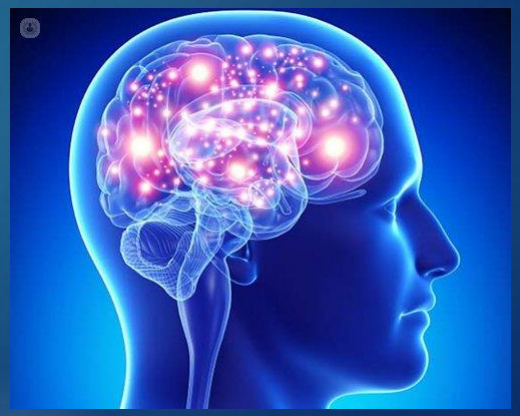
In the name of ALLAH

Principles of Psychopharmacotherapy

Dr. Amir Rezazadeh
Pharmacotherapy Specialist
Assistant Professor Of Clinical Pharmacy (IUMS)



Introduction

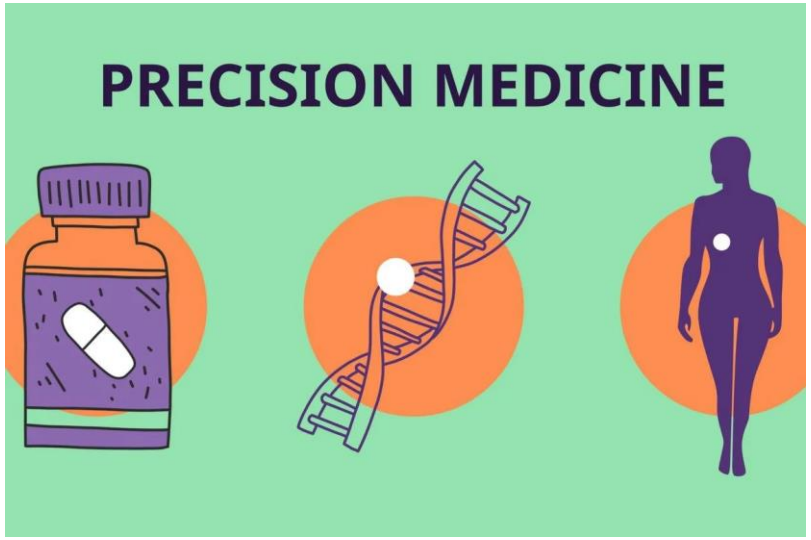
- **Common psychiatric conditions** such as depression, anxiety, and substance use disorders are known to negatively impact overall treatment outcomes for chronic medical conditions and subsequently increase healthcare costs

- **In the United State**, depression, diabetes and substance use disorders are among the top 10 health burdens

- **Iran: 10-20% (variable)**
- **Pharmacotherapy:** is cornerstone of treatment in depression ,anxiety ,…

Principles of pharmacotherapy

- Psychotropic medications, such as antipsychotic agents used for the treatment of mental illness can also cause or exacerbate medical conditions, such as diabetes mellitus, hyperlipidemia
- **Baseline and follow-up assessments** are needed to help document future adverse medication reactions
- **Every patients is a piece of art**



1.Collect: PMH/PDH/Social history/ previous response
2.Assess: Cognitive and emotional status /vital sign

3.Plan: Medication therapy regimen including specific psychiatric medication(s), dose, route, frequency, and duration

- **Monitoring parameters (TDM , lab tests)**

3.Implement:
Provide verbal and written patient education regarding all elements of treatment plan

5.Follow up
Resolution of behavioral health symptoms
Adherence /side effects

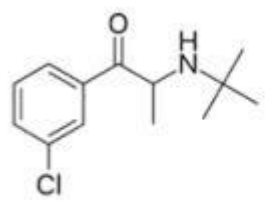
General Principles (Example antidepressants)

- The patient should be informed that **adverse effects** might occur immediately, while symptoms of depression may take 2 to 4 weeks to improve and up to 3 months for full resolution.
- **Adherence** to the treatment plan is essential for a successful outcome, and tools to help increase medication adherence should be discussed with each patient.
- **SSRIs is the first choice in many cases for depression**

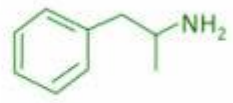
- **Compelling diseases**
- **1.TCA:** neuropathic pain, migraine prophylaxis, IBS, fibromyalgia
- **2.SSRI /SNRI:** most of anxiety such as GAD, Panic attack ,...
  - **Venlafaxine:** GAD/ migraine prophylaxis

Knowledge of medications (Example Bupropion) Pharmacotherapy Arts…

- **Bupropion: Tab 75, 100 mg, Tab SR 150 mg (Zyban®, Wellbutrin®, Wellban®)**



Bupropion



Amphetamine

- **Bupropion : amphetamine like** it inhibits both the **NE and DA** reuptake that makes it one of the most activating antidepressant.
- This activation can be particularly helpful for decreased motivation, low energy, and fatigue.
- **Adverse effects associated** with bupropion include nausea, vomiting, tremor, insomnia, dry mouth and weight loss.
- **Seizure:** strongly dose related
- **Dose: 150- 450mg/d**

Can be a choice for Smoking Cessation, sexual dysfunction +low libido , fatigue and obesity (in combination with naltrexone)!

TDM (Example: lithium)

- Chronic lithium administration may modulate **gene expression** and have **neuroprotective** effects.
- Lithium is a monovalent cation that is **rapidly absorbed**, and widely distributed with no protein binding. It is also not metabolized, and is excreted unchanged in the urine and in other body fluids.
- **Efficacy:** Lithium is considered a first-line agent for acute mania acute bipolar depression, and maintenance treatment of bipolar I and II disorders and suicidal idea.

- **Slow Onset (1-2 week)**
- **Dose:** initial 600 mg then 900-2,400 mg/day in two to four divided doses, preferably **with meals**
- Renal impairment: lower doses required with frequent serum monitoring

- **TDM:** There is wide variation in the dosage needed to achieve therapeutic response and **trough serum lithium concentration** (ie, 0.6-1.2 mEq/L [mmol/L]

TDM (Example: lithium)

- **Toxicity** Lithium is an extremely toxic medication if accidentally or intentionally taken in overdose.
  - Lithium toxicity usually occurs with blood levels greater than **1.5 mEq/L** (mmol/L), but elderly patients may experience toxicity at lower levels.

- **Several key symptoms**: *GI* (eg, vomiting, diarrhea, or incontinence), *coordination* (eg, fine to coarse hand tremor, unstable gait, slurred speech, and muscle twitching), and *cognition* (eg, poor concentration, drowsiness, disorientation, apathy, and coma)

Insomnia and Anxiolytics

Insomnia

- Insomnia is the **most common complaint** in general medical practice[8] as it frequently causes distress, due to the fear or a feeling of not being able to fall asleep at bedtime, leading to impaired work-related **productivity** because of daytime fatigue or drowsiness.
- Insomnia is classified as chronic when it has a duration of at **least three months, occurring at least three times per week.**

- **Transient (two or three nights**) and short-term (less than 3 months) insomnia is common.
- **Chronic insomnia** (more than 3 months duration) occurs in 9%–12% of adults and in up to 20% of older individuals.

TABLE 89-1 Common Etiologies of Insomnia

Situational

- Work or financial stress, major life events, interpersonal conflicts
- Jet lag or shift work

Medical

- Cardiovascular (angina, arrhythmias, heart failure)
- Respiratory (asthma, sleep apnea)
- Chronic pain
- Endocrine disorders (diabetes, hyperthyroidism)
- Gastrointestinal (gastroesophageal reflux disease, ulcers)
- Neurologic (delirium, epilepsy, Parkinson's disease)
- Pregnancy

Psychiatric

- Mood disorders (depression, mania)
- Anxiety disorders (eg, generalized anxiety disorder, obsessive-compulsive disorder)
- Substance abuse (alcohol or sedative-hypnotic withdrawal)

Pharmacologically induced

- Anticonvulsants
- Central adrenergic blockers
- Diuretics
- Selective serotonin reuptake inhibitors
- Steroids
- Stimulants

Drugs Associated With Sleep Disturbance	
Insomnia	Hypersomnia
Alcohol	Alcohol
Bupropion	Benzodiazepines
Fluoxetine	Antihypertensives
Sertraline	Clonidine
MAO inhibitors	α-Adrenergic blockers
TCA	ACE inhibitors
Thyroid supplements	β-Blockers
Calcium-channel blockers	Anticonvulsants
Decongestants	Analgesics
Appetite suppressants	Chloral hydrate
Theophylline	Antipsychotics
Corticosteroids	Antihistamines
Dopamine agonists	Opioids

Contributory factors

- **Time**:
- **A: Difficulty in falling asleep** is often a symptom of worry and anxiety. Sleep latency is the time taken to fall asleep (normally up to 30 min).
- **B: waking during sleep**: pain/ sleep apnea/ CV/ Asthma ,…
- **C: Early awaking:** depression/ light!

General Approach

- Clinical history should assess the **onset, duration, and frequency** of the symptoms
- **Management of all patients** with insomnia should include identifying the cause, patient education on sleep hygiene, and stress management .
- **Short-term insomnia (up to 4 weeks)**, which generally occurs as a result of acute stressors, is expected to resolve quickly and should be treated with **good sleep hygiene** and careful use of sedative-hypnotics.
- **Chronic insomnia (more than 4 weeks)** requires careful assessment for possible underlying medical causes, nonpharmacologic approaches, and careful use of sedative-hypnotics

Nonpharmacologic Therapy

- Nonpharmacologic interventions:
- Sleepy hygiene is cornerstone of insomnia treatment for insomnia frequently consist of short-term cognitive behavioral therapies, most commonly stimulus control therapy, sleep restriction, relaxation therapy, **cognitive therapy**, paradoxical intention, biofeedback, and **education** on good sleep hygiene.
- In patients aged 55 years and older, research indicates that cognitive behavioral therapy may be more effective than pharmacologic therapy at improving certain measures of insomnia.

Sleep Hygiene

- Avoid napping during the day as this reduces the 'drive to sleep' later.
- Avoid caffeine after midday; avoid nicotine, alcohol and large meals within 2 h of going to bed. Avoid using alcohol to try and help sleep.
- Avoid exercise within 4 h of bedtime (although exercise earlier in the day is beneficial).
- Avoid watching or checking the clock through the night; this increases anxiety.
- Avoid watching TV or using phones, tablets or computers for 2 h before going to bed.
- Avoid going to bed too early – go to bed when sleepy.
- Increase exposure to bright light in the morning.
- Using visual imagery in bed (mindfulness) can reduce 'racing' thoughts.

The sleep environment

- Maintain a comfortable sleeping environment: not too hot, cold, noisy or bright.
- Minimise bright light, including from electronic devices.
- Use thick curtains or blinds, an eye mask and earplugs to stop you being woken up by light and noise.
- Try to create a relaxation period before going to bed. Try taking a warm bath or listening to calming music. Relaxation exercises may help.
- Only use the bedroom for sleep and sexual activity.

Establish fixed times for going to bed and waking up every day, even after a poor night's sleep and at weekends.

Pharmacotherapy

- **Medications with regulatory approval for treatment of insomnia disorder fall into four categories of mechanism of action:**
- **Benzodiazepine receptor agonists (BZRAs),** which include the nonbenzodiazepine BZRAs (eszopiclone, zaleplon, and zolpidem) and five older benzodiazepine hypnotics (estazolam, flurazepam, temazepam, triazolam, and quazepam)
- **Dual orexin receptor antagonists** (DORAs: lemborexant, suvorexant, and daridorexant)
- **Histamine receptor antagonists** (low-dose doxepin)
- **Melatonin receptor agonists (ramelteon)**

General Approach

- **1.Antihistamines** (eg, diphenhydramine, doxylamine, and pyrilamine) are less effective than benzodiazepines, but side effects are usually minimal. Their anticholinergic side effects may be problematic, especially in Older individuals.
- **2.Antidepressants** are good alternatives for patients who should not receive benzodiazepines, especially those with depression, pain, or a history of substance abuse.
- ✓ Amitriptyline, doxepin, and nortriptyline are effective, but side effects include sedation, anticholinergic effects, adrenergic blockade effects, and cardiac condition.
- **Low-dose doxepin** is approved for sleep maintenance insomnia.
- **Mirtazapine** may improve sleep, but may cause daytime sedation and weight gain.
- **Trazodone**, 25–100 mg at bedtime, is often used for insomnia induced by selective
- serotonin reuptake inhibitors or bupropion and in patients prone to substance abuse.

Benzodiazepine (GABA A agonist)

Indications:

- **Acute stress, panic attack**
- **Insomnia:** including estazolam, flurazepam, and triazolam

- **Muscle relaxant**: diazepam/ clonazepam/ lorazepam
- **Withdrawal state (ethanol): l**onger acting benzodiazepines (eg, chlordiazepoxide, diazepam)
- **No metabolite** (good for elderly ang hepatic impairment): **oxazepam / lorazepam**

- **Clonazepam**: Tab 1, 2 mg (Relative Potency = 0. 5)
- Potent/ panic attack /Anti seizure ,muscle relaxant
- **Alprazolam**: Tab 0.5, 1 mg, (Xanax®) (relative potency :0.5 mg)
- **Lorazepam**: Tab 1, 2 mg (Ativan®) (Relative Potency = 1)

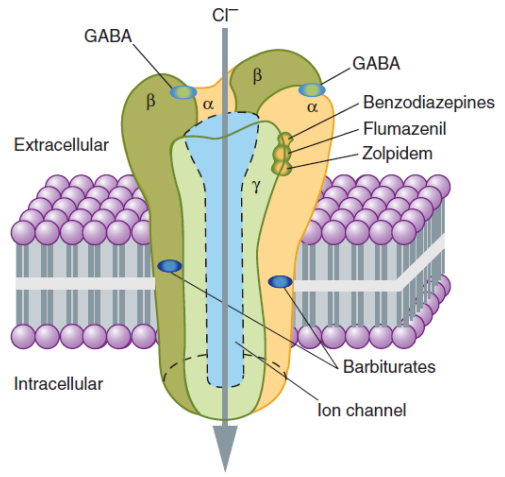
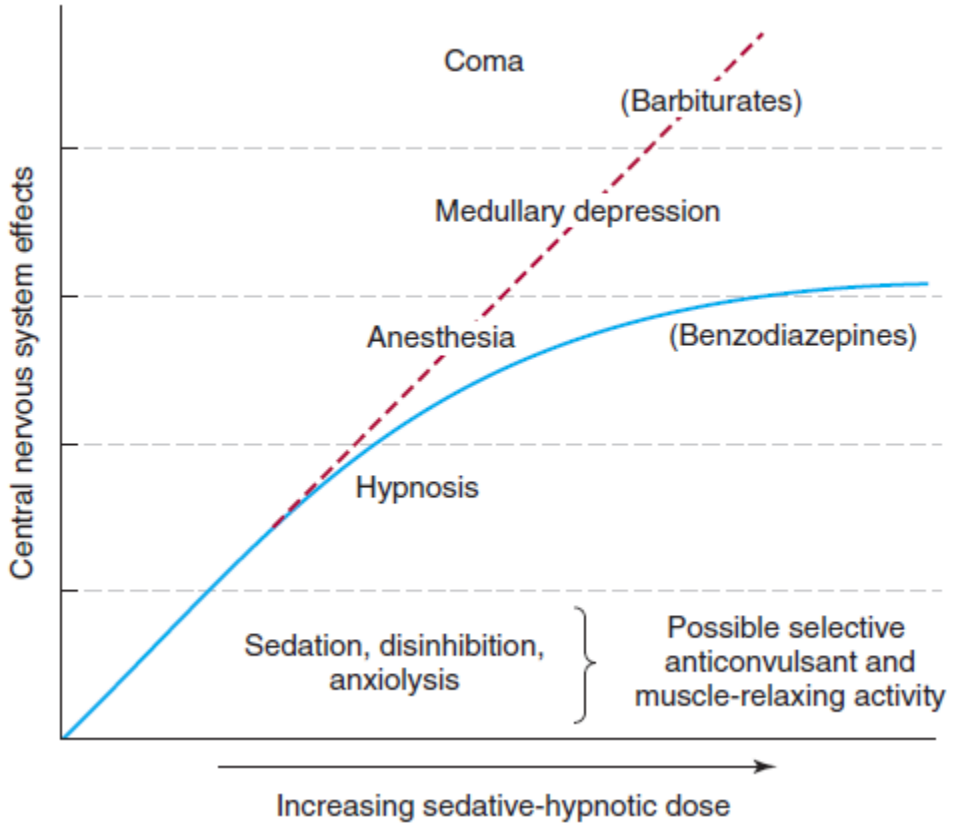


FIGURE 22–1 A model of the $GABA_A$ receptor-chloride ion channel macromolecular complex. A hetero-oligomeric glycopro-

Benzodiazepine

- **Diazepam**: Tab 2, 5, 10 mg, Amp 10 mg/2 ml (Valium®), Rectal Tube (Stesolid®) 5, 10 mg
- Muscle relaxent (2-10 mg/d), antisizure
- **Injection forms should not be diluted**
- **Chlordiazepoxide**: Tab 5, 10 mg (Librium®) (Relative Potency =10-25)
- Longer action/ less risk of abuse
- **Oxazepam**: Tab 10 mg (Oxpam®) potency: 10
- **Flurazepam**: Cap 15 mg potency: 15
- In insomnia (long act/ hang over!)
- **Midazolam**: Amp 5 mg/ml, 15 mg/3 ml
- Fast act,short act
- **In procedure such as endoscopy, agitation. ICU sedation**



- **ADRs**: risk of **abuse** (specially by fast acing : diazepam>alprazolm>lorazepam) anterograde **amnesia**/**tolerance** (not include anxiety)

Nonbenzodiazepine GABAA agonists

- Zolpidem, zaleplon, and eszopiclone are nonbenzodiazepine hypnotics that selectively bind to GABAA receptors and effectively induce sleepiness.
- **Zolpidem** has a duration of action of 6 to 8 hours[24] and is comparable in efficacy to benzodiazepine hypnotics, in that it is effective in reducing sleep latency and nocturnal awakenings, and increasing total sleep time.
- It does not appear to have significant effects on next day psychomotor performance.
- Zolpidem is less disruptive of sleep stages than benzodiazepines and adverse effects include drowsiness, amnesia, dizziness, headache, and GI complaints, which are dose-related. Sleep eating during zolpidem therapy can result in significant weight gain
- The recommended daily dose of zolpidem is 10 mg in male patients, **or 5 mg in female patients**, elderly patients, and those with hepatic impairment. Because food decreases its absorption, zolpidem should be taken on an empty stomach.

Nonbenzodiazepine GABAA agonists

- Zaleplon has a rapid onset of action with a half-life of 1 hour, and is metabolized to inactive metabolites.
- It is effective in decreasing **time to sleep onset**
- The recommended dose is 10 mg in adults and 5 mg in the elderly
- **Eszopiclone is** effective in reducing time to sleep onset, wake time after sleep onset, and number of awakenings, and increasing total sleep time and sleep quality. Eszopiclone's duration of action is up to 6 hours
- In general, the nonbenzodiazepine hypnotics seem to be associated with less withdrawal, tolerance, and
rebound insomnia than the benzodiazepine hypnotics. None of the nonbenzodiazepine GABAA agonists have significant active metabolites.

- **Onset: zaleplon> zolpidem>Eszopiclone**
- **Duration:?**

Buspirone and Z hypnotic

- **Buspirone**: Tab 5, 10 mg (Buspar®)
- 5HT1 agonist/ indication: GAD, augmentation in depression
- Dose: 10-60mg/d

- **Zolpidem**: Tab 5, 10 mg (Stilnox, Zoldem®)
- Dose: 5 mg (women. elderly) – 10 mg / day
- **It had Better be used just before sleep with empty stomach**
- **Should limit the use for 4-8 weeks**
- **ADRS: risk of complex behavior (not fully awake but do some work!)/ hallucination/ risk of abuse**

- **Zaleplon:** tab 5,10 mg

Faster act than zolpidem

CNS

- **Serotonin Syndrome:** SSRIs/SNRIs/MAOIs/ linezolid/Meperidine/ Tramadol/ Ondansetron
- **Anticholinergics:** TCA/ Clozapine/ 1st Gen Antihistamine/ dicyclomine/ Tolterodine
- **Additive effects: Carbamazepine/ lithium:** diplopia

- **Lithium:** ACEIs. NSAIDs, Thiazide (increase) , Caffein, Na, theophylline (Decrease)
- **Opioids+(Benzodiazepine, Barbiturate, alcohol):respiratory depression**
- **SSRIs:** Antiplatelet, Serotonin syndrome
- Paroxetine, fluoxetine and fluvoxamine have more interactions