Polypharmacy, Adverse Effects, and the Importance of Tapering Medications for People with Intellectual and Developmental Disabilities

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How did we get here?

1876 Methylene Blue
Insecticide
1937 B. Du Pont
Anthelmintic

France
1950 Antihistamine 1952 (largactil)
chlorpromazine (thorazine)

1939 Antimalaria 1952
USA

MALARIA Antimalarial Medicines
**Chlorpromazine Structure**

**Other Phenothiazines**

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mellaril</td>
<td>Thioridazine</td>
</tr>
<tr>
<td>Serentil</td>
<td>Mesoridazine</td>
</tr>
<tr>
<td>Prolixin</td>
<td>Fluphenazine</td>
</tr>
<tr>
<td>Loxatane</td>
<td>Loxapine</td>
</tr>
<tr>
<td>Compazine</td>
<td>Prochlorperazine</td>
</tr>
<tr>
<td>Stelazine</td>
<td>Trifluoperazine</td>
</tr>
<tr>
<td>Phenergan</td>
<td>Promethazine</td>
</tr>
<tr>
<td>Trilafon</td>
<td>Perphenazine</td>
</tr>
</tbody>
</table>

**Lorazepam Structure**

**Benzodiazepines (anxiolytics)**

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Librium</td>
<td>Chlordiazepoxide</td>
</tr>
<tr>
<td>Valium</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Ativan</td>
<td>Lorazepam</td>
</tr>
<tr>
<td>Tranxene</td>
<td>Clorazepate</td>
</tr>
<tr>
<td>Dalmane</td>
<td>Flurazepam</td>
</tr>
<tr>
<td>Klonopin</td>
<td>Clonazepam</td>
</tr>
<tr>
<td>Halcion</td>
<td>Triazolam</td>
</tr>
<tr>
<td>Xanax</td>
<td>Alprazolam</td>
</tr>
</tbody>
</table>
Benzodiazepines

- Not intended for long term usage
  - After being on for 8 weeks, 1/3 of people developed tolerances
- Highly addictive
- Withdrawal seizures when taper
- Increase in target behaviors when taper
- Utilize in acute short term or crisis situations
- Some experience paradoxical effects
- Can disrupt stage 4 sleep patterns
- Replace with SSRI’s for long term usage

Other Types of Antipsychotics

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haldol</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Navane</td>
<td>Thiothixene</td>
</tr>
</tbody>
</table>

Haldol

- Do NOT recommend as a routine drug
- Effective in emergency room settings to disrupt a psychotic episode
- Most likely to have side effects
- Not a great choice for most clients
- If not effective at lower dosages, do not continue to increase
- DO NOT mask with Cogentin

Tricyclic Structure
Tricyclic Antidepressants

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elavil</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Norpramine</td>
<td>Desipramine</td>
</tr>
<tr>
<td>Sinequan</td>
<td>Doxepin</td>
</tr>
<tr>
<td>Tofranil</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Pamelor</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Anafranil</td>
<td>Clomipramine</td>
</tr>
</tbody>
</table>

Carbamazepine Structure

![Carbamazepine Structure](image)

Antiepileptic Medications

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegretol</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Trileptal</td>
<td>Oxcarbazepine</td>
</tr>
</tbody>
</table>
2nd Generation Antipsychotics

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozaril</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Risperdal</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Zyprexa</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Geodon</td>
<td>Ziprasidone</td>
</tr>
<tr>
<td>Seroquel</td>
<td>Quetiapine</td>
</tr>
<tr>
<td>Abilify</td>
<td>Aripipazole</td>
</tr>
<tr>
<td>Invega</td>
<td>Paliperidone</td>
</tr>
<tr>
<td>Fanapt</td>
<td>Iloperidone</td>
</tr>
<tr>
<td>Latuda</td>
<td>Lurasidone</td>
</tr>
<tr>
<td>Saphris</td>
<td>Asenapine</td>
</tr>
</tbody>
</table>

*Antiparkinsons Medication | L-Dopa

Clozapine Structure

Second generation Antipsychotics: D2/5-HT2A Antagonism

1990s-2001: Introduction of risperidone, olanzapine, quetiapine, ziprasidone

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of positive and negative symptoms</td>
<td>Low rates of EPS, TD</td>
</tr>
<tr>
<td>Evidence of cognition improvement</td>
<td>Few anticholinergic effects</td>
</tr>
<tr>
<td>Broad range of efficacy (e.g., dementia and mania)</td>
<td>Emergence of drug specific side effects (e.g., pronounced weight gain, diabetes, QTc prolongation, prolactin elevation)</td>
</tr>
</tbody>
</table>

Clozaril

- Reserve for LAST RESORT
- Weekly blood tests
  - Decrease number of white blood cells
- Used mostly with schizophrenia
- Does not cause EPS or hyperprolactinemia
- High incidents of lowering seizure threshold
- Hypersalivation
- Metabolized by CYP/1A2
- Cuts level in half if a smoker (stimulates)
- Weight gain
- Seizures
**Risperdal**

- High incidents of EPS
- Sedating properties
- Dosing:
  - Can start at two times a day, however should eventually be given once a day for maintenance
  - Labs: prolactin levels once a year
  - When dose above 6mg, only get more side effects

**Zypraxa**

- Weight gain (can be 40lb-60lb in first year)
  - Changes how we store carbohydrates
  - Not dosage related
  - Prompted discussions about metabolic syndrome
  - Monitor at least quarterly for metabolic syndrome
  - Metabolized by CYP/1A2
  - If a smoker, cuts the level in half

**Geodon**

- “Cleaned up version of Risperdal.”
- If responded well to Risperdal but prolactin level increased, consider replacing with Geodon
- MUST be consumed with a 350 calorie meal
  - 60% bioavailability
- Dosing: most effective if given two times a day with equal dosages. Example 60mg at 7a and 60 mg at 5p) or with dinner)
  - Often it is given at 8pm, without sufficient calories
  - 120mg per day minimum
  - 160mg per day maximum
  - FDA approves 200mg for Bipolar

**Seroquel**

- Most sedating of the 2nd Generation Antipsychotics
- Weak receptor binding properties so side effects minimal
- Mid range as far as weight gain
- Dosing:
  - Ineffective and only experiencing sedation until reach 400mg-600mg
  - Go slow-only 100mg-200mg increases every week when initiating
  - Routine annual labs
Abilify

- Expensive
- Partial agonist (normal flow of dopamine)
- Least likely to cause weight gain
- Low incidents of EPS, QT prolongation

Dosing:
- If paired with another 2nd generation antipsychotic, wipe out agonist = Polypharmacy
- VERY low, VERY slow when initiating
  - Seen success at 5mg-10mg
  - 30mg max however not much success after 20mg

Invega

- The active metabolite of Risperidone (9-hydroxyrisperidone)
- Usual dose range 1.5mg to 12mg a day
- 6mg Invega equal to 2-3mg Risperidone

Latuda

- Must be given with at least a 350 calorie meal
- Dosage: 40mg – 160mg per day
- Can be given once daily

Fanapt

- Atypical antipsychotic approved for the treatment of schizophrenia
- Usual dosage: 12mg-24mg per day
- Give in divided doses with food to lessen orthostatic hypotension
- Common side effects: somnolence, dizziness, orthostatic hypotension
- Paxil and Prozac can increase levels

Saphris

- Start with 5mg BID for 7 days, then increase to 10mg BID
- Atypical antipsychotic approved for the treatment of schizophrenia and acute mania associated with bipolar disorder.
- Little weight gain compared to other atypicals.
- Very little anticholinergic activity.
- Is a sublingual tablet. *Sublingual tablets should not be split, chewed, crushed or swallowed.
- Patients should be instructed to not eat or drink for 10 minutes after administration.
- Most common side effect is somnolence
Conventional Antipsychotics or “Neuroleptics” – First Generation (fgap)

- Acute Dystonia
- Parkinsonism
- Akathisia
- Neuroleptic Malignant Syndrome
- Tardive Dyskinesia
- EPS & Hyperprolactinemia – D2 blockade
- Hypotension – alpha adrenergic blockade
- Sedation – histaminergic blockade
- Weight gain – histaminic and serotonergic blockade
- Muscarinic anticholinergic (dry mouth, etc.)

“Low-potency” agents have relatively higher affinities for these receptors

Shift in Risk Perception of Antipsychotics

Past Areas of Concern

Current Medical Realities

- EPS/TD
- QTc
- Weight Gain
- Insulin Resistance
- Hyperlipidemia
- CHD
- Prolactin
- Coronary heart disease

Hyperprolactinemia

- Females
  - 20% incidence of secondary amenorrhea
  - Infertility
  - Lactation
  - Mild hirsutism
  - Risk of osteoporosis due to estrogen deficiency
  - Risk of breast cancer

- Males
  - Erectile dysfunction
  - Decreased libido
  - Lactation
  - Hypogonadism
  - Gynecomastia
Effects of Atypical Antipsychotics on Prolactin Level

- Atypical antipsychotics can produce significant increases in prolactin levels (≥2-3 x normal)
- Clozapine and quetiapine have minimal or no effect
- Risperidone produces sustained elevation
- Olanzapine produces mild elevations at lower doses (5-10mg/d) and more significant increases at higher doses (15-30mg/d)

Comparing the symptoms of Parkinson’s Disease and patients with schizophrenia who receive antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Parkinson’s</th>
<th>Schizophrenia/ Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor: rigidity, tremor, akinesia</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blunted affect</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cognitive ‘dullness’</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Depression/ amotivation</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Neuroleptic Malignant Syndrome (NMS)

Potentially fatal condition characterized by:
- Autonomic instability
- Diaphoresis
- Hyperthermia
- Mental status change (confusion, hallucinations)
- Muscle rigidity
- Lab abnormalities
  - (elevated CPK, electrolyte abnormalities)
Atypical agents and d2 blockade

- Risperidone achieves 70% occupancy at approx 5mg/d
- Olanzapine achieves 70% occupancy at approx 20mg/d
- Clozapine and quetiapine do not exceed 60% occupancy
- Quetiapine is rapidly displaced from D2 receptors

Neuroleptic related movement disorders

Limited Reactions
- Acute dystonic reaction
  - Oculogyric crisis
  - Acute laryngospasm

Idiosyncratic Events
- Neuroleptic malignant syndrome

Toxic Effects
- Neuroleptic-induced parkinsonism
- Acute akathisia

Tardive Syndromes
Metabolic Syndrome

3 of the Following:

- Central Obesity
  - Waist >40in men
  - Waist >35in women
- Hypertension
- Elevated LDC cholesterol
- Low HDL
- Glucose intolerance
- 16-18% 10 year risk of CV event

Antipsychotic Weight Gain Risk

- High Risk
  - Clozapine
  - Olanzapine
  - Typical Antipsychotics
  - Risperidone
  - Quetiapine
  - Ziprasidone
- Low Risk
  - Abilify
Antipsychotic Medications and Healthy Outcomes

- Routinely consider health consequences of antipsychotic treatment:
  - Monitor weight, glucose, lipids
  - Monitor sexual function, breast changes, menstrual history
    - Consider prolactin level and referral if symptomatic
  - Monitor EPS/TD on physical exam
  - Inquire about subject response
    - Dysphoric response
    - Cognitive slowing/dulling

BUT NOBODY DOSES CORRECTLY AT FIRST

- Risperidone (Risperdal) too high (16mg down to 4-8mg)
- Olanzapine (Zyprexa) too low (10mg up to 15-20+ mg)
- Quetiapine (Seroquel) way too low (200-300mg up to 800+mg)
- Ziprasidone (Geodon) way too low (average dose still often <80mg; >50% of use is below 120 mg; dose needs to >120mg for optimal efficacy)
- Aripipazole (Abilify) (who knows yet? 20-30mg may be too high for children, mood disorders and those without prior antipsychotic dosing; 5mg?)
**Atypical Antipsychotic Agents**

- Dosing strategies should:
  - Be conservative – “start low, go slow, taper slowly”
  - Minimize use of emergency drug treatment (prn or stat)
  - Assess response and side effects on routine and systematic basis
  - Use atypical antipsychotic agent at adequate dose for appropriate period before making changes

**Features of Schizophrenia**

- Positive symptoms
  - Delusions
  - Hallucinations
  - Disorganized speech
  - Catatonia
- Negative symptoms
  - Anhedonia
  - Affective flattening
  - Avolition
  - Social withdrawal
  - Alogia
- Social/Occupational Dysfunction
  - Work
  - Interpersonal relationships
  - Self-care
- Cognitive Deficits
  - Attention
  - Memory
  - Executive function (e.g., abstraction)
- Comorbid Substance Abuse
- Mood symptoms
  - Depression
  - Anxiety
  - Aggression/Hostility
  - Suicidality
  - Hopelessness
  - Agitation

**Avoiding Polypharmacy**

- Avoid using multiple medications simultaneously whenever possible
- Reevaluate regimen of patient who does not experience decreased aggression while receiving multiple medications
- Consider tapering/discontinuing one or more medications if patient is on ≥4 medications without clear benefits
Evaluating Antipsychotic Therapies

- Reasons to Switch Between Atypical Antipsychotics
  - Partial response
  - Decrease in cognitive functioning due to sedation
  - Adverse effects, particularly weight gain, metabolic disturbances, or prolactin-associated side effects
  - Nonadherence to blood monitoring in patients taking clozapine

Discussion Questions

- Why does it appear as though a new medication is effective for about a month, then “stops/wears off”?
- When a new medication is first initiated, how long should we wait to see results before making a change?
- Why is Tegretol and Depakote a bad combination?
- Many of our clients are on multiple medications, and we do not feel like we have the ability to impact the psychiatrists’ decisions. What can we do about this?