

Antipsychotic Side Effects: Revisiting the Old Stuff

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Agenda:

- Intro: Dopamine and the antipsychotics
- Tardive Dyskinesia
- Akathisia
- Neuroleptic Malignant Syndrome
- Hyperprolactinemia
- Questions



**Area Man To Ask His
Doctor About Xenical,
Propecia, Claritin, Paxil,
Drixoral, Lipitor, Tavist-D**

see HEALTH page 11C

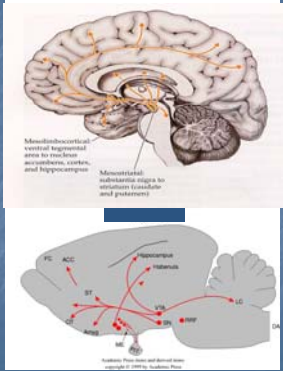
Schizophrenia

- **Positive Symptoms**
 - Hallucinations
 - Delusions
 - Illusions
- **Negative Symptoms**
 - Decreased spontaneity, motivation, persistence, speech, pleasure, affective flattening
- **Cognitive Deficits**
 - Verbal Memory Deficits
 - Executive Function Deficits
- **Affective Symptoms**
 - Depression or mood lability

Neurotransmitter systems that are dysregulated in schizophrenia

Dopamine

movement, motivation



Antipsychotic Medication

- “Older” and “Newer” medications
- Newer meds emerged over past ~15 years
- Newer meds better tolerated
- Newer meds may have advantages
- Newer meds considered **first-line** treatment for schizophrenia
- Newer agents **do** have side effects!!!

Antipsychotic Medication

- FDA indications: **Schizophrenia, Mood Disorders**
- Used for many indications which do not have FDA approval
- Often used inappropriately
- Controversy surrounding usage in dementia-related psychosis

Older Antipsychotics

Haldol (Haloperidol)
Prolixin (Fluphenazine)
Mellaril (Thioridazine)
Thorazine (Chlorpromazine)
Moban (Molindone)
Loxitane (Loxapine)
Navane (Thiothixene)

Older Antipsychotics

- They work!
- Work primarily by blocking **Dopamine** in the brain
- Thorazine was a revolution in psychiatric (1950s)
- All of the older agents carry a risk of TD
- Effective in treating hallucinations, delusions, disorganization, paranoia, etc.

Older Antipsychotic Risks

- More problems with certain side effects
 - stiffness
 - tremor
 - gait problems, slowness of movements
 - dystonia (contraction of certain muscles)
 - sedation
 - risk of Neuroleptic Malignant Syndrome
 - potential for cardiovascular side effects
 - **RISK OF TARDIVE DYSKINESIA**

Newer Antipsychotics

Clozaril (Clozapine)
Risperdal (Risperidone)
Invega (Paliperidone)
Zyprexa (Olanzapine)
Seroquel (Quetiapine)
Geodon (Ziprasidone)
Abillify (Aripiprazole)



**Toilet That Uses 50
Percent Less Water Must
Be Flushed Six Times**

see PRODUCTS page 3E

Newer Antipsychotics

- Less potential to cause Parkinsonian SFX
- May be better at treating "Negative" S/S
- Better tolerated -- Improves Compliance
- Less Risk of Tardive Dyskinesia
- Much more expensive
- Associated with more **weight gain** and development of **adult-onset diabetes**

Extrapyramidal Side Effects

- Abbreviated as "**EPS**" or "**EPSE**"
- Symptoms include:
 - Muscle stiffness/rigidity
 - Resting tremor
 - Slowness of movements (bradykinesia)
 - Akathisia
 - Acute Dystonia

Tardive Dyskinesia

- Involuntary movements of tongue, jaw, trunk, face, and extremities
- Associated with the use of antipsychotic medication over at least a several week period, often years
- Movements are **choreoathetoid**
- Prolonged usage of the agent may make condition worse over time

Tardive Dyskinesia

- Rarely occurs until after 6 months of treatment
- Movements of mouth, tongue and jaw most common
- Made worse by stress
- Disappears during sleep
- **10-20% treated for >1 year develop TD**
- There is a "spontaneous" dyskinesia rate in patients
- DISCUS rating scales should be conducted at least annually by clinicians

Tardive Dyskinesia

- Often a cosmetic issue
- If severe, can affect breathing, swallowing
- Risks:
 - long-term treatment with antipsychotics
 - female
 - increasing age
 - presence of a mood disorder
 - presence of a cognitive disorder
 - cigarette smoking

Three Basic Types of TD

- **MASKED TD:** TD is present but covered up by the antipsychotic and dose
- **PERSISTENT TD:** TD is present and the movements have been overt for 3 months or more
- **WITHDRAWAL TD:** TD is seen upon an antipsychotic reduction or discontinuation, but movements dissipate within 12 weeks of the reduction or discontinuation.

EARLY SIGNS

- Fine inner tongue movements
- Frequent blinking or "bursts" of blinking
- Tic-like movements of the lips or face
- Slight choreoathetoid movements of the fingers/hands

Severity

- Mild TD: 60-70%
- Moderate TD: 20-30%
- Severe TD: 10-15%
- Incapacitating TD: 3%

Simplified Diagnosis of TD

- History of a least **three months** total cumulative neuroleptic exposure. Be sure to include amoxapine and metoclopramide
- Scoring on the **DISCUS of FIVE or above**. Be alert to changes from baseline even if below 5 if "moderate" or "severe" levels appear. Also be alert if increase in at least two different body areas, even if mild.
- Other conditions are not responsible for the involuntary movements

Akathisia

'A-ka-thEzh-a'

From Greek, meaning
"never to sit down"

What is Akathisia?

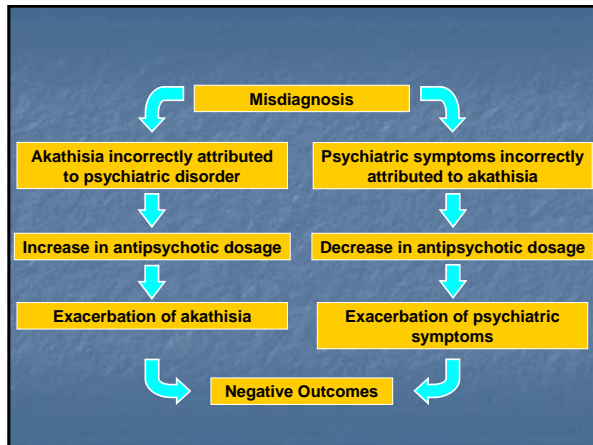
- An adverse effect of some antipsychotics and other medications
- A category of extrapyramidal symptoms (EPS)
- Subjective feelings of
 - inner restlessness
 - agitation
 - urge to move

Signs and Symptoms of Akathisia

- Pacing
- Fidgeting
- Irritability
- Repetitive leg movements
- Hyperactivity
- Agitation
- Subjective distress/dysphoria

Distinguishing Akathisia

- Akathisia may look like
 - agitation secondary to psychiatric disorders
 - psychomotor agitation
 - anxiety
 - drug withdrawal states
 - restless leg syndrome
 - neurological disorders



Potential Complications of Akathisia

- Depressive symptoms / dysphoria
- Nonadherence
- Cognitive impairment
- Violence / aggression
- Early EPS may herald tardive dyskinesia (TD)

Epidemiology

- Incidence of 10%-75%, variability due to differing diagnostic approaches
- Typical antipsychotics generally greater than atypical antipsychotics
- Primarily related to D₂ blockade; other neurotransmitters may be involved

Akathisia Rating Scale

- The Barnes Akathisia Rating Scale (BARS) is the most commonly used assessment tool
- BARS distinguishes akathisia from other disorders by incorporating both objective and subjective symptoms as well as global clinical components
- Quick: usually requires 10-15 minutes to complete
- Good inter-rater reliability

Treatment of Akathisia

- Clinicians have tried many available agents, including beta-blockers, benzodiazepines, and anticholinergic drugs
- Once akathisia is diagnosed, consider a reduction of antipsychotic dosage, if feasible
- Consider switching to an antipsychotic with a more favorable EPS profile

Neuroleptic Malignant Syndrome (NMS)

- A potentially fatal symptom complex
- First reported in 1956
- Severe adverse reaction to antipsychotics
- Cause related to abnormal dopamine blockade in brain
- Occurs with both older and newer drugs
- Symptoms develop over 24 – 72 hours

NMS

- **Clinical manifestations**
 - Hyperpyrexia (fever)
 - Muscle rigidity
 - Altered mental status
 - Autonomic instability
 - Diaphoresis (severe sweating)
 - Elevated creatine phosphokinase (CPK)
 - Myoglobinuria (rhabdomyolysis)
 - Acute renal failure
 - Death

NMS

- **F - Fever**
- **E - Encephalopathy** (confusion)
- **V - Vitals** unstable
- **E - Elevated enzymes** (elevated CPK)
- **R - Rigidity** of muscles

NMS

- More common within 2 weeks of starting new drug, or after a significant dosage increase
- Incidence under 0.5% within 30 days of starting medication
- Mortality up to 20%
- High rate of recurrence (25% – 75%)
- More common in men

NMS

■ Treatment Issues:

- Discontinuation of antipsychotic agent
- Supportive Medical Care (IV fluids, antipyretics, muscle relaxants.)
- Bromocriptine
- Dantrolene
- Avoid offending agent
- Early treatment is key

Prolactin (PRL)

- Hormone secreted by the pituitary gland
- Normal function is to enhance breast development during pregnancy and induce lactation
- In non-pregnant state, serum concentrations are low (<30 ng/ml)
- Dopamine suppresses PRL secretion

Hyperprolactinemia

- State of elevated serum prolactin (PRL)
- Causes include antipsychotic medications, other medications, pituitary tumors, hypothyroidism, chest wall trauma, renal failure, cirrhosis, post-ictal states
- If no obvious cause found, MRI should be performed to rule out tumor
- Tumors include micro- and macroadenomas

Signs and Symptoms of Hyperprolactinemia

- Gynecomastia (men)
- Galactorrhea (women)
- Amenorrhea/Infertility (women)
- Impotence/Infertility (men)
- If mass effect – headaches and vision problems

Epidemiology of Hyperprolactinemia

- Prevalence = 0.4% in health adults
- ~ 5% of patients in infertility clinics
- ~ 5% of men with impotence/infertility
- ~ 9% in women with amenorrhea
- ~ 25% in women with galactorrhea
- ~ 70% in women with galactorrhea + amenorrhea

Antipsychotic-Induced Hyperprolactinemia

- Varies depending upon agent
- In general newer agents = reduced risk
- **EXCEPT** for Risperidone
- Quetiapine and Aripiprazole = lowest risk
- Potential long-term risks = osteoporosis and breast cancer
