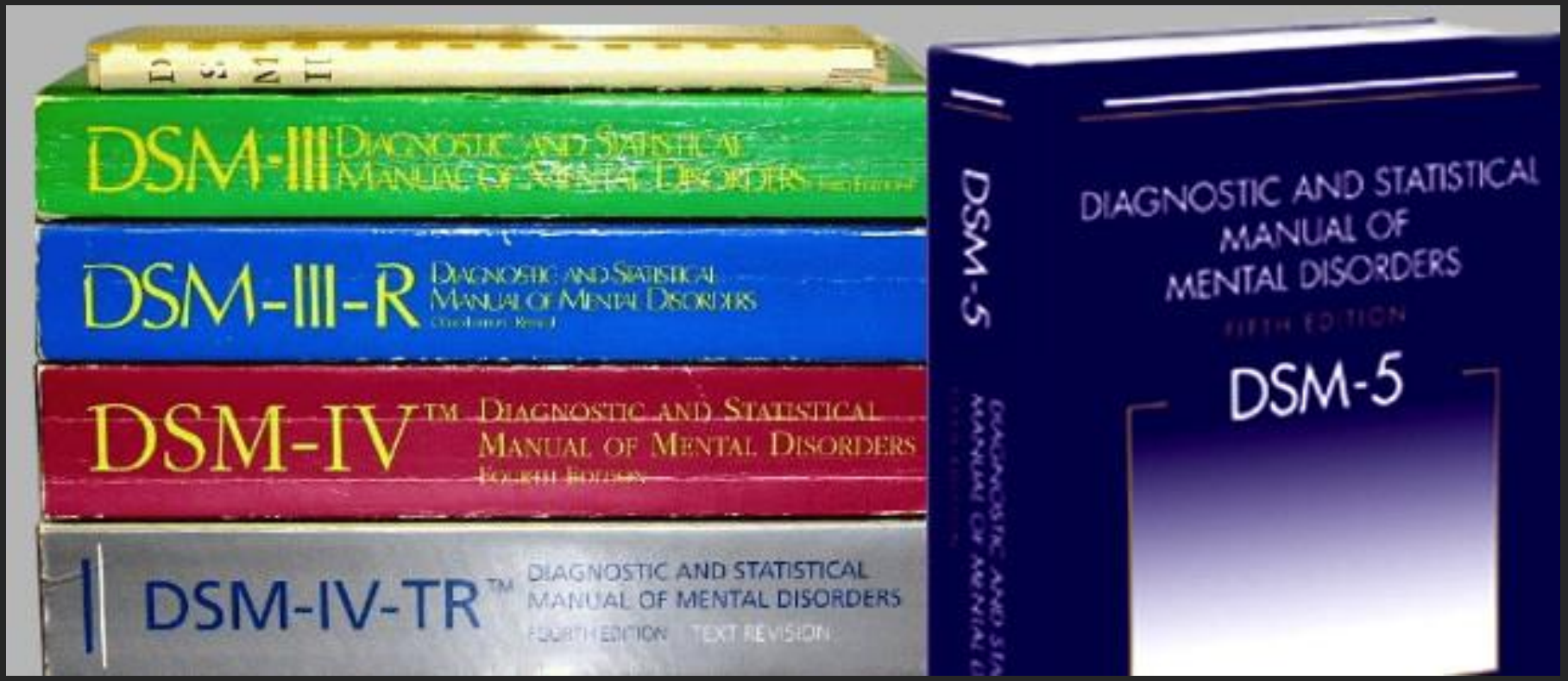
Anxiolytics

Anxiety

- physiological behaviour, visible in humans as well as in animals, in response to threatening stimuli

- important to generate a proper response in opposition of these stimuli

- it produces fear, defensive behaviours, activation of autonomic reflexes, generates the production of corticosteroids and of negative feelings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Generalized Anxiety Disorder

Diagnostic Criteria — 300.02 (F41.1)

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).

B. The individual finds it difficult to control the worry.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):

Note: Only one item is required in children.

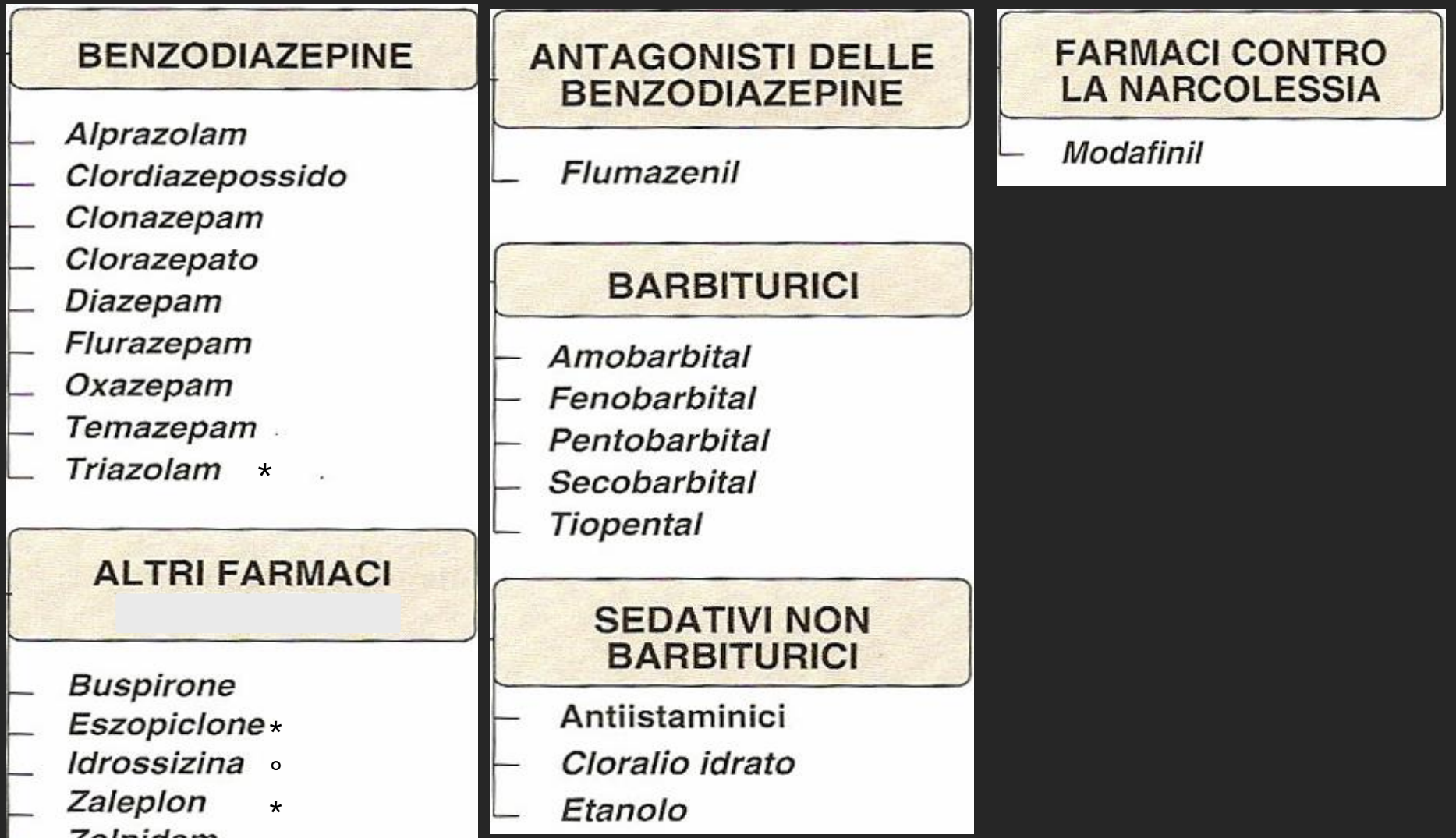
1. Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).

F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

Anxiolytic, Sedative and Hypnotic Drugs

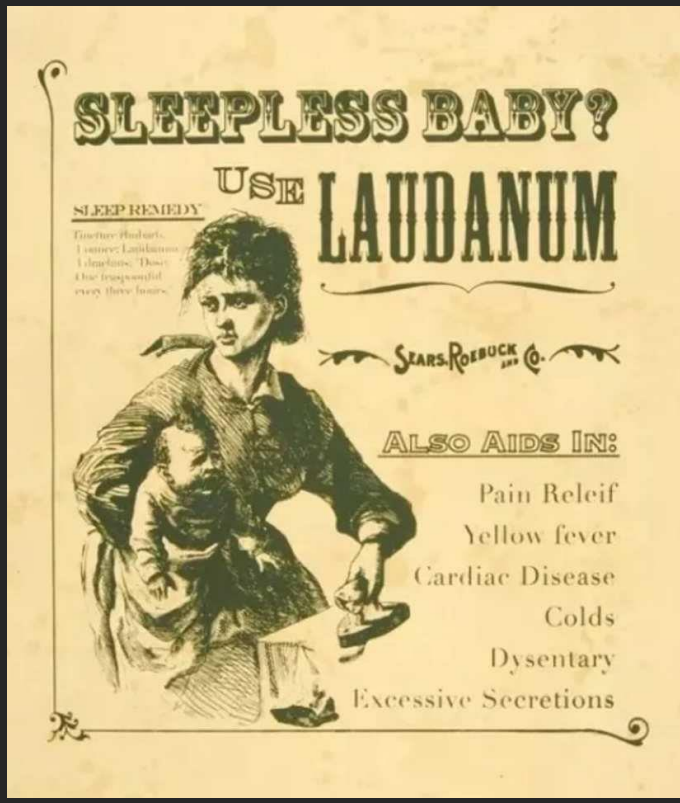


Sedatives/hypnotics

Laudanum (crocus opium tincture):

1% morphine, saffron, cinnamon, cloves

Chloral hydrate, paraldehyde….

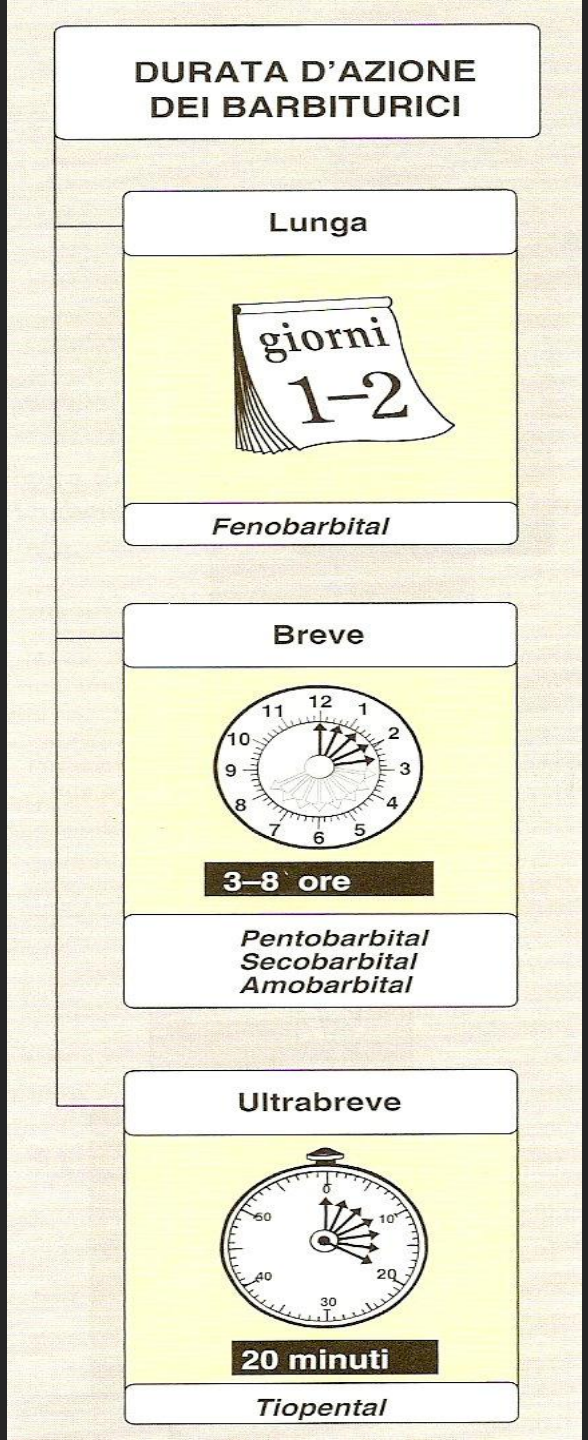


1903-12 Barbital e phenobarbital

1950 Chlordiazepoxide (1961 entry in the clinic)

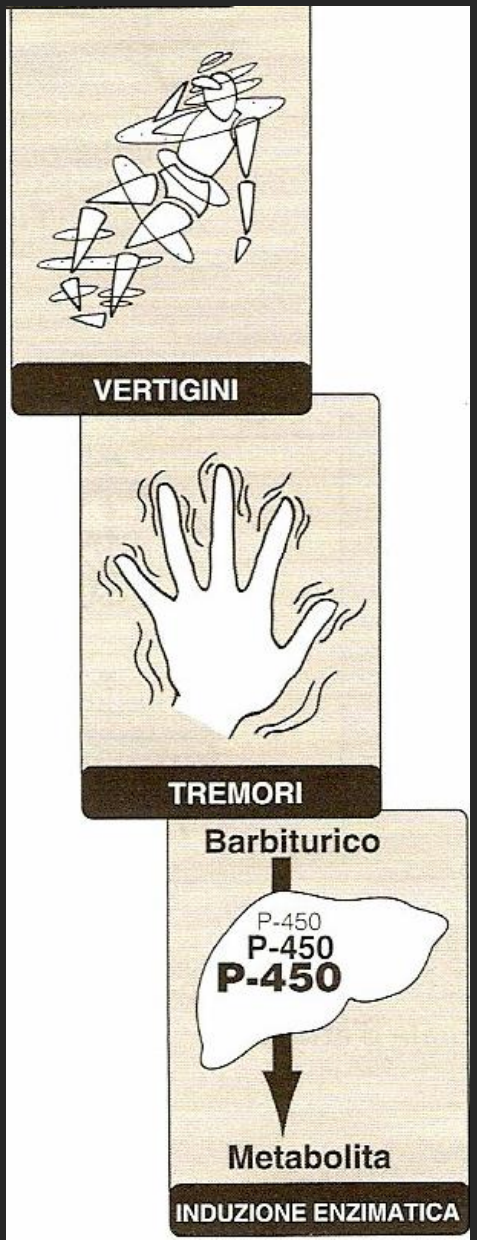
1990 Zolpidem, zaleplon, zolpicone (no BZ but binding a BZ-R)

Barbiturates

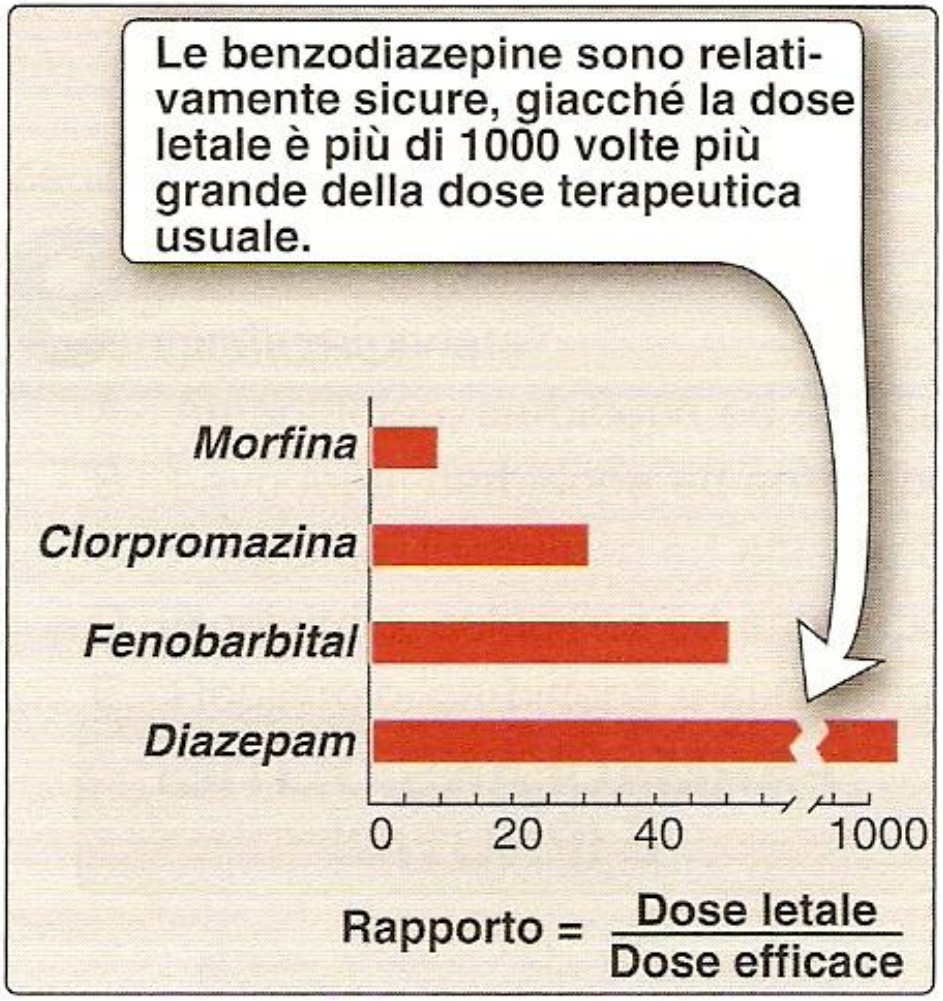


Duration of barbiturates

Side effects of barbiturates



Ratio lethal dose/ effective dose



Benzodiazepine

Table 44.1 Characteristics of benzodiazepines in humans

Drug(s)	Half-life of parent compound (h)	Active metabolite	Half-life of metabolite (h)	Overall duration of action	Main use(s)
Midazolam[a]	2–4	Hydroxylated derivative	2	Ultrashort (<6 h)	Hypnotic Midazolam used as intravenous anaesthetic
Lorazepam, oxazepam, temazepam, lormetazepam	8–12	No	–	Short (12–18 h)	Anxiolytic, hypnotic
Alprazolam	6–12	Hydroxylated derivative	6	Medium (24 h)	Anxiolytic, antidepressant Panic attack
Nitrazepam	16–40	No	–	Medium	Anxiolytic
Diazepam, chlordiazepoxide	20–40	Nordazepam	60	Long (24–48 h)	Anxiolytic, muscle relaxant Diazepam used as anticonvulsant
Flurazepam	1	Desmethyl-flurazepam	60	Long	Anxiolytic
Clonazepam	50	No	–	Long	Anticonvulsant, anxiolytic (especially mania)

[a]Another short-acting benzodiazepine, triazolam has been withdrawn from use in the UK on account of side effects.
[b]Zolpidem is not a benzodiazepine but acts in a similar manner. Zopiclone and zaleplon are similar.

Benzodiazepines

- Benzodiazepines cause:
  - * — reduction of anxiety and aggression
  - * — sedation, leading to improvement of insomnia
  - * — muscle relaxation and loss of motor coordination
  - * — suppression of convulsions (antiepileptic effect)
  - * — anterograde amnesia.
- Differences in the pharmacological profile of different benzodiazepines are minor; clonazepam appears to have more anticonvulsant action in relation to its other effects. Different $GABA_A$-receptor isoforms are believed to mediate sedative and anxiolytic effects.
- Benzodiazepines are active orally and differ mainly in respect of their duration of action. Short-acting agents (e.g. lorazepam and temazepam, half-lives 8–12 hours) are metabolised to inactive compounds and are used mainly as sleeping pills. Some long-acting agents (e.g. diazepam and chlordiazepoxide) are converted to a long-lasting active metabolite (nordazepam).

Anxiolytic effects

Major anxiety, short periods

Diazepam
Alprazolam (Panic attack)

Amnesia

Pre-medication (endoscopy, bronchoscopies, anesthesia)
Short duration

Muscular disturbances

Diazepam (spasticity)

Hypnotic effects

↓ Latency ↑ phase II non REM

↓ REM ↓ slow-wave

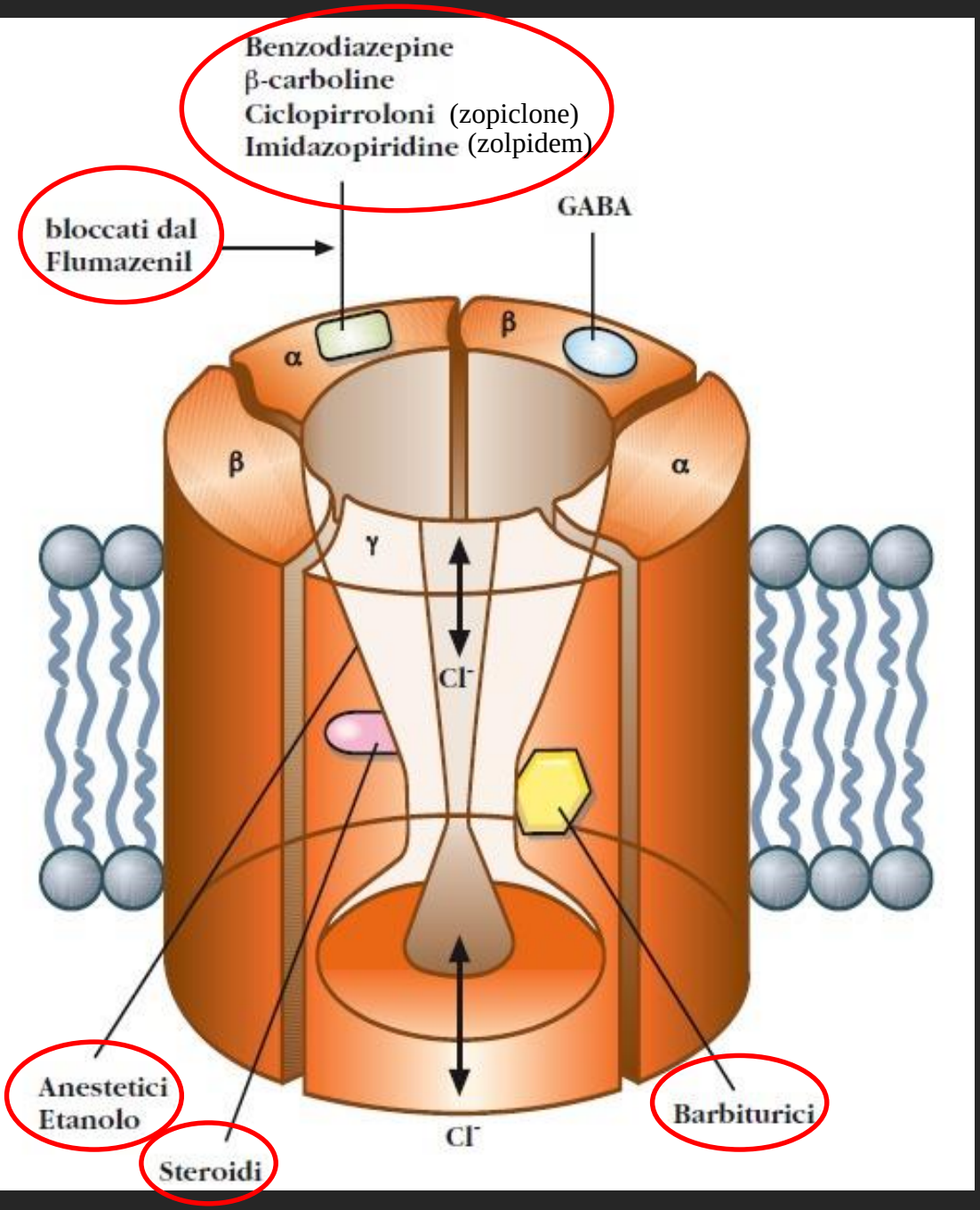
Flurazepam L
Temazepam M

Zolpidem, zaleplon (non BZ)

Epilepsy

Clonazepam
Diazepam

Alcohol withdrawal: clordiazepossido, clorazepato, diazepam, oxazepam



*alpha 1-subunit: sedative/hypnotic effects, amnesia, anticonvulsant effects, addiction

* alpha 2 subunit: anxiolytic and mio-relaxant effects

Table 44.2 $GABA_A$-receptor α-subunit selectivity of some therapeutically used benzodiazepines

Drug	Subunit selectivity
Diazepam	α1, α2, α3, α4, α5, α6
Flunitrazepam	α1, α2, α5
Midazolam	α1, α2, α3, α4, α5, α6
Zolpidem	α1
Flumazenil	Antagonist at α1, α2, α3, α4, α5, α6

(Adapted from Tan KR, Rudolph U, Lüscher C 2011 Hooked on benzodiazepines: $GABA_A$ receptor subtypes and addiction. Trends Neurosci 34, 188–197)

Tabella 24.2. Correlazione tra gli effetti farmacologici dei sedativi ipnotici ed il legame con le subunità a_1-a_6 del recettore del $GABA_A$.

EFFETTI FARMACOLOGICI	α_1	α_2-α_6
Ipnosi	+	–
Amnesia	+	–
Anticonvulsivante	+	+
Ansiolitico	–	+
Miorilassante	–	+

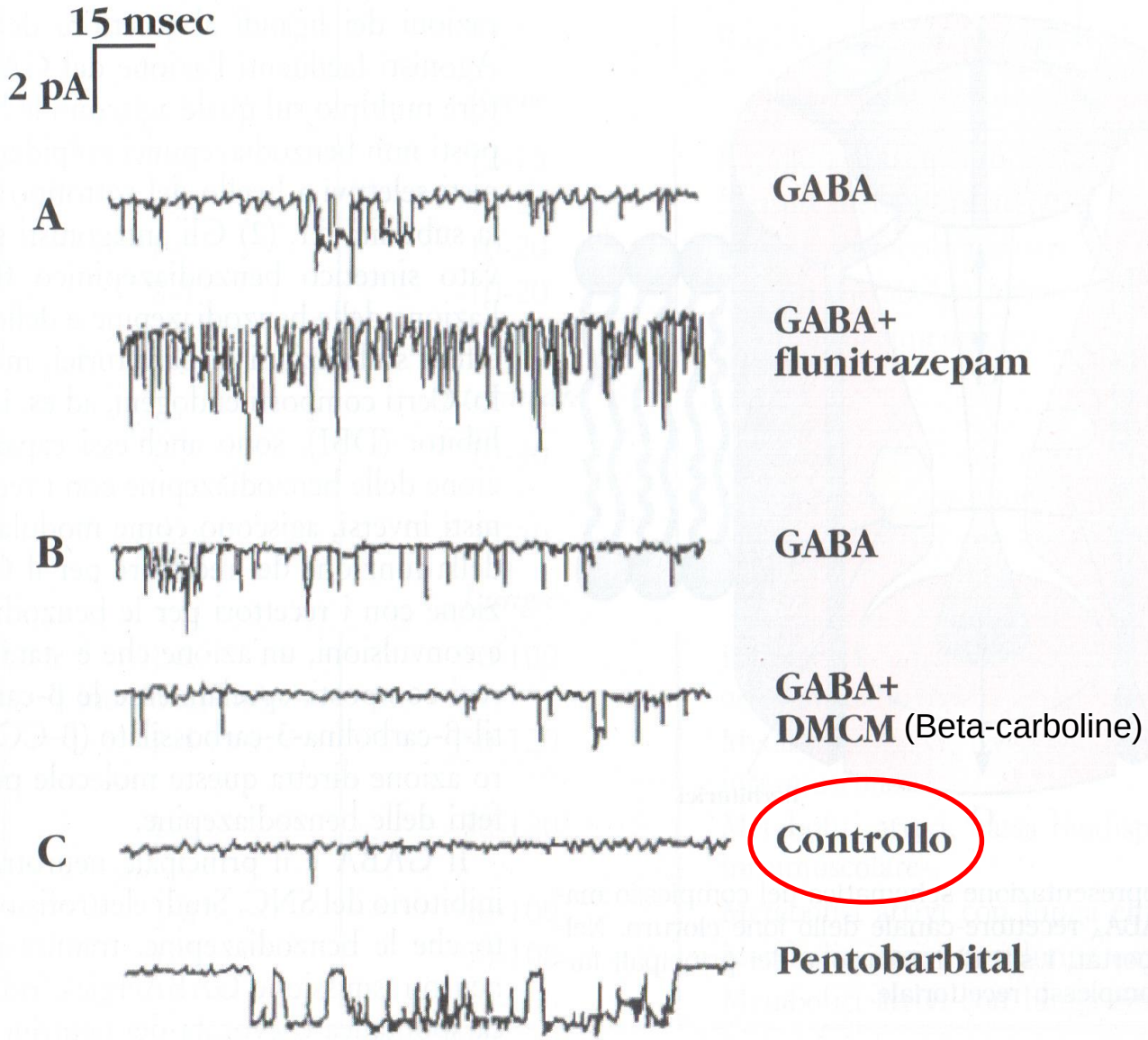
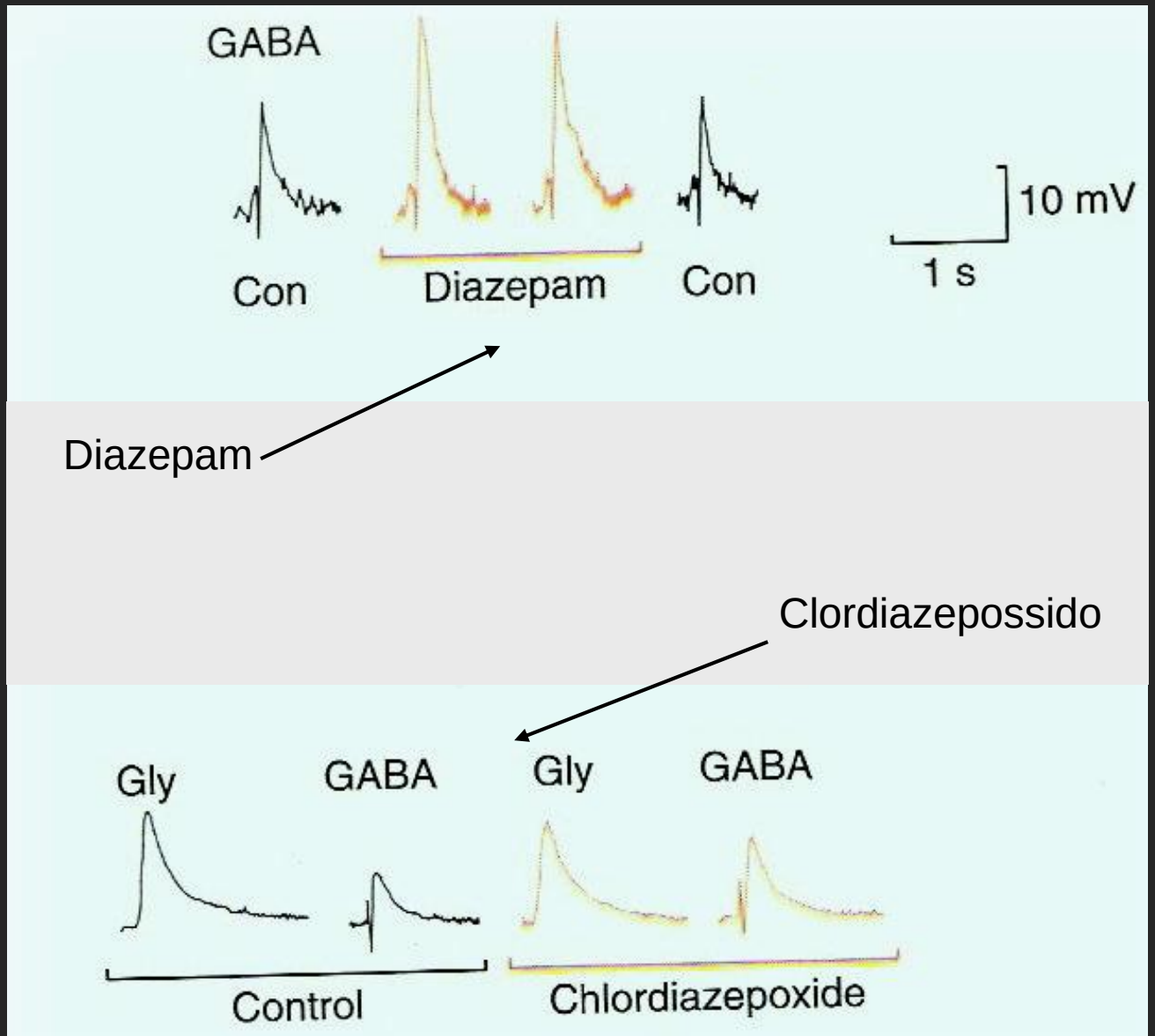


Figura 26.5. Correnti al Cl- attivate dal GABA e da vari modulatori del recettore GABAA misurate su singoli canali al Cl- su neuroni corticali di ratto (A e B) o neuroni spinali di ratto (C) con il metodo del patch-clamp. (A) La corrente attivata dal GABA (1 mM) è potenziata dalla benzodiazepina flunitrazepam (1 mM) attraverso un aumento della frequenza di apertura del canale. (B) La corrente attivata dal GABA (1 mM) è inibita dalla b-carbolina DMCM (5 mM) mediante una diminuzione della frequenza di apertura del canale. (C) Corrente attivata dal pentobarbital (150 mM) in assenza di GABA (vedi Rfs in Rogers et al., 1994).

Enhancing effect of benzodiazepines on the actions of GABA

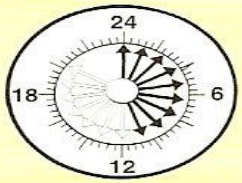


Duration of action of benzodiazepines

Lunga

Clorazepato
Clordiazepossido
Diazepam
Flurazepam
Quazepam

Intermedia



10–20 ore

Alprazolam
Estazolam
Lorazepam
Temazepam

Breve

3–8 ore

Oxazepam

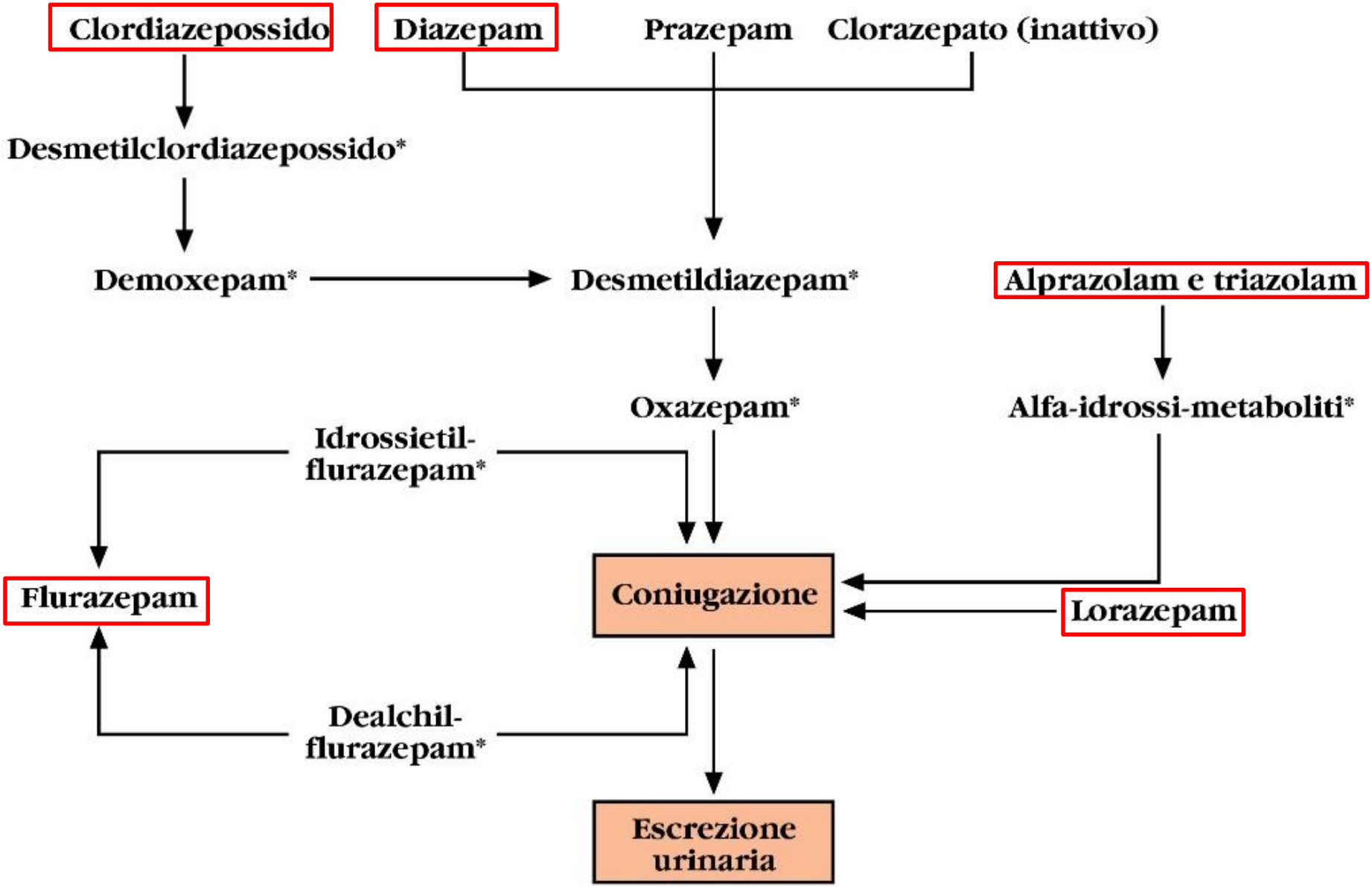


Figura 24.3. Biotrasformazione delle benzodiazepine (in neretto, farmaci disponibili per uso clinico, * metaboliti attivi).

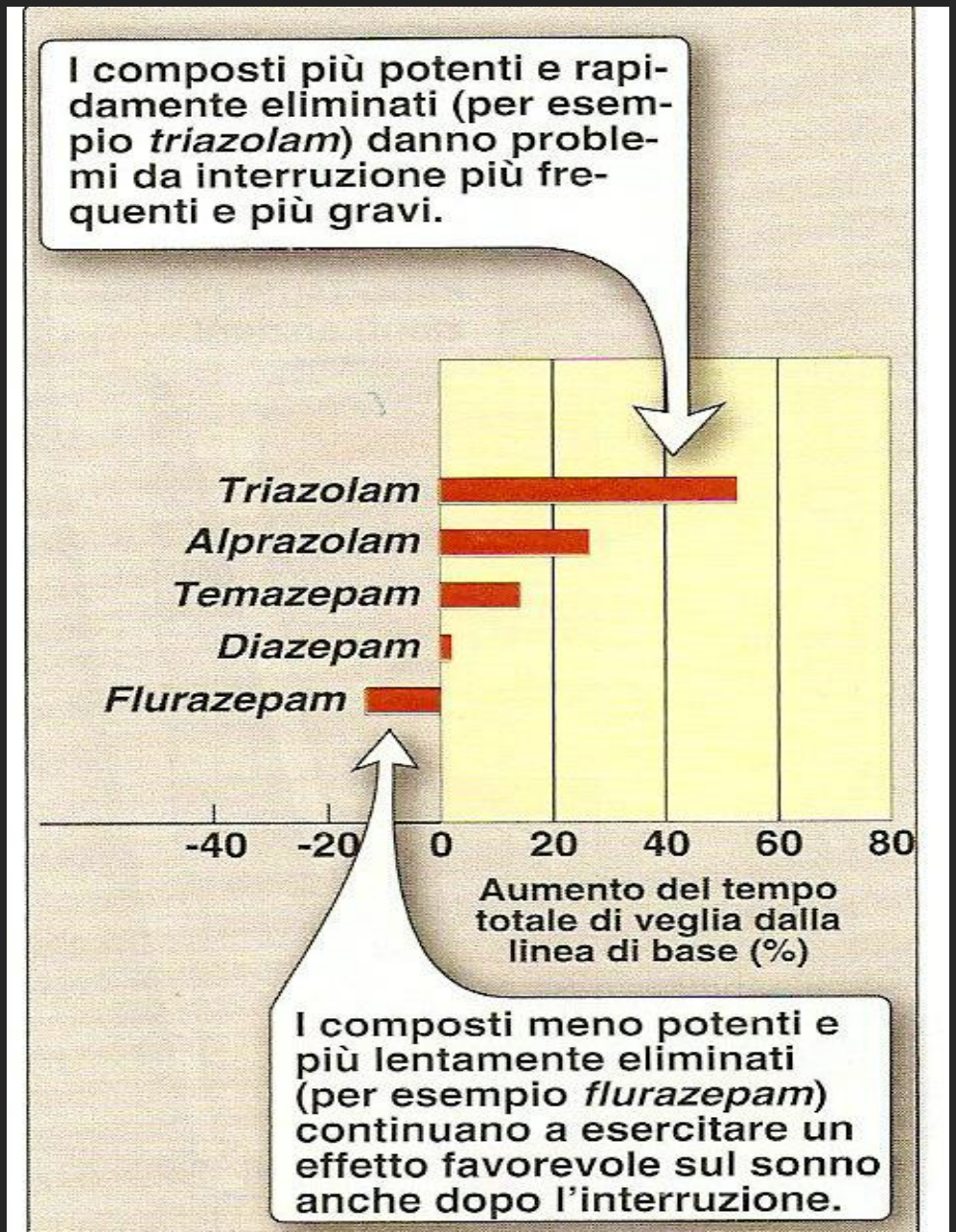
CYP3A4; CYP2C19 Cross Placenta and maternal milk

Benzodiazepines side effects

- **Acute toxicity** (lethal depression of the respiratory and cardiovascular systems) → Alcohol
- **Unwanted effects in daily tasks** during therapeutic use (drowsiness, confusion, amnesia, lack of coordination) → Manual work, Driving
- **Tolerance and dependence** → Withdrawal syndrome (anxiety, tremors, epilepsy, dizziness, insomnia)

	SSRIs (Selective serotonin reuptake inhibitors)	TCAs (Tricyclic antidepre-ssants)	MAOIs (Monomine oxidase inhibitors)	BDZs (Benzo-diazepines)
Onset of action	slow	slow	slow	fast
Initial exacerbation of anxiety	+/-	+/-	-	-
Therapeutic tolerance	-	-	-	little
Withdrawal	+	+	+	++
Abuse potential	-	-	-	+
Interactions with ethanol	+	+	++	+++
Dietary restrictions	-	-	+++	-
Sedation	-	++	-	++
Overdose risks	-	++	++	-

Rebound effects and insomnia



Classes of anxiolytic and hypnotic drug

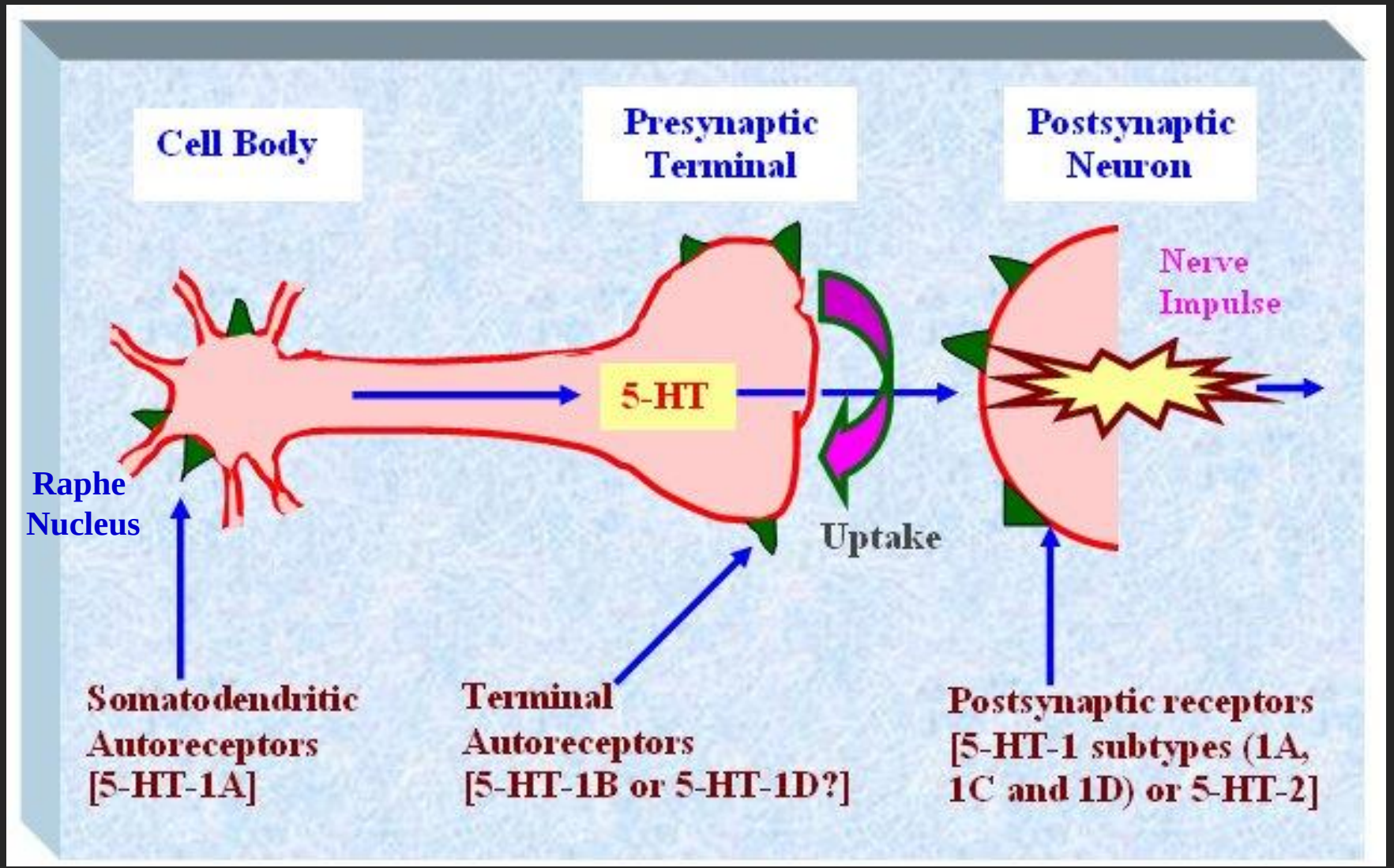
- Benzodiazepines, the most important class, are used for treating both anxiety states and insomnia.
- 5-HT_{1A}-receptor agonists have been recently introduced and show anxiolytic activity with little sedation.
- The β-adrenoceptor antagonists are used mainly to reduce physical symptoms of anxiety (tremor, palpitations, etc.); they have no effect on the affective component.

Other drugs

5-HT_{1A} agonists as anxiolytic drugs

- Buspirone is a potent (though non-selective) agonist at 5-HT_{1A}-receptors.
- Ipsapirone and gepirone are similar.
- Anxiolytic effects take days or weeks to develop.
- Side-effects appear less troublesome than with benzodiazepines; they include dizziness, nausea, headache, but not sedation or loss of coordination.

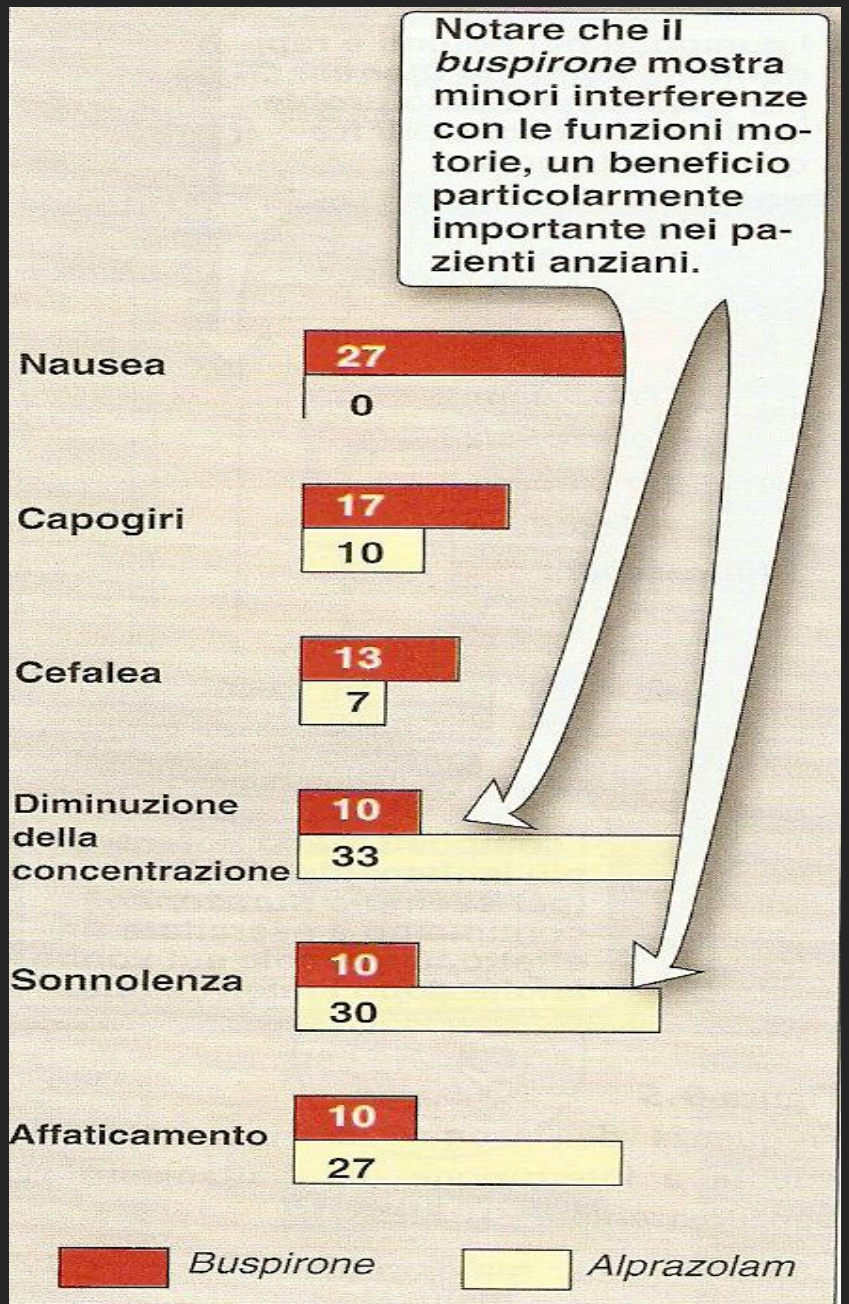
Anxiolitic effects and serotonin



Common side effects

buspirone

alprazolam



Contra

Pro

Benzodiazepine

- *Clonazepam*
- *Clorazepato*
- *Clordiazepossido*
- *Diazepam*
- *Flurazepam*
- *Quazepam*
- *Alprazolam*
- *Lorazepam*
- *Temazepam*
- *Triazolam* *

- Utile per trattare le assenze epilettiche.
- Questi composti meno potenti ed eliminati più lentamente non presentano insonnia da rimbalzo all'interruzione del trattamento.
- Farmaco di scelta per trattare i disturbi da panico.

- Le benzodiazepine possono disturbare le funzioni intellettive e l'abilità motoria.
- Le benzodiazepine possono dare dipendenza e possono presentarsi convulsioni da sospensione.
- La sospensione del farmaco spesso è seguita da insonnia da rimbalzo.

Altri composti

- *Buspirone*
- *Eszopiclone*
- *Idrossizina*
- *Zaleplon*
- *Zolpidem*

- Utile nella terapia di lungo periodo dell'ansia cronica con sintomi di irritabilità e ostilità.
  Non potenzia la depressione del SNC da alcol.
  Basso potenziale di tossicodipendenza.
- Efficace per 6-9 mesi.
- Non ha effetti all'interruzione.
- L'insonnia di rimbalzo è minima.
- Con l'uso prolungato si ha tolleranza scarsa o assente.

- Inizio dell'azione più lento di quello delle benzodiazepine.
- Mancanza dell'azione di rilassamento della muscolatura scheletrica e anticonvulsivante.
- Non hanno proprietà anticonvulsivanti o rilassanti muscolari.

Barbiturici

- *Fenobarbital*
- *Pentobarbital*
- *Secobarbital*
- *Amobarbital*
- *Tiopental*

- Inizio rapido dell'azione.

- I barbiturici causano tolleranza, induzione degli enzimi farmacometabolizzanti, dipendenza fisica e mostrano gravi sintomi da astinenza.

Interaction between anxiolytic/hypnotic and other drugs

(CYP3A4; CYP2C19)

Alcool - BDZ – barbiturici -sedativi

Zolpidem/ Zaleplon

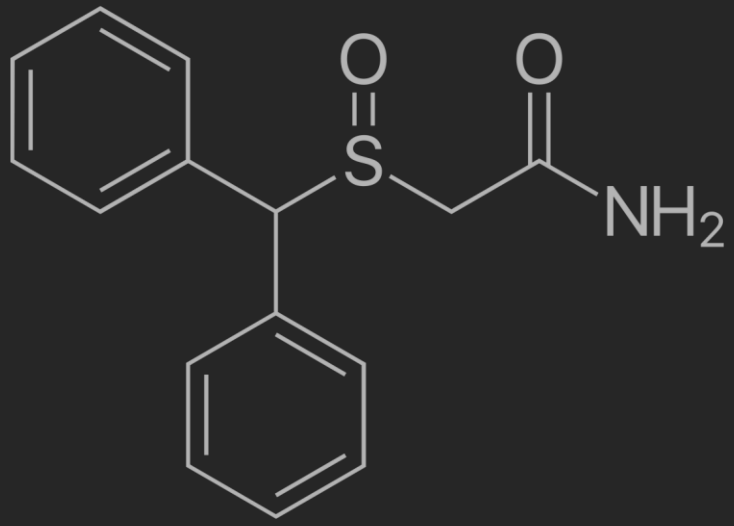
CYP3A4 ↑ rifampicina

Buspirone

eritromicina ↓ CYP3A4 ↑ rifampicina

Modafinil

To contrast Narcolepsy



Modafinil

- Commercialized as Provigil. It is a stimulant compound

- Approved for the treatment of narcolepsy, shift work - sleep disorders, sleep apnea and correlated disturbances

- As other stimulants, Modafinil elevates the release of monoamines in the brain

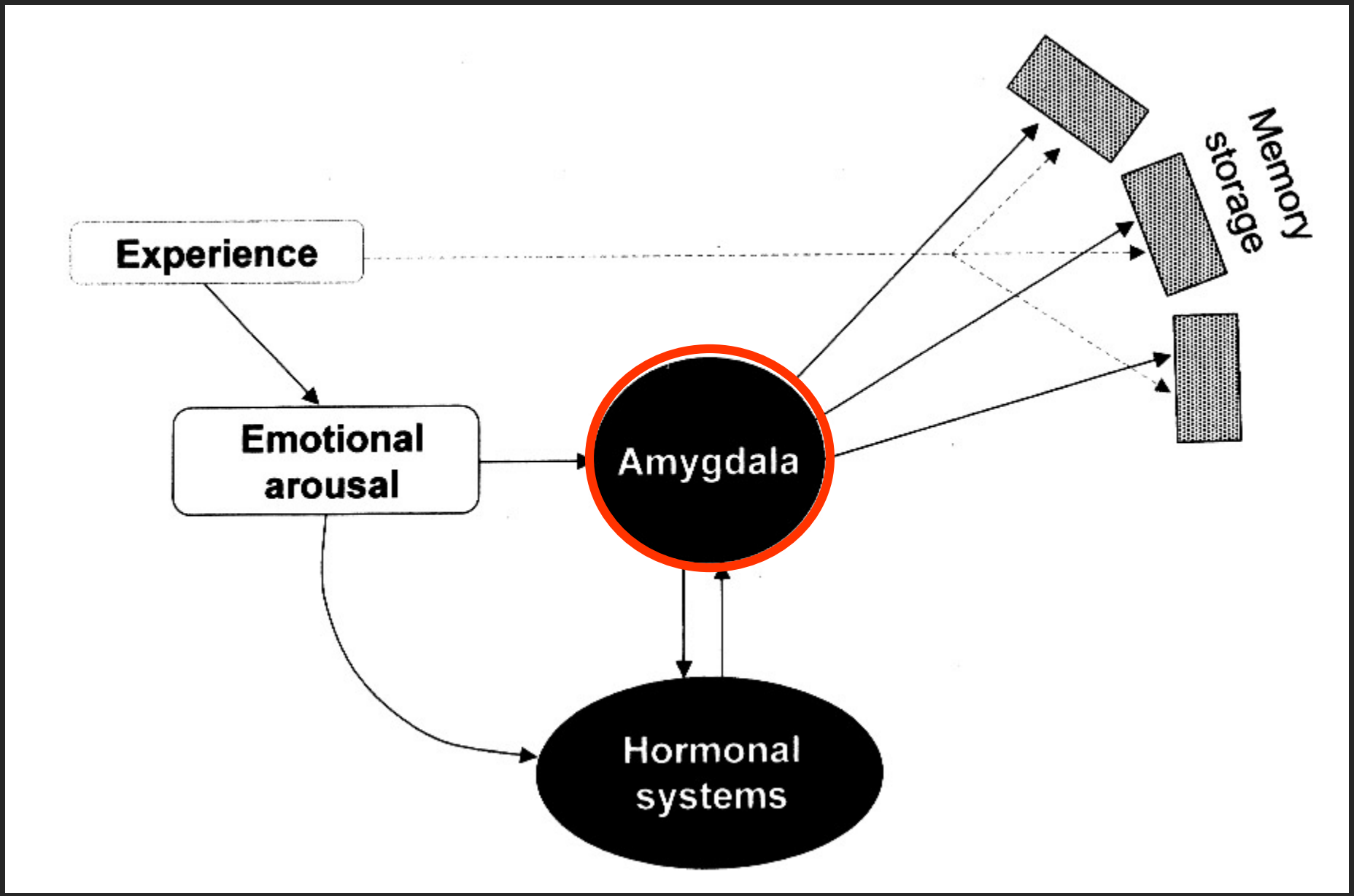
- Increased histamine levels in the hypothalamus

- Increases the orexin levels in the hypothalamus

Post-traumatic stress

This Palau stamp recreates a famous illustration of a U.S. Marine by Tom Lea, a writer and artist for *Life* magazine, who landed with Marines on Peleliu in September 1944.

Memory and emotions



Storage of memories in the brain

Memories having a strong emotinal component

Noradrenalina

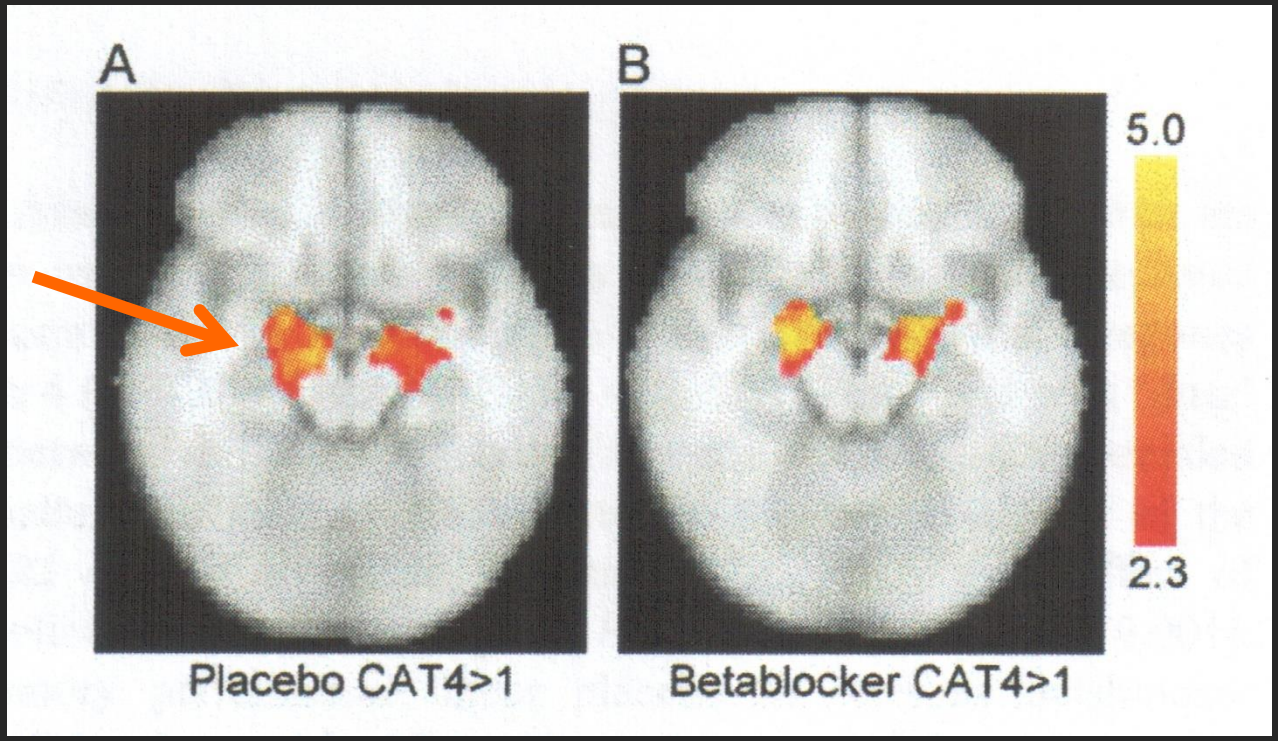
Beta receptor

Propranololo (80 mg)

SSRI inhibitors

Noradrenaline mediates the activation of the amygdala during the codification of stressful and emotional situations

amigdala



Van Stegeren et al. NeuroImage 2005