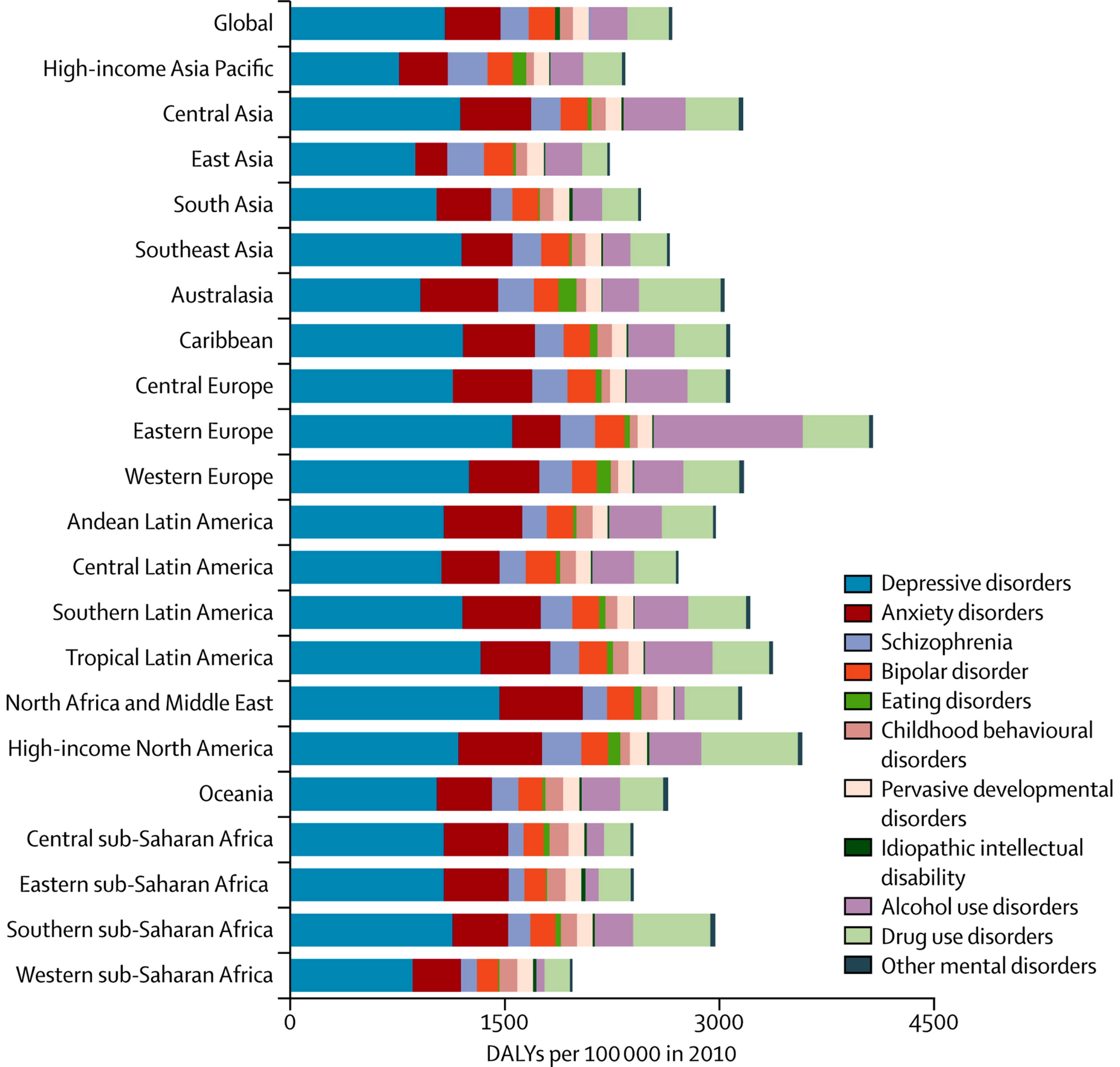
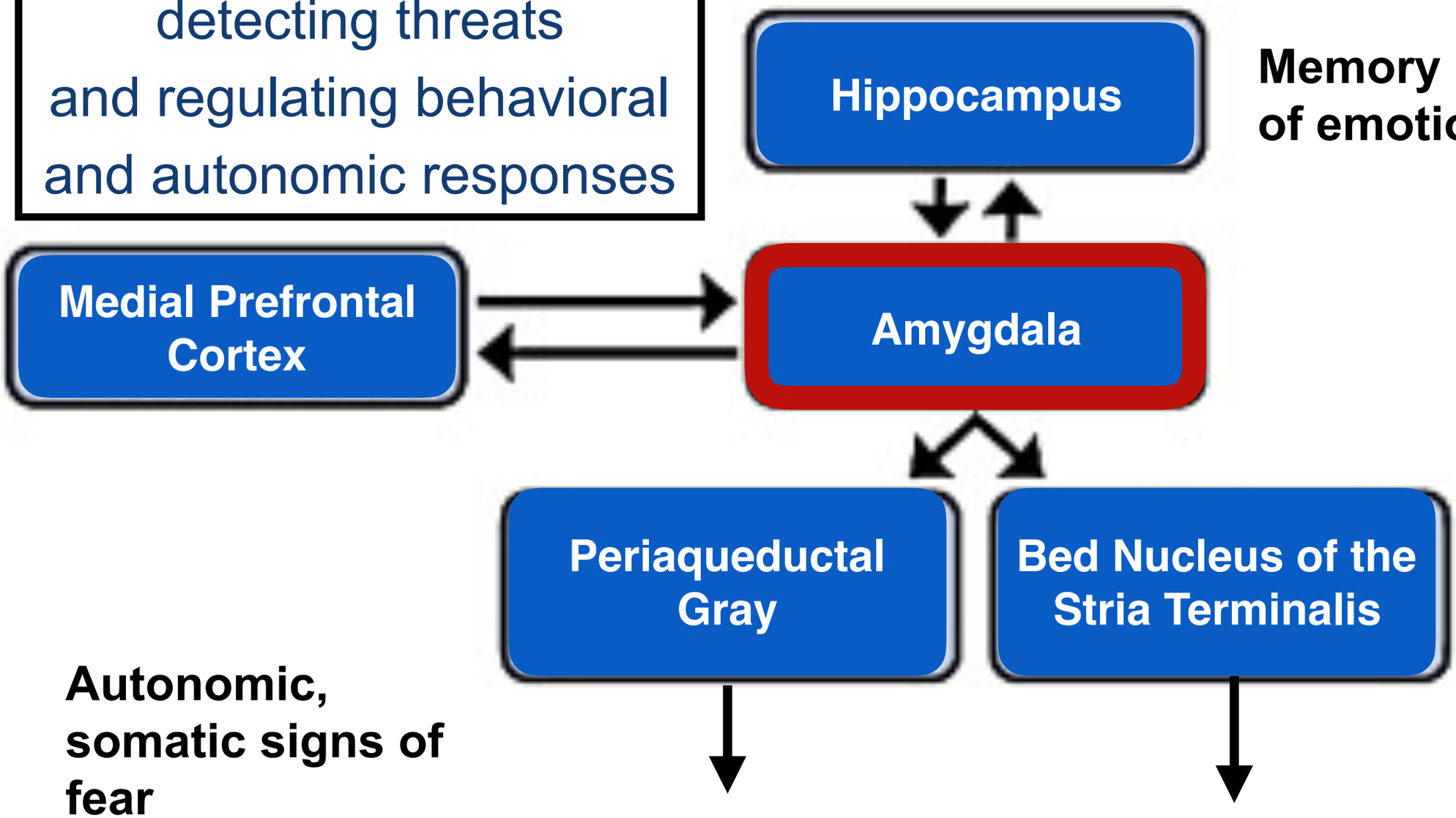

Global
High-income Asia Pacific
Central Asia
East Asia
South Asia
Southeast Asia
Australasia
Caribbean
Central Europe
Eastern Europe
Western Europe
Andean Latin America
Central Latin America
Southern Latin America
Tropical Latin America
North Africa and Middle East
High-income North America
Oceania
Central 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



Memory consolidation of emotional events

Autonomic, somatic signs of fear

stereotyped defensive reactions to threat (immobility and panic)

unconditioned (innate) anxiety responses

Autonomic, somatic signs of anxiety

autonomic and motor responses to threat (tachicardia, sweating)

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 inappropriate 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

- **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)

Second-line therapy

- **benzodiazepines** (early onset of action but adverse effects)
- **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:

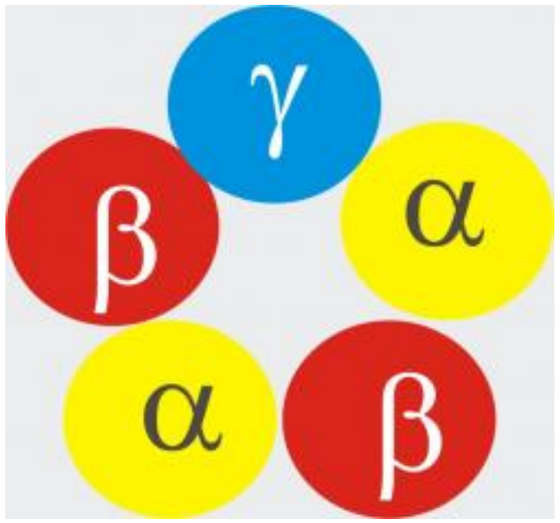
α (1–6), β (1–3), γ (1–3), δ, ε, ρ (1–3), θ and π

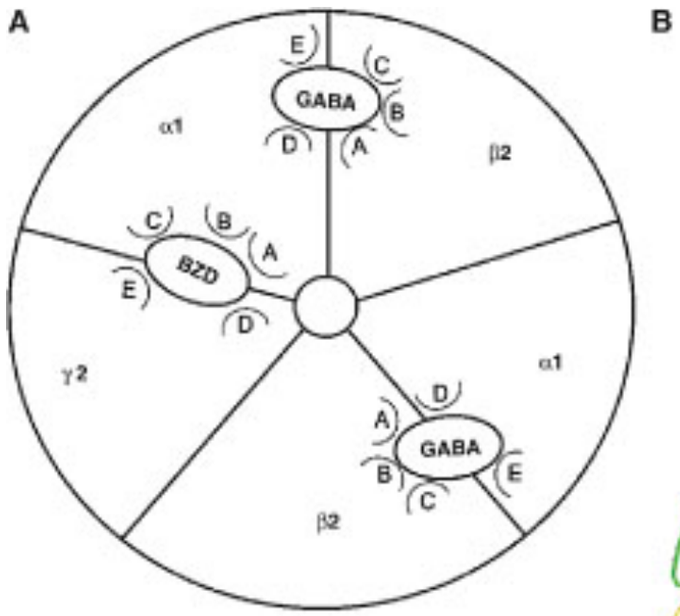
The majority of the native receptors are composed of α, β and γ subunits with at least one of 3 general compositions subunit in a 2:2:1 stoichiometry :

2α2β1γ

2α1β2γ

1α2β2γ



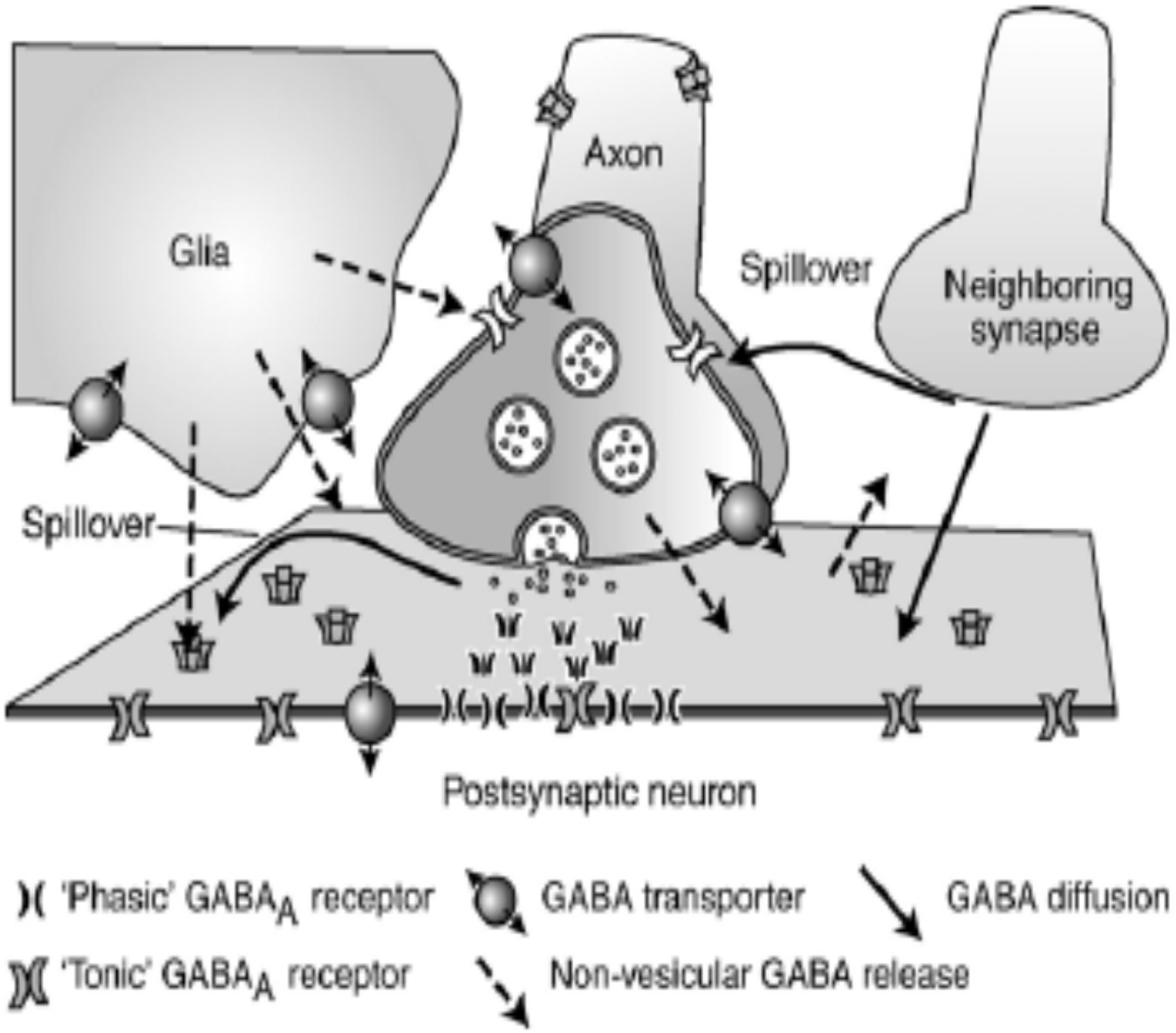


GABA-ergic synaptic and extrasynaptic neurotransmission

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

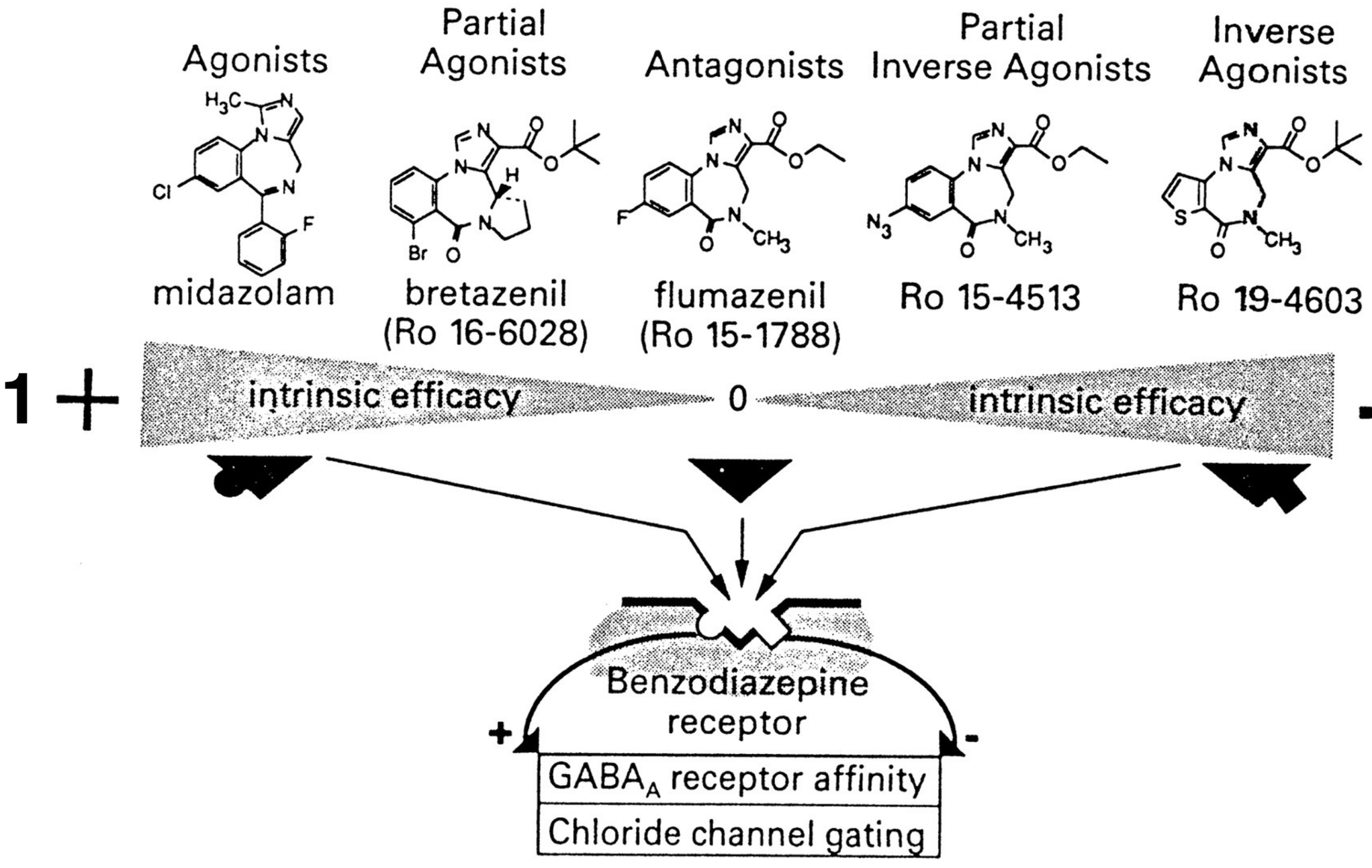
Tonic inhibition is mediated by GABA spillover from the synapse or nonvescicular pathways acting on receptors containing δ and α6 (and β) subunits with persistent conductance

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

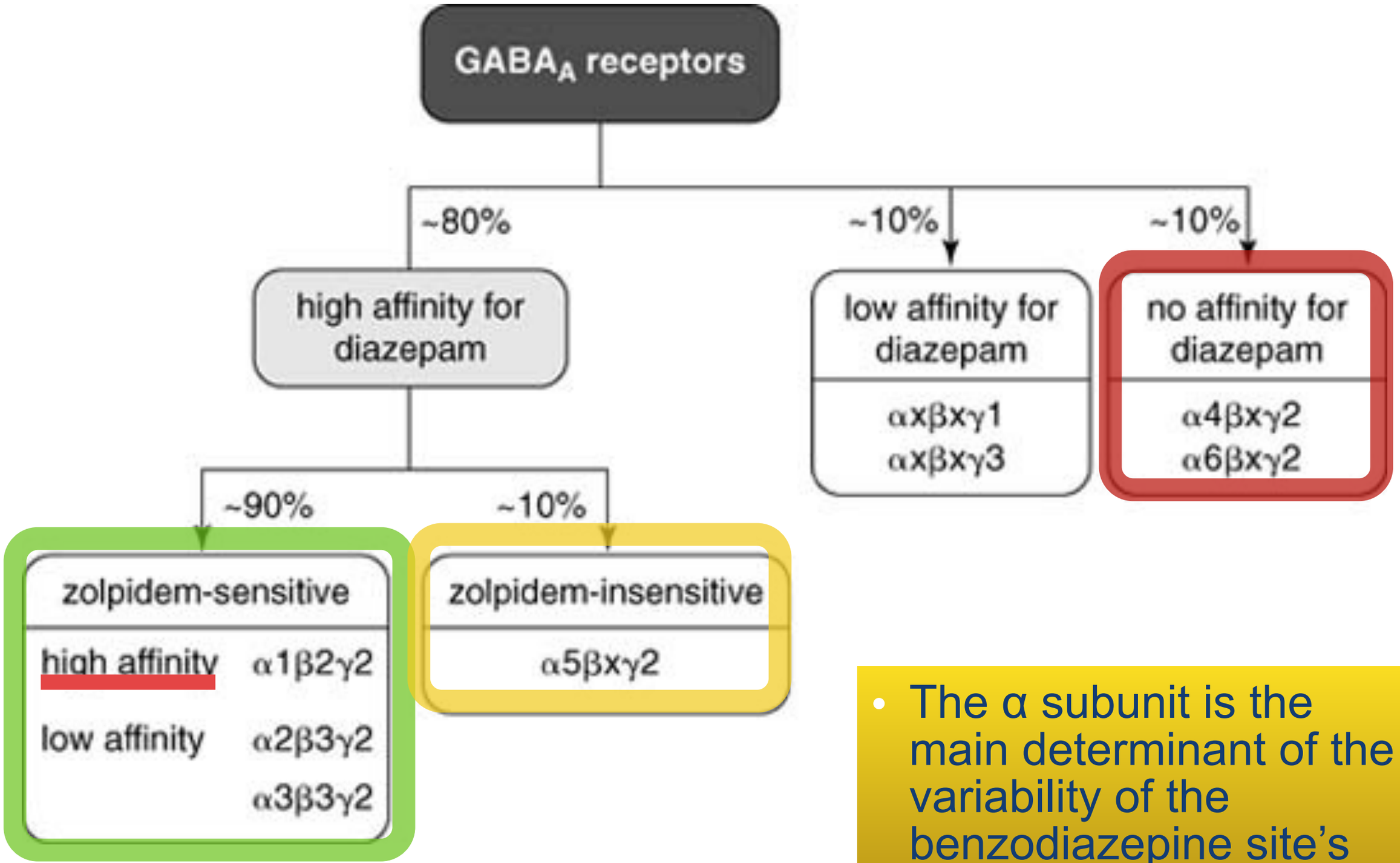


The benzodiazepine binding site

Spectrum of benzodiazepine receptor ligands

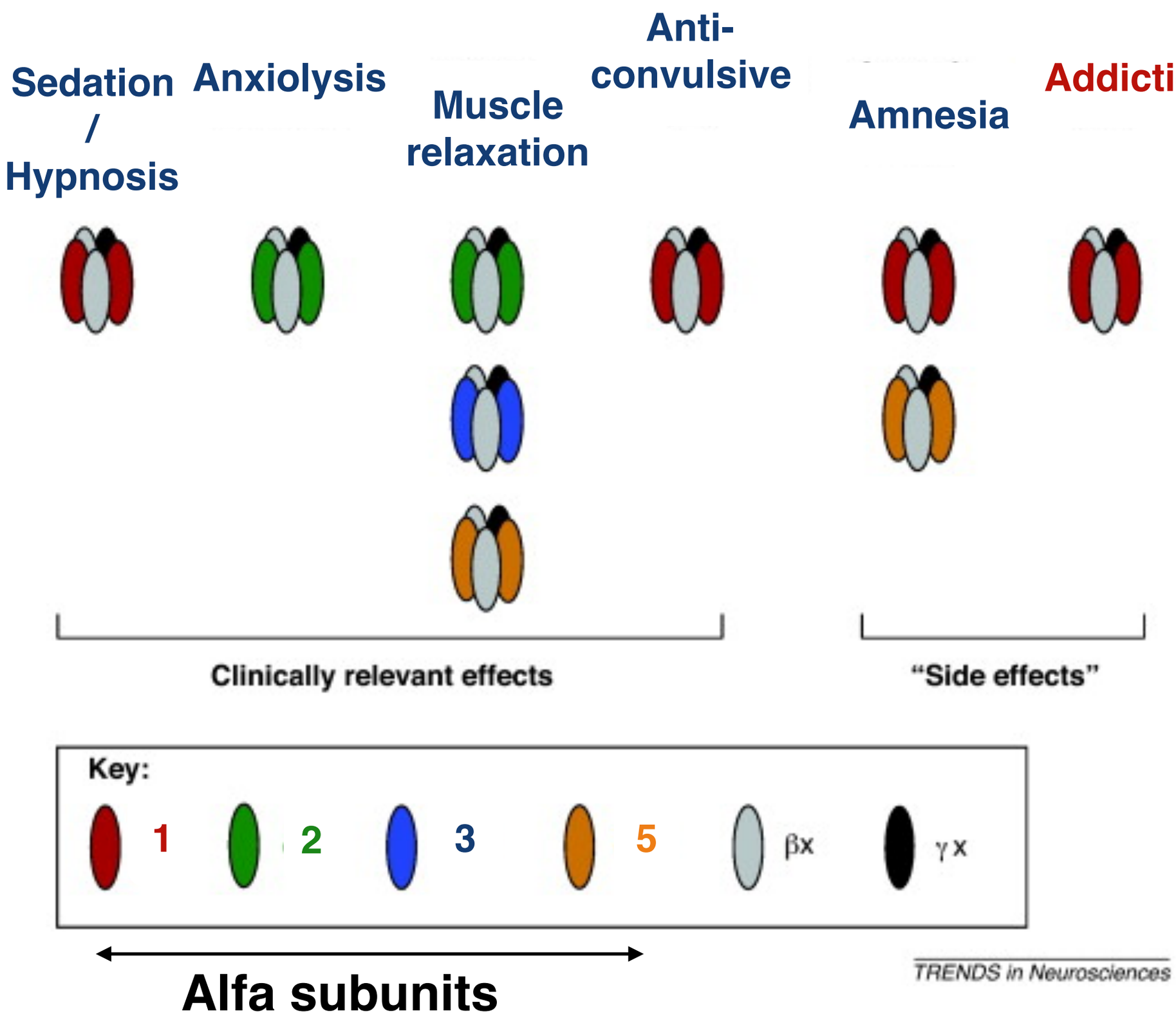


The benzodiazepine binding site



- 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



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

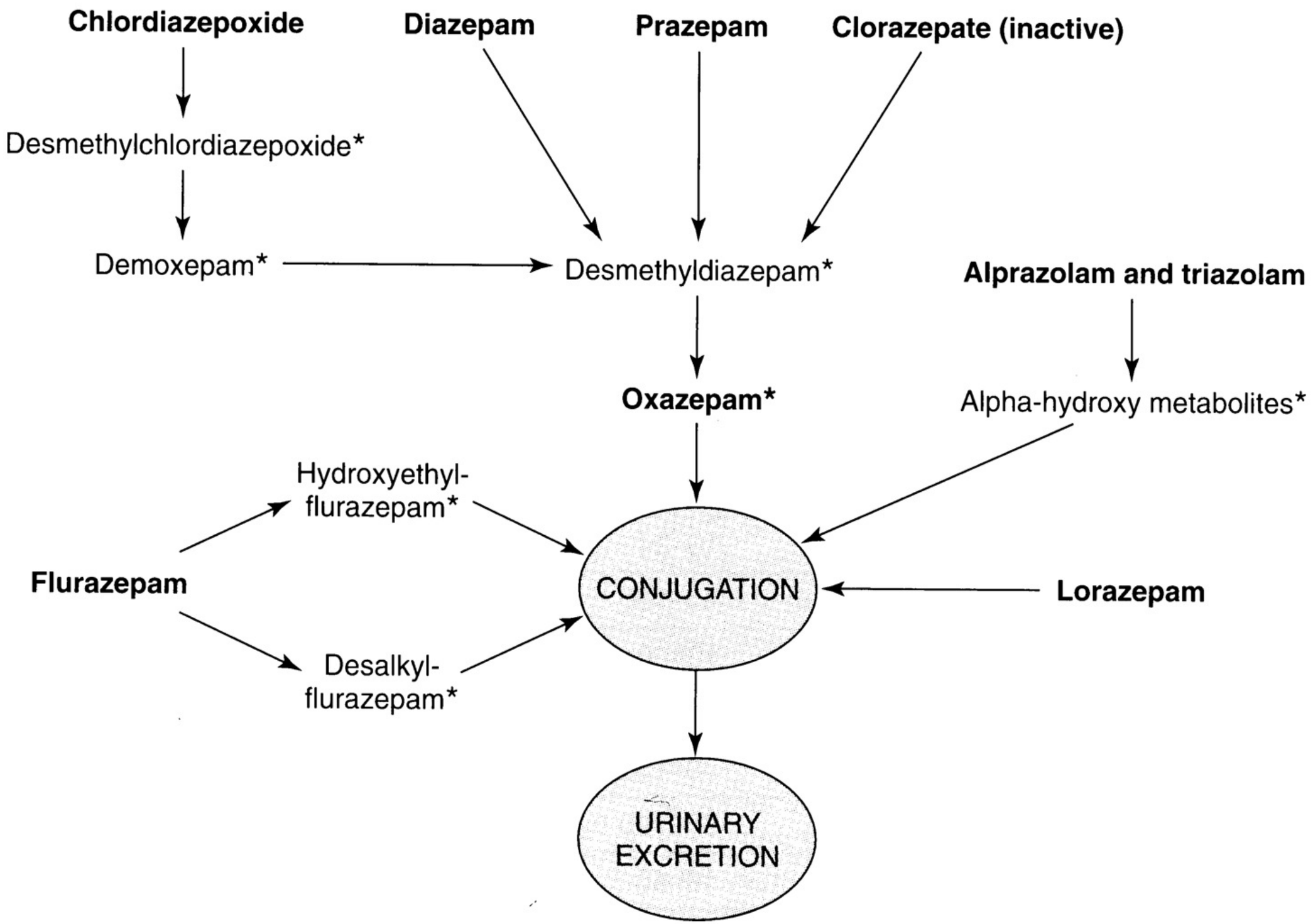
Hypnotic - Anxiolytic
Lorazepam, Oxazepam, Temazepam

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

Anticonvulsant - Anxiolytic
Diazepam, Clonazepam (mania)

	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

Biotransformation of BZDs



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

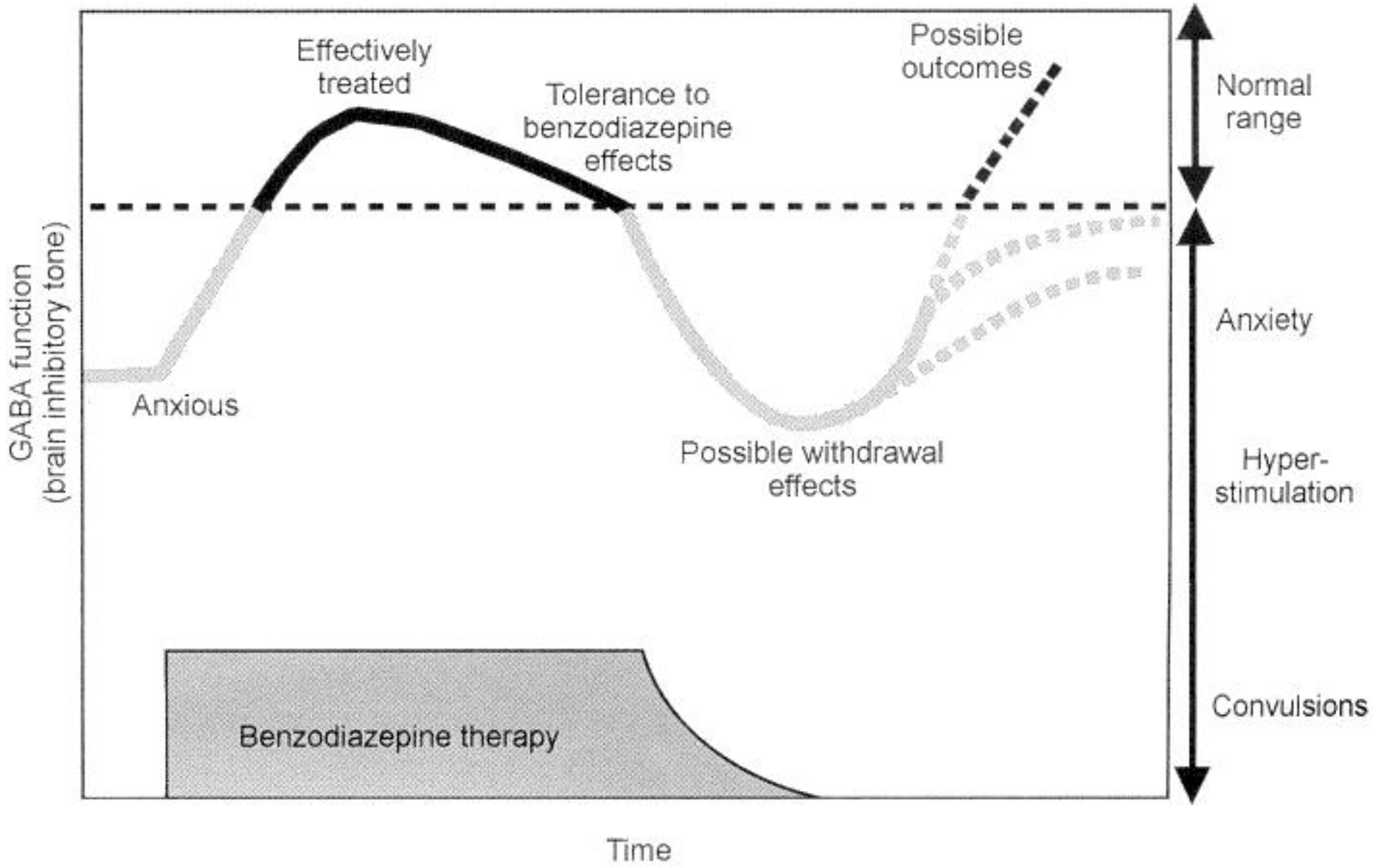
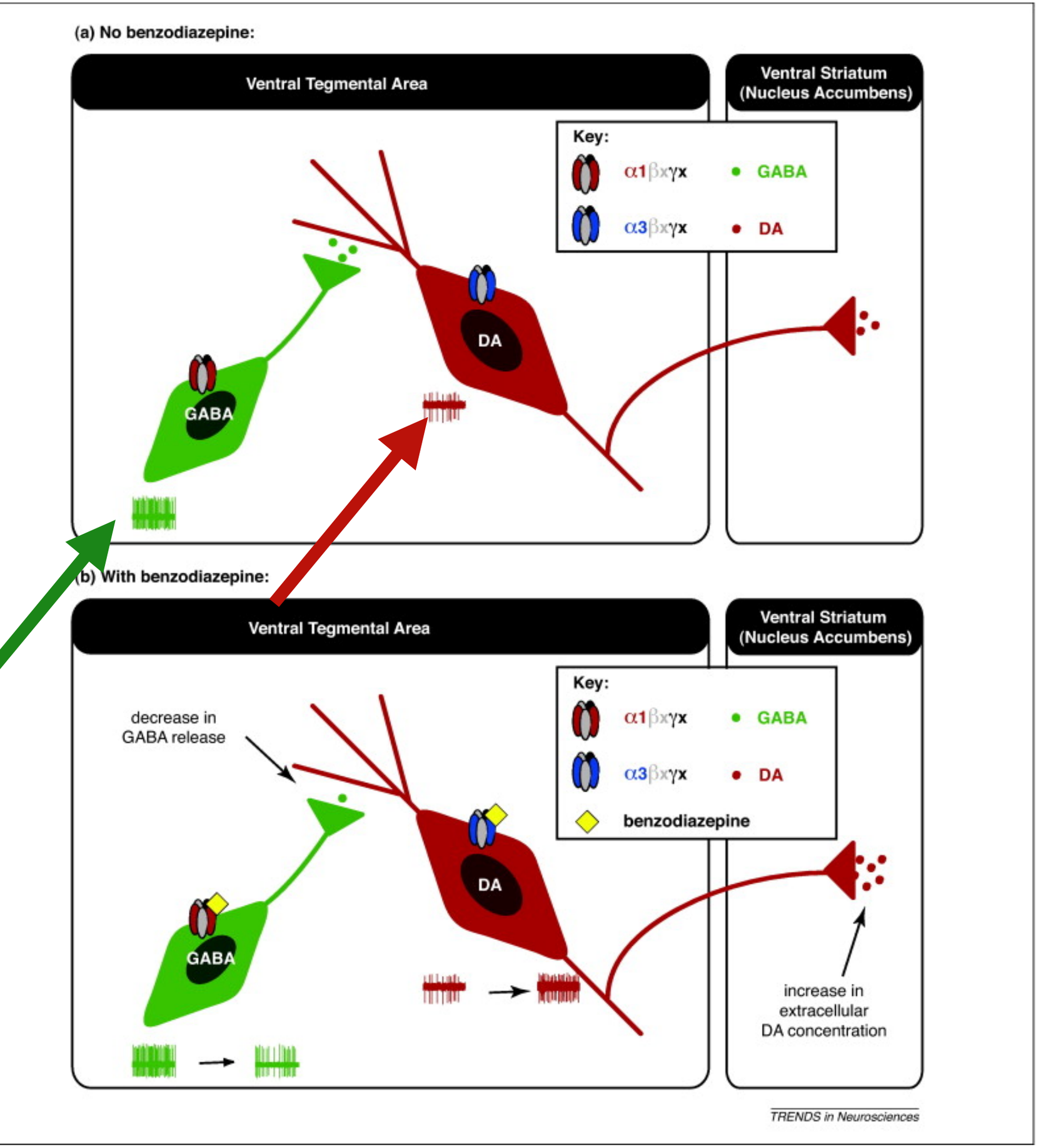


Fig. 7 Schematic



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