Medical Pharmacology

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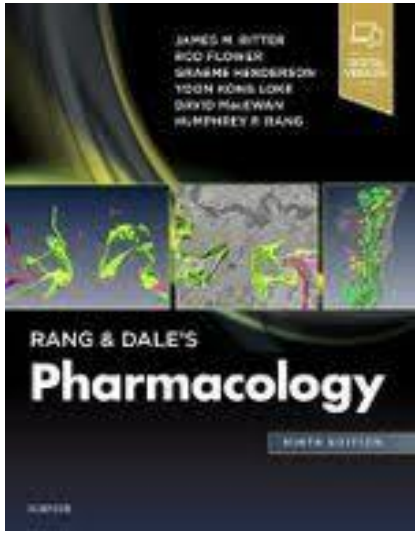
Celebrating 50 YEARS 1970 - 2020

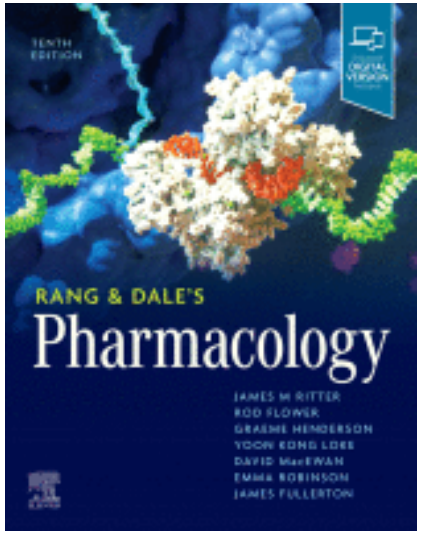
Psychotropic drugs 1
Anxiety & Associated Disorders



Rang & Dale's Pharmacology

9th edn 2019

Chap 45, 48



Rang & Dale's Pharmacology

10th edn 2023

Chap 45, 48

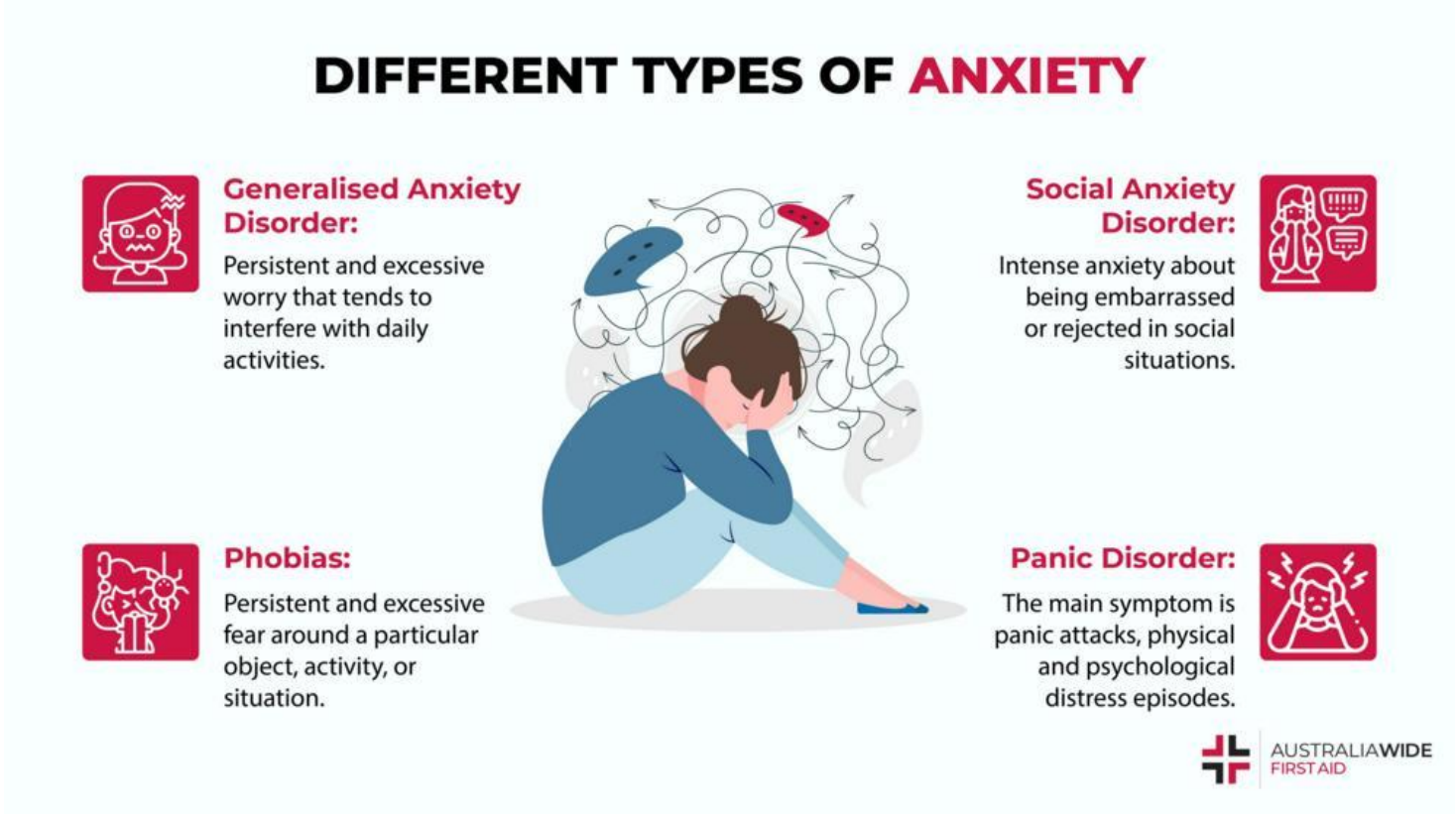
Introduction

- Anxiety disorder is a group of mental illnesses that relate to **physical and emotional symptoms of fear**
  - Considered as ‘functional psychiatric disorders’
    - Fear is part of the normal emotional, physical and behavioural response to recognisable external threat
    - The fear/anxiety response may be adoptive
      - i.e. to protect one from exposing from external threat that has previously encountered

Source: Anxiety at work https://workingwise.nz/anxiety-at-work/.

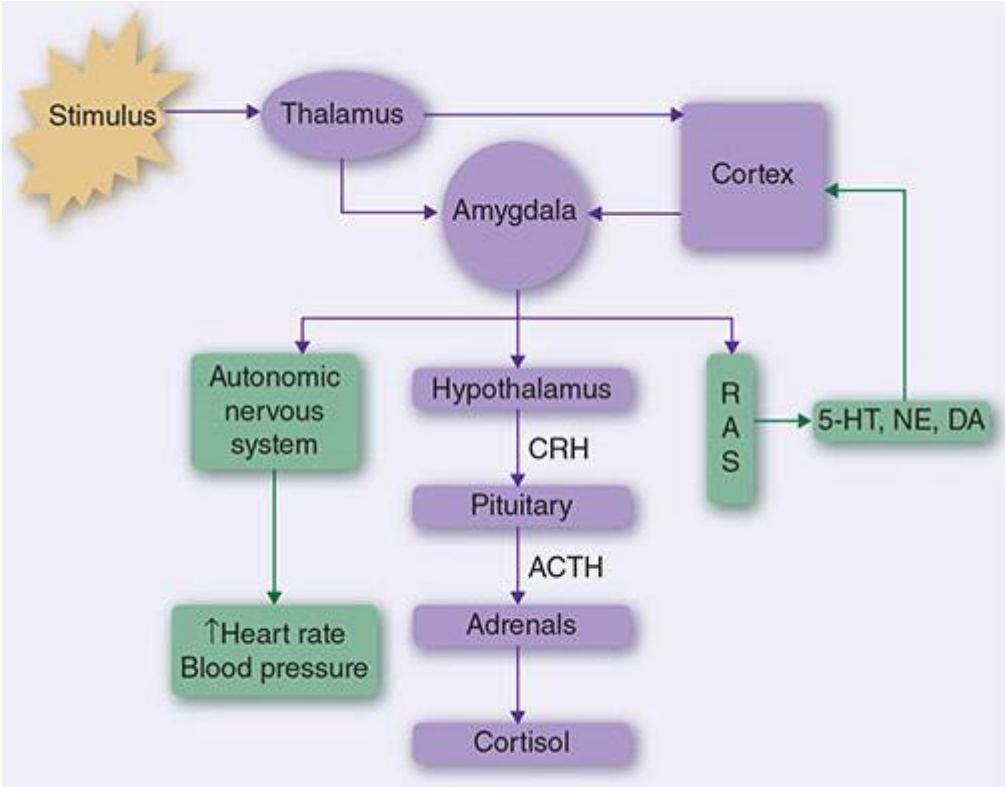
Anxiety – Subgroups

- Generalised anxiety disorder (GAD)
- Panic disorder
- Obsessive compulsive disorder (OCD)
- Acute stress disorder
- Post traumatic stress disorder (PTSD)
- Substance-induced anxiety disorder
- Secondary anxiety disorders (medical condition induced)
- Social phobias
- Specific phobia (e.g. arachnophobia, ophidiophobia, acrophobia, agoraphonia, etc.)
- Others



Pathogenesis

- The aetiologies of anxiety disorders are multi-factorial and not fully understood
- Different types of anxiety disorder appear to have different aetiology and/or pathophysiology
  - Current studies suggest wide variety of hypothesis/ theory
    - Some more common in one anxiety disorder than other
    - e.g. Serotonin (also NE, DA) abnormality and increase orbitofrontal cortex activity is observed



HPA axis/Neurocircuitry and key neurotransmitters involved in mediating anxiety disorders. (ACTH, CRH, DA, 5-HT, NE, RAS)
Source: Chisholm-Burns et al. Pharmacotherapy: Principles & Practice 5th ed. McGraw Hill. (online version)

Pathogenesis

- Common features among all types of anxiety disorders
  - Genetic-environment interaction
    - Genetic factors exhibit significant risk in developing anxiety disorder, but significant stressors are often observed
    - Some individuals appear to be resilient to stress, but others can be very vulnerable
    - Family history appears to be associated with most type of anxiety disorders
      - Consistent genetic factor(s) has not yet been identified, but disproportional higher prevalence is often observed in identical twins

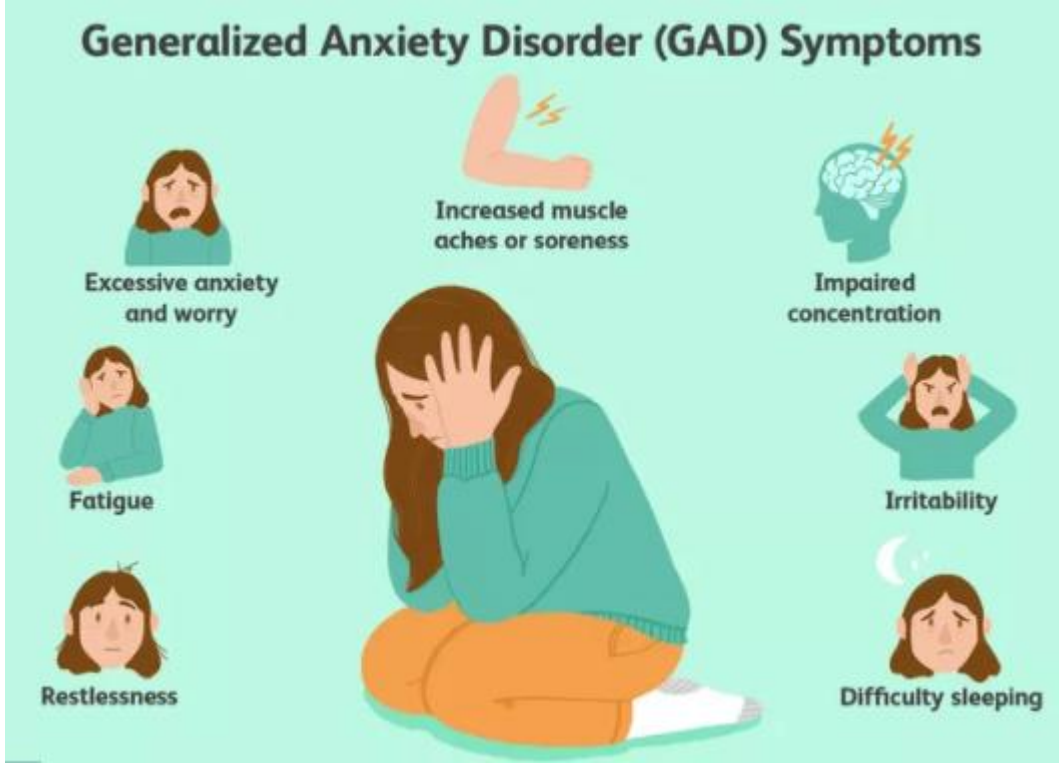
Various types of anxiety disorders

Generalised anxiety disorder

- Characterised as continuous excessive anxiety and worrying of many activities/event (> 6 months)
  - Common worries include health, safety, work, families, mortgage, etc
  - Onset usually during childhood
  - One of the most common anxiety disorders (lifetime prevalence around 5%)
    - Most common in adolescents
- Symptoms usually fluctuating, and worsen during stress

Generalised anxiety disorder

- Common symptoms
  - Restlessness or ‘on the edge’
  - Easily fatigue
  - Difficulty concentrating or ‘mind gone blank’
  - Irritability
  - Muscle tension
  - Sleep disturbance
- Pathogenesis largely unknown
  - Found associated with excessive alcohol use and other mental illness (esp. Depression)
- Prognosis
  - Usually fair to good
    - If treated appropriately
    - Especially in children and adolescents



Source: https://www.verywellmind.com/dsm-5-criteria-for-generalized-anxiety-disorder-1393147. Accessed September 2020.

Panic disorder

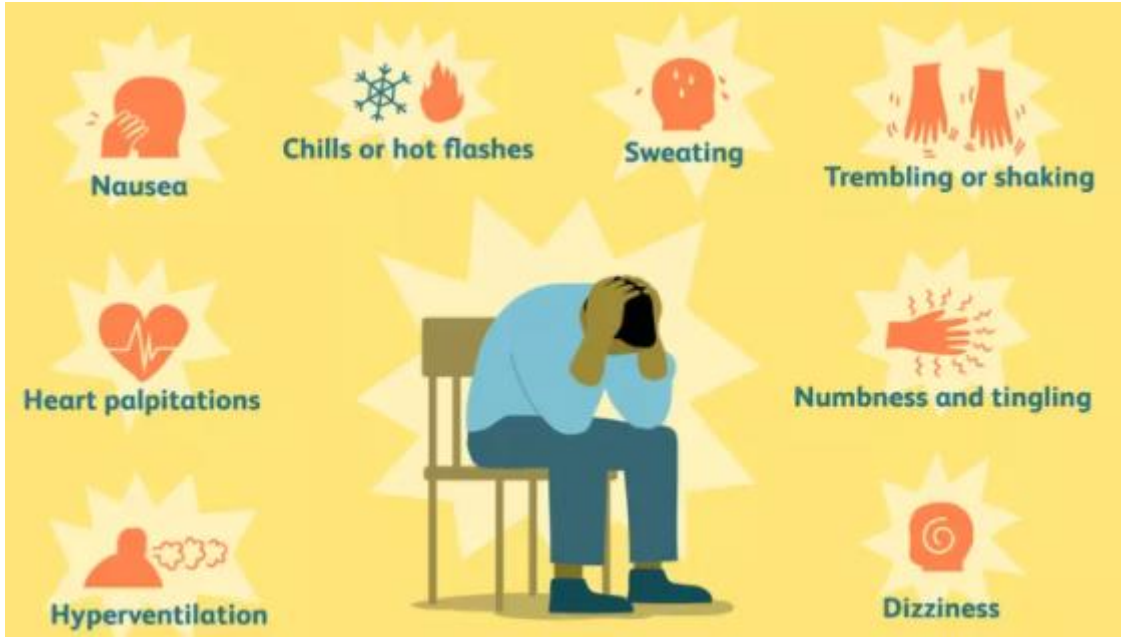
- is the reoccurrence of sudden onset of symptoms (panic episode/attack), such as fear of dying, fear of change or discomfort
  - May be presented with psychological induced physical symptoms, such as chest pain, SOB $\rightarrow$ regular visit to GP
    - Care required to exclude potential medical cause of the symptoms and or other mental illness
    - Patients who experience multiple panic episodes often develop personality changes e.g., avoidance behaviour, become very passive, dependence and withdrawn (social or mental)

Panic disorder

- Pathogenesis
  - Panic disorder is strongly associated with genetic predisposition and neurological dysfunction
    - E.g. catechol-O-methyltransferase gene polymorphism
    - Autonomic dysfunction, ↓ GABA-ergic tone, ↑ cortisol, etc...
  - Stimulants – common triggering factor for panic attack
    - Injury (accident and non-accident) and illness
    - Interpersonal conflict or illness
    - Use of stimulants
      - Caffeine, decongestant, cannabis, cocaine, amphetamine, etc...
    - Stimulant of social phobia or specific phobia
    - Sudden treatment withdrawn (e.g. SSRI)

Panic Attack/Episode – Signs and symptoms

- Palpitation
- Sweating, chill or hot flush
- Shaking/ trembling
- SOB/ hyperventilation
- Chest pain
- N &V or other GI symptoms
- Dizziness, headache
- Derealisation or depersonalisation
- Fear or loosing control or fear of dying



Source: https://www.verywellmind.com/top-symptoms-of-panic-attacks-2584270.

Panic disorder

- Panic attack ≠ panic disorder
  - Panic attack is relatively common in general population (~10%)
    - Can be one of the features of other anxiety disorder(s)
    - The panic episode induced by phobias are not usually consider as panic disorder
  - Most people recover without therapy and do not experience recurrence of symptoms
    - i.e. Not panic disorder

Post-traumatic stress disorder (PTSD)

- PTSD is an anxiety disorder develop after the patient involved in, or weakness, or being confronted by traumatic events
  - Injury, death or violation of one's personal integrity
  - Referred to ongoing stress outside the immediate period of traumatic experience
    - E.g. Weeks to month after exposure
- The severity and duration of PTSD varies widely among individuals

PTSD – Symptoms

- divided into 4 main groups
  - Develop the mentality of helplessness, intense fear or horror
  - Experience repeating ‘flush back’, or intense psychological distress when confronted by cues that symbolised the event (e.g. Image, smell, person)
  - Avoidance, detachment or numbing response, ‘false amnesia’ of the event
  - Irritation, sleep disorder, extra vigilant, exaggerated responses
    - Children may only exhibit irritation or and ‘unusual behaviour’, but with different characteristic symptoms at different age group

PTSD

- Pathogenesis
  - Development of PTSD is associated with
    - Genetic predisposition
    - Nature and proximity of trauma
    - Prior experience of trauma (esp. during childhood)
    - Posttraumatic factors (e.g. Social and psychological support)

Obsessive-compulsive disorder (OCD)

- A condition that is characterised of one or more anxiety-provoking ideas, impulses (obsessions) or urges (compulsion), and require taking specific/repeating actions until ‘it feels right’
  - Cleanliness or contamination
  - Safety
  - Doubting one’s memory or perception
  - Scrupulosity (psychological guilt, moral or religious issue)
  - Thing need to be arranged/done in specific order
  - Intrusive thought of sexual or physical aggression

OCD

- Common symptoms
  - Hand washing
  - Cleaning
  - Checking
  - Hoarding
  - Many different form of specific rituals
  - Avoiding people, environment or situation that will upset ‘the balance’

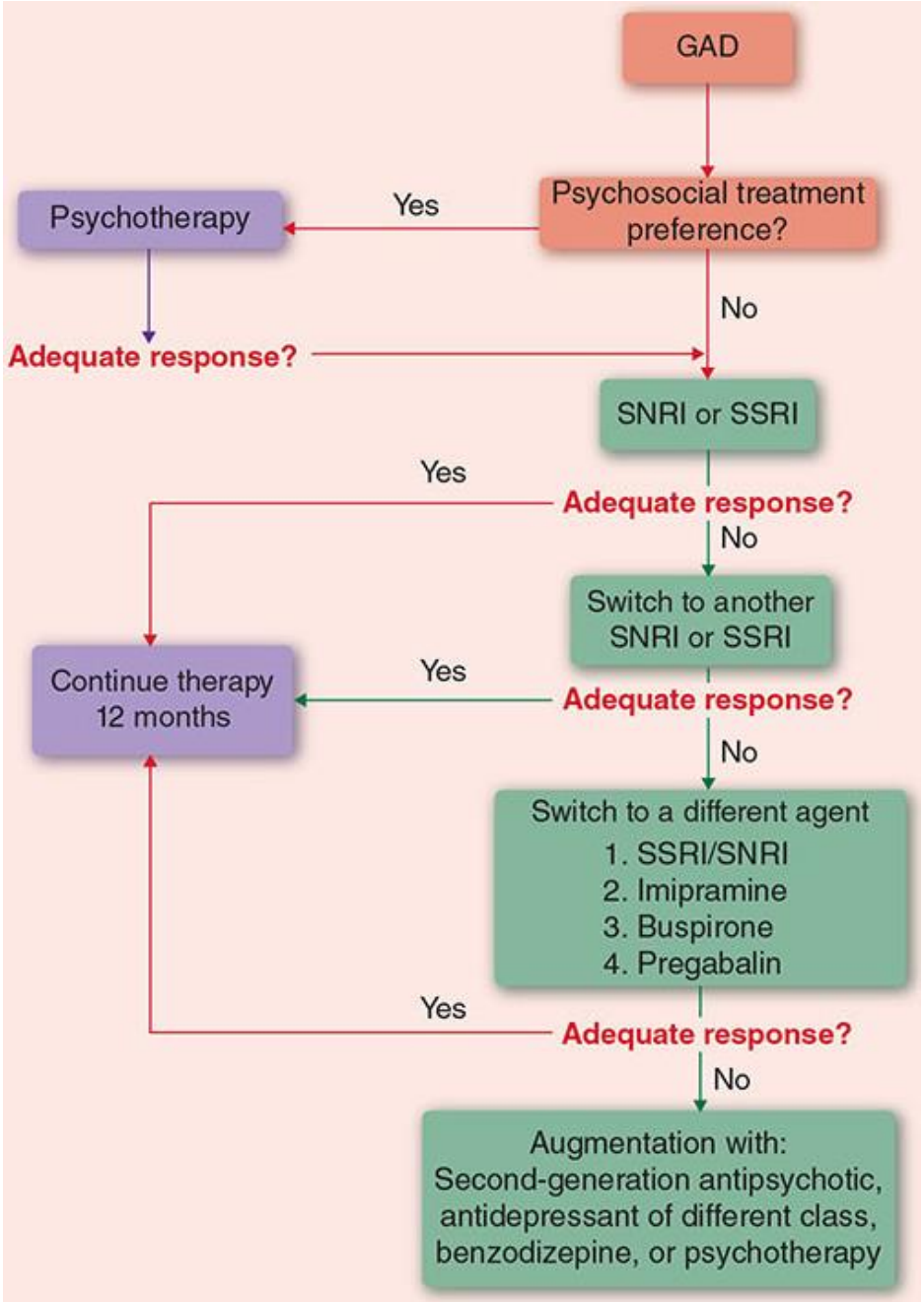
Phobias

- Social phobias
  - Often related to fear of social performance or at performing situations
    - Impaired in performance (e.g. work, school) when exposed to social situation
      - Severe symptom may significantly impact on one's function. E.g. eating at restaurant, using public toilet, speaking in public
    - Patients often choose to avoid social environment

Phobia	Definition
Acrophobia	Fear of heights
Amathophobia	Fear of dust
Astraphobia	Fear of thunder and lightning
Aviophobia	Fear of flying
Belonephobia	Fear of needles, pins, or other sharp objects
Brontophobia	Fear of thunder
Claustrophobia	Fear of confined spaces
Eurotophobia	Fear of female genitals
Gephyrophobia	Fear of crossing bridges
Hydrophobia	Fear of water
Odontiatophobia	Fear of dentists
Phartophobia	Fear of passing gas in a public place
Phasmophobia	Fear of ghosts
Phobophobia	Fear of having fears or developing a phobia
Spargarophobia	Fear of asparagus
Triskaidekaphobia	Fear of all things associated with the number thirteen
Trypanophobia	Fear of injections
Zoophobia	Fear of animals (usually spiders, snakes, or mice)
*There are over 500 named phobias, listed at the Phobia List web site. Most are extremely rare.	

Treatment and management

- General rule for managing anxiety disorders (some variations depend on nature of disorder)
  1. Identify the precipitating factor(s)
     - → avoid or eliminate the factors
     - Social support and reassurance may be all that required
  2. Psychotherapies
     - Consider as first line intervention therapy for all anxiety disorder
  3. Pharmacotherapy
     - Use as adjunct to psychotherapy
     - Solo therapy without psychological intervention is usually not recommended*
  4. Other adjunct therapies may be considered



Treatment algorithm for generalized anxiety disorder.
Source: Chisholm-Burns et al. Pharmacotherapy: Principles & Practice 5th ed. McGraw Hill. (online version)

Treatment and management

- Dietary
  - Avoidance of stimulants
    - Including caffeine, alcohol, nicotine, cannabis, amphetamine, other ‘recreational drugs’, herbal preparations (many herbal products contains adrenaline-like chemicals) and some prescription medications

Treatment and management

- Varies between different type of anxiety disorders
  - Psychological therapy vs. pharmacotherapy
    - Psychological therapy should be considered first for all type of anxiety disorders
    - Pharmacological therapy is found to have various effectiveness in anxiety disorders
- Combination of therapy
  - Psychotherapy + pharmacotherapy
    - Recommended for most anxiety disorders
      - Either therapy may be used alone, but often associated with less effective outcome
  - Adjunctive therapies also appear to provide benefits.
    - E.g. relaxation technique, life coaching

Treatment and management

- Pharmacological options
  - Antidepressants (already discussed)
    - The newer agents are usually preferred, although lacking quality clinical evidence
      - E.g. SSRI, SNRI, selective noradrenaline reuptake inhibitor
      - TCA can be utilised especially when sedative effect is beneficial
  - Efficacy mainly limited to some type of anxiety disorder
  - Other consideration
    - Fluctuation in neurotransmitter appear to trigger anxiety disorder
      - Avoid short acting agents
      - Initiating with low dose with slow titration
      - Avoid sudden withdrawal (even if not proven effective)
    - Medication with sedating effect may be beneficial

Treatment and management

- Pharmacological options (cont.)
  - Benzodiazepines (BZs)
    - Considered equally effective if use at equivalent dose
    - Usually indicated for acute anxiety
    - Cautions, especially for chronic use
      - Sedation, impaired coordination, dependence, abuse and conversion for illicit use
  - Atypical antipsychotics (2^{nd}-3^{rd} generation antipsychotics)
    - Second or third line options
    - Use when antidepressant therapy failed or when patient exhibit psychotic symptoms
      - Often with lower dose than treatment for schizophrenia
  - Mood stabiliser
    - Primarily anticonvulsants – similar to its use in depression

      (Details to be discussed in bipolar depression disorders)

Benzodiazepines & Barbiturates

Indications:

- Used as
  - Anxiolytics – to alleviate anxiety
  - Sedatives and hypnotics (agent to induce/maintain sleep)

- For anxiety disorders (some secondary due to other morbidities)
  - Generalised (no clear cause)
  - Panic disorder (can be treated with SSRI)
  - Phobias
  - Post-traumatic stress
  - Obsessive compulsive (also treated with SSRI)
  - ……
- Symptoms can be subjective (psychological) and include autonomic hyperactivity (sweating, tachycardia, trembling……)

Benzodiazepines & Barbiturates

Sedatives/Hypnotics

- Produce a dose-dependent CNS depression
- Agents include:
  - General anaesthetics
  - Barbiturates
  - Alcohol
  - Opioids
- Benzodiazepines have <u>limited</u> capacity in producing fatal CNS depression
  - At high doses, they produce
    - Amnesia, coma
    - No surgical anaesthesia
    - No CV/respiratory depression

CV/respiratory depression

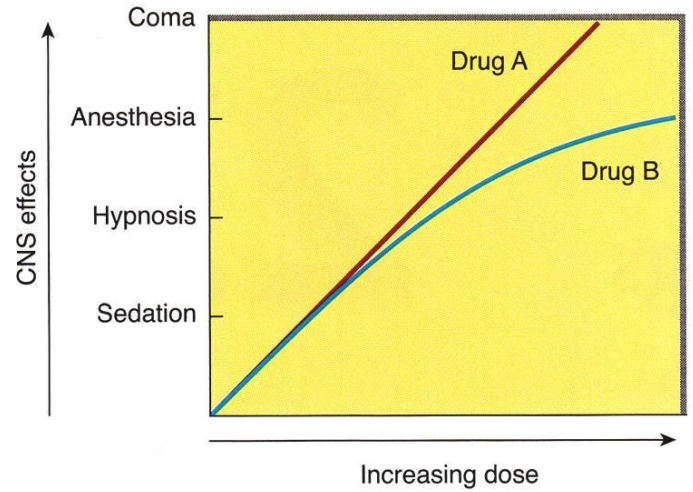


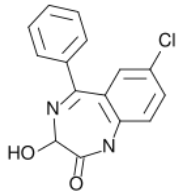
FIGURE 22–1 Dose-response curves for two hypothetical sedative-hypnotics.

from Katzung

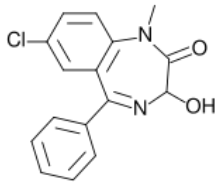
Benzodiazepines, Z drugs & Barbiturates

Benzodiazepines (BZs)

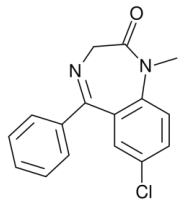
Remember "-zepam" suffix!



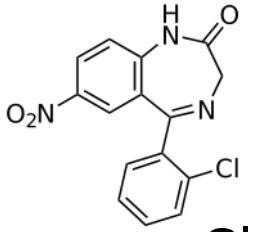
Oxazepam



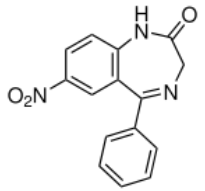
Temazepam



Diazepam (Valium®)



Clonazepam



Nitrazepam

Flunitrazepam (Rohypnol®) – "date-rape drug"

Others with "-zolam" suffix (different molecular structure)

e.g.

midazolam, alprazolam

Agents differ in pharmacokinetics!

Benzodiazepines & Barbiturates

Benzodiazepines (BZs)

- Some BZs are used for specific purposes
  - Midazolam (i.v.) → to induce anaesthesia
  - Diazepam (i.v.), clonazepam (prophylaxis) → as anticonvulsant, muscle relaxant for epilepsy
- These agents supersede older drugs such as barbiturates as they are:
  - Safer in OD (non-fatal unless co-administered with other CNS depressants)
  - Fewer adverse effects

Benzodiazepines & Barbiturates

Benzodiazepines (BZs) and $GABA_A$ Receptors

GABA Receptors

$GABA_A$	$GABA_B$
Ligand gated Cl^- channel	G-protein coupled receptor
Agonists open Cl^- channels	Agonists open K^+ channels
Cl^- influx	K^+ efflux
Hyperpolarisation	Hyperpolarisation
Both produce inhibitory effects	
Agonist: Muscimol	Agonist: Baclofen
Antagonist: Bicuculline	Antagonist: Phaclofen

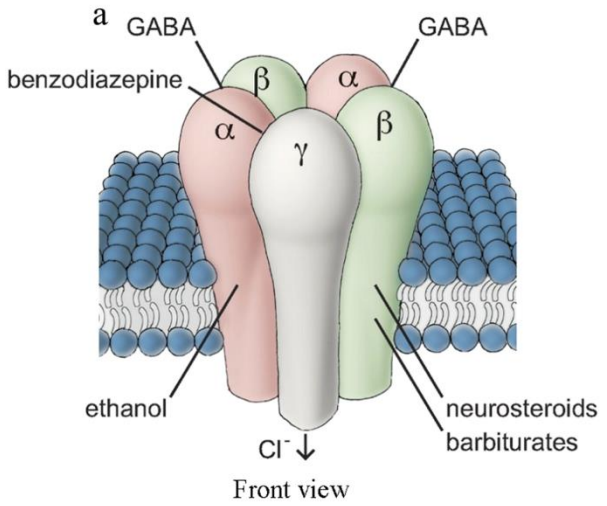
Baclofen is used clinically as spasmolytic to relieve muscle spasm in spinal cord injury, multiple sclerosis, hiccups……

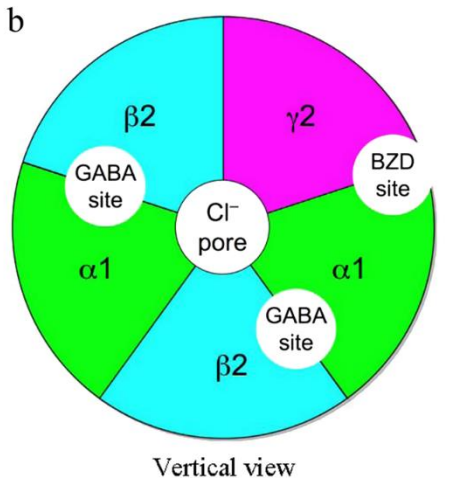
Benzodiazepines, Z drugs & Barbiturates

Benzodiazepines (BZs) and $GABA_A$ Receptors

$GABA_A$ Receptor – a Cl^- Ionophore

- Pentamer (5 subunits)
- From 7 subunit families (6α's, 3β's, 3γ's, δ, ε, π, θ)
- α, β, and γ subunits predominate
- Receptor containing only α or β subunits
  - GABA and barbiturates stimulate
  - BZs → no effect (therefore need γ)
- GABA and BZ bind different sites
- Each increases binding of the other





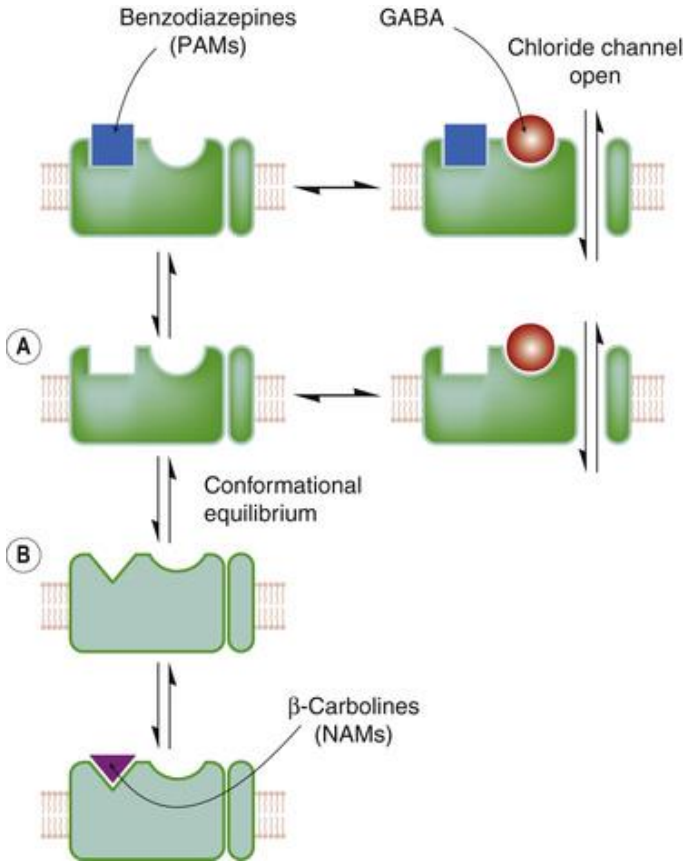
Only GABA and barbiturates can activate $GABA_A$ receptors and open Cl^- channels directly, NOT BZs

Benzodiazepines, Z drugs & Barbiturates

Benzodiazepines

Mechanism of Action

- Bind selectively to specific allosteric site in $GABA_A$ receptor
- Enhance affinity of GABA to $GABA_A$ receptor binding
- Facilitate (increase frequency) the opening of GABA-gated Cl^- channels
- Hyperpolarisation of neuronal cell membrane
- Inhibition of action potential generation
- Inhibition of neurotransmitter release



GABA is present at 30% of synapses in CNS

It inhibits many functions (or controls many stimulatory functions)

Benzodiazepines, Z drugs & Barbiturates

BZs – Effects

- Sedation (at low doses)
  - Euphoria (due to disinhibition)
  - Sleepiness
  - Decrease in activity
  - Impairment of psychomotor skills including driving
  - Can cause amnesia
- Sleep/Hypnosis (single, higher doses at bedtime)
  - Induce sleep
  - Prolong non-REM sleep
    - Use intermittently to avoid development of tolerance/dependence e.g. 1 in 3 nights

BZs reduce REM (rapid eye movement) sleep (less in Z-drugs)
→ less restful sleep leading to day-time sleepiness
Short-acting drugs (e.g. *temazepam*) → less day-time sleepiness

Benzodiazepines, Z drugs & Barbiturates

BZs – Effects

- Anaesthesia
  - Administered i.v. to induce anaesthesia or sedation for minor procedures such as endoscopy
  - Example: Midazolam (not other BZs!)
    - $t_{½}$ ~2 h, favour for short procedure
    - Also amnesic (as with other BZs)
- Anticonvulsion
  - i.v. diazepam for status epilepticus
  - Prophylaxis with clonazepam ($t_{½}$ ~50hrs)
- Skeletal muscle relaxation (may partly due to relief of anxiety)

Benzodiazepines, Z drugs & Barbiturates

BZs – Toxicities

- Impair performance/coordination
- Overdose (suicidal?)
  - Prolonged sleep and non-fatal unless combined with other CNS depressants (e.g. alcohol)
  - Flumazenil, a BZ antagonist, used to reverse BZ OD (short $t_{½}$, may require multiple administration)
- Development of tolerance (minor) and dependence (after chronic use) – mechanism not clear
- Desirable CNS effects may lead to compulsive misuse
- Withdrawal can be difficult
  - Symptoms include anxiety, insomnia, CNS excitability, convulsions
  - Gradual withdrawal required e.g. ↓ 10% dose per week

Benzodiazepines, Z drugs & Barbiturates

BZs – Clinical Preference?

- Depending on the PK of benzodiazepines (see the table below):
  - Ultra-short-acting
  - Short-acting
  - Intermediate-acting
  - Long-acting (active metabolites with long half-life)
- For short term use only

Adverse effects: different adverse effects are reported from different agents. The common adverse effects of BZs, Z drugs and barbiturates include drowsiness, impaired alertness the next morning, oversedation, light-headedness

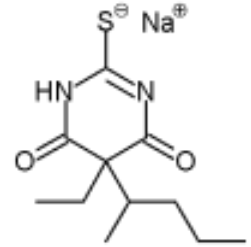
Length of action	Half-life	Drugs
very short	<6 hours	midazolam[1]
short	6–12 hours	alprazolam[1], oxazepam, temazepam[1]
medium	12–24 hours	bromazepam, lorazepam
long	>24 hours	clobazam, clonazepam, diazepam[1], flunitrazepam[1], nitrazepam

[1] rapid onset (<1 hour after oral administration)

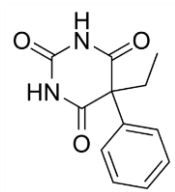
Benzodiazepines, Z drugs & Barbiturates

Barbiturates

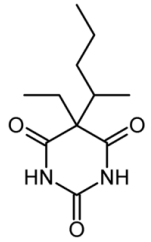
thiopental



Used for induction of general anaesthesia, rapid induction and short duration of action



phenobarbital



pentobarbital

(~one)

Lipophilicity of agent determines potency, speed of onset & $t_{½}$

- Mechanism of action
  - Bind directly to Cl^- channels, increase duration of channel opening independent of endogenous GABA
- Effects: similar to BZ
- Toxicities
  - Fatal in OD
  - Development of habituation/dependence