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Antipsychotic Medications: First Generation Antipsychotics (FGA's)

First Generation Antipsychotics (FGA's)

- Also called neuroleptics, conventional, or typical antipsychotics
- As a class, used for treating: psychotic disorders, acute agitation, bipolar mania, and other psychiatric conditions
- Significant potential to cause extrapyramidal side effects (EPS) and tardive dyskinesia (TD). This propensity to cause movements is the principle difference between FGA's and SGA's (second generation antipsychotics)

Mechanism of Action

- Appears to be post synaptic blockade of brain D2 receptors. Evidence that support this includes:
    - Strong antagonism of D2 receptors in both cortical and striatal areas
    - High correlation between D2 receptor binding and clinical potency
    - Consistent requirement of 65% D2 receptor occupancy for antipsychotic efficacy in functional imaging studies

High potency FGA's

- Are dosed in the range of 1 to 10's of milligrams
- Have **low activity at histamine and muscarinic receptors**; are associated with little sedation, weight gain, or anticholinergic activity, but have a **high risk for extrapyramidal side effects**

Low potency FGA's

- Are dosed in the 100's of milligrams
- Have **high histaminic and muscarinic activity** with a corresponding increased prevalence of sedation and anticholinergic effects, but have a lower risk of extrapyramidal side effects.

Metabolic Activation and Clearance

- All FGA's are subject of extensive metabolism via the **cytochrome P450 system**. This dependence on **hepatic clearance** make the drugs susceptible to liver impairment and drug-drug interactions

Side Effects

- Choice of an antipsychotic is often influenced by its side effect profile and its match with the patient's clinical status and vulnerabilities

- Extrapyramidal side effects
    - The defining **difference between FGA's and the newer SGA's is their higher incidence of the akathisia, rigidity, bradykinesia, tremor, and acute dystonic reactions that constitute extrapyramidal symptoms.** As dopamine D2 antagonists, these drugs have the potential to interfere with dopamine transmission via the nigrostriatal tract, which is involved in control of muscle movement, thereby producing symptoms similar to those seen in Parkinson's disease
    - Among the FGA's the high potency drugs, haloperidol (Haldol) are usually associated with the highest risk of extrapyramidal symptoms. Low potency medications, chlorpromazine (Thorazine), are less likely to cause extrapyramidal symptoms than are the high potency drugs
- Tardive Dyskinesia
    - Characterized by involuntary choreoathetoid movements of the mouth, tongue, face, extremities, or trunk, including lip smacking, tongue writhing or thrusting, jaw movements, facial grimaces, and trunk or extremity writhing. TD increases with age, time of exposure to the medications, and prior development of extrapyramidal symptoms
    - TD has been reported with all FGA's at a cumulative rate of 5% per year, with higher risk in the older population. The FGA's are considerably more likely to cause TD at all ages than the SGA's, a major reasons the newer drugs have largely supplanted them for maintenance use

- Metabolic syndrome
    - Although no FGA is entirely risk free of weight gain and metabolic effects, chlorpromazine (Thorazine) appears to carry relatively high risk whereas haloperidol (Haldol) shows the lowest risk. The potential morbidity of all FGA's to cause metabolic syndrome has led to recommendations for routine monitoring of weight, waist circumference, blood pressure, fasting glucose, and lipid profiles.

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- Anticholinergic effects
  - Low potency FGA's commonly result in dry mouth or constipation; less often in blurred vision or urinary retention. Tend to be mild or absent with high potency FGA's.

- Cardiovascular events
  - FGA antipsychotic medications are associated with an **increased risk of stroke, myocardial infarction, and death when used to treat behavioral symptoms in older adults with dementia**. The mechanism for this effect has not been firmly established.

- Neuroleptic Malignant Syndrome (NMS)
  - **Features of NMS are fever, muscle rigidity, mental status changes (confusion), and autonomic instability, generally accompanied by rhabdomyolysis and creatine kinase elevation.** NMS is rare but potentially **fatal and constitutes a medical emergency**. The physiological mechanism is unknown.
    - Single strongest predictor of NMS is a prior episode of NMS.
    - Other factors cited include recently initiated treatment, aggressive dosing, parenteral administration, acute medical illness, and dehydration.

- Prolactin elevation
  - All FGAs have been shown to increase prolactin, apparently through blockade of tuberoinfundibular dopamine receptors which results in uninhibited secretion of pituitary prolactin.
  - Both men and women typically have prolactin levels 2-3 times higher than normal
  - May lead to menstrual irregularities, infertility, galactorrhea, loss of libido, erectile and ejaculatory dysfunction

- Sexual dysfunction
  - Even in the absence of prolactin elevation, all FGAs have been associated with impaired sexual dysfunction

- Sedation
  - Low potency FGA's like chlorpromazine (Thorazine) have high levels of histaminic H1 receptor antagonism and is highly sedating

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Antipsychotic Medications: Second Generation Antipsychotics (SGA's)

Second Generation Antipsychotics (SGA's)

- Also called atypical antipsychotics, generally have **a lower risk of extrapyramidal side effects and tardive dyskinesia compared with first generation antipsychotics (FGA's)**
- FGA's and SGA's are more comparable in their clinical efficacy with the exception of clozapine (Clozaril) which is an SGA with unique efficacy in treatment resistant schizophrenia

Mechanism of Action

- As with FGA's, the mechanism of action of most SGA's appears to be post-synaptic blockade of brain dopamine D2 receptors. Notable exceptions:
    - Aripiprazole (Abilify) and brexpiprazole (Rexulti) are D2 receptor partial agonists
- Most SGA's differ from FGA's in that they have greater binding affinity for 5HT2 receptors than for D2 receptors.
    - 5HT2 activity has been suggested as a possible explanation for lower overall risk of extrapyramidal side effects for SGA's vs FGA's.
    - Other possible explanations for the lower overall risk of EPS from SGA use are:
        - *"loose" D2 receptor binding with rapid dissociation rates for SGA's*
        - *preferential binding of drugs to receptors in limbic and cortical brain regions rather than striatal areas*
    - *None of these hypotheses have been fully confirmed.*
- Additional receptor activities include blockade or partial agonist activity **at muscarinic, alpha-adrenergic, and histaminic receptors** with resultant anticholinergic, hypotensive, sedative, and metabolic effects.

Metabolic activation & clearance

- Most antipsychotic drugs are metabolized primarily by the **cytochrome P450 system**
    - an **exception is paliperidone (Invega) which is excreted unchanged by the kidneys;** as a result paliperidone is the only medication of this class for which no dose adjustment is recommended in patients with impaired liver function; the dose must be reduced with mild to moderate renal dysfunction and is not recommended with severe renal impairment

Drug-drug interactions with Dopamine system receptors

- Aripiprazole (Abilify)-dopamine D2 blockade may be unpredictable when the partial agonist aripiprazole is given simultaneously with other antipsychotics (all of which are dopamine antagonists) as might occur during a transition between medications. This can lead in some cases to a paradoxical reduction in dopamine blockade and reduced antipsychotic effect as the dose of aripiprazole is increased
- Brexpiprazole (Rexulti)-as with aripiprazole, the combination of this dopamine partial agonist with a dopamine antagonist can lead to unpredictable levels of dopamine D2 receptor blockade and a paradoxical reduction in efficacy when the drug is combined with a dopamine antagonist

Side Effects

- Common side effects with **second generation antipsychotics (SGA's) include weight gain and related metabolic effects, hypotension, sedation, anticholinergic symptoms, hyperprolactinemia, extrapyramidal symptoms (EPS), cardiac effects, and sexual dysfunction**. The rate and severity of these side effects vary across SGA's and these differences in side effect profiles often influence the selection among antipsychotic drugs

- Metabolic syndrome-weight gain, diabetes, and dyslipidemia are components of metabolic syndrome usually associated with SGA's. Mechanism is not entirely clear but there is evidence for both increased appetite and altered metabolic control with these drugs.
    - Highest risk SGA's: clozapine (Clozaril) and olanzapine (Zyprexa)
    - Moderate risk: All not listed in the line above or below
    - **Lowest risk SGA's: aripiprazole (Abilfy), lurasidone (Latuda), and ziprasidone (Geodon)**
    - Potential risk of all SGA's has led to **recommendation for routine short and long term monitoring of weight, waist circumference, blood pressure, fasting glucose, and lipid profiles for patients who take these drugs**

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- Anticholinergic effects
  - Mostly reported as dry mouth or constipation and less often as blurred vision or urinary retention
  - Clozapine (Clozaril) has the strongest affinity for muscarinic receptors among the SGAs and muscarinic side effects are most frequent and severe with this drug. For patients on clozapine, regular inquiries regarding urinary retention, blurred vision, and especially constipation should be made.

- Cardiovascular events
  - QTc interval prolongation
    - Ziprasidone (Geodon) have the greatest risk among SGA's of QT prolongation.
    - All other SGA's have low/mild risk with standard dosing usage
    - **Lurasidone (Latuda), Aripiprazole (Abilfy) and other partial dopamine agonist SGA's have the lowest risk of QTc prolongation**
    - An EKG is not routinely required in patients without cardiac risk factors but is recommended in patients with known cardiac risk factors

- Extrapyramidal side effects (EPS) & Tardive dyskinesia (TD)
  - Among SGA's, risperidone (Risperdal) carries the highest risk of EPS (8-25%) especially at doses greater than 4 mg per day
  - Quetiapine (Seroquel) and clozapine (Clozaril) are the preferred agents in patients at high risk for EPS including those with pre-existing movement disorders from other causes
  - There is evidence that with regards to various SGA's, the risk of tardive dyskinesia (TD) may be similar to the risk of EPS (see above)

- Neuroleptic Malignant Syndrome
  - See information in FGA section
  - No difference has been demonstrated in risk of NMS among the SGA's

- Prolactin elevation
  - For both men and women, controlled via the inhibitory effect of tuberoinfundibular dopamine on the pituitary. Direct blockade of pituitary dopamine receptors allows uninhibited prolactin
  - Clinical consequences include gynecomastia, menstrual disturbances, sexual dysfunction, and infertility
  - Risperidone (Risperdal) and paliperidone (Invega) are most strongly associated with elevated prolactin

- Sexual Side Effects
  - Several mechanisms are likely to contribute to sexual problems including through:
    - inhibition of dopaminergic motivation and reward pathways,
    - alpha adrenergic blockade and anticholinergic activity
    - prolactin elevation
  - Paliperidone (Invega) and risperidone (Risperdal) has the highest rates of sexual side effects, followed by Quetiapine (Seroquel)
  - **Aripiprazole (Abilify) has the lowest rate of sexual side effects**

- Sedation
  - All SGA's are histaminic H1 receptor antagonists and have the potential to cause drowsiness. The effect is most severe early in treatment and tolerance usually develops within a few days.
  - Most prominent with clozapine (Clozaril) and quetiapine (Seroquel) occurring in up to 50% of patients.
  - Least seen, < 10% of patients, in aripiprazole (Abilify), paliperidone (Invega), and risperidone (Risperdal).

- Agranulocytosis
  - Most common in the first few months of treatment with clozapine (Clozaril). About 3% will show evidence of leukocytosis and about 1% will develop agranulocytosis.
  - Lower rates of leukocytosis are found with other SGA's. Agranulocytosis with other SGA's has been reported but is rare.
    - For patients taking SGA's who have previously experienced drug induced leukocytopenia or have a pre-existing low WBC count or a low ANC, monitoring is recommended during the first few months of treatment.