Recent Pharmacological and Therapeutic Developments Related to Psychiatry

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Disclosure

¬ I have the following financial relationship to disclose:
  ¬ Speaker’s Bureau for Abbott Laboratories
¬ I will not discuss off-label use in my presentation.
¬ I will not discuss any investigational drugs.

Educational Objectives

¬ At the conclusion of this session, the participant should be able to:
  ¬ Identify and interpret essential information regarding newer drugs and changes in the therapeutic application(s) of drugs used in psychiatry.
  ¬ Compare and contrast the benefits and risks of atypical antipsychotics and antidepressants.
  ¬ Appropriately respond to questions and concerns from patients on recent reports in the pharmacologic literature.
Recent Pharmacological and Therapeutic Developments Related to Psychiatry

ETSU Department of Psychiatry
Grand Rounds
May 27, 2011

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**Top 15 Drugs for 2010 by Sales**
(in billions of US $ and % gain or loss)

1. Lipitor® 10.7 -6%
2. Plavix® 9.43 -4%
3. Remicade® 7.99 N/A
4. Advair® 7.94 +2%
5. Enbrel® 7.23 N/A
6. Abilify® 6.78 N/A
7. Humira® 6.55 +19%
8. Avastin® 6.22 +8%
9. Rituxan® 6.11 +9%
10. Diovan® 6.05 +1%
11. Crestor® 5.69 +26%
12. Seroquel® 5.3 +9%
13. Herceptin® 5.22 +7%
14. Zyprexa® 5.03 +2%
15. Singulair® 4.99 +7%

** america's Most Medicated States**
Retail prescriptions filled per capita for 2009

1. West Virginia 18.4
2. Tennessee 16.9
3. Alabama 16.7
4. Kentucky 16.5
5. Arkansas 16.4
6. South Carolina 16.3
7. Mississippi 15.9
8. Iowa 15.3
9. Missouri 15.0
10. Vermont 15.0

Forbes.com, August 16, 2010

**Use of Psychiatric Drugs in US Increased in all Age Groups**
- Prescriptions for psychoactive drugs increased from 1996 to 2006 as follows:
  - Doubled in people aged 65 years and older
  - Increased 73% in adults
  - Increased 50% in children

*Health Affairs, 28, no. 3 (2009): 637-648
doi: 10.1377/hlthaff.28.3.637, May 5, 2009*

**Drugs Make Up One-half of Spending for Mental-Health Care in U. S.**
- Drug costs account for 51% of spending for mental-health care.
  - The author suggested that the trend toward greater use of psychiatric drugs reflects better access to care and comparatively slower growth in the use of psychosocial therapies.

*Health Affairs, 28, no. 3 (2009): 637-648
doi: 10.1377/hlthaff.28.3.637, May 5, 2009*
The Most Expensive Chronic Condition? Bipolar

- A data review of health care claims over a four-year period showed patients with bipolar disorder had significantly higher total per member per month costs compared with patients who had chronic conditions such as diabetes, depression, asthma or coronary artery disease.

Annual Meeting of the American Psychiatric Association, May 22, 2009

Generic Drugs Continue to Grow

- Generics now account for 72% of the total US pharmaceutical market volume, reaching an all-time high in 2009.
- However, brand name drugs made up about 80% of dollars spent on prescription drugs.

ICIB.com, February 9, 2010

Are Generic Drugs Just As Good?

- The continuing claims of pharmaceutical manufacturers and others that generic drugs are inferior to brand-name originals still lack convincing documentation.
- Nevertheless, with levothyroxine and antiepileptic drugs, Medical Letter consultants recommend using one formulation (brand name or generic) consistently or, if consistency is not possible with generics, prescribing the brand name routinely.

The Medical Letter, October 19, 2009

Branded Products That Became Available Generic in 2010

- Cozaar®/Hyzaar® (losartan/losartan & HCTZ)
- Arimidex® (anastrozole)
- Effexor XR® (venlafaxine)
- Aricept® (donepezil)
- Flomax® (tamsulosin)

Branded Products Going Generic in 2011 & 2012

2011
- Lipitor® (atorvastatin)
  - Generic atorvastatin became available in Canada in May 2010
- Plavix® (clopidogrel)
- Actos® (pioglitazone)
- Zyprexa® (olanzapine)

2012
- Lexapro® (escitalopram)
- Avandia® (rosiglitazone)
- Advair® (salmeterol/fluticasone)
- Diovan® (valsartan)
- Zometa® (zoledronic acid)
- Viagra® (sildenafil)


New Atypical Antipsychotic: Lurasidone (Latuda®)
- The 10th atypical is a dopamine type 2 (D2) AND serotonin type 2 (5-HT2A) antagonist approved for schizophrenia.
- Adverse effects (≥ 5%)
  - Somnolence
  - Akathisia
  - Nausea
  - Parkinsonism
  - Agitation

Prescriber’s Letter, February 2011

Lurasidone (Latuda®)
- Supplied as 40 & 80 mg tablets
- Cost ~$15-$20/day
- Dosing
  - Start 40 mg once daily with food
  - Maximum 80 mg once daily with food
  - Limit to 40 mg daily
    - CrCl 10 to 50 mL/min
    - Moderate to severe hepatic impairment

Prescriber’s Letter, February 2011
New Atypical Antipsychotic: Asenapine (Saphris®)

- Approved 2009 for schizophrenia and bi-polar.
- **Sublingual** tablet that is inactive if swallowed.
- Patients who may "cheek" other antipsychotics to avoid therapy, can just swallow this one.

Prescriber's Letter, October 2009

New Atypical Antipsychotic: Asenapine (Saphris®)

- Supposedly less drug interactions and less likely to cause weight gain than clozapine (Zyprexa®).
- **Disadvantages:**
  - Some studies show it to be less effective
  - Causes some QT prolongation, but not as much as some others
  - Administered twice a day
  - Cost ~$500/month

Prescriber's Letter, October 2009

### Adverse Effects for Atypicals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Diabetes</th>
<th>EPS</th>
<th>Prolactin</th>
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</table>

Treatment Guidelines from *The Medical Letter*, August, 2010
Prescriber's Letter, February 2011

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<th>QTc</th>
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Treatment Guidelines from *The Medical Letter*, August, 2010
Prescriber's Letter, February 2011
Efficacy of Atypicals

<table>
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<th>Atypical Antipsychotic &amp; Daily Dose</th>
<th>Efficacy</th>
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<tr>
<td>Aripiprazole (Abilify®) 10-30 mg</td>
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<tr>
<td>Clozapine (Clozaril®) 25-900 mg</td>
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</tr>
<tr>
<td>Olanzapine (Zyprexa®) 3.5-20 mg</td>
<td>+++</td>
</tr>
<tr>
<td>Quetiapine (Seroquel®) 150-800 mg</td>
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</tr>
<tr>
<td>Risperidone (Risperdal®) 0.5-6 mg</td>
<td>+++</td>
</tr>
<tr>
<td>Ziprasidone (Geodon®) 40-160 mg</td>
<td>++</td>
</tr>
</tbody>
</table>

Treatment Guidelines from *The Medical Letter*, May, 2010

Pros and Cons of Atypical Antipsychotics: Efficacy

- For schizophrenia, clozapine works best.
  - But save it for resistant cases, due to possible agranulocytosis.
- For mood disorders, use one that has some evidence of a benefit, and only when an antipsychotic is needed.
  - For resistant depression: Abilify®, Seroquel®, or Zyprexa®.
  - For bipolar disorder: Abilify®, Seroquel®, Zyprexa®, risperidone, Saphris®, or Geodon®.

Pros and Cons of Atypical Antipsychotics: Side Effects

- To minimize weight gain and metabolic effects: Abilify®, Latuda®, Saphris®, or Geodon®.
  - Not Zyprexa®, clozapine, or Seroquel®.
- To minimize EPS: Seroquel® or Fanapt®.
  - Not risperidone or Invega®.
- To minimize cardiac problems such as QT prolongation: Abilify® or Latuda®.
  - Not Geodon®, Fanapt®, or Invega®.
- To minimize sedation: Abilify®, risperidone, Invega®, or Geodon®.
- For insomnia or agitation: Zyprexa® or Seroquel®.
- To minimize hyperprolactinemia, avoid risperidone or Invega®.
"Substantial" Weight Gain in Children Treated with Atypical Antipsychotics

- Treatment-naive children who took atypical antipsychotics for 11 weeks had mean weight gain ranging from 4.4 kg to 8.5 kg, depending on the drug prescribed.
- Lead author Christoph Correll commented that "weight gain was pervasive even in medications usually considered to be weight neutral in adults."
- The study involved 272 children aged 4 years to 19 years of age with bipolar disorder, schizophrenia or other behavioral disorders.

JAMA. 2009;302(16):1811-1812

Risk of TD with Typical v. Atypical Antipsychotic Agents

- Traditional thinking has been that atypical antipsychotics represent an advance in the treatment of psychosis—not so much from the efficacy standpoint—but from the safety standpoint, primarily lack of EPS and TD.
- However, some studies are beginning to question if there really is a clinically significant decreased risk.


"Substantial" Weight Gain in Children Treated with Atypical Antipsychotics

- Specifically, weight gain was reported as follows:
  - Zyprexa® (olanzapine) = 8.5 kg (18.7 pounds)
  - Seroquel® (quetiapine) = 6.1 kg (13.4 pounds)
  - Abilify® (anipiprazole) = 4.4 kg (9.7 pounds)
  - Risperdal® (risperidone) = 3.5 kg (11.7 pounds)

JAMA. 2009;302(16):1811-1812

Risk of TD with Typical v. Atypical Antipsychotic Agents

- A study examining the incidence rate of TD among 352 outpatients receiving atypical and/or typical antipsychotic medications at a community mental health center concluded that the incidence of TD with atypicals was more similar to that of conventional antipsychotics than has been reported in most previous studies.

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Alternative Agents No Safer Than Atypicals in the Elderly
- BZDs, antidepressants, and conventional antipsychotic medications, frequently used as an alternative to atypical antipsychotics, may be no safer in vulnerable nursing home residents.
  - Admitting the study had some limitations, lead author Dr. Roca said the message is that "all medications can have serious adverse side effects in elderly people and should be prescribed only after considering the risks and costs of using these agents versus the risks and costs of not using them."
  
  CMAJ. Published online March 28, 2011

Long-term Antipsychotic Treatment and Loss of Brain Cells
- Progressive brain volume changes in schizophrenia are thought to be due principally to the disease.
  - However, recent animal studies indicate that antipsychotics may also contribute to brain tissue volume decrement.

Long-term Antipsychotic Treatment and Loss of Brain Cells
- A small human study (211 patients) with schizophrenia suggests that antipsychotics have a subtle but measurable influence on brain tissue loss over time.
  - With increasing use of these agents in non-schizophrenic patients, e.g., depression, this small study raises questions about the advisability of this practice.

Class Labeling: Antipsychotics Increase Risk of Abnormal Movements or Withdrawal Symptoms in Newborns
- The FDA updated the labels for all antipsychotic drugs to reflect a potential risk in newborns born to mothers taking the drugs during the third trimester.
- The FDA has received several reports of abnormal muscle movement or withdrawal among newborns whose mothers took antipsychotics.

FDA.gov, February 22, 2011

Arch Gen Psychiatry. 2011;68(2):128-137

Arch Gen Psychiatry. 2011;68(2):128-137
Class Labeling: Antipsychotics Increase Risk of Abnormal Movements or Withdrawal Symptoms in Newborns

- Specifically, these drugs may cause abnormal muscle movements and withdrawal symptoms in newborns, including agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding.
- The agency noted that “in some newborns, the symptoms subside within hours or days and do not require specific treatment; other newborns may require longer hospital stays.”

FDA.gov, February 22, 2011

New Antidepressant: Vilazodone (Viibryd®)

- Approved 2011, vilazodone (Viibryd®) is the first and only SSRI and 5HT1A receptor partial agonist.
- Claims to be “dual-action”

http://www.viibryd.com/

New Antidepressant: Vilazodone (Viibryd®)

- The marketing niche is that it may not interfere with sexual desire.
- Like other antidepressants, Viibryd® carries a boxed warning describing the increased risk of suicidal thinking and behavior in children and young adults ages 18 to 24 during initial treatment, as well as suicide ideation.

http://www.viibryd.com/

Antidepressant Benefits May Vary Depending on Severity of Symptoms

- A meta-analysis of 6 placebo-controlled studies of antidepressants.
- Those with severe symptoms derived the most benefit, while those with less-severe symptoms experienced minimal or no benefit.
- Conclusion: “There is little evidence to suggest that [antidepressants] produce specific pharmacological benefit for the majority of patients with less severe acute depression.”

JAMA. 2010;303(1):47-53
Antidepressants and Bone Mineral Density

- A Canadian study found that osteoporosis was associated with SSRIs, mood stabilizers other than lithium, and benzodiazepines.
  - Use of tricyclic antidepressants was protective.
  - There was a 40% increased risk for low BMD with SSRIs and a 37% reduced risk with TCAs.

American Psychiatric Association 2010 Annual Meeting, Abstract NR4-5, May 25, 2010

Antidepressants and Atherosclerosis

- Antidepressant medications might be associated with atherosclerosis as measured by carotid intima-media thickness (CIMT), according to new observational data.
  - The study looked at a large cohort of male twins, and found that a twin taking an antidepressant had ~5% in CIMT.

American College of Cardiology, 2011 Scientific Sessions, New Orleans, April 2, 2011

Antidepressants and Atherosclerosis

- Dr. Amit Shah of Emory stated: Increased atherosclerotic burden of the carotid artery is not on the radar of practicing clinicians, including psychiatrists, and that most are instead concerned with sleep, appetite, and sexual side effects as well as weight gain. While these data should not be used to take patients off medications, the clinician needs to assess the benefits and risks on a patient-by-patient basis.

American College of Cardiology, 2011 Scientific Sessions New Orleans, April 2, 2011

Suicide Risk Is Same for All Antidepressants

- A nine-year cohort study collected data on 20,906 children aged 10 to 18 years who had been diagnosed with depression and were prescribed SSRIs or tricyclics.
  - The risk of suicidal behavior among children taking antidepressants was consistent across all drugs.

Suicide Risk Is Same for All Antidepressants

- Lead researcher Sebastian Schneeweiss said "the main finding is essentially a non-finding, meaning that there is no difference in risk for a suicide between different drugs."
- In the first year of receiving the drugs, 266 attempted suicides were recorded as well as 3 completed suicides.


FDA Warns of Suicidality with all Antiepileptic Drugs

- A FDA meta-analysis of nearly 200 clinical studies involving 11 anti-seizure drugs found a doubling of the risk of suicidal thinking or behavior.
- Patients receiving antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation (0.43%) compared to patients receiving placebo (0.22%).


Not All Epilepsy Drugs Raise Suicide Risk

- The FDA requires that all epilepsy drugs bear a warning label about an increased risk of suicidal behaviors, but a German study reports that only certain medications may increase the risk of self-harm.

Neurology, July 27, 2010

These Are Likely

- The study of more than 44,000 epilepsy patients in the UK revealed that those who took relatively new antiepileptic drugs with a higher risk of causing depression were three times more likely to harm themselves or attempt suicide than those who weren't taking any epilepsy medications.
  - levetiracetam (Keppra®)
  - topiramate (Topamax®)
  - vigabatrin (Sabril®)

Neurology, July 27, 2010
These Are Not Likely

- The researchers found that patients who took conventional epilepsy medications or those with a low risk of depression faced no increased risk of self-harm or suicidal behavior:
  - divalproex (Depakote®, Depakote ER®, Depakene®)
  - phenytoin (Dilantin®)
  - gabapentin (Neurontin®)
  - lamotrigine (Lamictal®)

Neurology, July 27, 2010

Antiepileptic Drugs Do Not Increase Suicide

- The current use of antiepileptic drugs was not associated with an increased risk of suicide-related events among patients with epilepsy.
  - However, it was associated with an increased risk of such events among patients with depression.


Antiepileptic Drugs Do Not Increase Suicide

- Study author Alejandro Arana said "in our opinion, in the long term, it is not the drugs themselves that raise the risk of suicide, but the underlying disease for which these drugs are prescribed."
- He added that "treatment with antiepileptic drugs helps to control the psychiatric syndromes that are at the root of suicidal behavior in these patients."


New Formulation and Indication: Silenor® (doxepin) for insomnia
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New Formulation: Oleptro® extended-release trazodone

Intuniv® (Guanfacine) For ADHD
- The alpha-2A adrenergic receptor agonist guanfacine is approved as Intuniv® to treat ADHD in children and adolescents aged 6 to 17 years.
- Guanfacine under the brand name Tenex® has long been approved for hypertension.

FDA.gov, September 3, 2009

Clonidine (Kapvay®) Approved for ADHD
- In October 2010, the FDA approved clonidine, the second alpha2 agonist non-stimulant for ADHD.
- Kapvay® is in an extended-release, twice daily oral formulation as add-on therapy to stimulants in children and adolescents ages 6-17 years.

FDA.gov, October 4, 2010

How Do Alpha2 Adrenergic Agonists Treat ADHD?
- While the mechanism of action of alpha2 agonists in ADHD is not known, it is believed to involve the pre-frontal cortex (PFC) of the brain.
- Studies suggest that the PFC regulates attention and plays a critical role in impulse control, working memory and executive function.

Shionogi Inc., Press Release, October 4, 2010
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Clonidine Abuse
- Clonidine is often used in opioid detox programs to reduce withdrawal symptoms such as anxiety, restlessness, insomnia.
- But some people are abusing it for its sedative effects or to ease withdrawal symptoms when they can’t afford street drugs.

Prescriber’s Letter, March 2010

“Bath Salts” are not for Bathing; Similar to Methamphetamine
- These aren’t really bath salts, they’re designer stimulants, such as mephedrone or 3,4-methylenedioxypyrovalerone (MDPV).
- These small powder packs are labeled "bath salts" or "plant food."
- They go by various brand names...Cloud 9, Blizzard, Ivory Snow, Ivory Wave, Vanilla Sky, Red Dove, and others.
- They are snorted, smoked, injected, or taken orally.

Prescriber’s Letter, March 2011

Questions?