Psychopharmacologic Updates

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My mother used to puke in my mouth.
"But if YOU see yourself as grim, that's the way other people will see you."
YOU DWELL ON THINGS TOO MUCH
History of Psychiatric drug development

- Mid-20th century showed the birth of modern psychopharmacology; the discovery of the first medicines that treated specific disorders.
- In 1949, lithium was tested on manic patients after John Cage noticed lithium urate salts sedating his guinea pigs.
- In 1950, chlorpromazine was initially used for its sedating properties, but the true benefit was really its ability to reduce hallucinations and delusions of patients with schizophrenia.
- In 1951, imipramine was initially developed for patients with schizophrenia, but was found to elevate mood, and became the prototype for antidepressant development.
- Fluoxetine was the first marketed SSRI in 1987 in the USA (Fluvoxamine was approved in 1983 in Switzerland and West Germany).
The advent of drug discoveries in the 1950’s and 1960’s, motivated the research to understand the mechanism of actions that led to success of these medications.

- Julius Axelrod won the Nobel Prize in 1970 for discovering neurotransmitter reuptake mechanisms.
- Arvid Carlsson won the Nobel Prize in 2000 for discovering that antipsychotic drugs work by blocking dopamine receptors.
HI BATMAN! I'M ON MY WAY TO MAKE BALLOON ANIMALS FOR KIDS IN GOTHAM GENERAL CHILDREN'S HOSPITAL. I LIKE TO GIVE THEM SOMETHING TO SMILE ABOUT!

When the Joker Takes His Anti-Psychotic Meds
Antipsychotics

- “Golden era” of the 1950’s led to development of what we now refer to as the typical antipsychotics. Despite initial excitement, the side effects of this class of medications limited their effectiveness.
- Clozaril was introduced in 1990, which began the research to find novel agents for the treatment of psychosis.
- Olanzapine was the first antipsychotic to get FDA approval for mania, and aripiprazole was the first antipsychotic to get FDA approval for adjunct treatment of major depressive disorder.
- Most antipsychotics that have been developed in the past decade now get indications for more than just psychotic disorders.
Antipsychotics of the last decade

- 2006-Invega (paliperidone)
- 2009-Invega sustenna (paliperidone extended release)
- 2009- Sapris (asenapine)
- 2009- Fanapt (iloperidone)
- 2009- Zyprexa Relprevv (olanzapine extended release injectable)
- 2010- Latuda (lurasidone)
- 2015- Invega trinza (paliperidone extended release injectable)
- 2015- Vraylar (cariprazine)
- 2015- Rexulti (brexpiprazole)
- 2015- Aristada (aripiprazole lauroxil)
Antipsychotics (con’t)

- **Number One:**
- **Invenga (paliperidone) 2006:** Indication for the treatment of schizophrenia. Paliperidone is an active metabolite of risperidone. Dosage range is 3mg to max 12mg.
- **Invenga sustenna intramuscular monthly injection was approved in 2009:** monthly dose range is 39mg to 234mg (depending on oral invenga dosage).
- **Invenga trinza intramuscular THREE MONTH injection was approved in 2015:** dosage range is 273mg to 819mg (depending on monthly invenga sustenna dosage).
- **Adverse side effects include:** parkinsonism, akathisia, dyskinesia, tachycardia, headache, somnolence, anxiety, hyperkinesia, extrapyramidal disorder, dystonia.
Doses of INVEGA® and INVEGA® SUSTENNA® needed to attain similar paliperidone exposure during maintenance treatment

<table>
<thead>
<tr>
<th>Formulation</th>
<th>INVEGA® Extended-Release Tablet</th>
<th>INVEGA® SUSTENNA® Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Frequency</td>
<td>Once daily</td>
<td>Once every 4 weeks</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>12</td>
<td>234</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>39-78</td>
</tr>
</tbody>
</table>
**INVEGA TRINZA® DOSES FOR ADULT PATIENTS ADEQUATELY TREATED WITH INVEGA SUSTENNA®**

<table>
<thead>
<tr>
<th>If the last INVEGA SUSTENNA® dose was:</th>
<th>Initiate INVEGA TRINZA® at the following dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td>78 mg</td>
<td>273 mg</td>
</tr>
<tr>
<td>117 mg</td>
<td>410 mg</td>
</tr>
<tr>
<td>156 mg</td>
<td>546 mg</td>
</tr>
<tr>
<td>234 mg</td>
<td>819 mg</td>
</tr>
</tbody>
</table>

Arrows illustrate the corresponding dose conversion from INVEGA SUSTENNA® to INVEGA TRINZA®.

*Conversion from the INVEGA SUSTENNA® 39-mg dose was not studied.*
Antipsychotics (con’t)

- **Number Two:**
  - Saphris (Asenapine) 2009: Indication for the treatment of schizophrenia and acute mania in bipolar disorder. Dosage range is 5mg to 10mg twice a day as a sublingual formulation.
  - Asenapine is currently working on a depot formulation, so you may see this come out in a couple of years.
  - Adverse side effects include: insomnia, somnolence, extrapyramidal symptoms, akathisia, constipation, oral hypoesthesia (numbness), vomiting, diarrhea.

- **Number Three:**
  - Fanapt (Iloperidone) 2009: Indication for the treatment of schizophrenia. Dosage range is 1mg to 12mg twice a day. Related to risperidone.
  - Adverse side effects include: dizziness, somnolence, dry mouth, tachycardia, nausea, diarrhea, orthostatic hypotension, weight gain.
Antipsychotics (con’t)

- **Number Four:**
  - Zyprexa Relprevv (olanzapine) 2009: Indication for the treatment of schizophrenia. Dosage range is 150mg to 300mg IM.
  - This injection can only be given if a patient is enrolled in a care program which must be specifically certified to offer this injection.
  - Approximately 0.7% of patients have post injection delirium/sedation syndrome (PDSS) which requires at least 3 hours of monitoring post-injection. There have been approximately 3-4 deaths on this medication, hence the strict monitoring and certification required to prescribe this formulation.
<table>
<thead>
<tr>
<th>Target Oral ZYPREXA Dose</th>
<th>Dosing of ZYPREXA RELPREVV During the First 8 Weeks</th>
<th>Maintenance Dose After 8 Weeks of ZYPREXA RELPREVV Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/day</td>
<td>210 mg/2 weeks or 405 mg/4 weeks</td>
<td>150 mg/2 weeks or 300 mg/4 weeks</td>
</tr>
<tr>
<td>15 mg/day</td>
<td>300 mg/2 weeks</td>
<td>210 mg/2 weeks or 405 mg/4 weeks</td>
</tr>
<tr>
<td>20 mg/day</td>
<td>300 mg/2 weeks</td>
<td>300 mg/2 weeks</td>
</tr>
</tbody>
</table>
Antipsychotics (con’t)

- **Number Five:**
  - Latuda (Lurasidone) 2010: Indication for the treatment of schizophrenia. Dosage range is 40 to 80mg once a day.
  - Recommended to be taken with food.
  - Adverse side effects include: somnolence, akathisia, nausea, parkinsonism, and agitation.

- **Number Six:**
  - Vraylar (cariprazine) 2015: Indication for the treatment of schizophrenia and mania. Dosage range is 1.5mg to 6mg once daily.
  - Adverse side effects include: extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, restlessness.
Antipsychotics (con’t)

- **Number Seven:**
  - Rexulti (brexpiprazole) 2015: Indication for treatment of schizophrenia and adjunct treatment for major depression. Dosage range from 1mg to 4mg once daily.
  - Adverse side effects include: akathisia, weight gain.
  - Has a black box warning for elderly patients with dementia related psychosis and potential risk of suicidal thoughts and behaviors in patients younger than 24.

- **Number Eight:**
  - Aristada (aripiprazole lauroxil) 2015: Indication for the treatment of schizophrenia. Dosage ranges from 441mg to 1064mg (see next page table for details).
  - Adverse side effects include: akathisia.
  - Has a black box warning for elderly patients with dementia related psychosis (increased risk of death).
<table>
<thead>
<tr>
<th>Oral Aripiprazole Dose</th>
<th>Intramuscular ARISTADA Dose</th>
<th>Concomitant Oral Aripiprazole (duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg per day</td>
<td>441 mg every month</td>
<td>First 21 days</td>
</tr>
<tr>
<td>15 mg per day</td>
<td>662 mg every month 882 mg every 6 weeks 1064 mg every 2 months</td>
<td>First 21 days</td>
</tr>
<tr>
<td>20 mg or higher per day</td>
<td>882 mg every month</td>
<td>First 21 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose</th>
<th>Dosing Frequency</th>
<th>Site of Intramuscular Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>441 mg</td>
<td>Monthly</td>
<td>Deltoid or Gluteal</td>
</tr>
<tr>
<td>662 mg</td>
<td>Monthly</td>
<td>Gluteal</td>
</tr>
<tr>
<td>882 mg</td>
<td>Monthly or every 6 weeks</td>
<td>Gluteal</td>
</tr>
<tr>
<td>1064 mg</td>
<td>Every 2 months</td>
<td>Gluteal</td>
</tr>
</tbody>
</table>
“It’s a new anti-depressant—instead of swallowing it, you throw it at anyone who appears to be having a good time.”
Antidepressants

- In the 1950’s, isoniazid was used to treat for tuberculosis, and it was found to have antidepressant properties. Researchers found that MAO inhibition was the reason for this, and began creating the first MAO-inhibitors.

- The tricyclics were discovered next, with imipramine being found to impact mood more than psychosis (initially trialed as a drug for the treatment of schizophrenia).

- Dr Arvid Carlsson was the first to develop a selective-serotonin re-uptake inhibitor (his medication was taken off the European market due to serious Guillian-Barre syndrome side-effect in a few patients, and never made it to the USA.)


Antidepressant of the last decade

- 2008 Aplenzin (bupropion hydrobromide)
- 2010 Oleptro (trazadone hydrochloride)
- 2011 Viibryd (vilazodone hydrochloride)
- 2013 Fetzima (levomilnacipran)
- 2013 Brintellix (vortioxetine)
Antidepressants (con’t)

- **Number One:**
  - Aplenzin (bupropion hydrobromide) 2008: Indication for treatment of major depression. Dosage is from 174mg-522mg once daily.
  - Difference between Wellbutrin and aplenzin is that Wellbutrin is made with bupropion hydrochloride by GlaxoSmithKline, and aplenzin is bupropion hydrobromide made by Sanofi-Aventis.
  - Both are expected to have similar efficacies and thought to impact the noradrenergic and/or dopaminergic systems.
  - Adverse side effects include: dry mouth, nausea, insomnia, dizziness, pharyngitis, abdominal pain, agitation, anxiety, tremor, palpitation, sweating, tinnitus, myalgia, anorexia, urinary frequency, and rash.
Antidepressants (con’t)

- **Number Two:**
  - Oleptro (trazadone hydrochloride) 2010: Indication for the treatment of major depressive disorder. Dosage range is 150mg to 375mg once daily.
  - This is a once a day controlled release formulation of trazadone. Believed to potentiate serotonergic activity in the CNS.
  - Adverse side effects include: somnolence, sedation, dizziness, constipation, vision blurred, and headache. Priapism?

- **Number Three:**
  - Viibryd (vilazodone hydrochloride) 2011: Indicated for the treatment of major depressive disorder. Dosage range is 10mg to 40mg once daily.
  - Viibryd is a selective serotonin reuptake inhibitor and a 5HT1A receptor partial agonist.
  - Adverse side effects include: diarrhea, nausea, vomiting, insomnia.
Antidepressants (con’t)

- **Number Four:**
  - Fetzima (levomilnacipran) 2013: Indication for the treatment of major depressive disorder. Dosage range is 40mg to 120mg once daily.
  - Fetzima is an extended release selective norepinephrine and serotonin reuptake inhibitor.
  - Adverse side effects include: nausea, constipation, hyperhidrosis (excessive sweating), heart rate increase, erectile dysfunction, tachycardia, vomiting, palpitations.

- **Number Five:**
  - Brintellix (vortioxetine) 2013: Indication for the treatment of major depressive disorder. Dosage range is 10mg to 20mg once daily.
  - Brintellix is a serotonin modulator and stimulator. Tested in geriatric patients.
  - Adverse side effects include: nausea, constipation, vomiting.
Other new psychotropic medications

- **Number One:**
  - Nuplazid (pimavanserin) 2016: Indication for the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis. Dosage is 34 mg once daily.
  - Thought to work by the combination of inverse agonist and antagonist activity at serotonin 5-HT2A receptors.
  - Still has a black box warning against use in elderly, and is not indicated for use in the treatment of patients with dementia-related psychosis.
  - Adverse side effects include: peripheral edema, confusion state.
Other drugs (con’t)

- **Number Two:**

  - Ingrezza (Valbenazine) 2017: Indication for treatment of adults with tardive dyskinesia. Dosage range is 40-80mg once daily.
  - INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor.
  - Trial study was done for 6 weeks.
  - Adverse side effects include: sleepiness and QT prolongation.
Case Study #1

- 52 yo swm who has DMII, homelessness, schizophrenia, HIV, and is not willing to engage with mental health, but has a relationship with his primary care provider and shows up almost daily to PCP’s office. Refuses any medications including antibiotics for his ulcers on his legs due to persistent paranoia.

What would be your first choice in regards to treatment?
- In a perfect world, I would consider oral antipsychotics, but due to patient’s current mental status, that is not an option.

What are the alternatives?
- I think you have to decide on an atypical IM antipsychotic despite risk of no oral trials.
- Zyprexa Relprevv is out as a choice due to the restrictions on it; I would also rule out any 3 month formulation as a starting option.
- BUT, I would consider a medication that I could start with monthly, that would then be given every 2-3 months if patient does well (no side effects, some efficacy seen).
- My two choices would be Invega sustenna or Aristada.
Case Study #2

- 19 yo swm with depression, anxiety, and IBS. Has had trials of Prozac, Zoloft, and Lexapro with very little impact on his symptoms.

- What are your considerations?
  - Tricyclic antidepressants (TCA’s) can help with IBS, and so can Viibyrd (vilazodone).

- How to choose between them?
  - In general, due TCA being limiting at higher doses due to muscarinic and anticholinergic side effects, it would not be my first choice.
  - I would choose viibyrd due to the 5-HT4 receptor on which vilazodone acts is present in the gastrointestinal (GI) tract which may impact the IBS positively.
“Honestly, Doctor, I tried to keep the channels of communication open, but it was so much easier just to eat him.”
References

- McDonnell et al. BMC Psychiatry 2010, 10:45 [http://www.biomedcentral.com/1471-244X/10/45](http://www.biomedcentral.com/1471-244X/10/45).
- [https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm552418.htm](https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm552418.htm)