Antipsychotic Drugs

Blanton Lecture script

SLIDE 1:

Introduction:

Good Day! Let me start by introducing myself, Michael Blanton, I am a Professor in the Department of Pharmacology and Neuroscience

Our focus today is on antipsychotic drugs, also known as neuroleptics or major tranquilizers. This class of drugs is primarily used to manage psychosis, principally in schizophrenia and bipolar disorder.

Note: *My lecture script is available on sakai*

SLIDE 2:

Learning Objectives:

Dr. Nelson covered the clinical presentation of psychosis and schizophrenia- my focus will be primarily on the pharmacology.

1. Discuss role of dopamine and serotonin in the pathophysiology of psychotic disorders.
2. Describe some of the consequences of dopamine blockade, *here we will talk about Extrapyramidal Symptoms and Neuroleptic Malignant Syndrome .*
3. List drugs used in the treatment of psychotic disorders, grouped as "typical" (high vs low Potency) and "atypical"
4. Discuss the mechanism of action, selection and adverse effects of each of the antipsychotic drugs.
5. Compare and contrast differences in typical and atypical antipsychotic drugs.
6. Describe the "mood-stabilizing" effects of lithium, its low therapeutic index and associated adverse effects and the now commonly used mood-stabilizers, valproic acid and carbamazepine.

Suggested background reading: Chapter 16, Pharmacotherapy of Psychosis. Goodman and Gilman's The Pharmacological Basis of Therapeutics 12th Edition (Brunton, Chabner, Knollman); Chapter 29, Antipsychotic Agents and Lithium. Basic and Clinical Pharmacology 13th Edition (Lange).

SLIDE 3:

Psychotic Disorders:

Long time theory rests on dopamine driven pathology.

- It is now clear that multiple receptor/neurotransmitter systems are involved, including both dopamine and serotonergic mechanisms, and likely glutamate receptors are also involved.

  *A simplistic view is that increased dopamine/ serotonin results in psychosis; decreased dopamine/ serotonin results in depressio*n

  DSM-V:

- Positive symptoms- delusions, hallucinations, disorganized speech/ thought, catatonic behavior, bizarre behaviors
- Negative symptoms- (neurovegetative)- flat affect, poor eye contact and lack of goal-directed activity.

- Most patients exhibit both types of symptoms

SLIDE 4:

Antipsychotic Drugs:

Other names: neuroleptics, antischizophrenia drugs, antipsychotic, and major tranquilizers)-

Used to treat schizophrenia and other psychotic states

Side note: Electroconvulsive Therapy (ECT) is a very effective treatment for schizophrenia and other psychotic disorders, but is very expensive and generally reserved for patients that don't respond well to antipsychotic drug treatment.

MOA : older neuroleptic drugs "Typical Antipsychotics" are competitive blockers of dopamine receptors (D2)
MOA : newer agents "Atypical Antipsychotics" are blockers of serotonin receptors (5HT2A) and to a lesser extent dopamine receptors (D2)

-The antipsychotic drugs also relieve the manic phase of bipolar affective disorder.
-Many also block muscarinic, alpha adrenergic and histamine receptors to a varying degrees

-These medications do not cure the underlying disease but they may permit the psychotic patient to function. *With that said- approximately 15% of schizophrenic patients are able to be employed and as Dr. Nelson pointed out 50% of patients with schizophrenia attempt suicide at some point. So while the introduction of*

antipsychotic drugs is a huge step forward- we still have a long way to go in terms of developing truly effective medications.

-All have Equivalent Therapeutic Efficacies. *This is certainly the case for treating the positive symptoms, there is some evidence that the atypicals may be slightly more effective in treating the negative symptoms*

SLIDE 5:

Antipsychotic Drug List:

- First generation Antipsychotic Agents (Low Potency):
  - Chlorpromazine – Prototype
  - Prochlorperizine (Compazine)
  - Thioridazine (Mellaril)
- First generation Antipsychotic Agents (High Potency):
  - Fluphenazine (Prolixin)
  - Haloperidol (Haldol)
  - Thiothixene (Navane)
- Miscellaneous
  - Pimozide (Orap) *only used for Tourette's Syndrome*
- Second Generation Antipsychotic Agents"Atypical":
  - Clozapine (Clozaril)
  - Risperidone (Resperdal)
  - Olanzapine (Zyprexa)
  - Quetiapine (Seroquel)
  - Ziprasidone (Geodone)
  - Aripiprazole (Abilify)

SLIDE 6:

Antipsychotic Drug Actions:

- All reduce "positive" symptoms hallucinations and agitation by blocking dopamine receptors
  - First generation most effective against "positive" Symptoms.
  - Newer (atypical) agents are arguably more effective in treating "negative" symptoms
  - The antipsychotic effects take several weeks to be effective
  - Calming effect ("Tranquilizers")
  - Used to handle agitated and disruptive behavior
    - parenteral administration for *acute* agitation
  - Reduce spontaneous physical movement

SLIDE 7:

Other actions that can be useful:

- Antiemetic effect:
  - Due to blockage of D2 in the chemoreceptor trigger zone (CTZ) of the medulla
  - Second generation less effective
- Anticholinergic effects:
  - Helps minimize the risk of extra pyramidal symptoms (EPS) with first generation
- Intractable Hiccups: (Chlorpromazine)
- Pain control: (No Analgesic Effect!)

SLIDE 8:

Adverse Effects of Dopamine Blockade:

- **Typical >>Atypical**: Haloperidol (high potency), Fluphenazine > Thioridazine, Chlorpromazine >> Risperidone, Clozapine
- 80% show adverse effects but therapeutic index is high
  - Use lowest dose possible

- **Extra Pyramidal Symptoms**-(EPS)- dopamine/ acetylcholine imbalance.
  - ***Akathisia***- feeling of restlessness, inability to sit still.
  - ***Parkinson's Disease*** (bradykinesia (slow moving, tremor, rigidity)
  - ***Tardive Dyskinesia*** (TD) – stereotyped, repetitive oral facial dyskinesia, choreiform movements of limbs. (May be irreversible)
  - Agents with higher potency for D2 receptor have greater propensity to induce EPS
  - For agents with high EPS, can use antimuscarinic drugs(blunts excitatory tone).

- **Gynecomastia, amenorrhea and galactorrhea**- prolactin release increased with D2 blockade.

SLIDE 9:

Adverse Effects of Dopamine Blockade, Neuroleptic Malignant Syndrome:

- Idiosyncratic (*might develop after 2 weeks or 20 years of antipsychotic drug treatment*)
- Rare (0.5-1% receiving high potency neuroleptics)
- Potentially fatal (mortality rate as high as 20%).
- **Presentation:**
    - Stupor,
    - High fever,
    - autonomic instability – hypertension, altered pulse rate
    - muscle rigidity,
    - stress leukocytosis (not related to infection),
    - diaphoresis (sweating)
    - elevated creatinine kinase.

SLIDE 10:

Other Adverse Effects:

- **Anticholinergic (antimuscarinic)**:
    - Xerostomia (dry mouth), urinary retention, constipation, Loss of accommodation, aggravation of glaucoma
- **Antiadrenergic (α1R blockade) :**
    - orthostatic hypotension, sexual dysfunction
- **Antihistaminic (H1R blockade):**
    - sedation
- **Antiserotonergic:**
    - weight gain(?), *more prominent with atypicals*
- **Diabetes Mellitus:**
    - hyperglycemia, *more prominent with atypicals*

SLIDE 11:

Cautions/Warnings:

- **FDA Black Box** – not to be used for dementia-related psychosis- increased risk of mortality in elderly dementia patients.
- May cause drowsiness
- Avoid alcohol and other depressants
    - Acute agitation with alcohol may be aggravated with neuroleptics – benzodiazepines are preferred
- Do not give to patients with glaucoma or prostatic hypertrophy
- Caution in CVD or hepatic disease
- Safety in pregnancy has not been established (Class C)

SLIDE 12:

Chlorpromazine (Thorazine)

Introduced in 1959, First generation (low potency), antipsychotic

- Uses:
  - Antipsychotic,
  - control manifestations of mania,
  - intractable hiccups
- (not used much anymore due to side effects)
- Highest occurrence of sedation

SLIDE 13:

Haloperidol (Haldol)

Introduced in 1967, First generation (high potency), antipsychotic

- Uses:
- Antipsychotic:
  Recommended first-line drug for treatment of schizophrenia
  Acute agitation (rapid acting).
  Common Extra-Pyramidal-Syndrome (EPS) due to dopamine receptor Blockade and low anticholinergic action.
  Less drowsiness than other antipsychotics
  Caution Neuroleptic malignant Syndrome
  Available as po, im, decanoate (IM depot).

SLIDE 14:

Fluphenazine (Prolixin)

Introduced in 1959, First generation (high potency), antipsychotic

- Uses:
- Antipsychotic:
  Good in patients refusing oral medications because it comes in depot injection (4 weeks)

- Available as IM, decanoate (depot).

SLIDE 15:

Pimozide (Orap)

Miscellaneous category- approved in1985 for Tourette's syndrome

- Use:
  - **Tourette's syndrome**
  - used for suppression of motor and phonic tics
  - second line after failure to respond to haloperidol

- Contraindications:
  - congenital long QT interval syndrome & long history of cardiac arrhythmias

SLIDE 16:

Atypical Antipsychotics:

- **Becoming the drugs of choice for treatment of Psychosis**
- *High affinity as 5-HT$_{2A}$ (serotonin) receptor antagonists or partial agonists*
  Dopamine D$_2$ receptor antagonists or partial agonists.
  -

  Bind less avidly to D$_2$ receptors in the striatum and hypothalamus than the Conventional antipsychotics therefore produce less EPS and endocrine Disturbance.

- Somewhat better therapeutic profile
- Appear to improve cognitive function as compared to conventional drugs**.**

SLIDE 17:

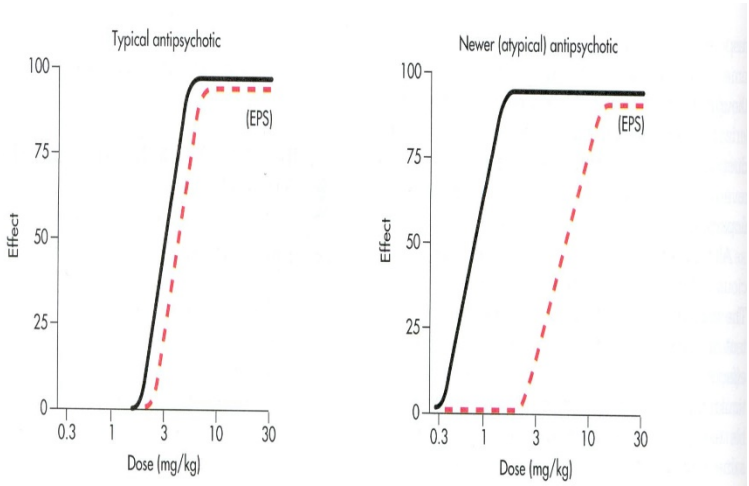

FIGURE 25-6 Antipsychotic and extrapyramidal syndrome *(EPS)* dose-response curves for typical and newer antipsychotic drugs.

SLIDE 18:

Atypical Antipsychotics:

Clozapine (Clozaril), 1989
Risperidone (Risperdal), 1994
Olanzapine (Zyprexa), 1996
Quetiapine (Seroquel), 1997
Ziprasidone (Geodon), 2001
Aripiprazole (Abilify), 2002 (*5-HT2A and D2 receptor partial agonists*)
Paliperidone (Invega), 2006

Asenapine (Saphris), 2009; Lurasidone (Latuda), 2010; …….

SLIDE 19:

Atypical Antipsychotics:
Clozapine (Clozaril):

Use: Antipsychotic (very effective)
Excellent for negative symptoms.
Low risk for EPS or tardive dyskinesia.

Reserved for refractory patients due to High risk for agranulocytosis (can be deadly). Must have weekly CBC.

Last resort but Drug of Choice (DOC) for refractive schizophrenia

SLIDE 20:

Atypical Antipsychotics:
Risperiodone (Risperdal):

USE: Antipsychotic with fewer side effects than Clozapine, No agranulocytosis risk.
1st line therapy
Paliperidone (Invega)– major metabolite
Adverse Effects – weight gain, orthostatic hypotension and reflex tachycardia at start of treatment
Fewer problems with EPS and TD

SLIDE 21:

Atypical Antipsychotics:

- •Olanzapine (Zyprexa)*
  - Weight gain is a major problem – 30% of patients on olanzapine gain more than 20 pounds.
  - Diabetes can occur
- •Quetiapine (Seroquel)*
  - Less weight gain noted
  - Extra Black Box Warning- Suicidality in Children
  - Diabetes can occur
  - QT prolongation
- •Ziprasidone (Geodon)*
  - No weight gain
  - Diabetes can occur
  - QT prolongation
  - Available as both oral and injectable
- •Aripiprazole (Abilify)*
  - **Extra Black Box Warning- Suicidality in Children**
  - Weight gain (less weight gain)
  - Diabetes can occur

* Low risk for EPS or TD with no agranulocytosis risk.

SLIDE 22:

Guidelines for Treatment:

- **Use Atypicals if at all possible.**
- Contraindications include pregnancy, refractory patient and hypersensitivity.
- **Black Box Warning – ALL**:
  - *Not approved for elderly or dementia related psychosis – increased mortality (CVD/infections?)*
- Always try to decrease dose needed after acute period.
- Educate patient and assess compliance.
- Watch closely for adverse effects.

SLIDE 23:

FDA Requests Diabetes Information on Antipsychotic Drug Labels

The FDA has asked drug makers to include information on hyperglycemia and diabetes on the labels of all atypical antipsychotic treatments.

According to Eli Lilly, which received an agency letter, the FDA recognizes the relationship between hyperglycemia and antipsychotic drug use is vague and not entirely understood, but believes labeling should reflect medical concerns nonetheless. The drugs affected by the requested labeling change include Lilly's Zyprexa (olanzapine), Pfizer's Geodon (ziprasidone), Bristol-Myers Squibb's Abilify (aripiprazole), AstraZeneca's Seroquel (quetiapine), Novartis' Clozaril (clozapine) and Janssen's Risperdal (risperidone).

SLIDE 24:

TABLE 76-6 Relative Incidence of Antipsychotic Drug Adverse Effects

	Sedation	EPS	Anticholinergic	Orthostasis	Seizures	Prolactin Elevation	Cognitive Improvement	Weight Gain
Low Potency								
Chlorpromazine	++++	+++	+++	++++	+++	+++	d	++
Thioridazine	++++	++	++++	++++	++	+++	d	+++
High Potency								
Trifluoperazine	++	++++	++	++	+++	+++	?	
Fluphenazine	++	+++++	++	++	++	+++	?	
Thiothixene	++	++++	++	++	++	+++	?	++
Haloperidol	+	+++++	+	+	++	+++	?	++
Loxapine	+++	++++	++	+++	++	+++	?	+
Molindone	+	++++	++	++	++	+++	?	+
Atypicals								
Clozapine	++++	+	++++	++++	++++[c]	0	?/++	++++
Risperidone	+++	+[a]	++	+++	++	0 to +++[c]	?/++	++
Olanzapine	+++	+[b]	+++	++	++	0	?	+++
Quetiapine	+++	+	++	++	++	0	e	++

[a]Very low at dosages <8 mg/day.
[b]With dosages <20 mg/day.
[c]Dose related.
[d]May worsen.
[e]Case report.
+, very low; ++, low; +++, moderate; ++++, high; +++++, very high; EPS, extrapyramidal side effects.
Adapted from references 23, 25, 49, 53, and 144.

SLIDE 25:

Bipolar Disorder: (*see also Blanton Antidepressant lecture that covers Bipolar Disorders***)**

Since the 1970's **lithium carbonate** has been the treatment for bipolar disorder. At therapeutic levels, Lithium has a mood-stabilizing effect, hence its value for treating bipolar disorder (~70% of patients respond) The mechanism of action is really not understood yet.

Unfortunately the therapeutic window for lithium is very small; the SE include: memory problems, weight gain, tremor, poluria, drowsiness, hypothyroidism, cardiac effects,etc

The therapeutic index is 1-2 and acute intoxication can cause vomiting, profuse diarrhea, ataxia, coma, and convulsions.

Treatment is mostly supportive and dialysis.

SLIDE 26:

Bipolar Disorder Treatment:
Because of the low therapeutic index for lithium in recent years there has been increased use of alternative mood-stabilizing agents: these include several of the anticonvulsant agents, including **valproic acid**, **carbamezepine, lamotrignine (only used for maintenance)**, etc.

These anticonvulsants are nearly as effective as lithium and are far safer. How they stabilize mood is also not understood at all.

Option 1: **Mood Stabilizer** (lithium/valproic acid/carbamazepine) ***+/-***

.. during depressive phase- add **SSRI antidepressant** (e.g. fluoxetine)

… during manic phase- add **Atypical antipsychotic (**e.g. aripiprazole)

Option 2: **Olanzapine** (Pyrexia) + **Fluoxetine** (Prozac) [combination Symbax].. *paradoxical-SSRI combined with 5-HTR blocker?*

SLIDE 27:

A 40-year-old woman presents with a 6-month history of missed menstrual periods; she describes a milky secretion from her breasts. She is not sexually active. She states that she is on antipsychotics. A pregnancy test is negative and TSH is normal. What medication is she most likely responsible?

A. Aripiprazole (Abilify)
B. Haloperidol (Haldol).. most likely- first generation, high potency, EPS
C. Olanzapine (Zyprexa)
D. Quetiapine (Seroquel)
E. Thioridazine (Mellaril)…..next likely,-first generation, low potency, less EPS

SLIDE 28:

A 33-year-old woman is brought into the emergency room by ambulance. She has been diagnosed as having schizophrenic disorder, disorganized type, since the age of 17. She has been on antipsychotic medications since that time, which have controlled her symptoms well. Physical examination reveals a well-nourished female with a temperature of 103.2 degrees F, BP of 180/99, HR of 97, and copious perspiration. She is mute, has muscular rigidity, and appears to be obtunded. What is the likely diagnosis?

A. Acute dystonia
B. Akathisia
C. Dementia
D. ***Neuroleptic malignant syndrome*** *(fever, perspiration, rigidity, etc)*
E. Tardive dyskinesia

SLIDE 29:

Patient who has schizophrenia refractive to other medications is put on Thioridazine (Mellaril). Within days, patient complains of severe orthostatic hypotension. What is the mechanism of action responsible for this adverse effect?

A. Alpha-1-adrenoceptor blockade
B. Dopamine-2 receptor blockade
C. Histamine-1 receptor blockade
D. Muscarinic receptor blockade
E. Serotonin-(5HT-2A) receptor blockade

SLIDE 30:

Based upon previous vignette, what medication would the patient with refractive schizophrenia ultimately be placed upon, being the only medication known to be effective?

A. Aripiprazole (Abilify)
B. Clozapine (Clozaril)
C. Haloperidol (Haldol)
D. Olanzapine (Zyprexa)
E. Quetiapine (Seroquel)

SLIDE 31:

FDA "Black Box Warning" associated with all antipsychotics (low and high potency - typical and atypical antipsychotics) deals with

A. Agranulocytosis/neutro-penia.
B. ***Dementia and increased mortality***.
C. Diabetes Mellitus.
D. Suicidality in young patients.
E. Tardive Dyskinesia.