Wisconsin Public Psychiatry Network Teleconference (WPPNT)

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WPPNT Reminders

• Call 877-820-7831 before 11:00 a.m.
• Enter passcode 107633#, when prompted.
• Questions may be asked, if time allows.
• To ask a question, press *6 on your phone to un-mute yourself. Please *6 to re-mute your line.
• Ask questions for the presenter, about their presentation.

• The link to the evaluation for today’s presentation is on the WPPNT webpage, under today’s date: https://www.dhs.wisconsin.gov/wppnt/2020.htm. Complete the evaluation to receive the CEH.
Antipsychotic Medications Update
7/23/20
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Four out of five doctors recommend. . .
Evidence Based Practice (Modified from PORT Recommendations)

- Family psycho-education
- ACT and Clubhouse psychosocial programs
- Integrated supported work programs
- Skill training
- Integrated Mental Health and AODA Treatment
- Cognitive Behavioral Therapy
- Cognitive Remediation

Clubhouse not part of current PORT recommendations
What is the purpose of taking this antipsychotic medication?

- May increase stability
- May decrease positive symptoms
- May help people improve function and quality of life

Medication can be part of a solution to a problem, but first we need to be very clear about the consumer’s goal, the nature of the problem, and how medication may help.
Cost of Antipsychotic Medication

Cost of 30 tabs (from drugs.com)

• Aripiprazole 15 mg (generic):  $ 21
• Abilify 15 mg (branded form): $ 940
• Olanzapine 20 mg (generic)  $ 7.50
• Zyprexa (branded form)      $ 1,370
Relapse Rate on Placebo: Schizophrenia

8% Relapse / month over 24 months

Prien, Cole and Belkin, 1969
“Paper or plastic?”
A brief discussion about time:

Absorption

Half-life

Crossing blood-brain barrier

Time to take Effect

**Figure 1.**
*Example of a 12-hour half-life*

- Peak serum level
- Half of peak serum level
- Serum Level
- Hours
Same Dose ≠ Same Serum Level

Distribution Curve of Dopamine Receptor Occupancy in 100 Patients Treated with Risperidone 4 mg

RIS=risperidone; D=dopamine.

Smoking

Induced CYP 1A2

- Can decrease clozapine levels by up to 50%, and may also decrease olanzapine to some extent


Improvement Per Week

Meta-analysis of 114 trials with > 8000 patients

Refractory patients and acute emergency patients excluded

Agid et al Arch Gen Psych 2003
Antipsychotic Dose-Response Curve

Clinical Response Curve

Toxicity Curve

Therapeutic window

Dose/Plasma level of antipsychotic medication
Dose Escalation:

Medication Dose

Symptoms

Time
Antipsychotic Medications: Indications

- **Schizophrenia:**
  - + positive symptoms
  - x Negative symptoms
  - x Cognitive dysfunction

- **Depression**
  - + psychotic depression
  - + Some (quetiapine)

- **Bipolar disorder**
- **OCD**
- **Autism related behaviors**
- **Aggression**
Antipsychotic Medications: other uses (NOT FDA indicated)

• Psychosis associated with dementia
  ➢ Black Box warning when used in people with dementia

• Borderline Personality Disorder
• Conduct disorder/childhood aggression
• Anti-anxiety

• Hiccups
• Nausea
Antipsychotic Medications: What do we really know?

• All are much more effective for positive sx than for negative sx

• Clozapine is more effective than any other antipsychotic

• None of the others is clearly more effective than any other, but they are different and different people respond differentially

• They are equally effective, but have very different side effect risks.

• The data on lifetime need is problematic and may be wrong, at least for some patients
Dopamine Pathways

- Nigrostriatal EPS
- Mesolimbic psychosis
- Infundibular Prolactin elevation
- Mesocortical Negative and cognitive sx
Second Generation Antipsychotic Medications

clozapine

risperidone

quetiapine

olanzapine

ziprasidone

aripiprazole

paliperidone monthly

paliperidone

ziprasidone microspheres injection

asenapine

Clozapine

- Other side effects
  - Severe neutropenia
  - Heat Related Deaths
  - Cardiomyopathy
  - Pulmonary embolism
  - Gastric hypomotility
  - Diabetes
  - Diabetic ketoacidosis
  - Drooling
  - Seizures

- Very effective
  - positive and negative
  - good mood stabilizer
  - very low EPS
  - very low TD
Risperidone (Risperdal)

- Dose related EPS
- Less is better
- Prolactin Elevation
- Weight Gain

- Positive and negative efficacy
- Mood stabilizer
- Decreased TD

Adapted from Stahl
Essential Psychopharmacology
Paliperidone (Invega)

- Major metabolite of risperidone
- More gradual release than risperidone [but risperidone converted into paliperidone]
- Fewer drug-drug interactions (metabolized primarily in kidneys, little P450 interaction)
- More QTc prolongation [not significant]
- Similar prolactin elevation to risperidone
- ? Similar weight gain
Olanzapine (Zyprexa)

- Some dose related EPS
- Slight prolactin Elevation
- **Big** Weight Gain
- Diabetes (?)
- Somewhat sedating

- Positive and negative efficacy
- Mood stabilizer
- Decreased TD

Adapted from Stahl
Essential Psychopharmacology
Quetiapine (Seroquel)

- More is Better
- 400 mg up to 1200 mg
- Very low EPS
- Very low TD risk
- Some weight gain
- Sedating
- Needs dose titration to decrease dizziness

- Low dose may be useful in people with borderline disorder

Adapted from Stahl
Essential Psychopharmacology
Ziprasidone (Geodon)

Newest antipsychotic
NO WEIGHT GAIN
Very low diabetes risk
Higher dose often better than low

QTc prolongation
Activating/agitating
Antidepressant activity

Nausea, sleep disturbance
EPS dose related

Adapted from Stahl
Essential Psychopharmacology
Dose Ziprasidone With Food to Maximize Absorption

- AUC Fasted
- AUC Fed

Data on file, Pfizer Inc.
Intrinsic Activity: Ability to Stimulate Receptors

- **Full agonist (dopamine)**: Full receptor activity
- **Antagonist (haloperidol, etc)**: No receptor activity
- **Partial agonist (aripiprazol)**: Partial receptor activity

Iloperidone (Fanapt): Problems

• Dose dependent increase in QTc (9.1 msec at 20-24mg/day) which may or may not be an issue

• Must be titrated gradually to prevent dizziness

• Start 1 mg BID, then increase 2mg/day til 12-24 mg

• 2D6 inhibitors can increase serum level (fluoxetine, paroxetine)

• Several negative effectiveness studies
Asenapine (Saphris)

• Sublingual tablet
  • 35% bio-available sublingual <2% oral
  • Bid dosing-- sublingual tablet
  • Avoid food 10 min after dose

• 5HT 2D2 antagonist

• Also antagonist at D1,D3,D4, 1-HT1A, 5-HT2A,5-HT2C, alpha 1 and H1

• Less wt gain than olanzapine

• VERY LITTLE data published
Lurasidone (Latuda) (FDA approved Oct 2010)

- **Weight Neutral**

- FDA indications for schizophrenia and Bipolar depression

- High Affinity for: $D_2$, $5-HT_{2A}$, $5-HT_7$, $5-HT_{1A}$, $NE_{\text{alpha} 2c}$

- Low Affinity for: $NE_{\text{alpha} 1}$ and $\text{alpha} 2a$, $H_1$, $M_1$

- EPS similar to risperidone

- 160 mg had better clinical outcomes than 80 mg

- **[MORE IS BETTER]**
New antipsychotic medications

All are very expensive, have no long-term data, and no data demonstrating better efficacy than older better known medications.

• Brexpiprazole (Relpaturated): D2 partial agonist, in some ways similar to aripiprazole

• Cariprazine (Vraylar): D2 and D3 partial agonist with preferred binding to D3

• Lumateperone (Caplyta): much more serotonin rather than D2 binding
1st Generation Antipsychotic Meds

- Chlorpromazine ------------- Thorazine
- Fluphenazine --------------- Prolixin
- Haloperidol --------------- Haldol
- Thiothixene ------------- Navane
- Perphenazine -------------- Trilafon
- Loxapine -------------- Loxatane
- Molindone -------------- Moban
Receptor Binding of Currently Available Atypical Antipsychotic Meds
Percentage of Patients With Clinically Significant Weight Gain in Short-Term Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Aripiprazole</td>
<td></td>
</tr>
<tr>
<td>Zipraside</td>
<td></td>
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<tr>
<td>Risperidone</td>
<td></td>
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<tr>
<td>Quetiapine</td>
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<tr>
<td>Olanzapine</td>
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Patients who gained >7% of their body weight (%)

Antipsychotics

Obesity and Mortality Risk

Mortality Ratio

BMI

Antipsychotic Side Effects

• Dytonias (muscle cramps)
• Tremor--coarse Parkinsonian type tremor
• Akinisia--decreased movement/spontaneity
• Akathisia--motor restlessness
• Tardive Dyskinesia: MAY BE PERMANENT

Metabolic Side Effects:
• Weight gain, diabetes, cardiovascular disease
Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy: Wunderink et al 2013

128 pts remitted on antipsychotic meds for 6 months, then randomized to maintenance dose or slow dose reduction

• Initial relapse rates twice for DR Vs MT in first 2 years

• Relapse = between two groups > 3 yrs

• Recovery (Andreason criteria) all PANSS items 1-3 on 7 point scale

• Function (Groningen Social Disability Schedule (GSDS) all 7 subscales 1 or lower
Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy: Wunderink et al 2013

• The DR patients experienced twice the recovery rate of the MT patients (40.4% vs 17.6%).

• Logistic regression showed an odds ratio of 3.49 (P = .01).

• Better DR recovery rates were related to higher functional remission rates in the DR group but were not related to symptomatic remission rates.
Time to first relapse after first remission (t6) during 7 years of follow-up in patients assigned to 18 months (547 days) of dose reduction/discontinuation (DR) or maintenance treatment (MT).