Managing Psychotropic Drug Side Effects

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Disclosure of Conflicts

- Advisor: Avanir, Mylan Pharmaceuticals
- Consultant: Frontline Medical Communications, Medscape
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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 effects[1]

[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

"I've been taking this medication for 50 years and I'm going to sue! The side effects made me wrinkled, fat and bald!"

TREATMENT-EMERGENT ADVERSE REACTION INCIDENCE RATES BY BODY SYSTEM IN ADULT OCD PATIENTS AND ANOTHER STUDIED POPULATION[1]

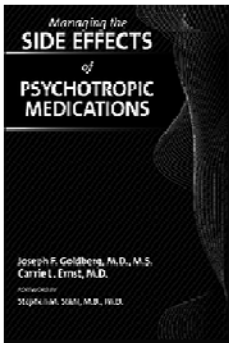
	PERCENTAGE OF PATIENTS REPORTING REACTION			
	OBSESSIVE COMPULSIVE DISORDER		OTHER STUDIED POPULATION	
BODY SYSTEM/ ADVERSE REACTION	LUVOX CR N = 124	PLACEBO N = 124	LUVOX CR N = 279	PLACEBO N = 276
BODY AS A WHOLE				
Headache	32	31	35	30
Asthenia	26	8	24	10
Pain[2]	10	8	–	–
Abdominal Pain	--	--	5	4
Accidental Injury	5	3	–	–
Chest Pain	--	--	3	1
Viral Infection	2	<1	–	–

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

- Cardiac
- Renal
- Systemic
- Sexual
- Weight
- Sedation
- Sleep
- Cognition
- Motor



Alopecia
Angioedemia
Blood dyscrasias
Bone demineralization
Bruxism
Discontinuation Syndromes
Dry mouth
Edema
Electrolyte abnormalities
Headache
Hyperammonemia
Hyperhidrosis
Hyperprolactinemia
Hypothyroidism
Myalgias
Palpitations
Pancreatitis
Paresthesias
Priapism
Pruritis
Rashes
Seizures
Serotonin syndrome
Sialorrhea
Suicidality
Sweating
Tics
Tinnitus
Transaminitis
Urinary retention
Yawning

Cardiac

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death

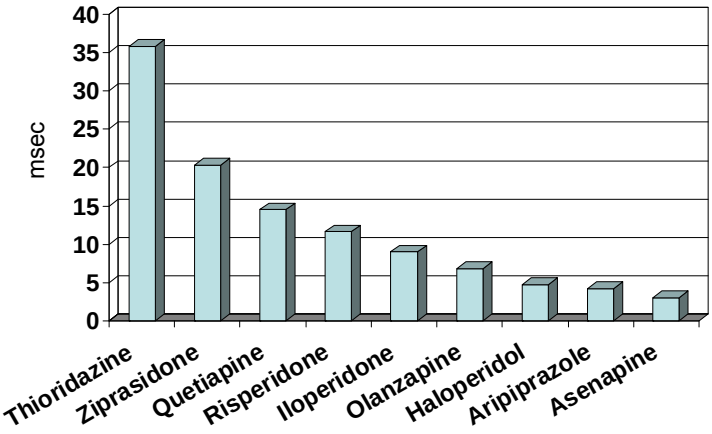
RESULTS

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). Former users of antipsychotic drugs had no significantly increased risk (incidence-rate ratio, 1.13; 95% CI, 0.98 to 1.30). 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, 2.25 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

Cardiac

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

Cardiac

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

Cardiac Adverse Effects

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

Renal

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 m^2
  - St 2: GFR 60-89 mL/min/1.73 m^2
  - St 3: GFR 30-59 mL/min/1.73 m^2
  - St 4: GFR 15-29 mL/min/1.73 m^2
  - GFR <15 mL/min/1.73 m^2

LITHIUM
- APA Guidelines: semi-annual monitoring of lithium levels and serum creatinine
- Long-term risk for CKD:4%[1] – 20%[2]
- Once-daily dosing minimizes glomerular sclerosis
- Rises > 25% warrant measurement of 24^o urine for creatinine clearance

- DIABETES INSIPIDUS
- Amiloride 5 mg BID to ↑ concentrating ability (K^+ sparing) [3,4]

[1] Gitlin, 1993; [2] Lepkifiker 2004; [3] Finch et al., 2003; [4] Bedford et al., 2008

Systemic

Discontinuation Syndromes

Serotonergic Antidepressants:
As many as 46% of patients taking short $t_{½}$ SSRIs[1,2]
Hypothesized mechanisms:
• cholinergic rebound (after prolonged blockade) (e.g.,
paroxetine, 3° amine TCAs)
• Increased catecholaminergic activity
• Rostral anterior cingulate choline/creatine metabolite ratio ↓[3]

Change to fluoxetine

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

Systemic

Common Symptoms of SSRI Discontinuation

N=242 remitted MDD patients

Abrupt 5-8 day Interruption of SSRI continuation treatment

Symptoms as reported by ≥10% of patients

Symptom	Fluoxetine (n = 63)	Sertraline (n = 63)	Paroxetine (n = 59)
Worsened mood	22	28	45
Irritability	17	38	35
Agitation	16	37	31
Dizziness	3	29	50
Confusion	14	23	42
Headache	14	31	34
Nervousness	9	31	34
Crying	6	26	40
Fatigue	16	23	32
Emotional lability	13	31	26
Trouble sleeping	9	22	39
Dreaming	6	25	37
Anger	5	28	29
Nausea	6	14	40
Amnesia	8	17	24
Sweating	8	17	24
Depersonalization	8	17	21
Muscle aches	6	14	23
Unsteady gait	5	15	23
Panic	2	15	21
Sore eyes	6	14	15
Diarrhea	5	6	24
Shaking	2	11	21
Muscle tension	8	14	11
Chills	2	11	18

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

Systemic

Hypersensitivity Reactions

- Anticonvulsants: **D**rug **R**eactiom with **E**osinophilia and **S**ystemic **S**ymptoms
- 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)

Systemic

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

Sexual Dysfxn

SSRI-Associated Sexual Dysfunction

30-70% incidence

Agent	Rationale
Amantadine	DA agonism
Bupropion	?DA agonism
Buspirone	5-HT_{1A} partial agonism
Cyproheptadine	5-HT blocker
Gingko Biloba	?
Maca Root	?
Methylphenidate	DA agonism
PDE-5 Inhibitors (Sildenafil, Tadafenil, Vardenafil)	NO
Yohibmibe (+/- L-arginine glutamate)	α_2 blockade ↑'s NE tone
Trazodone	Postsynaptic $5HT_{2A}$ blocker
Mirtazapine	Postsynaptic $5HT_{2A}$ blocker

Sexual Dysfxn

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

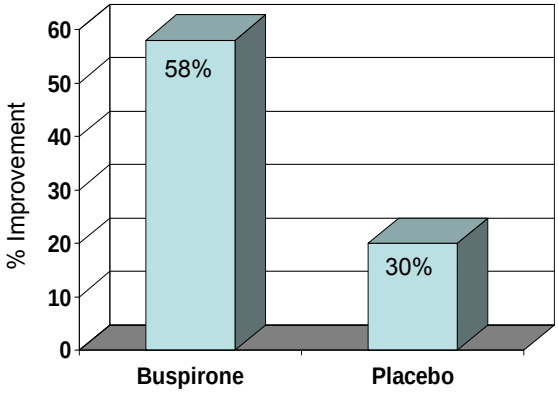
Michelson et al., *Am J Psychiatry* 2000; 157: 239-243

Sexual Dysfxn

LABEL

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

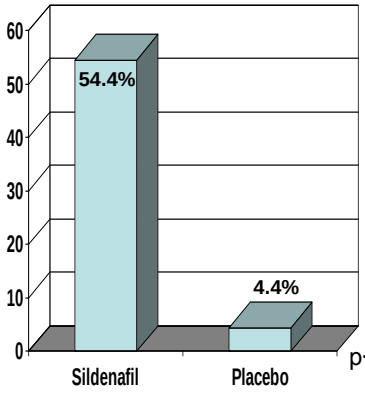
Sexual Dysfxn

LABEL

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"



p<.001

Significant improvements vs. placebo in:

- Erectile dysfunction (p=.004)
- Arousal (p=.01)
- Ejaculation (p<.001)
- Orgasm (p=.007)
- Intercourse satisfaction (p<.001)
- Overall satusfaction (p=.02)

Nurnberger et al., *JAMA* 2003; 289: 56-64

Sexual Dysfxn

LABEL

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

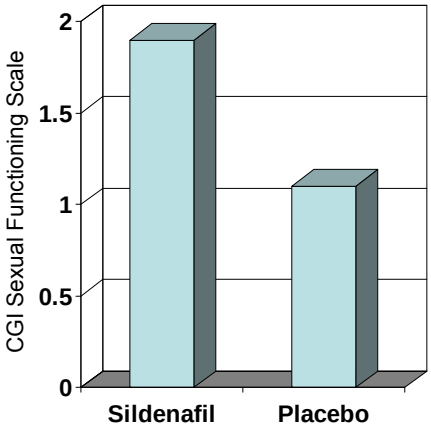
Fava et al., *J Clin Psychiatry* 2006; 67: 240-246

Sexual Dysfxn

LABEL

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 2° sexual dysfunction



- 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

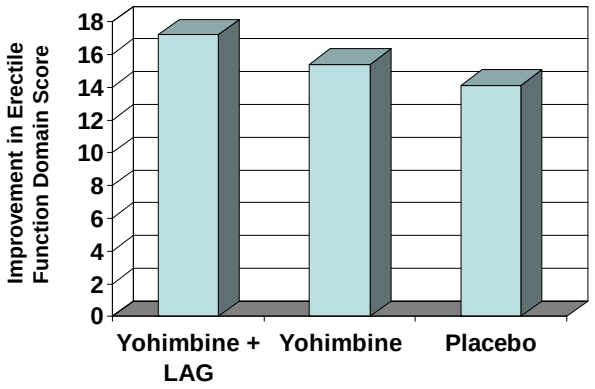
Nurnberg et al., *JAMA* 2008; 300: 395-404

Sexual Dysfxn

LABEL

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)



p=.006

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

Sexual Dysfxn

LABEL

Adjunctive Bupropion for SSRI-Associated Sexual Dysfunction

- Open trial of bupropion SR 75-150 mg 1-2^{o} before sex or TID if no response
- N=47

66% overall improved (38% of those on PRN regimen)

Ashton & Rosen, *J Clin Psychiatry* 1998; 59: 112-115

6-week randomized comparison (N=41) of Bupropion SR 150 mg/day or placebo X 6 weeks

No significant between-group differences On ASEX

DeBattista et al., *J Clin Psychiatry* 2005; 66: 844-848

- 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=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

Sexual Dysfxn

LABEL

Mixed or Preliminary Results

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

[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

Weight

Psychotropic-Induced Weight Gain

LABEL

- Severity of illness
- Unique efficacy?
- Alternate tx's?
- Viable to manage?
- Weight gain 2º to psychiatric illness, concomitant meds or medical/psychiatric comorbidity?

- Extent of weight gain
- Other metabolic risks

STRATEGIES:

- Diet and exercise
- Metformin
- Topiramate
- Zonisamide
- Lamotrigine
- H_2 blockers
- Bupropion (+/- NTX)
- Orlistat
- Amantadine
- Stimulants
- Chromium picolinate

Weight

Lifestyle Modification for Psychotropic Weight Gain

Authors	Duration	N	Outcome
Centorrino [1]	24 weeks	22	13.2# wt loss (5.7% of baseline); 77% completed
Chen [2]	10 weeks	33	↓4.6# @ 10 weeks; 8.1# @ 6 mos; 5.9# @ 12 mos; ↓ TGs
Paulin [3]	18 mos	110	3.5% ↓ BW, ↓ LDL, ↓ TGs, ↓ FBS, ↑ HDL
Vreeland [4] Menza [5]	12 week	31	6# wt ↓; 87% completed; 65% completede 40-week extension, w/ ↓ HbA_1C
Kwon [6]	12 week	48	8.8# lost @ 8 weeks; no lipid Δ's; 75% completed

[1] Centorrino et al., *Int J Obesity (Lond)* 2006; 30: 1011-1016; [2] Chen et al., *Psychiatry Clin Neurosci* 2009; 63: 17-22. [3] Poulin et al., *Aus N Z J Psychiatry* 2007; 41: 980-989; [4] Vreeland et al., [5] Menza et al., J Clin Psychiatry 2004; 65: 471-477; [6] Kwon et al., *J Clin Psychiatry* 2006; 67: 547-553

Weight

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

Treatment	Δ BMI	Insulin Resistance Index	Δ in waist circumference
Lifestyle + metformin*	1.8	3.6	↓ 2.0 cm
Metformin	1.2	3.5	↓ 1.3 cm
Lifestyle + placebo	0.5	1.0	↑ 1.2 cm

Wu et al., *JAMA* 2008; 299: 185-193

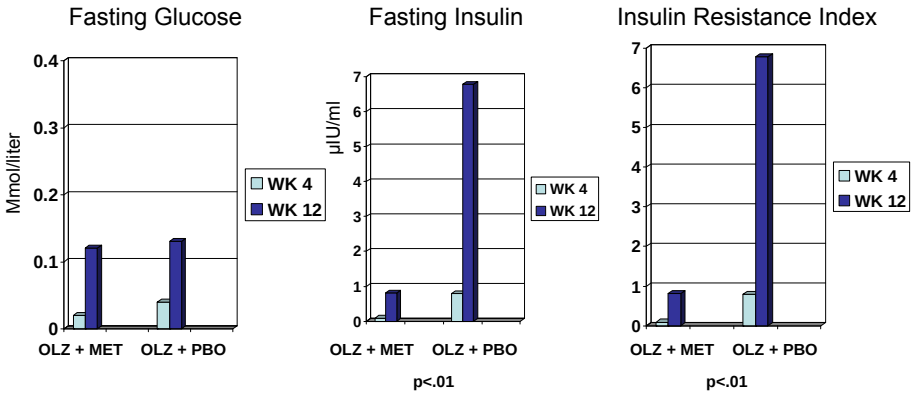
* BMI: L + M > M or L; M > L or PBO; L > PBO
* IRI: L + M > L or PBO; M > L or PBO; L > PBO
* Waist: L + M > M or L or PBO; M > L or PBO; L >PBO

Weight

Metabolic Dysregulation: Hyperglycemia and Metformin

LABEL

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



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

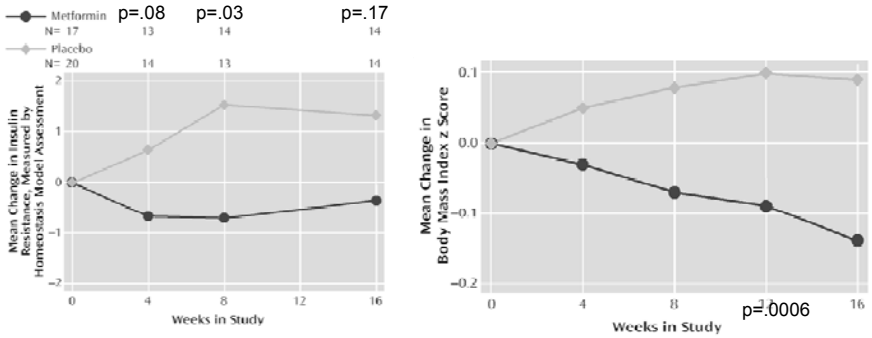
Weight

Metformin for Atypical-Antipsychotic-Induced Weight Gain in Adolescents

LABEL

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



Subjects taking placebo continued to gain 0.31 kg/week

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

Weight

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

Weight

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

24-week open randomized trial

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

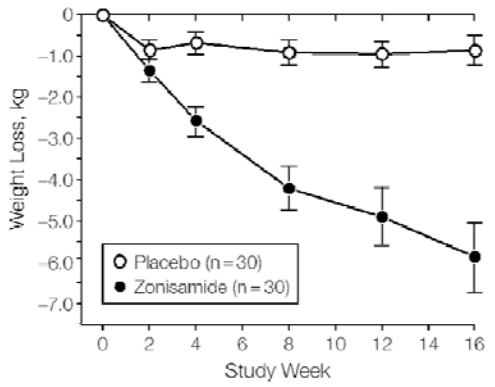
McElroy et al., *Bipolar Disord* 2007; 9: 426-434

Weight

Zonisamide vs. Placebo for Weight Loss in Obese Adults

LABEL

- 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

Weight

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

LABEL

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

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

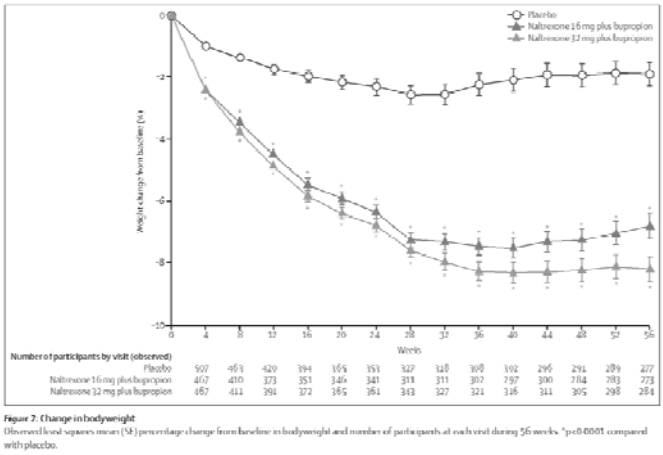


Figure 2: Change in bodyweight

Greenway et al., *Lancet* 2010; 376: 595-605

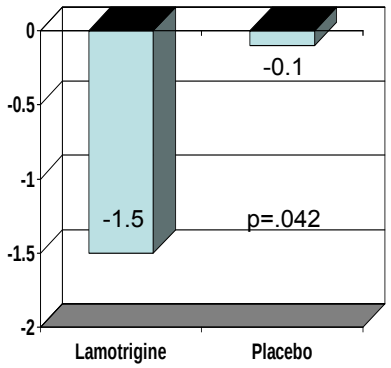
Weight

Lamotrigine or Placebo for Weight Loss in Obese Adults

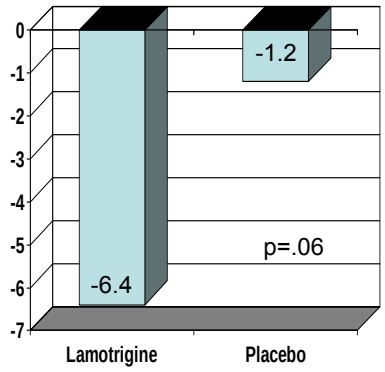
LABEL

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

Mean Δ in BMI from Baseline



Weight Loss (pounds) (LOCF)



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

Weight

Nizatidine for Olanzapine-Associated Weight Gain

KOREAN SAMPLE [1]

LABEL

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

Lilly sample [2]

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

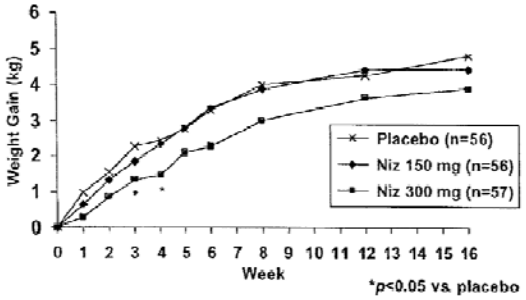


Fig. 1. Weight gain reduced at weeks 3 and 4 in patients treated with Olz+Niz 300 mg b.i.d.

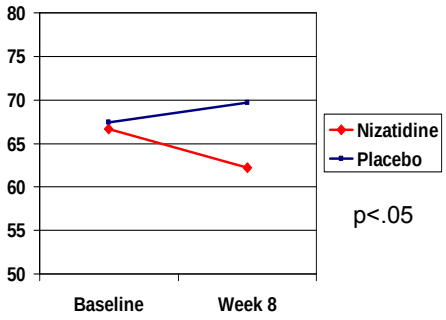
[1] Pae et al., *Hum Psychopharmacol* 2003; 18: 435-456; 2 Cavazzoni et al., *Eur Neuropsycho-Pharmacol* 2003; 13: 81-85

Weight

Nizatidine and Olanzapine-Associated Weight Gain

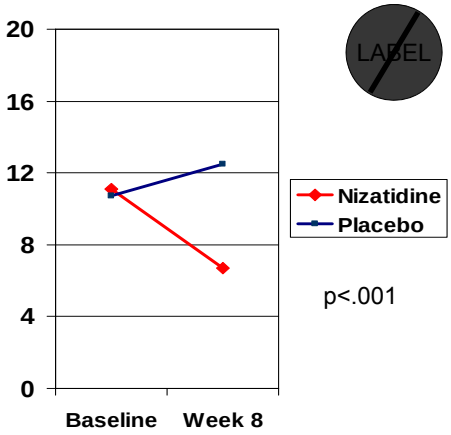
8-week randomized placebo comparison in 35 SZ patients who gained >2.5 kg

Changes in Weight (kg)



p<.05

Changes in serum Leptin Levels (mg/dL)



p<.001

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

Weight

LABEL

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)

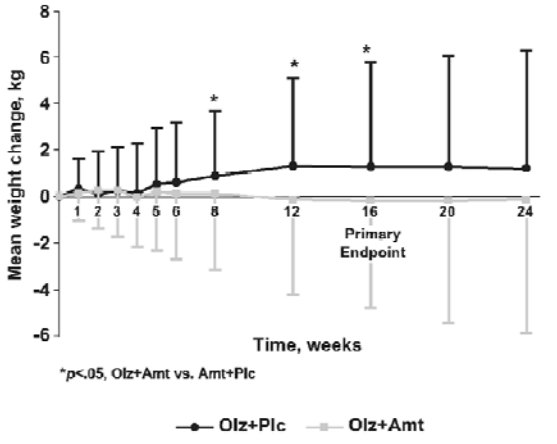


Fig. 2. Weight change during study period 1. *N*=123; Olz+Plc, *n*=64; Olz+Amt, *n*=59. Data are presented as mean±S.D. Abbreviations: Olz=olanzapine; Plc=placebo; Amt=amantadine.

Deberdt et al., *Eur Neuropsychopharmacol* 2005; 15: 13-21

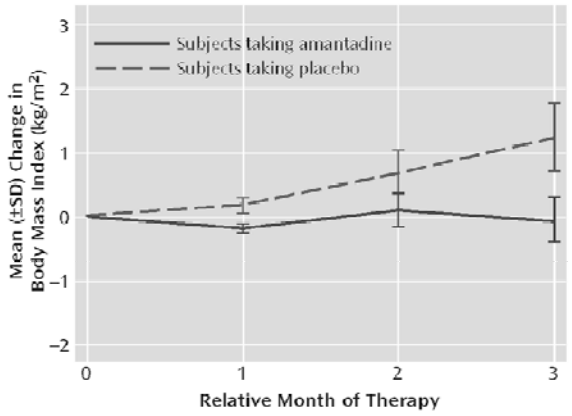
Weight

LABEL

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)

FIGURE 1. Monthly Mean Change in Body Mass Index From Baseline in Subjects Taking Amantadine or Placebo With Olanzapine[a]



[a] Last-observation-carried-forward analysis.

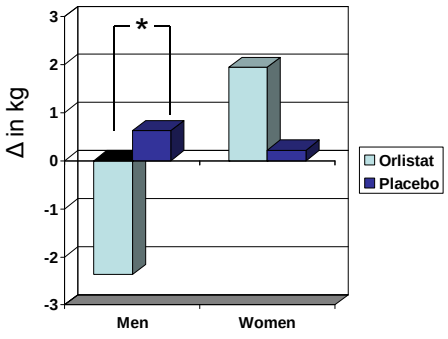
Graham et al., *Am J Psychiatry* 2005; 162: 1744-1746

Weight

LABEL

Orlistat for Clozapine- or Olanzapine-Associated Weight Gain

- 16-week randomized placebo comparison
- Baseline BMI: 28-43 kg/m^2
- Dosing: 120 mg TID
- Response (>5% loss of baseline weight): 16% orlistat vs. 6% PBO (ns)



* p=.011

Joffe et al., *J Clin Psychiatry* 2008; 9: 706-711

Weight

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

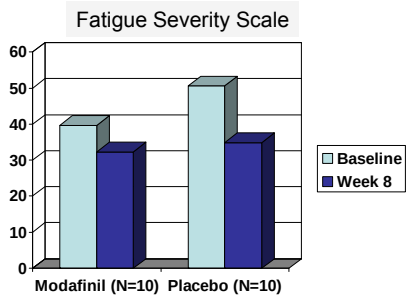
Sedation

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

Serge Sevy, M.D., M.B.A.; Murray H. Rosenthal, D.O.; Jose Alvir, Dr.P.H.; Sabina Meyer, B.A.; Hema Visweswaraiah, B.A.; Handan Gunduz-Bruce, M.D.; and Nina R. Schooler, Ph.D.

(J Clin Psychiatry 2005;66:839–843)

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



No significant differences

Common side effects: agitation, insomnia, dry mouth

Sleep

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

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] Londborg et al., *J Affect Disord* 2000; 61(1-2): 73-79

Sleep

Insomnia

Agent	Comment
Benzodiazepines	More time in light sleep (St 2), reduction in slow wave sleep and REM; tolerance, withdrawal, abuse
Chloral Hydrate	↓'s sleep latency; $t_{½}$ 4-6^{o}; tolerance
Eszopiclone (Lunesta®)	GABA-A subunit selectivity; does not alter slow wave sleep or REM
Gabapentin	↑'s slow wave sleep
Mirtazapine	↑ time in St 2, REM and slow wave sleep
Melatonin	0.1-0.3 mg = physiologically relevant;minimal disruption of sleep architecture
Quetiapine	↓ REM time, ↑ total time in non-REM sleep & ↑ 'd duration of St 2 sleep
Ramelteon	↑'s REM and slow wave sleep
Doxepin (Silenor®)	H_1 antagonist; 25-50 mg @ HS
Trazodone	↓'s St 1 & 2 sleep; little effect on REM
Zaleplon	$t_{½}$=1^{o}; better for sleep initiation than maintenance
Zolpidem	Preserves slow wave sleep

Sleep

Benzo's or Non-Benzo's?

BENZO'S

- More disruption of sleep architecture
- Rebound insomnia and withdrawal
- Abuse potential
- Tolerance
- Respitatory 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

Wagner & Wagner, *Sleep Med Rev* 2000; 4: 551-581

Cognition

Adverse Cognitive Effects

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

Cognition

Cognitive Enhancers?

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

Cognition

Other Possible Cognitive Enhancers?

- Pramipexole
- thyroxine
- Glycine
- D-serine
- D-cycloserine
- Ampakines
- Acamprosate

- COX-2 inhibitors
- Buspirone
- Sibutramine
- Ginko biloba
- Omega-3 fatty acids
- Estrogen
- Vitamin E
- Taurine

Motor

Motor Side Effects

- Rates of EPS
- Tremor: β-blockers, primidone
- Akathisia: β -blockers, benzodiazepines

Motor/TD

LABEL

Tardive Dyskinesia and Vitamin E

Study	Findings
12-week randomized comparison of Vit E 1200 IU vs. placebo (N=41) [1]	AIMS reduction: 46% Vit E vs. 4% PBO
2-month randomized comparison of Vit E 800 IU BID vs. placebo (N=35) [2]	AIMS reduction: 24% Vit E
2-Year 9-site VA trial comparing Vit E 1600 IU/day vs. placebo (N=158) [3]	No total or subscale differences on AIMS
6-week comparison of Vit E 1600 IU/day vs. placebo (N=18) [4]	No differences on AIMS scores

[1] Zhang et al., J Clin Psychopharmacol 2004; 24: 83-86; [2] Lohr & Calagiuri, *J Clin Psychiatry* 1996; 57: 167-173; [3] Adler et al., *Arch Gen Psychiatry* 1999; 56: 836-841; [4] Egan et al., *Am J Psychiatry* 1992; 149: 773-777

Motor/TD

LABEL

Tardive Dyskinesia

Interventions with at Least One (+) Randomized Controlled Trial

Agent	Outcome
Vitamin B6 (N=50); 1200 mg/day or placebo x 26 weeks	Greater ↓ in EPS, Parkinsonism, dyskinesia (p<.001) [1]
Levetiracetam (N=50; 500-3000 mg/day (mean= 2156 mg/day)	AIMS decline 44% with LEV vs. 19% PBO (p=.022) [2]
Amantadine (N=32, 100 mg BID) x 2 wks	Biperiden = amantadine >PBO for Parkinsonism and AIMS [3]
Biperiden (N=32, 2 mg BID) x 2 wks	Biperiden = amantadine >PBO for Parkinsonism and AIMS [3]
Melatonin (N=22, 10 mg x 6 weeks)	AIMS decline 2.5 points with MEL vs. 0.1 with PBO (p<.001) [4]

[1] Lerner et al., *J Clin Psychiatry* 2007; 68: 1648-1654; [2] Woods et al., *J Clin Psychiatry* 2008; 69: 546-554; [3] Silver et al., *J Clin Psychiatry* 1995; 56: 167-170; [4] Shamir et al., *Arch Gen Psychiatry* 2001; 58: 1049-1052

Motor/TD

Clozapine and Tardive Dyskinesia

- 20 chronic SZ patients given clozapine x 18 weeks
- 74% TD improvement, 69% Parkinsonism improvement, 78% akathisia improvement [1]

[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