Psychopharmacology in Psychiatry

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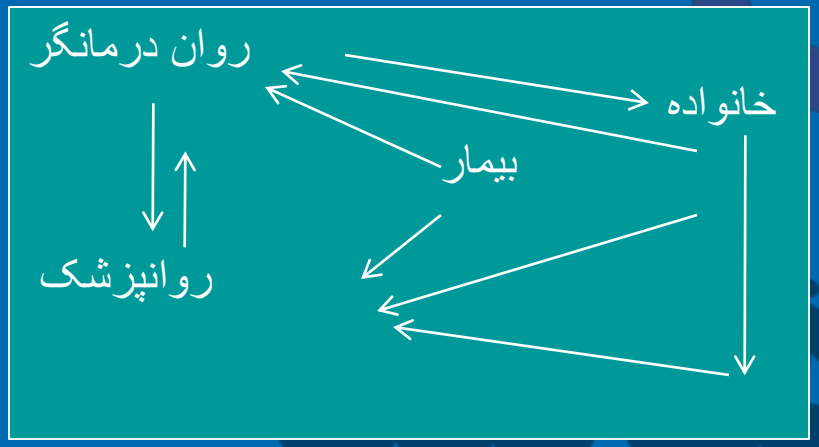
Over view

- هم فکری و هم بینی
- دانش همه جانبه نگر
- مدیریت زیست روانی اجتماعی
- درمان دارویی رکن اساسی در بسیاری از اختلالات
- درمان غیر دارویی رکن اساسی در بسیاری از مشکلات

TEAM WORK



- بیمار
- رواندرمانگر
- روانپزشک
- خانواده

ترس های بیماران

- وابستگی یا اعتیاد
- ناتوانی در باروری
- چاقی
- خواب آلودگی
- آسیب های کبدی و کلیوی

Objectives: At the end of this session you should be able to:

- Identify general pharmacologic strategies

- Discuss antidepressants including indications for use and side effects
- Describe mood stabilizers
- Review antipsychotics
- Identify anxiolytic

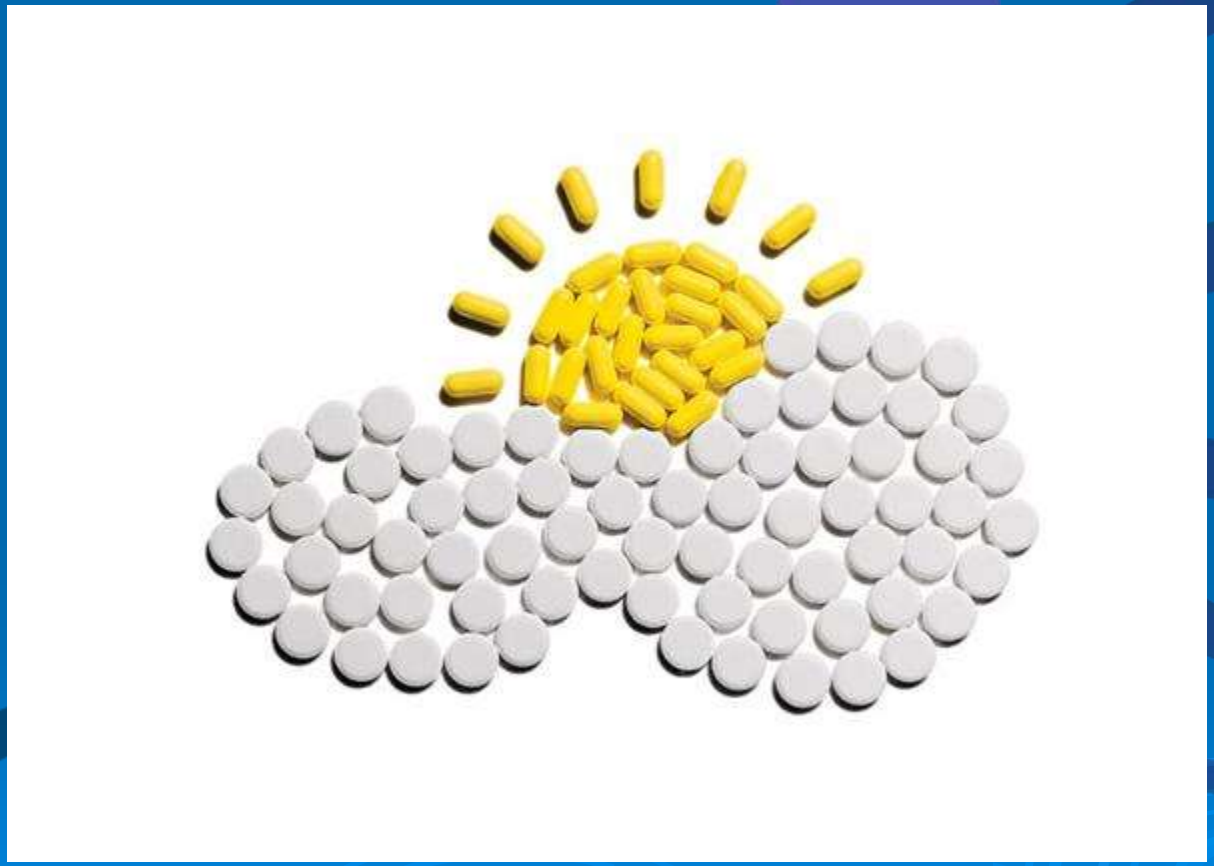
General Pharmacology strategies

- Indication: Establish a diagnosis and identify the target symptoms that will be used to monitor therapy response.
- Choice of agent and dosage: Select an agent with an acceptable side effect profile and use the lowest effective dose.
- Remember the delayed response for many psych meds and drug-drug interactions.

- Establish informed consent: The patient should understand the benefits and risks of the medication.
- Make sure to document this discussion including pt understanding and agreement. In fertile women make sure to document teratogenicity discussion

- Management: Adjust dosage for optimum benefit, safety and compliance.
- Use adjunctive and combination therapies if needed however always strive for the simplest regimen.
- Keep your therapeutic endpoint in mind.

Antidepressants



Antidepressants

- **Indications**: Unipolar and bipolar depression, organic mood disorders, schizoaffective disorder, anxiety disorders including OCD, panic, social phobia, PTSD, premenstrual dysphoric disorder and impulsivity associated with personality disorders.

General guidelines for antidepressant use

- Antidepressant efficacy is similar so selection is based on past history of a response, side effect profile and coexisting medical conditions.

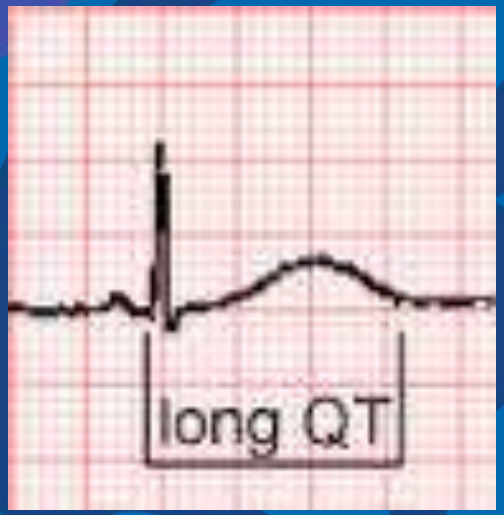
- There is a delay typically of 3-6 weeks after a therapeutic dose is achieved before symptoms improve.
- If no improvement is seen after a trial of adequate length (at least 2 months) and adequate dose, either switch to another antidepressant or augment with another agent.

Antidepressant Classifications

- Tricyclics (TCAs)
- Monoamine Oxidase Inhibitors (MAOIs)
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)
- Novel antidepressants

TCAs

- Very effective but potentially unacceptable side effect profile i.e. antihistaminic, anticholinergic, antiadrenergic
- Lethal in overdose (even a one week supply can be lethal!)
- Can cause QT lengthening even at a therapeutic serum level



Tertiary TCAs

- Have tertiary amine side chains
- Side chains are prone to cross react with other types of receptors which leads to more side effects including antihistaminic (sedation and weight gain), anticholinergic (dry mouth, dry eyes, constipation, memory deficits and potentially delirium), antiadrenergic (orthostatic hypotension, sedation, sexual dysfunction)
- Act predominantly on serotonin receptors
- Examples:Imipramine, amitriptyline, doxepin, clomipramine
- Have active metabolites including desipramine and nortriptyline

Secondary TCAs

- Are often metabolites of tertiary amines
- Primarily block norepinephrine
- Side effects are the same as tertiary TCAs but generally are less severe
- Examples: Desipramine, notrtriptyline

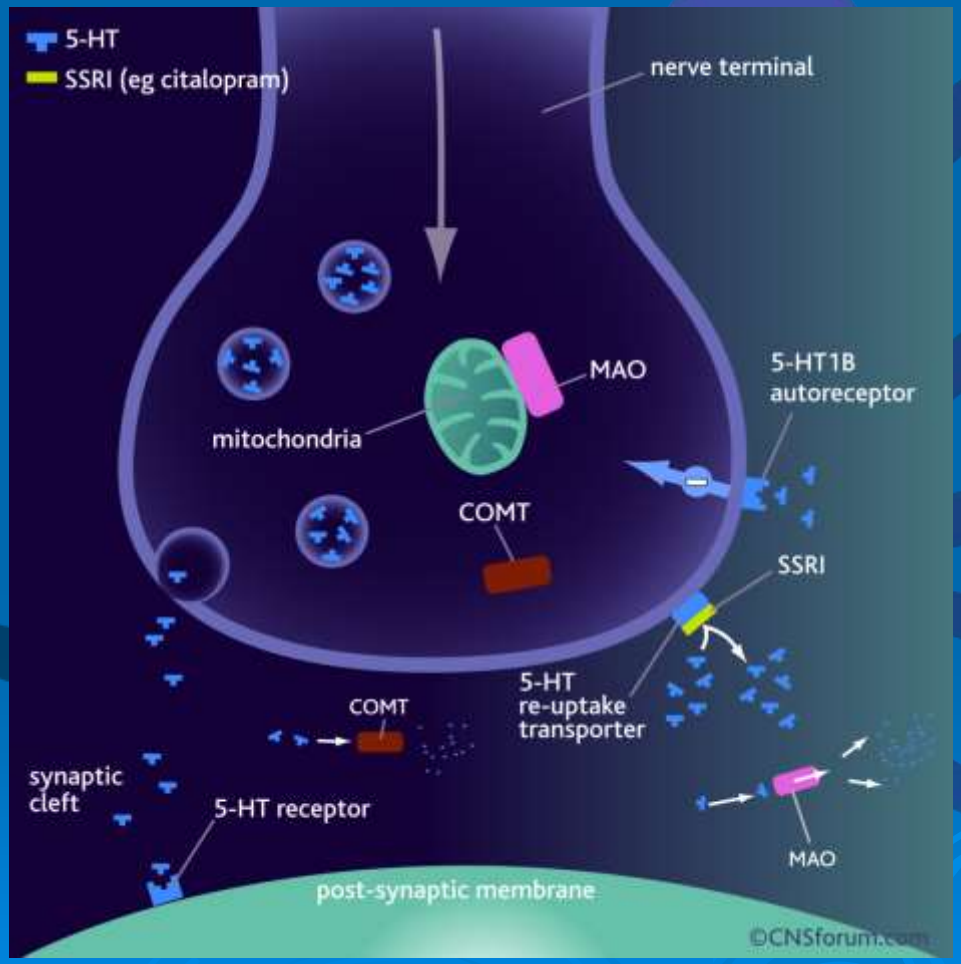
Monoamine Oxidase Inhibitors (MAOIs)

- Bind irreversibly to monoamine oxidase thereby preventing inactivation of biogenic amines such as norepinephrine, dopamine and serotonin leading to increased synaptic levels.
- Are very effective for depression
- Side effects include orthostatic hypotension, weight gain, dry mouth, sedation, sexual dysfunction and sleep disturbance
- Hypertensive crisis can develop when MAOI's are taken with tyramine-rich foods or sympathomimetics.

MAOIs cont.

- Serotonin Syndrome can develop if take MAOI with meds that increase serotonin or have sympathomimetic actions. Serotonin syndrome sx include abdominal pain, diarrhea, sweats, tachycardia, HTN, myoclonus, irritability, delirium. Can lead to hyperpyrexia, cardiovascular shock and death.
- To avoid need to wait 2 weeks before switching from an SSRI to an MAOI. The exception of fluoxetine where need to wait 5 weeks because of long half-life.

SSRIs


5-HT
SSRI (eg citalopram)
nerve terminal
MAO
5-HT1B
autoreceptor
mitochondria
COMT
SSRI
5-HT
re-uptake
transporter
COMT
synaptic
cleft
5-HT receptor
MAO
post-synaptic membrane
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Selective Serotonin Reuptake Inhibitors (SSRIs)

- Block the presynaptic serotonin reuptake
- Treat both anxiety and depressive sx
- Most common side effects include GI upset, sexual dysfunction (30%+!), anxiety, restlessness, nervousness, insomnia, fatigue or sedation, dizziness
- Very little risk of cardiotoxicity in overdose
- Can develop a discontinuation syndrome with agitation, nausea, disequilibrium and dysphoria

Paroxetine (Paxil)

- Pros
  - Short half life with no active metabolite means no build-up (which is good if hypomania develops)
  - Sedating properties (dose at night) offers good initial relief from anxiety and insomnia
- Cons
  - Significant CYP2D6 inhibition
  - Sedating, wt. gain, more anticholinergic effects
  - Likely to cause a discontinuation syndrome

Sertraline (Zoloft)

- Pros
  - Very weak P450 interactions (only slight CYP2D6)
  - Short half life with lower build-up of metabolites
  - Less sedating when compared to paroxetine
- Cons
  - Max absorption requires a full stomach
  - Increased number of GI adverse drug reactions

Fluoxetine (Prozac)

- Pros
  - Long half-life so decreased incidence of discontinuation syndromes. Good for pts with medication noncompliance issues
  - Initially activating so may provide increased energy
  - Secondary to long half life, can give one 20mg tab to taper someone off SSRI when trying to prevent SSRI Discontinuation Syndrome
- Cons
  - Long half life and active metabolite may build up (e.g. not a good choice in patients with hepatic illness)
  - Significant P450 interactions so this may not be a good choice in pts already on a number of meds
  - Initial activation may increase anxiety and insomnia
  - More likely to induce mania than some of the other SSRIs

Citalopram (Celexa)

- Pros
  - Low inhibition of P450 enzymes so fewer drug-drug interactions
  - Intermediate ½ life
- Cons
  - Dose-dependent QT interval prolongation with doses of 10-30mg daily- due to this risk doses of >40mg/day not recommended!
  - Can be sedating (has mild antagonism at H1 histamine receptor)
  - GI side effects (less than sertraline)

Escitalopram (Lexapro)

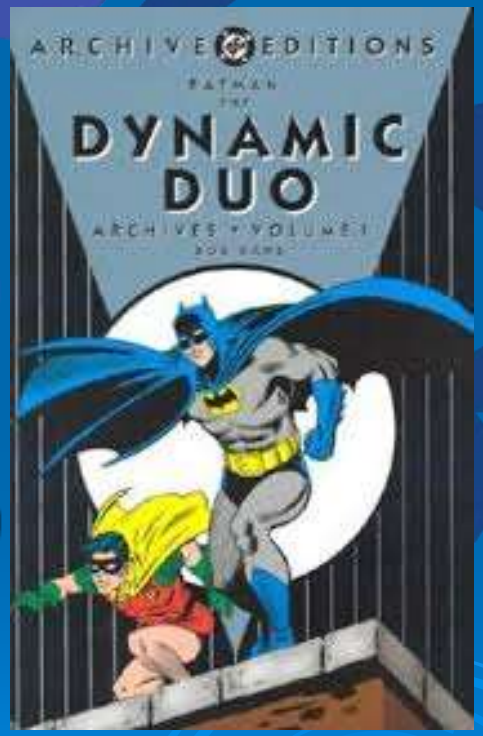
- Pros
  - Low overall inhibition of P450s enzymes so fewer drug-drug interactions
  - Intermediate 1/2 life
  - More effective than Citalopram in acute response and remission
- Cons
  - Dose-dependent QT interval prolongation with doses of 10-30mg daily
  - Nausea, headache

Fluvoxamine (Luvox)

- Pros
  - Shortest ½ life
  - Found to possess some analgesic properties
- Cons
  - Shortest ½ life
  - GI distress, headaches, sedation, weakness
  - Strong inhibitor of CYP1A2 and CYP2C19

Serotonin/Norepinephrine reuptake inhibitors (SNRIs)

- Inhibit both serotonin and noradrenergic reuptake like the TCAS but without the antihistamine, antiadrenergic or anticholinergic side effects
- Used for depression, anxiety and possibly neuropathic pain



Venlafaxine (Effexor)

- Pros
  - Minimal drug interactions and almost no P450 activity
  - Short half life and fast renal clearance avoids build-up (good for geriatric populations)
- Cons
  - Can cause a 10-15 mmHG dose dependent increase in diastolic BP.
  - May cause significant nausea, primarily with immediate-release (IR) tabs
  - Can cause a bad discontinuation syndrome, and taper recommended after 2 weeks of administration
  - Noted to cause QT prolongation
  - Sexual side effects in >30%

Desvenlafaxine (Pristiq)

- Pros
  - Minimal drug interactions
  - Short half life and fast renal clearance avoids build-up (good for geriatric populations)
- Cons
  - GI distress in 20%+
  - Dose related increase in total cholesterol, LDL and triglycerides
  - Dose related increase in BP

Duloxetine (Cymbalta)

- Pros
  - Some data to suggest efficacy for the physical symptoms of depression
  - Thus far less BP increase as compared to venlafaxine, however this may change in time
- Cons
  - CYP2D6 and CYP1A2 inhibitor
  - Cannot break capsule, as active ingredient not stable within the stomach
  - In pooled analysis had higher drop out rate

Novel antidepressants Mirtazapine (Remeron)

- Pros
  - Different mechanism of action may provide a good augmentation strategy to SSRIs. Is a 5HT2 and 5HT3 receptor antagonist
  - Can be utilized as a hypnotic at lower doses secondary to antihistaminic effects
- Cons
  - Increases serum cholesterol by 20% in 15% of patients and triglycerides in 6% of patients
  - Very sedating at lower doses. At doses 30mg and above it can become activating and require change of administration time to the morning.
  - Associated with weight gain (particularly at doses below 45mg

Buproprion (Wellbutrin)

- Pros
  - Good for use as an augmenting agent
  - Mechanism of action likely reuptake inhibition of dopamine and norepinephrine
  - No weight gain, sexual side effects, sedation or cardiac interactions
  - Low induction of mania
  - Is a second line ADHD agent so consider if patient has a co-occurring diagnosis
- Cons
  - May increase seizure risk at high doses (450mg+) and should avoid in patients with Traumatic Brain Injury, bulimia and anorexia.
  - Does not treat anxiety unlike many other antidepressants and can actually cause anxiety, agitation and insomnia
  - Has abuse potential because can induce psychotic sx at high doses

Case 1

- Mrs S. has a nonpsychotic unipolar depression with no history of hypomania or mania. She has depressed mood, hyperphagia, psychomotor retardation and hypersomnolence. What agent would you like to use for her?
- Establish dx: Major depressive disorder
- Target symptoms: depression, hyperphagia, psychomotor retardation and hypersomnolence

- For a treatment naive patient start with an SSRI.
- Using the side effect profile as a guide select an SSRI that is less sedating. Good choices would be Citalopram, Fluoxetine or Sertraline.
- Buproprion would also have been a reasonable choice given her hypersomnolence, psychomotor retardation and hyperphagia.

- Less desirable choices include Paxil and Mirtazapine because of sedation and wt gain.
- Not a duel reuptake inhibitors because she is treatment naïve and may not need a "big gun".
- Not a TCA because of side effects

Case 2

- Mr. B. is a 55 year old diabetic man with mild HTN and painful diabetic neuropathy who has had previous depressive episodes and one suicide attempt. He meets criteria currently for a major depressive episode with some anxiety.
- He has been treated with paroxetine, setraline and buproprion.
- His depression was improved slightly with each of these meds but never remitted. What would you like to treat him with?

Case 2 continued

- Establish dx: Major depressive disorder with anxious features
- Target symptoms: depressive sx, anxiety and possibly his neuropathic pain
- Assuming he received adequate trials previously would move on to a duel reuptake inhibitor as he had not achieved remission with two SSRIS or a novel agent.

Case 2 continued

- Given his mild HTN would not choose Venlafaxine. TCA's can help with neuropathic pain and depression however not a good choice given the SE profile and lethality in overdose. Duloxetine is a good choice since it has an indication for neuropathic pain, depression and anxiety. Three birds with one stone!!
- Keep in mind Duloxetine is a CYP2D6 and CPY1A2 inhibitor and has potential drug-drug interactions.

Mood Stabilizers

Mood stabilizers

- Indications: Bipolar, cyclothymia, schizoaffective, impulse control and intermittent explosive disorders, Migraine.
- Classes: Lithium, anticonvulsants, antipsychotics
- Which you select depends on what you are treating and again the side effect profile.

Lithium

- Only medication to reduce suicide rate.
  - Rate of completed suicide in BAD ~15%
- Effective in long-term prophylaxis of both mania and depressive episodes in 70+% of BAD I pts
- Factors predicting positive response to lithium
  - Prior long-term response or family member with good response
  - Classic pure mania
  - Mania is followed by depression

Lithium- how to use it

- Before starting :Get baseline creatinine, TSH and CBC.
- In women check a pregnancy test- during the first trimester is associated with Ebstein's anomaly 1/1000 (20X greater risk than the general population)
- Monitoring: Steady state achieved after 5 days- check 12 hours after last dose. Once stable check q 3 months and TSH and creatinine q 6 months.
- Goal: blood level between 0.6-1.2

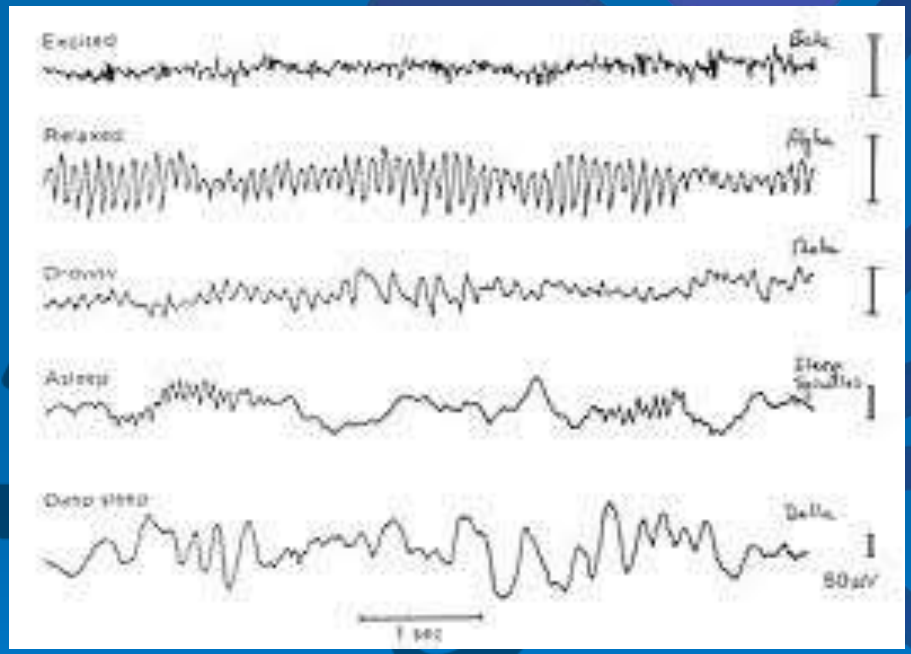
Lithium side effects

- Most common are GI distress including reduced appetite, nausea/vomiting, diarrhea
- Thyroid abnormalities
- Nonsignificant leukocytosis
- Polyuria/polydypsia secondary to ADH antagonism. In a small number of patients can cause interstitial renal fibrosis.
- Hair loss, acne
- Reduces seizure threshold, cognitive slowing, intention tremor

Lithium toxicity

- Mild- levels 1.5-2.0 see vomiting, diarrhea, ataxia, dizziness, slurred speech, nystagmus.
- Moderate-2.0-2.5 nausea, vomiting, anorexia, blurred vision, clonic limb movements, convulsions, delirium, syncope
- Severe- >2.5 generalized convulsions, oligouria and renal failure

Anticonvulsants



Valproic acid (Depakote)

- Valproic acid is as effective as Lithium in mania prophylaxis but is not as effective in depression prophylaxis.
- Factors predicting a positive response:
  - rapid cycling patients (females>males)
  - comorbid substance issues
  - mixed patients
  - Patients with comorbid anxiety disorders
- Better tolerated than Lithium

Valproic acid

- Before med is started: baseline liver function tests (lfts), pregnancy test and CBC
- Start folic acid supplement in women
- Monitoring: Steady state achieved after 4-5 days -check 12 hours after last dose and repeat CBC and lfts
- Goal: target level is between 50-125

Valproic acid side effects

- Thrombocytopenia and platelet dysfunction
- Nausea, vomiting, weight gain
- Transaminitis
- Sedation, tremor
- Increased risk of neural tube defect 1-2% vs 0.14-0.2% in general population secondary to reduction in folic acid
- Hair loss

Carbamazepine (Tegretol)

- First line agent for acute mania and mania prophylaxis
- Indicated for rapid cyclers and mixed patients

- Before med is started: baseline liver function tests, CBC and an EKG
- Monitoring: Steady state achieved after 5 days -check 12 hours after last dose and repeat CBC and lfts
- Goal: Target levels 4-12mcg/ml
- Need to check level and adjust dosing after around a month because induces own metabolism.

Carbamazepine side effects

- Rash- most common SE seen
- Nausea, vomiting, diarrhea, transaminitis
- Sedation, dizziness, ataxia, confusion
- AV conduction delays
- Aplastic anemia and agranulocytosis (<0.002%)
- Water retention due to vasopressin-like effect which can result in hyponatremia
- Drug-drug interactions!

Lamotrigine (Lamictal)

- Indications similar to other anticonvulsants
- Also used for neuropathic/chronic pain
- Before med is started: baseline liver function tests
- Initiation/titration: start with 25 mg daily X 2 weeks then increase to 50mg X 2 weeks then increase to 100mg- faster titration has a higher incidence of serious rash
- If the patient stops the med for 5 days or more have to start at 25mg again!

Lamotrigine: Side effects

- Nausea/vomiting
- Sedation, dizziness, ataxia and confusion
- The most severe are toxic epidermal necrolysis and Stevens Johnson's Syndrome. The character/severity of the rash is not a good predictor of severity of reaction. Therefore, if **ANY** rash develops, discontinue use immediately.
- Blood dyscrasias have been seen in rare cases.
- Drugs that increase lamotrigine levels: **VPA (doubles concentration, so use slower dose titration)**, sertraline.

Antipsychotics as mood stabilizers

FDA approved indications in Bipolar disorder

Generic name	Trade name	Manic	Mixed	Maintenance	Depressed
Aripiprazole	Abilify	X	X	X	
Ziprasidone	Geodon	X	X	X*	
Risperdone	Risperdal	X	X		
Asenapine	Saphris	X	X		
Quetiapine	Seroquel	X		X*	
Quetiapine XR	Seroquel XR	X		X*	X
Chlorpromazine	Thorazine	X			
Olanzapine	Zyprexa	X	X	X	
Olanzapine fluoxetine comb	Symbyax				X

*denotes FDA approval for adjunct therapy not mono-therapy

Case 3

- 33 yo woman hospitalized with her first episode of mania. She has no previous history of a depressive episode. She has no drug or ETOH history and has no medical issues. What medication would you like to start?

- Given her first presentation was a manic episode statistically she will do better on lithium.
- Make sure to check a pregnancy test, serum creatinine and TSH prior to initiation of treatment.
- Discuss with her what she will use for birth control and document this discussion.

- You start her at 300mg BID (average starting dose) and when she comes to see you in one week she is complaining about stomach irritation and some diarrhea. What do you think is going on and what should you do?

- GI irritation including diarrhea is common particularly early in treatment. Encourage pt to drink adequate fluid, leave at current dose and see if side effects resolve.

Case 4

- 27 y male is admitted secondary to a manic episode. In reviewing his history you find he has 5 to 6 manic or depressive episodes a year. He has also struggled on and off with ETOH abuse. What medication would you like to start?

- Depakote would be a good choice because pt is a rapid cycler (4 or more depressive or manic episodes/year) and because of comorbid ETOH abuse.
- You start 250mg BID and titrate to 500mg BID. His depakote level is 70. You check his lfts and compared to baseline they have increased as follows:

- ALT 48 →115
- AST 62→140
- ALK PHOS 32→80

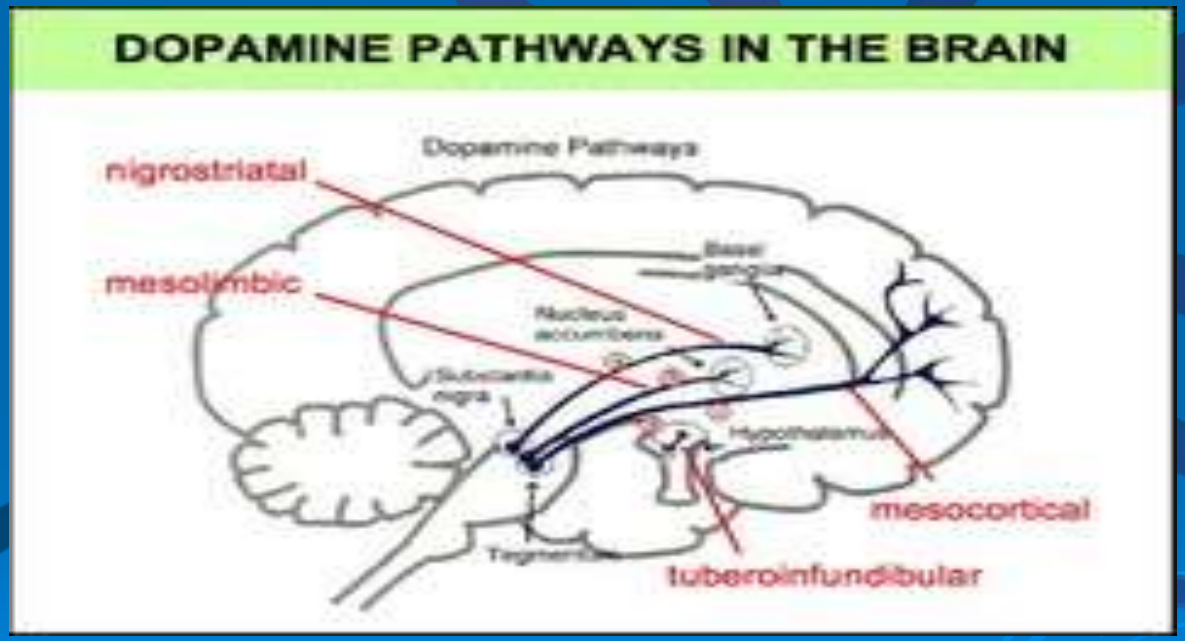
- What happened and what do you want to do??

- It is not unusual for patients on anticonvulsants to experience an increase in lfts and as long as they do not more than triple no change in therapy is indicated.
- Continue to monitor over time

Antipsychotics

- Indications for use: schizophrenia, schizoaffective disorder, bipolar disorder- for mood stabilization and/or when psychotic features are present, delirium, psychotic depression, dementia, trichotillomania, augmenting agent in treatment resistant anxiety disorders.

Key pathways affected by dopamine in the Brain



- **MESOCORTICAL**- projects from the ventral tegmentum (brain stem) to the cerebral cortex. This pathway is felt to be where the negative symptoms and cognitive disorders (lack of executive function) arise. Problem here for a psychotic patient, is **too little** dopamine.

- **MESOLIMBIC**-projects from the dopaminergic cell bodies in the ventral tegmentum to the limbic system. This pathway is where the positive symptoms come from (hallucinations, delusions, and thought disorders). Problem here in a psychotic patient is there is **too much** dopamine.

- **NIGROSTRIATAL**- projects from the dopaminergic cell bodies in the substantia nigra to the basal ganglia. This pathway is involved in movement regulation. Remember that dopamine suppresses acetylcholine activity. **Dopamine hypoactivity** can cause Parkinsonian movements i.e. rigidity, bradykinesia, tremors), akathisia and dystonia.

- **TUBEROINFUNDIBULAR**-projects from the hypothalamus to the anterior pituitary. Remember that dopamine release inhibits/regulates prolactin release. Blocking dopamine in this pathway will predispose your patient to hyperprolactinemia (gynecomastia/galactorrhea/decreased libido/menstrual dysfunction).

Antipsychotics: Typicals

- Are D2 dopamine receptor antagonists
- High potency typical antipsychotics bind to the D2 receptor with high affinity.
- As a result they have higher risk of extrapyramidal side effects.

- Examples include Fluphenazine, Haloperidol, Pimozide.

- Low potency typical antipsychotics have less affinity for the D2 receptors but tend to interact with nondopaminergic receptors resulting in more cardiotoxic and anticholinergic adverse effects including sedation, hypotension.
- Examples include chlorpromazine and Thioridazine.

Antipsychotics: Atypicals

- **The Atypical Antipsychotics -** atypical agents are serotonin-dopamine 2 antagonists (SDAs)
- They are considered atypical in the way they affect dopamine **and** serotonin neurotransmission in the four key dopamine pathways in the brain.

Risperidone (Risperdal)

- Available in regular tabs, IM depot forms and rapidly dissolving tablet
- Functions more like a typical antipsychotic at doses greater than 6mg
- Increased extrapyramidal side effects (dose dependent)
- Most likely atypical to induce hyperprolactinemia
- Weight gain and sedation (dosage dependent)

Olanzapine (Zyprexa)

- Available in regular tabs, immediate release IM, rapidly dissolving tab, depo form
- Weight gain (can be as much as 30-50lbs with even short term use)
- May cause hypertriglyceridemia, hypercholesterolemia, hyperglycemia (even without weight gain)
- May cause hyperprolactinemia (< risperidone)
- May cause transaminitis (2% of all patients)

Quetiapine (Seroquel)

- Available in a regular tablet form only
- May cause transaminitis (6% of all patients)
- May be associated with weight gain, though less than seen with olanzapine
- May cause hypertriglyceridemia, hypercholesterolemia, hyperglycemia (even without weight gain), however less than olanzapine
- Most likely to cause orthostatic hypotension

Ziprasidone (Geodon)

- Available regular tabs and IM immediate release form
- Clinically significant QT prolongation in susceptible patients
- May cause hyperprolactinemia (< risperidone)
- No associated weight gain
- Absorption is increased (up to 100%) with food

Aripiprazole (Abilify)

- Available in regular tabs, immediate release IM formulation and depo form
- Unique mechanism of action as a D2 partial agonist
- Low EPS, no QT prolongation, low sedation
- CYP2D6 (fluoxetine and paroxetine), 3A4 (carbamazepine and ketoconazole) interactions that the manufacturer recommends adjusted dosing. Could cause potential intolerability due to akathisia/activation.
- Not associated with weight gain

Clozapine (Clozaril)

- Available in 1 form- a regular tablet
- Is reserved for treatment resistant patients because of side effect profile but this stuff works!
- Associated with agranulocytosis (0.5-2%) and therefore requires weekly blood draws x 6 months, then Q-2weeks x 6 months)
- Increased risk of seizures (especially if lithium is also on board)
- Associated with the most sedation, weight gain and transaminitis
- Increased risk of hypertriglyceridemia, hypercholesterolemia, hyperglycemia, including nonketotic hyperosmolar coma and death with and/or without weight gain

Iloperidone (Fanapt)

- Comes in regular tabs
- Needs BID dosing
- **Titrate over 4 days** to 12mg/day in order to minimize risk of orthostatic hypotension
- Low EPS, akathisia, wt gain and metabolic disturbances
- **Inhibitors of 3A4** (ketoconazole) **or 2D6** (fluoxetine, paroxetine)-Can increase blood levels two-fold!
- QT Prolongation- mean increase of 19msec at 12mg BID
- Not recommended for patients with hepatic impairment

Citrome L, Postgraduate Medicine 2011

Asenapine (Saphris)

- Sublingual (no food or liquid for 10 min)
- BID dosing required
- Can start at therapeutic dose
- Low wt gain and metabolic disturbances
- Sedation, somnolence, akathisia
- Not recommended for patients with severe hepatic impairment
- Be careful with co-administration of (**CYP1A2 inhibitor**)

Lurasidone (latuda)

- Can dose once daily and start at therapeutic dose
- No QT prolongation warning
- Less treatment emergent weight gain and metabolic disturbances
- Must administer with food (>350kcals)
- Is associated with akathisia, sedation
- Dose should not exceed 40mg day in patients with moderate to severe renal or hepatic impairment
- Contraindicated co-administration with CYP 3A4 inhibitors and inducers

New Meta-Analyses Demonstrate the Heterogeneity for Antipsychotic Response

"All antipsychotics are equal, but some are more equal than others"

- Volavka J, Citrome L. J Clin Psychiatry 2009;70:429-430.

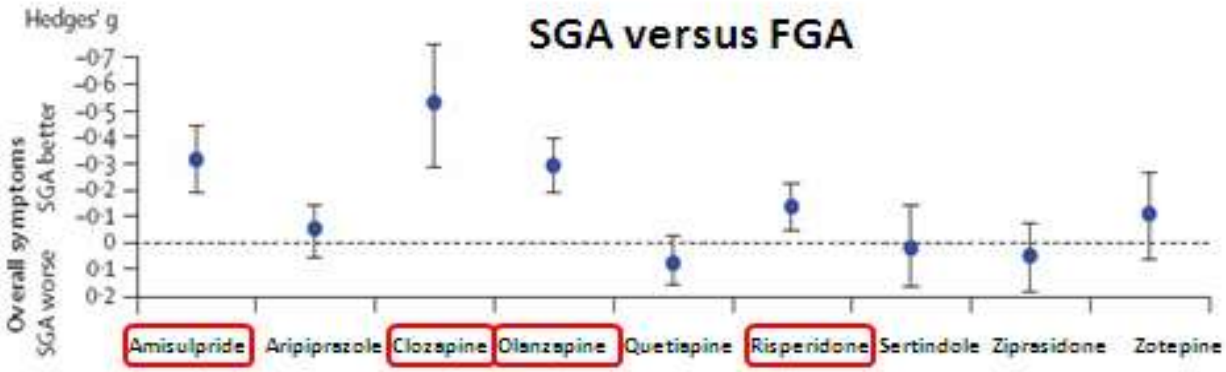


Figure 2: Second-generation versus first-generation antipsychotic drugs—efficacy in various domains
Data are Hedges' g (95% CI). Note that the results are significant at p<0·05 if the 95% CIs do not overlap the x axis. SGA=second-generation antipsychotic drug.

Leucht S, et al. *Lancet* 2009; 373(9657):31-41.

Leucht S, et al. *Lancet* 2009; 373(9657):31-41. Slide courtesy of Dick Miyoshi

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TABLE 1. Summary of Results of Comparisons of Primary Outcome Measure in Meta-Analysis of Second-Generation Antipsychotics[a]

	Amisulpride	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Sertindole	Ziprasidone	Zotepine
Aripiprazole									
Clozapine									
Olanzapine	↔(N=701)	Olanzapine ↑ (N=794)	↔ (N=619)						
Quetiapine			↔ (N=232)	Olanzapine ↑ (N=1,449)					
Risperidone	↔ (N=291)	↔ (N=372)	↔ (N=466)	Olanzapine ↑ (N=2,404)	Risperidone ↑ (N=1,953)				
Sertindole						↔ (N=491)			
Ziprasidone	↔(N=122)		↔ (N=146)	Olanzapine ↑ (N=1,291)	↔ (N=710)	Risperidone ↑ (N=1,016)			
Zotepine			Clozapine ↑ (N=59)						

SGA versus SGA

Advantages for:

Clozapine
Olanzapine
Risperidone

[a] The primary outcome measure was change in total score on the Positive and Negative Syndrome Scale. Blank cells indicate that no study is available. Ns refer to the total number of patients in the comparison. ↑=statistically significantly superior; ↔=no significant difference between groups.

Leucht S, et al. *Am J Psychiatry* 2009; 166(2): 152-63.

Leucht S, et al. *Lancet* 2009; 373(9657):31-41. Slide courtesy of Dick Miyoshi

Antipsychotic adverse effects

- Tardive Dyskinesia (TD)-involuntary muscle movements that may not resolve with drug discontinuation- risk approx. 5% per year
- Neuroleptic Malignant Syndrome (NMS): Characterized by severe muscle rigidity, fever, altered mental status, autonomic instability, elevated WBC, CPK and lfts. Potentially fatal.
- Extrapyramidal side effects (EPS): Acute dystonia, Parkinson syndrome, Akathisia

Agents for EPS

- Anticholinergics such as benztropine, trihexyphenidyl, diphenhydramine
- Dopamine facilitators such as Amantadine
- Beta-blockers such as propranolol
- Need to watch for anticholinergic SE particularly if taken with other meds with anticholinergic activity ie TCAs

Case

- 21 yo AA male with symptoms consistent with schizophrenia is admitted because of profound psychotic sx. He is treatment naïve. You plan to start an antipsychotic- what baseline blood work would you obtain?

- Many atypical antipsychotics can cause dyslipidemia, transaminitis and elevated blood sugars and there is a class risk of diabetes unrelated to weight gain so you need the following:
- Fasting lipid profile
- Fasting blood sugar
- Lfts
- CBC

- His labs come back as follows:
- Total Cholesterol:215 HDL:30 LDL:145
- Glucose 88
- Lfts, CBC WNL

- What agent would you like to start?

- Pt has mildly elevated total cholesterol and a low HDL for his age. Would not choose Olanzapine or Quetiapine given risk of dyslipidemia. Risperidone, Ziprasidone or Aripiprazole are good choices.
- You start Risperidone and titrate to 3mg BID (high average dose). He starts to complain that he “feels uncomfortable in my skin like I can’t sit still”. What is likely going on and what are you going to do about it?

- He is likely experiencing akathisia. This is not uncommon with Risperidone. Given he was very ill reducing the dose may not be the best choice so likely treat with an anticholinergic agent or propranolol. You need to treat akathisia because it is associated with an increase risk for suicide!

Anxiolytics

- Used to treat many diagnoses including panic disorder, generalized Anxiety disorder, substance-related disorders and their withdrawal, insomnias and parasomnias.
- In anxiety disorders often use anxiolytics in combination with SSRIS or SNRIs for treatment.

Buspirone (Buspar)

- Pros:
  - Good augmentation strategy- Mechanism of action is 5HT1A agonist. It works independent of endogenous release of serotonin.
  - No sedation
- Cons:
  - Takes around 2 weeks before patients notice results.
  - Will not reduce anxiety in patients that are used to taking BZDs because there is no sedation effect to "take the edge off.

Benzodiazapines

- Used to treat insomnia, parasomnias and anxiety disorders.
- Often used for CNS depressant withdrawal protocols ex. ETOH withdrawal.
- Side effects/cons
  - Somnolence
  - Cognitive deficits
  - Amnesia
  - Disinhibition
  - Tolerance
  - **Dependence**

Drug	Dose Equivalency (mg)	Peak Blood Level (hours)	Elimination Half-Life[1] (hours)	Comments
Alprazolam (Xanax)	0.5	1-2	12-15	Rapid oral absorption
Chlordiazepoxide (Librium)	10.0	2-4	15-40	Active metabolites; erratic bioavailability from IM injection
Clonazepam (Klonopin)	0.25	1-4	18-50	Can have layering effect
Diazepam (Valium)	5.0	1-2	20-80	Active metabolites; erratic bioavailability from IM injection
Flurazepam (Dalmane)	30.0	1-2	40-100	Active metabolites with long half-lives
Lorazepam (Ativan)	1.0	1-6	10-20	No active metabolites
Oxazepam (Serax)	15.0	2-4	10-20	No active metabolites
Temazepam (Restoril)	30.0	2-3	10-40	Slow oral absorption
Triazolam (Halcion)	0.25	1	2-3	Rapid onset; short duration of action

- Please refer to the Mood Disorder, Psychosis, Anxiety Disorder and Substance-Related Disorder lectures for further discussions of medications for specific psychiatric diagnoses
- Also the web-based cases have pharmacologic discussions that may be helpful

Take home points

- Be clear on the diagnosis you are treating
- Any comorbid diagnoses when you are selecting an agent to treat- often can get 2 birds with 1 stone!
- Select the agent based on patients history, current symptom profile and the side effect profile of the medication- there is no one correct answer in most cases.

- Monitor for efficacy and tolerance and adjust as indicated.
- Relativity of response
- If the patient does not improve step back, rethink your diagnosis and treatment plan!
- Keep an eye on drug-drug interactions

مرکز طب پیشگیری و ارتقاء سلامت

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