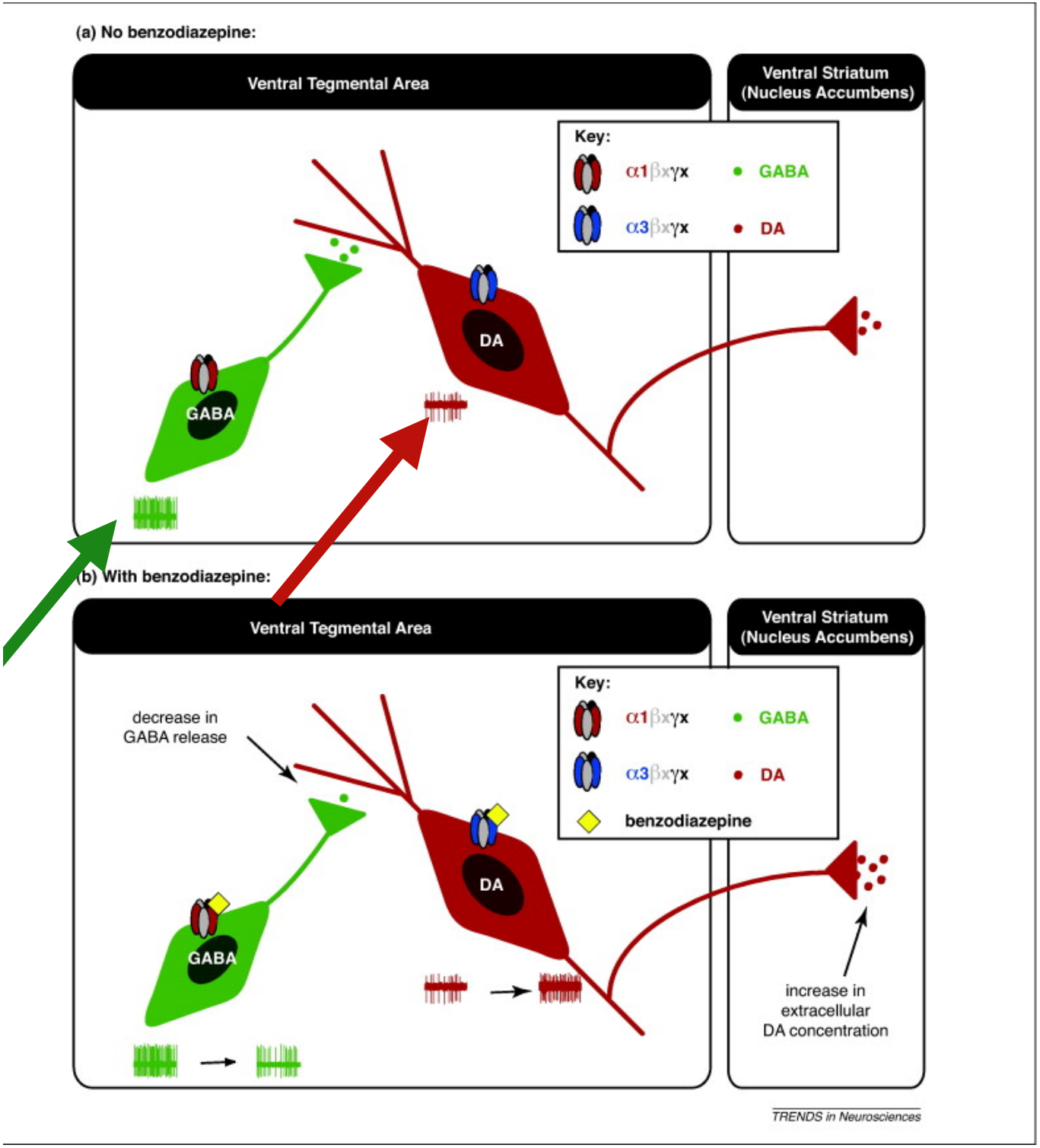


Fig. 7 Schematic



BDZs receptors in the VTA dopaminergic reward circuit

Hypnotic drugs

Short-acting benzodiazepines Lorazepam, temazepam
Allosteric modulator of GABA-A receptor Zolpidem, Zopiclone (BDZs site) Chlormethiazole
Melatonin receptor agonists Melatonin, Ramelteon
Orexin receptor antagonists Suvorexant
Histamine H1 receptor antagonists Prometazine, Doxepin