Managing Psychotropic Drug Side Effects

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Disclosure of Conflicts

- Advisor: Avanir, Mylan Pharmaceuticals
- Consultant: Frontline Medical Communications, Medscape
- Speakers’ Bureau: AstraZeneca, Mylan Pharmaceuticals, Novartis, Takeda, Sunovion
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Objectives

• To gain familiarity with risks and benefits of psychotropic drug therapy and strategies for managing adverse side effects.
• To understand factors that impact the emergence of adverse psychotropic drug effects

Off Label Uses

• Virtually every intervention available is capitalizing on the pharmacodynamic profile of a compound that has not been approved by the FDA for the purpose of counteracting another drug’s side effect
Basic Concepts

• Risk-benefit analyses
  – Alternative efficacious treatments
  – Unique efficacy (eg, lithium, clozapine); effect size, NNH
  – Antidotes versus changing treatment, dangerous vs. annoying
• Time course to adverse effects vs. efficacy (rashes; NMS; TD)
• Attribution and causality
  – Primary illness vs. iatrogenic signs
  – Plausible mechanisms (eg, dry mouth + diarrhea)
  – Paradoxical vs. lack of efficacy (eg, psychosis from antipsychotics)
  – Side effect rates vary across illnesses (eg SSRIs: MDD vs. GAD)
  – Nocebo effects
• Generic vs. branded/extended release vs. immediate release
• At-risk populations (eg, antidepressant-induced mania; Han Chinese CBZ)
• Parsing effects within drug combinations
• Pharmacokinetic effects (eg, slow metabolizers), opposing mechanisms
• Pharmacologic parsimony/minimization of toxic polypharmacy
• Manufacturers’ PIs/spontaneous reporting
• Nocebo effects¹

¹ Barsky et al., JAMA 2002; 287: 622-627

Risk-Benefit Analyses

“This prescription doesn’t cure anything, but it has fewer side effects than other drugs.”
Time Course for Side Effects and the Natural Course of Illness

Nocebo Effects:
Most common (>10% in depression RCTs): dizziness, headache, nausea, diarrhea, sedation, insomnia, anorexia, nervousness, anxiety

Predisposing factors: neuroticism, phobic-obsessive traits, suggestibility, alexithymia
## End-Organ Effects

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Alopecia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Angioedema</td>
</tr>
<tr>
<td>Systemic</td>
<td>Blood dyscrasias</td>
</tr>
<tr>
<td>Sexual</td>
<td>Bone demineralization</td>
</tr>
<tr>
<td>Weight</td>
<td>Bruxism</td>
</tr>
<tr>
<td>Sedation</td>
<td>Discontinuation Syndromes</td>
</tr>
<tr>
<td>Sleep</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Cognition</td>
<td>Edema</td>
</tr>
<tr>
<td>Motor</td>
<td>Electrolyte abnormalities</td>
</tr>
</tbody>
</table>

### Cardiac

- Ray et al., NEJM 2009; 360: 225-235

### Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death

**Results**

Current users of typical and of atypical antipsychotic drugs had higher rates of sudden cardiac death than did nonusers of antipsychotic drugs, with adjusted incidence-rate ratios of 1.99 (95% confidence interval [CI], 1.68 to 2.34) and 2.26 (95% CI, 1.88 to 2.72), respectively. The incidence-rate ratio for users of atypical antipsychotic drugs as compared with users of typical antipsychotic drugs was 1.14 (95% CI, 0.93 to 1.39). For both classes of drugs, the risk for current users increased significantly with an increasing dose. Among users of typical antipsychotic drugs, the incidence-rate ratios increased from 1.31 (95% CI, 0.97 to 1.77) for those taking low doses to 2.42 (95% CI, 1.91 to 3.06) for those taking high doses (P<0.001). Among users of atypical agents, the incidence-rate ratios increased from 1.59 (95% CI, 1.03 to 2.46) for those taking low doses to 2.86 (95% CI, 2.23 to 3.65) for those taking high doses (P<0.01). The findings were similar in the cohort that was matched for propensity score.

Ray et al., NEJM 2009; 360: 225-235
QTc Prolongation Among Antipsychotics

- If QTc > 500: avoid antipsychotics
- If QTc is prolonged (i.e., 450-499 msec): benefit may outweigh risk of using an antipsychotic with lower potential for QTc prolongation
  - Collaboration with cardiologist
  - Assure no other medications are present that could independently prolong QTc

Marder et al., Schizophr Res 2003; 61: 123-135
Glassman & Biggers, Am J Psychiatry 2001; 158: 1774-1783

Risk Factors for QTc Prolongation

- Alcohol
- Antiarrhythmics (amiodarone, flecainide, quinidine)
- Antibiotics (azithromycin, ciprofloxacin, erythromycin, levofloxacin)
- Ondansetron
- Ketoconazole
- Citalopram >40 mg/day
- cyclobenzaprine
- Methadone
- TCAs
- Trazodone
- vardenafil
Cardiac Adverse Effects

<table>
<thead>
<tr>
<th>Agent</th>
<th>EKG Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Heart block, ventricular arrhythmias in OD</td>
</tr>
<tr>
<td>Divalproex</td>
<td>↑ or ↓ heart rate</td>
</tr>
<tr>
<td>Lithium</td>
<td>Reversible T-wave changes, sinus bradycardia, heart block</td>
</tr>
<tr>
<td>Second Generation Antipsychotics</td>
<td>QTc↑ (ziprasidone: 20.3 msec, quetiapine 14.5 msec, risperidone 11.6 msec, olanzapine 6.8 msec, haloperidol 4.7 msec)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>myocarditis</td>
</tr>
<tr>
<td>SSRIs</td>
<td>QTc ↑ (rare) w/fluoxetine, paroxetine, sertraline</td>
</tr>
<tr>
<td>SNRIs</td>
<td>↑ HR, minor QT or QES prolongation on OD</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>↑PR and QRS interval, ST-T changes</td>
</tr>
</tbody>
</table>

Renal Function

GFR: (normal):
- Normally declines by ~10 ml/min/year beyond age 40
- Chronic Kidney Disease stages:
  - St 1: GFR >90 mL/min/1.73 m²
  - St 2: GFR 60-89 mL/min/1.73 m²
  - St 3: GFR 30-59 mL/min/1.73 m²
  - St 4: GFR 15-29 mL/min/1.73 m²
  - GFR <15 mL/min/1.73 m²

LITHIUM
- APA Guidelines: semi-annual monitoring of lithium levels and serum creatinine
- Long-term risk for CKD: 4% – 20%
- Once-daily dosing minimizes glomerular sclerosis
- Rises > 25% warrant measurement of 24-hour urine for creatinine clearance

DIABETES INSIPIDUS
- Amlodipine 5 mg BID to ↑ concentrating ability (K⁺ sparing)

1 Gitlin, 1993; 2 Lepkifker 2004; 3 Finch et al., 2003; 4 Bedford et al., 2008
Discontinuation Syndromes

Serotonergic Antidepressants:
As many as 46% of patients taking short t½ SSRI1,2
Hypothesized mechanisms:
• cholinergic rebound (after prolonged blockade)
(e.g., paroxetine, 3⁰ amine TCAs)
• Increased catecholaminergic activity
• Rostral anterior cingulate choline/creatine
  metabolite ratio ↓

MAOI discontinuation: hallucinations, anxiety, agitation, paranoia, delirium
Gradual taper

Antipsychotic withdrawal dyskinesias

Prazosin (and other α1 blockers): rebound hypertension

1 Tint et al., J Psychopharmacol 2008; 22: 330-332
2 Perahia et al., J Affect Disord 2005; 89(1-3): 207-212
3 Kaufman et al., Biol Psychiatry 2003; 54: 534-539

Common Symptoms of SSRI Discontinuation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Fluoxetine</th>
<th>Sertraline</th>
<th>Paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=242 remitted MDD patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abrupt 5-8 day interruption of SSRI continuation treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms as reported by ≥10% of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>46</td>
<td>31</td>
<td>45</td>
</tr>
<tr>
<td>Irritability</td>
<td>35</td>
<td>31</td>
<td>36</td>
</tr>
<tr>
<td>Agitation</td>
<td>31</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>Dizziness</td>
<td>50</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>Confusion</td>
<td>42</td>
<td>42</td>
<td>36</td>
</tr>
<tr>
<td>Headache</td>
<td>34</td>
<td>34</td>
<td>22</td>
</tr>
<tr>
<td>Nervousness</td>
<td>34</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td>Crying</td>
<td>40</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>32</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Trouble sleeping</td>
<td>39</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>Daydreaming</td>
<td>17</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Anger</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Nausea</td>
<td>40</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>24</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Sweating</td>
<td>24</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Depersonalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle aches</td>
<td>23</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Unsteady gait</td>
<td>23</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Panic</td>
<td>21</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Shaking</td>
<td>21</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Muscle tension</td>
<td>11</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Chills</td>
<td>18</td>
<td>18</td>
<td>11</td>
</tr>
</tbody>
</table>

Rosenbaum et al., Biol Psychiatry 1998; 44: 77-87
Hypersensitivity Reactions

- **Anticonvulsants**: Drug Reaction with Eosinophilia and Systemic Symptoms
- Aseptic meningitis (lamotrigine) – 40 cases, mean onset @ 16 days
- Drug-induced Lupus Erythematosus: carbamazepine, oxcarbazepine, lithium, clonidine, first generation antipsychotics
  - Flu-like symptoms, fever, myalgias/arthralgias
  - (rash is rarer than in SLE)

Serotonin Syndrome

- Hunter criteria: clonus, agitation, diaphoresis, tremor, diarrhea, hyperreflexia
- MAOIs + serotonergic antidepressants, meperidine, dextromethorphan
- SSRIs + buspirone, triptans
- Amphetamines (which release serotonin)
- 3,4-methylenedioxymethamphetamine (Ecstasy)
- Tramodol + SSRIs or SNRIs
**SSRI-Associated Sexual Dysfunction**

30-70% incidence

<table>
<thead>
<tr>
<th>Agent</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>DA agonism</td>
</tr>
<tr>
<td>Bupropion</td>
<td>DA agonism</td>
</tr>
<tr>
<td>Buspirone</td>
<td>5-HT$_{1A}$ partial agonism</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>5-HT blocker</td>
</tr>
<tr>
<td>Gingko Biloba</td>
<td>?</td>
</tr>
<tr>
<td>Maca Root</td>
<td>?</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>DA agonism</td>
</tr>
<tr>
<td>PDE-5 Inhibitors (Sildenafil, Tadalafil, Vardenafil)</td>
<td>NO</td>
</tr>
<tr>
<td>Yohimbine (+/- L-arginine glutamate)</td>
<td>$\alpha_2$ blockade $\uparrow$’s NE tone</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Postsynaptic 5HT$_{2A}$ blocker</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Postsynaptic 5HT$_{2A}$ blocker</td>
</tr>
</tbody>
</table>

**Amantadine vs. Buspirone vs. Placebo in Women with SSRI-Associated Sexual Dysfunction**

- Fluoxetine treatment for MDD x at least 8 weeks + subsequent emergence of sexual dysfunction
- Randomization to amantadine (N=18), buspirone (N=19) or placebo (N=20)
- No significant between-group differences in interest/desire, lubrication, orgasm, pleasure, discomfort

Buspirone for SSRI-Induced Sexual Dysfunction

- 4-week randomized comparison of buspirone (mean dose 49 mg/day) or placebo added to paroxetine or citalopram
- 47 men and women, trend toward better outcomes in women

Landén et al., J Clin Psychopharmacol 1998; 19: 268-271

Sildenafil for SSRI-Associated Sexual Dysfunction

- 6-week randomized placebo-controlled trial of sildenafil 50-100 mg/day in 90 remitted male depressed outpatients with SSRI-associated sexual dysfunction
- % "very much improved" or "much improved"

Nurnberger et al., JAMA 2003; 289: 56-64
Sildenafil for SSRI-Associated Sexual Dysfunction

6-week randomized comparison of sildenafil (N=71) or placebo (N=71)
In remitted depressed men with SSRI-associated erectile dysfunction

• Significantly improved frequency of penetration, maintained erections
  after penetration, more successful intercourse attempts per week

Fava et al., *J Clin Psychiatry* 2006; 67: 240-246

Sildenafil for SSRI-Associated Sexual Dysfunction in Women

• 8-week placebo-controlled randomized study of sildenafil 50-100 mg/day
• 98 premenopausal women with SSRI-remitted depression but 2o sexual dysfunction

LABEL

1

1.5

2

Greater ability to achieve orgasm (p=.01)
Greater improvement in quality of orgasm (p=.03)

Note: in women, PDEIs improve anorgasmia but not desire, arousal-sensation, or arousal-lubrication

Adverse effects: headache, flushing, dyspepsia, nasal congestion, blurry vision

Numberg et al., *JAMA* 2008; 300: 395-404
**Yohimbine**

- 3-way crossover: Yohimbine 6 mg vs. Yohimbine 6 mg + L arginine glutamate 6 gms or placebo
- 45 men with erectile dysfunction (non-iatrogenic)

Lebret et al., *Eur Urol* 2002; 41: 608-613

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**Adjunctive Bupropion for SSRI-Associated Sexual Dysfunction**

- Open trial of bupropion SR 75-150 mg 1-2x before sex or TID if no response
  - N=47
  - 66% overall improved (38% of those on PRN regimen)

- 234 euthymic SSRI-treated men
  - Bupropion SR 150 mg BID vs. placebo x 12 weeks
  - Better global sexual functioning (ASEX, IIEF, CGI-SF)
  - Safarinejad, *BJU Int* 2010; 106: 840-847

- 6-week randomized comparison (N=41) of Bupropion SR 150 mg/day or placebo X 6 weeks
  - No significant between-group differences on ASEX

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- 6-week randomized comparison (N=30) of bupropion SR 150 mg or placebo q 6 PM x 3 weeks
  - No significant between-group differences on ASEX
  - Masand et al., *Am J Psychiatr* 2001; 158: 06-807
Mixed or Preliminary Results

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyproheptadine</td>
<td>Case reports</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Case reports, but negative double-blind data ¹</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Open trial (N=20), 50-100 mg/day improved desire, arousal, orgasm in ♂ and ♀ ²</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>8-week open trial (N=33), 15-30 mg/day; 49% reported significant improvement ³</td>
</tr>
<tr>
<td>Gingko Biloba</td>
<td>Case reports, but negative double-blind data ⁴,⁵</td>
</tr>
</tbody>
</table>

¹ Pae et al., 2009 ² Stryjer et al., Clin Neuropsychopharmacol 2009; 32: 82-84; ³ Ozmenler et al., Hum Psychopharmacol 2008; 23: 321-326; ⁴ Kang et al., Hum Psychopharmacol 2002; 17: 279-284; ⁵ Wheatley et al., Hum Psychopharmacol 2004; 19: 545-548

Psychotropic-Induced Weight Gain

STRATEGIES:
- Diet and exercise
- Metformin
- Topiramate
- Zonisamide
- Lamotrigine
- H₂ blockers
- Bupropion (+/- NTX)
- Orlistat
- Amantadine
- Stimulants
- Chromium picolinate

- Severity of illness
- Unique efficacy?
- Alternate tx’s?
- Viable to manage?
- Weight gain ² to psychiatric illness, concomitant meds or medical/psychiatric comorbidity?
- Extent of weight gain
- Other metabolic risks
### Lifestyle Modification for Psychotropic Weight Gain

<table>
<thead>
<tr>
<th>Authors</th>
<th>Duration</th>
<th>N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centorrino 1</td>
<td>24 weeks</td>
<td>22</td>
<td>13.2# wt loss (5.7% of baseline); 77% completed</td>
</tr>
<tr>
<td>Chen 2</td>
<td>10 weeks</td>
<td>33</td>
<td>↓4.6# @ 10 weeks; 8.1# @ 6 mos; 5.9# @ 12 mos; ↓TGs</td>
</tr>
<tr>
<td>Paulin 3</td>
<td>18 mos</td>
<td>110</td>
<td>3.5% ↓BW, ↓LDL, ↓TGs, ↓FBS, ↑HDL</td>
</tr>
<tr>
<td>Vreeland 4</td>
<td>12 week</td>
<td>31</td>
<td>6# wt ↓; 87% completed; 65% completedede 40-week extension, w/ ↓HbA1c</td>
</tr>
<tr>
<td>Menza 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kwon 6</td>
<td>12 week</td>
<td>48</td>
<td>8.8# lost @ 8 weeks; no lipid Δ’s; 75% completed</td>
</tr>
</tbody>
</table>


### Metformin + Lifestyle Modification

- 12 week comparison of metformin 750 mg/day or placebo, +/- lifestyle modification
- 128 schizophrenia patients who gained >10% of baseline body weight w/SGAs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Δ BMI</th>
<th>Insulin Resistance Index</th>
<th>Δ in waist circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle + metformin*</td>
<td>1.8</td>
<td>3.6</td>
<td>↓ 2.0 cm</td>
</tr>
<tr>
<td>Metformin</td>
<td>1.2</td>
<td>3.5</td>
<td>↓ 1.3 cm</td>
</tr>
<tr>
<td>Lifestyle + placebo</td>
<td>0.5</td>
<td>1.0</td>
<td>↑ 1.2 cm</td>
</tr>
</tbody>
</table>

* BMI: L + M > M or L; M > L or PBO; L > PBO  
* IRI: L + M > L or PBO; M > L or PBO; L > PBO  
* Waist: L + M > M or L or PBO; M > L or PBO; L >PBO

Wu et al., *JAMA* 2008; 299: 185-193
Metabolic Dysregulation: Hyperglycemia and Metformin

• 40 drug-naïve, 1st episode SZ patients
• 12 weeks of OLZ 15 mg/day + metformin 750 mg/day or placebo

Fasting Glucose
Fasting Insulin
Insulin Resistance Index

Wu et al., Am J Psychiatry 2008; 165: 352-358

Metformin for Atypical-Antipsychotic-Induced Weight Gain in Adolescents

16-week double-blind placebo-controlled trial of metformin in 39 adolescents who gained >10% of baseline weight with olanzapine, risperidone or quetiapine

Dosing: 500 mg @ HS x 1 week, then 500 mg BID, then 850 mg BID

Klein et al., Am J Psychiatry 2006; 163: 2072-2079
**Metformin: Negative RCT**

- 40 SZ patients beginning olanzapine
- 14-week comparison of adjunctive metformin (850-1700 mg/day) or placebo
- Mean serum glucose levels decreased significantly
- No significant differences in waist circumference, body weight gain, BMI, fasting glucose, insulin, lipids

Baptista et al., *Can J Psychiatry* 2006; 51: 192-196

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**Topiramate vs. Sibutramine for Psychotropic-Induced Weight Gain in Bipolar Disorder**

24-week open randomized trial

<table>
<thead>
<tr>
<th></th>
<th>Sibutramine 5-15 mg/day</th>
<th>Topiramate 25-600 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=18</td>
<td></td>
<td>N=28</td>
</tr>
<tr>
<td>Mean weight loss</td>
<td>4.1 kg</td>
<td>2.8 kg</td>
</tr>
<tr>
<td>Δ BMI</td>
<td>-1.4</td>
<td>-1.1</td>
</tr>
<tr>
<td>% body weight lost</td>
<td>-4%</td>
<td>-3%</td>
</tr>
<tr>
<td>Completers</td>
<td>22%</td>
<td>21%</td>
</tr>
</tbody>
</table>

McElroy et al., *Bipolar Disord* 2007; 9: 426-434
Zonisamide vs. Placebo for Weight Loss in Obese Adults

- 60 randomized adults
- 16-week randomized trial
- Dosing: 100-600 mg/day
- Zonisamide: 57% lost 5% of baseline body weight (cf. 10% lost 5% w/ placebo)
- Extension to 32 weeks: Zonisamide group lost 9.2 kg (9.4% loss) vs. 1.5 kg (1.8% loss w/ placebo)

Data from the last observation carried forward, intent-to-treat analysis. Error bars indicate SE.

Gadde et al., JAMA 2003; 289: 1820-1825

Naltrexone (16 or 32 mg/day) + Bupropion SR (360 mg/day) for Overweight and Obesity

- N=1742
- 34 USA sites
- 56 weeks
- Healthy obese pts

Weight Loss:
- PBO: -1.3%
- NTX 16: -5.0%
- NTX 32: -6.1%

Greenway et al., Lancet 2010; 376: 595-605
**Lamotrigine or Placebo for Weight Loss in Obese Adults**

26 week randomized comparison of lamotrigine (200 mg/day) or placebo in 40 obese psychiatrically healthy adults

<table>
<thead>
<tr>
<th>Mean Δ in BMI from Baseline</th>
<th>Weight Loss (pounds) (LOCF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>Placebo</td>
</tr>
<tr>
<td>-1.5</td>
<td>-0.1</td>
</tr>
<tr>
<td>p = .042</td>
<td>p = .06</td>
</tr>
</tbody>
</table>

Meredith, *J Clin Psychiatry* 2006; 67: 258-262

**Nizatidine for Olanzapine-Associated Weight Gain**

**KOREAN SAMPLE**

- 8-week open-label trial in 10 SZ patients
- 3.5% down in weight, 3.7% down in BMI

**Lilly sample**

- 16-week RCT
- OLZ + nizatidine 150 or 300 mg BID
- NO SIGNIFICANT DIFFERENCES

*Fig. 1. Weight gain reduced at weeks 3 and 4 in patients treated with OLZ + Niz 300 mg b.i.d.*

Nizatidine and Olanzapine-Associated Weight Gain

8-week randomized placebo comparison in 35 SZ patients who gained >2.5 kg

Changes in Weight (kg)

Changes in serum Leptin Levels (mg/dL)

Atmaca et al., *Hum Psychopharmacol* 2003; 18: 457-461

Amantadine for Olanzapine-Associated Weight Gain in SZ

- 16-week randomized comparison of 300 mg/day of amantadine (N=60) or placebo (N=65) in psychosis patients who gained >5% of baseline body weight with olanzapine
- Greater weight loss with amantadine (-0.19 ± 4.58 kg) than placebo (+1.28 ± 4.26 kg)

Amantadine for Olanzapine-Associated Weight Gain in SZ

- 12-week randomized comparison of amantadine (300 mg/day) or placebo
- 21 adults with SZ who had gained >5 lbs with olanzapine
- Amantadine recipients lost a mean of 0.8 lbs (cf. placebo: gain of 8.7 lbs)


Orlistat for Clozapine- or Olanzapine-Associated Weight Gain

- 16-week randomized placebo comparison
- Baseline BMI: 28-43 kg/m²
- Dosing: 120 mg TID
- Response (>5% loss of baseline weight): 16% orlistat vs. 6% PBO (ns)

Stimulants and Weight Loss

- Adipex (phentermine) – short-term (12 weeks)
- Qsymia (topiramate and phentermine)
- Amphetamine
- Methylphenidate
- No clear pro-anorectic effect with modafinil or armodafinil

Sedation

Double-Blind, Placebo-Controlled Study of Modafinil for Fatigue and Cognition in Schizophrenia Patients Treated With Psychotropic Medications


- Adjunctive modafinil 200 mg/day added to olanzapine, risperidone, quetiapine or ziprasidone ± typical antipsychotics ± mood stabilizers ± antidepressants ± anticholinergics ± benzodiazepines ± zolpidem

No significant differences

Fatigue Severity Scale

Common side effects: agitation, insomnia, dry mouth
Insomnia

Diagnostic Considerations:
- Simple insomnia vs. mania/hypomania
- Akathisia
- Restless Legs Syndrome/periodic limb movement disorder
- Sleep Apnea
- Circadian rhythm disturbances
- Substance use withdrawal

Evaluation:
- Sleep log
- Sleep hygiene

Sleep and Mood

- Depression ↑’s sleep latency, ↑’s waking after sleep onset, ↑’s REM latency and density, ↑’s early morning awakenings, ↓’s stages 3 and 4 (slow wave) sleep, shifts REM sleep to earlier in the night

- Co-therapy with fluoxetine + clonazepam (0.5-1 mg/HS) for MDD x 1st 21 days = better sleep + less anxiety + faster global improvement ¹

- Antidepressants generally suppress REM except bupropion and mirtazapine

¹ Lønberg et al., J Affect Disord 2000; 61(1-2): 73-79
### Insomnia

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>More time in light sleep (St 2), reduction in slow wave sleep and REM; tolerance, withdrawal, abuse</td>
</tr>
<tr>
<td>Chloral Hydrate</td>
<td>↓'s sleep latency; t½ 4-6h; tolerance</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta®)</td>
<td>GABA-A subunit selectivity; does not alter slow wave sleep or REM</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>↑'s slow wave sleep</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>↑ time in St 2, REM and slow wave sleep</td>
</tr>
<tr>
<td>Melatonin</td>
<td>0.1-0.3 mg = physiologically relevant; minimal disruption of sleep architecture</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>↓ REM time, ↑ total time in non-REM sleep &amp; ↑ 'd duration of St 2 sleep</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>↑'s REM and slow wave sleep</td>
</tr>
<tr>
<td>Doxepin (Silenor®)</td>
<td>H₁ antagonist; 25-50 mg @ HS</td>
</tr>
<tr>
<td>Trazodone</td>
<td>↓’s St 1 &amp; 2 sleep; little effect on REM</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>t½=1h; better for sleep initiation than maintenance</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Preserves slow wave sleep</td>
</tr>
</tbody>
</table>

### Benzo’s or Non-Benzo’s?

**BENZO’S**
- More disruption of sleep architecture
- Rebound insomnia and withdrawal
- Abuse potential
- Tolerance
- Respiratory suppression
- Daytime cognitive impairment

**NON-BENZO’S**
- Less disruption of sleep architecture
- Rarer rebound insomnia and withdrawal
- Lower abuse potential
- Less rapid tolerance during long-term tx
- Less risk for respiratory suppression
- Less retrograde memory impairment

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Adverse Cognitive Effects

- Illness with known cognitive AEs
  - Domains: attention, memory, executive function
- Parsing multiple sedating agents
- Anticholinergic, antihistaminergic, BZDs
- Drug toxicity states
  - Corroborative signs of neurotoxicity
- EtOH, depression, anxiety
- Amantadine vs. benztropine

Cognitive Enhancers?

<table>
<thead>
<tr>
<th>Agent</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>67% “global improvement” as open-label add-on</td>
</tr>
<tr>
<td></td>
<td>No benefit vs. placebo in Sz or SzAff disorder</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Same as placebo in studies in SZ</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Favorable case reports in BP disorder</td>
</tr>
<tr>
<td></td>
<td>Improved processing speed in SZ (16 mg/day)</td>
</tr>
<tr>
<td>Modafinil</td>
<td>May improve attentional set-shifting, working memory, response inhibition, executive function, immediate verbal recall, short-term visual memory</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>May improve working memory, language production</td>
</tr>
<tr>
<td>Memantine</td>
<td>Favorable open-label self-report data</td>
</tr>
</tbody>
</table>
### Other Possible Cognitive Enhancers?

<table>
<thead>
<tr>
<th>Cognition</th>
<th>COX-2 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramipexole</td>
<td></td>
</tr>
<tr>
<td>thyroxine</td>
<td>Buspirone</td>
</tr>
<tr>
<td>Glycine</td>
<td>Sibutramine</td>
</tr>
<tr>
<td>D-serine</td>
<td>Ginko biloba</td>
</tr>
<tr>
<td>D-cycloserine</td>
<td>Omega-3 fatty acids</td>
</tr>
<tr>
<td>Ampakines</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>Vitamin E</td>
</tr>
<tr>
<td></td>
<td>Taurine</td>
</tr>
</tbody>
</table>

### Motor Side Effects

- Rates of EPS
- Tremor: \( \beta \)-blockers, primidone
- Akathisia: \( \beta \)-blockers, benzodiazepines
### Tardive Dyskinesia and Vitamin E

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-week randomized comparison of Vit E 1200 IU vs. placebo (N=41)</td>
<td>AIMS reduction: 46% Vit E vs. 4% PBO</td>
</tr>
<tr>
<td>2-month randomized comparison of Vit E 800 IU BID vs. placebo (N=35)</td>
<td>AIMS reduction: 24% Vit E</td>
</tr>
<tr>
<td>2-Year 9-site VA trial comparing Vit E 1600 IU/day vs. placebo (N=158)</td>
<td>No total or subscale differences on AIMS</td>
</tr>
<tr>
<td>6-week comparison of Vit E 1600 IU/day vs. placebo (N=18)</td>
<td>No differences on AIMS scores</td>
</tr>
</tbody>
</table>


### Tardive Dyskinesia

<table>
<thead>
<tr>
<th>Agent</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B6 (N=50); 1200 mg/day or placebo x 26 weeks</td>
<td>Greater ↓ in EPS, Parkinsonism, dyskinesia (p&lt;.001)</td>
</tr>
<tr>
<td>Levetiracetam (N=50; 500-3000 mg/day (mean= 2156 mg/day)</td>
<td>AIMS decline 44% with LEV vs. 19% PBO (p=.022)</td>
</tr>
<tr>
<td>Amantadine (N=32, 100 mg BID) x 2 wks</td>
<td>Biperiden = amantadine &gt;PBO for Parkinsonism and AIMS</td>
</tr>
<tr>
<td>Biperiden (N=32, 2 mg BID) x 2 wks</td>
<td>Biperiden = amantadine &gt;PBO for Parkinsonism and AIMS</td>
</tr>
<tr>
<td>Melatonin (N=22, 10 mg x 6 weeks)</td>
<td>AIMS decline 2.5 points with MEL vs. 0.1 with PBO (p&lt;.001)</td>
</tr>
</tbody>
</table>

Clozapine and Tardive Dyskinesia

- 20 chronic SZ patients given clozapine x 18 weeks
- 74% TD improvement, 69% Parkinsonism improvement, 78% akathisia improvement

1 Spivak et al., J Clin Psychiatry 1997; 58: 318-322

Conclusions

- Effective management of adverse drug effects requires careful overall assessment and evaluation of relative drug risks and benefits
- Variable and ever-changing evidence-base to support pharmacologic and other strategies to manage specific iatrogenic effects