CNS pharmacology / Final
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Antidepressants

Antidepressants

- Depression is not well understood ... we don't really know if there is a biological cause for it ⇒ This is Why ... treatment is complicated

- Depression symptoms
  - Cognitive : Thoughts of hopelessness, poor confidence, negative thoughts, lack of motivation
  - Emotional : Feeling Sad, irritability
  - psychomotor / physical : Decreased libido & energy, Sleep changes (more or less), Appetite changes (more or less)

- Drugs & Hypothesis

  1. MAO Hypothesis

     it's believed that, Dopamine + Serotonin + Norepinephrine, are the main chemical controllers of mood

     So, a decrease in them will cause depression ⇒ any drug that increases them is supposed to treat depression

     - Clinical trials on MAO inhibitors showed the following :

       1- MAO inhibitors efficacy was slightly higher than placebo ... & both were low [30-45%]

       2- SE of the drugs appear within a short period ... While the maximal wanted effect may take up to 8 weeks

       ↳ This was confusing ... bc it contradicts the initial hypothesis of depression being caused by a deficiency of monoamines

  2. Neurotrophic theory

     long time needed for treatment with MAO inhibitors ⇒ So, they're having a long term effect, rather than simply raising monoamines

     Explanation : the long term use of MAO inhibitors appears to increase the transcription of BDNF (Brain derived neurotrophic factor)

     BDNF is normally responsible of enhancing the neuronal placticity & connectivity ... & it exerts it's effect by binding to the tyrosine kinase B receptor.

     ⇒ So, the new theory explains depression by either decrease in BDNF or it's receptor.

     Which leads to stress, pain, atrophic structural changes in the hippocampus, frontal cortex & cingulate.

     This also explains why antidepressants need a long time to reach the maximal benefit.

Drug name	Commercial name	Drug class	Total prescriptions
Sertraline	Zoloft	SSRI	33,409,838
Citalopram	Celexa	SSRI	27,993,635
Fluoxetine	Prozac	SSRI	24,473,994
Escitalopram	Lexapro	SSRI	23,000,456
Trazodone	Desyrel	SARI	18,786,495
Venlafaxine (all formulations)	Effexor (IR, ER, XR)	SNRI	16,110,606
Bupropion (all formulations)	Wellbutrin (IR, ER, SR, XL)	NDRI	15,792,653
Duloxetine	Cymbalta	SNRI	14,591,949
Paroxetine	Paxil	SSRI	12,979,366
Amitriptyline	Elavil	TCA	12,611,254
Venlafaxine XR	Effexor XR	SNRI	7,603,949
Bupropion XL	Wellbutrin XL	NDRI	7,317,814
Mirtazapine	Remeron	TeCA	6,308,288
Venlafaxine ER	Effexor XR	SNRI	5,526,132
Bupropion SR	Wellbutrin SR	NDRI	4,588,996
Desvenlafaxine	Pristiq	SNRI	3,412,354
Nortriptyline	Sensoval	TCA	3,210,476
Bupropion ER	Wellbutrin XL	NDRI	3,132,327
Venlafaxine	Effexor	SNRI	2,980,525
Bupropion	Wellbutrin IR	NDRI	753,516

- currently used Antidepressants :

1. SSRIs → Serotonin Specific reuptake inhibitors
2. SNRIs → Serotonin , Norepinephrine reuptake inhibitors
3. NDRIs → Norepinephrine , Dopamine reuptake inhibitors
4. TCA → Tricyclic antidepressants [inhibit the reuptake of all three]

- How are they used ?

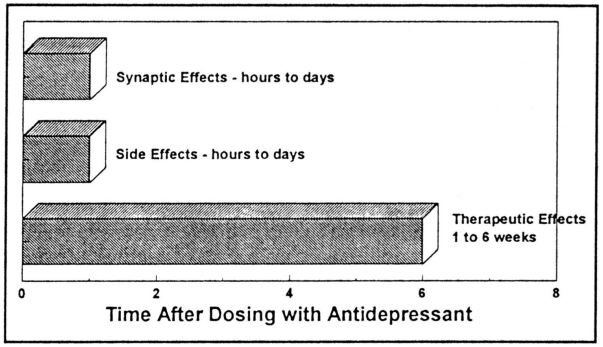
Therapy trials :

SSRI —(8 weeks, No effect)→ increase dose OR switch to SNRI —(8 weeks, No effect)→ increase dose OR switch to NDRI —(8 weeks, No effect)→ increase dose or switch to TCA [use in resistant cases]

- When the treatment is successful ⇒ 6-12 maintenance period
- If the pt. experienced 2 episodes of major depression ⇒ give life long

- Nowadays , antidepressants are of the most widely prescribed medications worldwide...

problems
- The chemicals we're playing with have many other functions in the body ⇒ ↑ expected SE
- Their efficacy isn't much higher than placebo (30-40 %) ⇒ combine with psychotherapy & exersize (↑ 60-70 %)
- Therapy trials take a very long time



SSRIs (1st drugs in the therapy trial)

Drug	General description	Use & specific description
Sertraline (Zoloft)	**MOA** Inhibit the reuptake of serotonin without seriously affecting the reuptake of dopamine & norepinephrine. **Other uses for SSRIs** OCD, Anxiolytics& Hypnotics **SE** (results of increased serotonin) →GI upset (nausea, vomiting, diarrhea) - serotonin have a major effect in GI →Sexual dysfunction >30% -dose dependent SE -serotonin has an inhibitory effect on dopamine … which is associated with sexual function. -reversible after discontinuation →Anxiety & insomnia -increased serotonin will bind to all 5HT receptors … the antidepressant effect is reached by serotonin binding to 5HT1 receptor, which is the inhibitory receptor … BUT, binding to 5HT2a,b will cause an excitatory effect → anxiety & insomnia. -this effect is temporary … until the excitatory receptors get desensitized within 1-2 weeks (Note: inhibitory receptors like 5HT1A do not desensitize) -this is a major cause of drug noncompliance →Sedation & dizziness -contradictory to the previous SE … its patient dependent →suicidal thoughts →Personality changes **→ only use when benefits outweigh risks**	- has increased number of GI adverse effects → so, if your pt, already has GI problems … do not use Sertraline
Paroxetine (Paxil)		- has sedating properties & offers good initial relief from anxiety & insomnia → use for depressed pts with insomnia !! problem: inhibits CYP2D6 → Do not use with polypharmacy pts. Who are taking more than 1 drug
Fluoxetine (Prozac)	**Serotonin discontinuation syndrome FINISH** -Flu like symptoms: fatigue, muscle aches, headache, diarrhea -Insomnia -Nausea -Imbalance: gait, dizziness, vertigo -Sensory disturbances: paresthesia, electric shock sensation, visual disturbances -Hyperarousal: anxiety, agitation → onset: 24- 72 hrs Resolution: 1- 14 days Incidence: 20- 40% (who have been treated for > 6 weeks) → they do not cause addiction **Why there are many of them?** Different SE → different use	-Due to its longer t1/2 , has less discontinuation symptoms !!problems: 1. interacts with CYP450 → Do not use with polypharmacy pts. 2. initially increases anxiety & insomnia 3. more likely to induce mania than other SSRIs → Avoid using it in bipolar pts.

SNRIs (we started with SSRIs … we waited for 8 weeks, increased the dose … still no effect)

Drugs	General description	Specific description
Venlafaxine	-slightly greater efficacy than SSRIs -slightly fewer serotonin SE than SSRIs -more discontinuation symptoms (now we are discontinuing 2 chemicals) … tapering is recommended after 2 weeks (while its 6 weeks for SSRIs)	Most drug causing nausea
Duloxetine	**SE** (new SE resulting from increasing norepinephrine) → increased BP → more significant nausea	

5 HT2 antagonists (increasing serotonin by SSRI or SNRI both can cause anxiety and insomnia by binding to the excitatory receptor 5HT2)

Drugs	General description	Specific description
Nefazodone	- inhibiting 5 HT2 receptor = antianxiety, antipsychotic, antidepressant effects	-Weak inhibitor of both SERT & NET (reuptake of serotonin & norepinephrine, respectively)
Trazodone	-Have sedative effect → use for pts. with depression & insomnia → no CYP450 effect … can be used to polypharmacy pts instead of *Paroxetine* → dose at bedtime -SE: dose dependent GI symptoms	-Weak but selective inhibitor of SERT - low doses have been used concurrently with SSRIs or SNRIs to treat insomnia
Mirtazapine		-causes weight gain

NDRI (this drug has no effect on serotonin, but serotonin is the major player in depression… SO, in the next step of therapy trial we can ADD Buproprion to SSRI OR SNRI)

Drug	Description
Buproprion	**Use** -As an augmenting agent … not used alone -gives a similar effect of increasing all monoamines by TAC or MAO inhibitors … but less efficient & less SE **Advantages (results of not affecting serotonin)** -no weight gain -no sexual side effects -no sedation -no cardiac interactions **disadvantages** -low induction of mania (do not use in bipolar) -does not treat anxiety like other antidepressants … can actually cause anxiety, agitation & insomnia -like other antidepressants… needs 4-6 weeks to give maximal effect

TCA / MOA inhibitors (next step of therapy trial … resistant cases)

Drug	MOA	SE	Use
TCA (Amitriptyline)	- non selective monoamine reuptake inhibitor - blocks Ach, α adrenergic, H1 (histamine) receptors	-sedation (due to blocking H1 receptor) -orthostatic hypotension (due to blocking α adrenergic receptors) -cardiac effects → SE: palpitation, tachycardia Toxicity: prolong QT interval -anticholinergic effects (dry mouth, constipation, blurred vision, urinary retention)	-resistant types of depression -fibromyalgia (generalized pain associated with depression)
MAO inhibitors **-phenelzine (non selective)** **-moclobemide (MAO A inhibitor/ reversible)** **-selegiline (MAO B inhibitor)**	**What is MOA** - MAO A → oxidizes epinephrine, norepinephrine, serotonin, dopamine → inhibitors can be used as antidepressants - MAO B → oxidizes phenylethylamine & dopamine → inhibitors cant be used as antidepressants (but they have a role in Parkinson treatment)	-weight gain -insomnia -edema -hypertension crisis → due to accumulation of tyramine (a dietary amine found in cheese, which is normally metabolized by MAO) accumulated tyramine leads to excess norepinephrine release & HTN crisis	-Atypical depression -resistant depression

Drug Combinations

1. SSRI or SNRI with 5HT2 antagonist
2. SSRI or SNRI with Bupropion (NDRI)

⇒ Notice : we never combine 2 S together … otherwise, Serotonin Syndrome

Antipsychotics

Schizophrania

1 What ?

- A Chronic psychatric disorder ⇝ Symptoms are continuous, not in episodes
- caused by ⟶ dysfunction of dopaminergic activity in the brain
  - ⟶ Mesolimbic tract - ↑ Dopamine ⇒ positive symptoms
  - ⟶ Mesocortical tract - ↓ Dopamine ⇒ Negative Symptoms

2 Why ?

Genetic predisposition (only 10%) + Environmental trigger ⇝ Affecting epigenetics

So, is it genetic ? NO , but genetic polymorphism is a risk factor

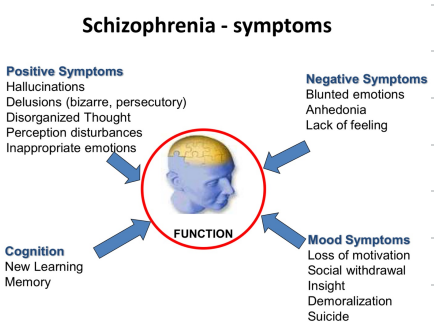
↳ multiple genes are involved

3 Who ?

2M : 1F

♂ ⇝ At age 21

♀ ⇝ At age 28



- Treatment :

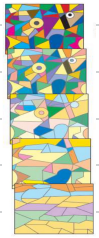
1. We are dealing with a disease caused by increased & decreased dopamine at the same time
   - Solution : ① give a drug to increase dopamine (But not at the mesolimbic area)
     - Serotonin normally inhibits dopamine release through 5HT2A receptor
     - give 5HT2A antagonist ⇒ more dopamine at mesocortical area - less negative symptoms
   - ② give dopamine receptor D_2 antagonist ⇒ less dopamine at mesolimbic - less positive symptoms
     - less dopamine at Nigrostriatal area → motor SE related to extrapyramidal tracts
     - less dopamine at tuberoinfundibular → more prolactin → gynecomastia, galactorrhea ...

* Note : old "Typical" Schizophrania drugs were more oriented on blocking D_2 & are highly specific
  New "Atypical" Drugs are combined, but more oriented on blocking 5HT2A & are less specific (more SE)

2. So, at the end ... a schizophrenic pt. has
   - positive symptoms ~ decreased by D_2 antagonism
   - Negative Symptoms ~ decreased by 5HT2A antagonism
   - Endocrine Symptoms ~ Due to D_2 antagonism
   - Motor Symptoms ~ Due to D_2 antagonism
     - This needs to be controlled by adding other drugs
       - Anti-parkinsonism
       - Benzo
       - Propranolol

   Drugs are not a cure
   There is no remission
   Drugs only prevent psychotic episodes
   Drugs are taken for life.

3. Response to drugs will need time, while SE are faster to appear



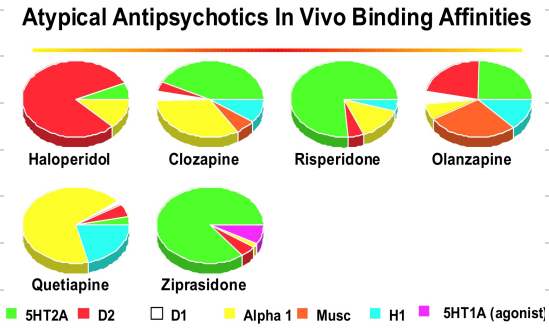
~ pt. gets better gradually

4] Addiction ⇒ No addiction to antipsychotic drugs

5] Tolerance ⇒ No tolerance to antipsychotic effect ... only to sedative effect

6] physical dependence & Withdrawal symptoms
- Relapse in psychosis happens when the drug is abruptly discontinued
  ↳ Tapering
- withdrawal symptoms → Nause, vomiting, Insomnia, Headache
  → persist for 2 weeks
  → Minimized by tapering

7] Effect vs. SE



Different antipsychotic drugs ... With affinities to different receptors

D_2 → Anti-positive symptoms + Motor (EP) SE

5HT2A → Anti-Negative Symptoms + ↓ Motor (EP) SE

α_1 → SE: orthostatic hypotension

H_1 → Sedation

⇒ The binding affinities to each drug gives it its effects & SE.

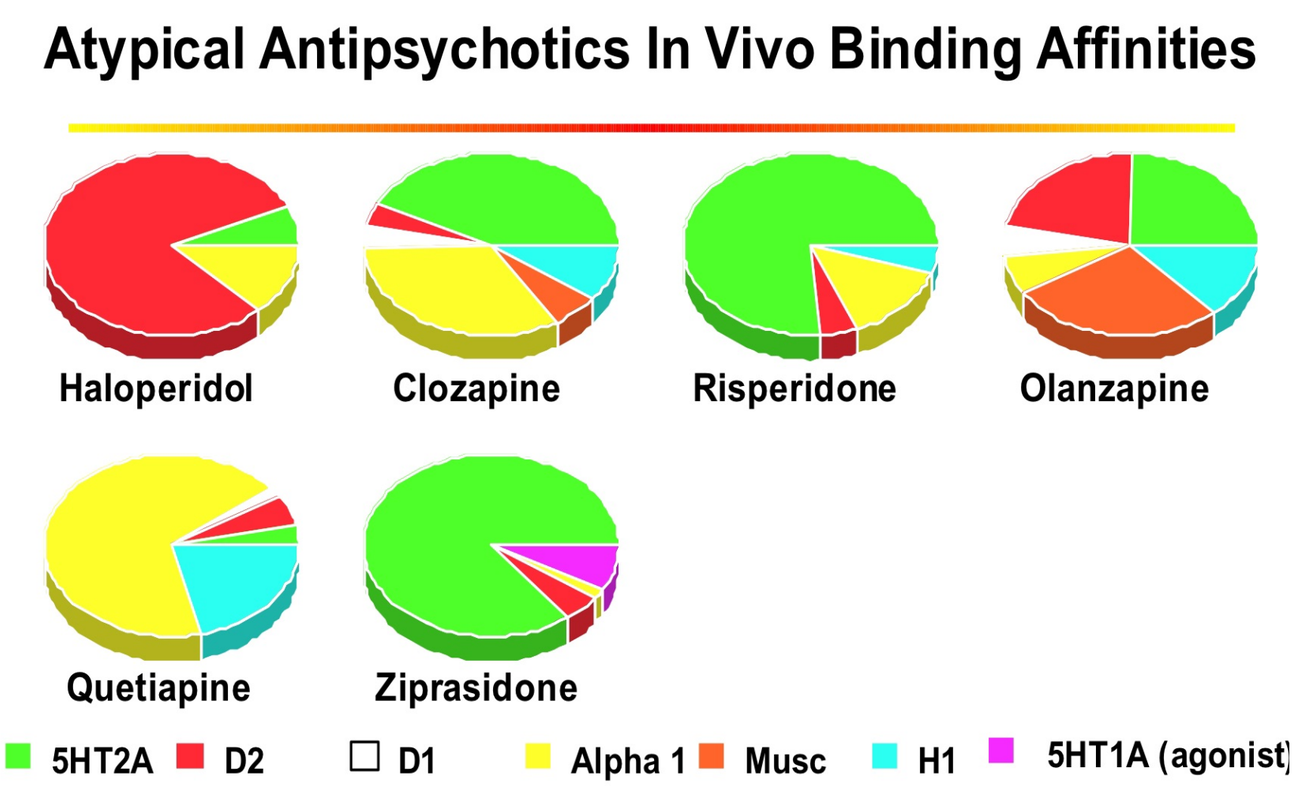
Example: The typical anti-psychotic "Haloperidol" has the highest affinity to D_2 ⇒ prominant motor SE

Classification of Antipsychotic drugs

- Main categories are:
  - *Typical antipsychotics*
    - Phenothiazines (**chlorpromazine, perphenazine, fluphenazine, thioridazine et al**)
    - Thioxanthenes (**flupenthixol**, **clopenthixol**)
    - Butyrophenones (**haloperidol, droperidol**)
  - *Atypical antipsychotics* (e.g. **clozapine**, **risperidone**, **sulpiride**, **olanzapine**)

Typical Antipsychotic drugs	Description	SE	Notes
Haloperidol	**Forms** Injectable & oral Sedation + Hypotension + Motor EP effects ++++	**Proportional to D2 specificity** REACTION / FEATURES / TIME OF MAXIMAL RISK / PROPOSED MECHANISM / TREATMENT Acute dystonia — Spasm of muscles of tongue, face, neck, back; may mimic seizures; *not* hysteria — 1 to 5 days — Unknown — Antiparkinsonian agents are diagnostic and curative Akathisia — Motor restlessness; *not* anxiety or "agitation" — 5 to 60 days — Unknown — Reduce dose or change drug: antiparkinsonian agents,b benzodiazepines or propranololc may help Parkinsonism — Bradykinesia, rigidity, variable tremor, mask facies, shuffling gait — 5 to 30 days — Antagonism of dopamine — Antiparkinsonian agents helpful Tardive dyskinesia — Oral-facial dyskinesia; widespread choreoathetosis or dystonia — After months or years of treatment (worse on withdrawal) — Excess function of dopamine hypothesized — Prevention crucial; treatment unsatisfactory	**Tardrive dyskinesia** (after long time use) - happens when D2 receptors get hypersensitized & the given antagonist is no more enough -what to do ? We neeed to change the drug… but if you change it or reduce it abruptly, dyskinesia will be worse … So, increase the dose acutely to get rid of dyskinesia symptoms, then start tapering & substituting the drug -when to do that ? Whenever the early symptoms of dyskinesia appear (oral & facial numbness) -keep in mind … we don't want to reach this stage, bc it means the drug is no more working for this pt. at the time they need to take it for life
Fluphenazine	Sedation + Hypotension + Motor EP effects ++++ → same as haloperidol		
Chlorpromazine	Sedation +++ Hypotension ++ Motor EP effects ++ → less specificity towards D_2		

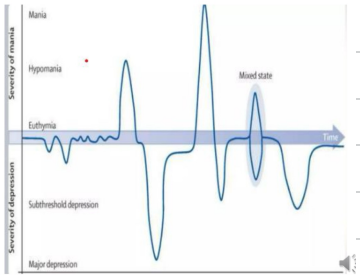
Atypical antipsychotic drugs	Description	SE	Notes
Risperidone	Sedation ++ Hypotension +++ Motor effects +/ ++ (dose dependent) → one of the most prescribed drugs in Jordan	**Endocrine** (effect of increased prolactin) -in women → galactorrhea, loss of libido, amonorrhea -in men → gynecomastia, impotence	problem of concern : Motor EP SE ↑ prolactin
Clozapine & olanzapine ↳ the best one , Especially regarding Negative Symptoms But, last drug resort ↳ !! Agranulocytosis	Sedation ++ Hypotension ++ Motor effects – (very little D2 affinity) → greater binding to 5HT2A = greater efficacy against negative symptoms	**Agranulocytosis** 4% -fatal SE for *Clozapine* **Metabolic** 1. weight gain (H1 blockade increases appetite) 2. DM (by reducing insulin sensitivity) By binding 5HT2C receptor → no increase in prolactin	problem of concern : Agranulocytosis – Clozapine DM & Weight gain
Quetiapine	Sedation ++ Hypotension ++ Motor effects 0 ↳ very low affinity to D_2	**Metabolic** Less weight gain and DM risk than Clozipine & olanzapine **Anticholinergic** -orthostatic hypotension -dry mouth -constipation → no increase in prolactin	problem of concern : Strong anticholinergic effect
Ziprasidone	Similar	Argued not to cause weight gain	
Aripiprazole	Sedation 0/+ Hypotension 0/+ Motor effects 0/+ (less effect + needs time; less SE) → This drug is different -a partial agonist at D2 receptor -acts as an agonist when dopamine is low (mesocortical) ⇒ Anti - negative symptoms Acts as an antagonist when dopamine is high (mesolimbic) ⇒ Anti - positive symptoms -also has affinity to muscarinic, α1, serotonin and histamine receptors →effect needs time … solution: Augmentation ~ Drug is given orally, with an IV loading dose (at the same time) for 1-2 months	Weight gain → least Feeling dizzy	Aripiprazole is a prodrug activated by CYTP450 (CYP2D6 & CYP3A4) → we dose according to the activity of those metabolizers … Taking in consideration if the pt. takes any inhibitors or Activators.



Drugs for Bipolar

Bipolar

Definition : disorder characterized by extreme mood swings that go in cycles between → Mania "overstimulation"
→ Depression "understimulation"



pathophysiology → Neurotransmitter imbalance : Glutamate is linked to both bipolar & major depression
Catecholamines → ↑ epinephrine & norepinephrine ⇒ Manic episodes
→ ↓ epinephrine & norepinephrine ⇒ Depression episodes
→ Hormonal imbalance : Disruption of the hypothalamic-pituitary-adrenal axis ⇒ increased cortisol levels contributes to both mania & depression
Thyroid levels dysregulation → Hypothyroidism contributes to depression episodes
→ Hyperthyroidism contributes to manic attacks

Treatment guide :

give one of those choices →

1- Lithium [0.6 - 1.2]
2- Lithium [0.4] + valproic acid / carbamazepine / Lamotrigine [Anti-epileptic]
3- Valproic acid + Atypical antipsychotic

Drug	Description	SE & toxicity	Notes	Alternatives
Lithium (mood stabilizer)	**Pharmacodynamics** -regulates neurotransmitter levels like serotonin -stabilizes neuronal excitation by affecting nerve membranes, receptor systems & intracellular 2nd messengers and signal transduction. -regulates CNS gene expression, stabilizing neurons. → not well understood → has no psychotic effects on non bipolars **Pharmacokinetics** -therapeutic window is very narrow = 0.6 – 1.2 mEq/L Below → no effect Above → high toxicity at 1.5 … fatal at 2.5 -excretion: -Li is filtered by glomerulus then reabsorbed by proximal tubules … same as Na. -So, Li follows Na in the kidneys… when Na is retained, Li is retained… when Na is excreted, Li is excreted.	**Dose dependent** -effect and SE of lithium are highly dependent on its plasma levels … so, monitoring is essential. **Generally** Neurological, gastrointestinal, enlarged thyroid, rash, weight gain, memory difficulty, kidney dysfunction, cardiovascular. **1. Fine tremors** -most common SE at therapeutic doses -treated by propranolol or atenolol (blocking β2) **2. leukocytosis** -benign & reversible after treatment is stopped **3. Hypothyroidism** -benign, reversible & non progressive -However, we always prefer to keep thyroid levels within upper limits, as hypothyroidism may contribute to the psychological state of pts. -So, we add Levothyroxine as a part of the psychiatric treatment… not to treat pathological state of thyroid gland. **4. inhibition of ADH (diabetes insipidus)** -causes polyuria -polyuria → dehydration →compensatory increase in Na & H2O retention towards plasma → Li follows Na → higher Li levels in plasma. ** **to overcome this side effect : pt. should be well hydrated to decrease Na reabsorption**. **5. Contraindicated In pregnancy** -causes fetal goiter & Ebsteins (cardiac) anomaly → 1-5 all happen within therapeutic dose → over therapeutic dose = toxicity -nephrotoxic, neurotoxic, cardiotoxic	**A patient taking lithium should be told to:** **1. well hydration** - drink more water to prevent dehydration & elevation of Li levels. **2. stable Na intake** - Since Na & Li are highly related in terms of retention and excretion… we dose the pt. depending on their Na intake. - Pt. should not change Na intake - More Na intake → more Na excretion → more Li excretion → under therapeutic Li levels - Less Na intake → more Na retention → more Li retention → toxic Li levels. **3. add propranolol** - to overcome the fine tremor **4. add levothyroxine** -to overcome psychiatric side effects of hypothyroidism **Antidote** - there Is no antidote for Li … in cases of toxicity → hemodilation	-40% of bipolars are resistant to lithium, or side effects hinder its effectiveness. Therefore, we must consider alternative agents for treatment. -new guides advice not starting with Li **1. Valproic acid (Depakote)** **2. Carbamazepine (Tegratol)** **3. Lamotrigine** **4. Atypical antipsychotics**

Alternatives

Drug	MOA	Use	SE
Valproic acid	-An antiepileptic -depresses the CNS by augmenting GABA effect	- best for rapid cycling & acute mania -most widely used anti-manic -used for anxiety, mood and personality disorders -used in combination with either low dose Li or atypical Antipsychotic.	-GI upset -sedation & lethargy -tremors -loss of hair -metabolic liver changes
Carbamazepine	-An antiepileptic	-superior to lithium for rapid cycling -second line treatment for mania -used in combination with low dose Li	-GI upset -sedation -ataxia -cognitive effects
Lamotrigine	-An antiepileptic	-effective in bipolar, border line personality, schizophrenia, post-traumatic stress disorders. -used in combination with low dose Li	-dizziness -tremors -headache -nausea -rash
Atypical antipsychotics **-Clozapine** **-Risperidone** **-Olanzapine** **-Aripiprazole**		-Risperidone : more antidepressant than antipsychotic. Remember (high 5HT2A antagonism) - Clozapine : not readily used due to serious SE -Olanzapine : short term use in acute mania -Aripiprazole : acute manic episodes in adults	

General anesthesia

General anesthesia

- use : In surgeries → we need to induce →
  - unconsciousness
  - Analgesia
  - Autonomic Stabilization ⇒ less secretions
  - Skeletal muscle relaxation & inhibition of reflexes ⇒ Allows the surgion to work without muscle resistance.

⇒ Do we use a single agent to induce all those effects ? previously, they did. Ether was used alone for general anesthesia

But... SE ↑↑, Mortality ↑↑

Now we use combinations of drugs ⇒ ↓ SE

- phases of anesthesia -overview

premedication

- Anxiolytic ⇒ Benzo
- Analgesia
- Atropine ⇒ to reduce Salivation
  - Anti - muscarinic

During Surgery

- Induction
  - Short acting IV anesthetic + Muscle relaxant
    - Propofol, Thiopental
    - ketamine
  - Aim : Induce unconsciousness + prepare for Intubation

- Maintenance
  - Inhaled anesthetic is delivered to pt. lungs continuously during the surgery to maintain unconsciousness
  - Aim : Inhaled anesthetics go from lungs → Blood → Brain → lungs → Exhaled
    Bypassing Metabolism ⇒ less SE
    - Halothane
    - Enflurane
    - Isoflurane
    - Sevuflurane
    - + N_2O

- Control
  - Vitals should always be undercontrol
    - BP
      - ↑ : give β blocker [Esmolol]
      - ↓ : give Norepinephrin, vasopressen
    - pain : give analgesic [Fentanyl]

Recovery

- Reversing anesthesia
  - Neostigmine ⇒ Reverse neuromuscular block
  - ondansetron ⇒ Antiemetic [Blocks 5HT3 receptor]

The Anesthetic machine

→ has 3 tubes

- O_2 tube ~ = 30 % ⇒ to ensure tissue oxygenation & prevent hypoxia
- Anesthetic → ≈ 1-2 % ⇒ percentage depends on MAC "Explained later"
- N_2O tube ~ ≈ 70 % ⇒ Is not an anesthetic by it's own
  But is used as an adjuvent →
  1. Analgesic effect (that anesthetics don't have)
  2. 2nd gas effect "Explained later"

Induction phase/ IV anesthetics (REMEMBER: they work fast, finish fast → only used to induce anesthesia)

Drug	MOA	Features	SE
Thiopental / Barbiturate	- activates GABA receptor → more Cl- influx → CNS depression -remember → to reach anesthetic effect you need to increase the dose .	-weak analgesic effect (supplementary analgesics are required) -ultra short acting → not the first choice… propofol have replaced it	-vasodilation → Hypotension (remember: controlled by norepinephrine) -cough -chest wall spasm -bronchospasm (do not use in asthmatic pt.) -causes post anesthetic nausea
Propofol (حليب) 	-activates GABA receptor (?)	-weak analgesic effect (supplementary analgesics are required) -no post anesthetic nausea & vomiting (& its considered antiemetic) -no cardiac depression -no increased ICP (bc it reduces cerebral blood flow) -no bronchospasm → widely used and is the 1st choice	-vasodilation → Hypotension -promotes bacterial growth… should not be used after 24hrs of opening the bottle… otherwise, contamination may cause septicemia.
Ketamine (صديقك الأمين)	-blocks NMDA channel → less Ca++ influx → CNS depression	-induces a **dissociation state**, in which the pt. is unconscious, feels no pain, has no reflexes… BUT, appears to be awake, open eyes, may speak (hallucinate). -strong analgesic -no hypotension -no bronchospasm **Use** **1. Anesthetic** -patients with hypotension, heart failure, low ejection fraction… -short procedures in children **2. Antidepressant** -at low doses, it has very nice effect -works immediately (while other antidepressants need weeks) **3. Pain management** -due to its effect on NMDA receptor -used for resistant type of pain, that doesn't respond to morphine nor methadone.	-stimulates the sympathetic outflow → increased BP & cardiac output (special property… other anesthetics cause hypotension) -increases ICP (bc it increases cerebral blood flow) **Contraindications** -hypertensive, stroke pts

Now that our pt. is unconscious… the next step is to intubate… so the maintenance anesthetics take over → to intubate, we need a muscle relaxant (ex. succinylcholine)

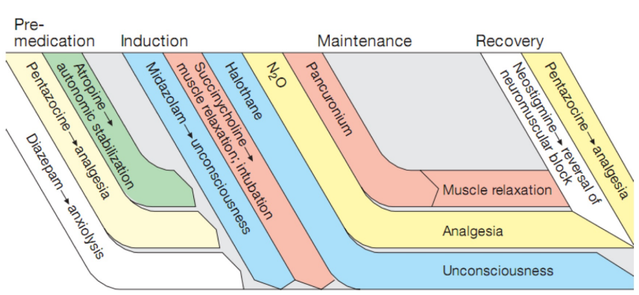
Maintenance phase / inhaled anesthetics

Drug	General description	Specific features	SE
Halothane/ prototype	**Efficacy** -No one anesthetic agent is superior in all circumstances **Potency** -defined quantitatively as MAO (median alveolar concentration) -MAC is the minimum alveolar con. that produces immobility in 50% of pts. -MAC is expressed as the percentage of anesthetic in the gas mixture. -the lower the MAC, the higher the potency **MOA** -old theory → they are lipophilic agents that embed in the plasma membrane of neurons & decrease its conductivity -new theory → they might have effects on ion channels such as GABA, NMDA, K+ channels… leading to CNS depression	-works fast, finishes fast (quick recovery) -potent anesthetic, but weak analgesic (combined with N20 or opioids- fentanyl) -bronchodilator -no hepatotoxicity in children (due to underdeveloped metabolism) **Use** -due to SE, it has largely been replaced -asthmatic & COPD pts. -children	-20% of the dose is not exhaled & causes liver toxicity in adults -bradycardia -hypotension -cardiac arrhythmias (due to catecholamine sensitization) -potential to induce malignant hyperthermia
Enflurane		-works fast, finishes fast -less potent than halothane -fewer arrhythmia than halothane → not used due to SE	-2% is metabolized to fluoride ion, which is excreted by kidneys -hepatotoxic -neurotoxic (seizures) **Contraindications** -kidney failure pts.
Isoflurane		-little metabolized → much lower risk of hepatitis -no cardiac arrhythmias → most widely used inhaled anesthetic	-hypotension (but no bradycardia)
Sevoflurane		Slightly better than Isoflurane, but very expensive	

This is what goes in the anesthetic tube of the machine … percentage depends on potency (MAC)

Gas	use in maintenance	N2O in recovery
N2O	-weak anesthetic (cannot produce surgical anesthesia at 80%) -potent **analgesic** (while inhaled anesthetics are not) -**2nd gas effect** -its fast diffusion from alveoli has a suction effect on the halogenated anesthetic… enhancing their penetration speed -has the least effect on cardiovascular & hepatic systems → particularly used with O2 in dental surgery	- its fast diffusion is a problem in recovery… When the intubation is removed, N20 gets out quickly… occupying the alveoli & compromising O2 diffusion → diffusion hypoxia → how do we manage that? By increasing O2 concentration to 100% during recovery

Don't forget… muscle relaxation is also a part of maintenance (use Pancuronium)



Regimen for balanced anesthesia

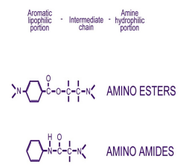
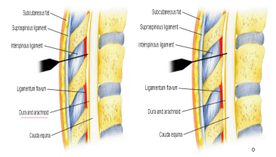
Local anesthetics

local anesthesia - overview

- In local anesthesia, our goal is to block **pain receptors** (→ free nerve endings), the pt. is still gonna be awake & motor function isn't affected.
  - How can we do that? Block Na^+ channels of the nerve terminal → No propagation of pain signals
  - Why aren't the motor nerves also blocked? Due to fiber size & myelination
    - ⇒ Small unmyelinated fibers (pain) are blocked first ⇒ the given anesthetic dose isn't enough to block motor fibers
  - Why is the pt. still awake? Drug doesn't reach the CNS (nor the blood - Explained later)

⇒ this is the local anesthetic cartidge

⇒ Components
- local anesthetic "Caine"
- Vasoconstrictor "Dose is coded by the color"
- $NaHCO_3$ - Sodium bicarbonate.

Local anesthetic	Description	Notes
Caines Lidocaine Tetracaine Bupivacaine Procaine Prilocaine Articaine	**MOA** -blocking the inactive Na+ channel present in the inner side of the neuronal cell membrane + nonspecifically stabilizing the membrane → no depolarization → no action potential propagation → no pain transmission. → reflexes are also inhibited All local anesthetics contain **structural components**: an aromatic ring (usually substituted) a connecting group which is either an ester (e.g., novocain or an amide (e.g. lidocaine) an ionizable amino group Chemical structure of local anesthetics  **2 types depending on structure** -Esters → broken down by esterases … short DOA … rarely used -Amides → longer DOA … wider usage **Administration** -most commonly through injecting the cartridge subcutaneously -there are 2 types: 1. nerve block → very close to the nerve fiber … very painful … more localized area … deeper injection 2. infiltration → wider area … more superficial injection … more need to vasoconstrict **Site of action** -local anesthetic needs to alternate between different states: -in the cartridge → water soluble -in the tissue → lipid soluble (to be able to **penetrate** the plasma membrane & reach the inactivated Na+ channels) -in the nerve terminal → water soluble (to be able to **bind the Na+ channel** & inactivate it) → this alternation in ionization depends on the relation between pH in the environment & pKa of the anesthetic. **pH & pKa** -local anesthetics are weak bases (pKa= 7.5- 9.5) -pKa = the pH in which the molecule is 50% ionized & 50% non ionized -higher pH → less ionization lower pH → more ionization -pH in tissue is higher than the neuronal cell → more drug gets ionized in the nerve terminal → binds to Na+ channel **DOA** -depends on the 2 important features mentioned above: 1. penetration 2.protein binding -why do we care about DOA? we need it to be long enough that we only inject once. -where is the problem if we inject more than once? Higher chance of reaching the blood **Blood access** -blood flow to the area under local anesthesia should be as low as possible … why? 1. we don't want the anesthetic to be washed out quickly 2. we don't want the anesthetic to reach the systemic circulation … due to bad SE -vasodilation & hypotension -cardiac effects (decreased pacemaker excitability, prolonged effective refractory period) -CNS effects (increased excitability (due to initial inhibition of inhibitory neurons), followed by generalized depression that can reach RS depression) → for this reason, the anesthetic cartridge contains a vasoconstrictor, usually Epinephrine: -to decrease washout & prolong DOA -to decrease systemic SE **Value (dose) of vasoconstrictor** -we need to induce vasoconstriction that is high enough to decrease washout + access & low enough to prevent tissue necrosis -we need to take in consideration the variability of blood flow between different areas -we need to take in consideration the variability of cardiac states of different patients… a pt. with cardiac problems (arrhythmia, HTN) should be given the lowest possible dose → for this reason, the color system was invented, in which each color indicates a different value of Epi Examples of values → 1g/50k ml, 1g/200k ml (generally low doses)	**Inflammation in the area** - if your gingiva is inflamed, the dentist cannot give you local anesthetic… why? Inflammation = acidic environment = lower pH Lowe pH = more ionization = less penetration = dose isn't enough to block pain -what do we do… Increase the dose? Dangerous… bc this increases the chance of blood access Make the environment alkaline (higher pH)? Perfect idea → for this reason, anesthetic cartridges may have a 3rd component … NaHCO3 **Variations between anesthetics** -they differ in the chemical structure → pKa → lipid solubility & protein binding → DOA & potency -choosing one of them depends of the desired DOA -Lidocaine is the most widely used **Bupivacaine** -longest DOA → used for long operations such as obstetrics **Prilocaine** -contraindicated in obstetrics bc it causes mythhemoglobinemia & possible baby death **Topical agents** -applying the anesthetic directly on the mucous membrane (conjunctiva, nose, throat, urethra) -Agents of choice → tetracaine, lidocaine, proparacaine -onset of action = 20 sec DOA = 8 min -topical agents contain high concentrations of anesthetic (2-5%) → less blood access **Injection (IV) agents** -used when decreasing blood flow to the area isn't possible -example: limb surgeries -since we can't give a VC, we use a cuff proximal to the area to be injected… to arrest the blood flow -the anesthetic remains effective until the circulation is restored -Agents of choice → Lidocaine, Prilocaine **Spinal anesthesia** -injected intrathecally into the CSF -used for abdomen, pelvis, leg surgeries when general anesthesia isn't appropriate -Agents of choice → Lidocaine, Tetracaine **Epidural anesthesia** -used in obstetrics → keep in mind: the deeper you inject, the more blood access & SE • Length of time from induction until the reversal process is complete. • **Short-acting:** – Local anesthetic agent lasts less than 30 minutes. • **Intermediate-acting:** – Local anesthetic agent lasts about 60 minutes. • **Long-acting:** – Local anesthetic agent lasts longer than 90 minutes. Epidural Spinal 

Good luck