

A CE- Accredited Scientific Symposium to be Covered During the 2009 American College of Clinical Pharmacy Annual Meeting  
**OPTIMIZING PHARMACOTHERAPY**  
in Depressed Patients with Residual Symptoms

## Adjunctive Treatment of Residual Symptoms in Resistant Depression

**Brent Solvason, PhD, MD**  
**Stanford University School of Medicine**

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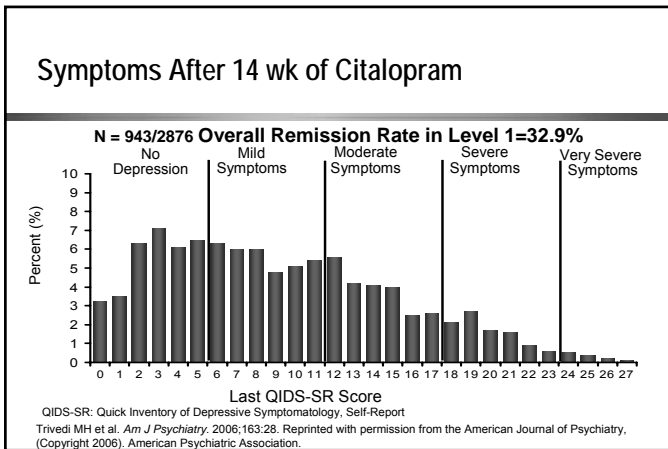
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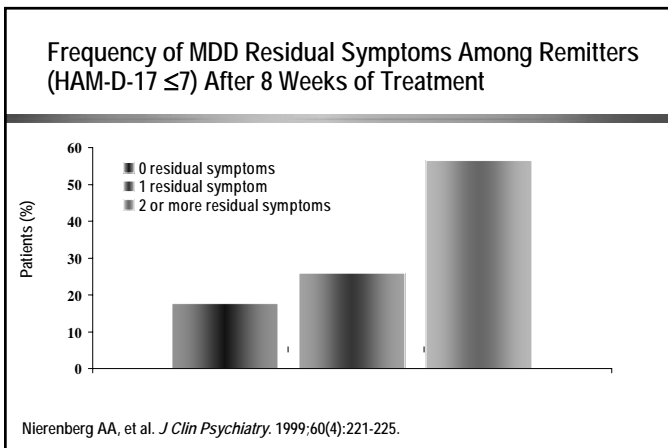
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### Targeted Sleep Rx of Residual Insomnia, Anxiety, Agitation

- Benzodiazepines
- Non-benzodiazepine hypnotics
- Trazodone
- Eplivanserin
- Mirtazapine
- SGAs

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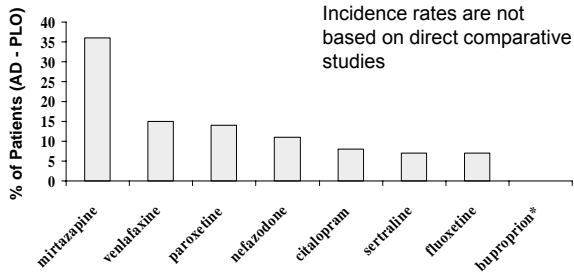
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### Incidence of Somnolence/Sedation During Antidepressant Management



PDR 2001: Incidence on Active (AD) - Incidence on Placebo (PLO);  
 \*No difference for bupropion

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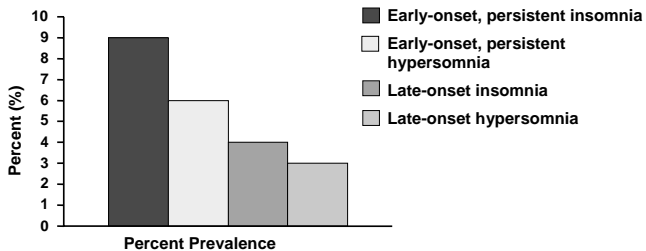
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### Rates of Sleep Disturbances During 6 Months of Fluoxetine Treatment



Zajacka J, et al. J Clin Psychiatry. 1999; 60(6):389-394.

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## Residual Symptoms: Cognitive Deficits in Major Depression

DSM IV: " Diminished ability to think or concentrate, or indecisiveness, nearly every day"

Neuropsychological evaluation of MDD patients

- Attention deficits
- Short-term and working memory deficits (verbal and visual)
- Executive dysfunction

Castaneda et al, J Affective Dis. 2008;106: 1-27.

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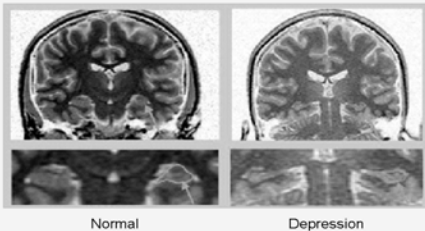
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## Brain atrophy in depression?

Atrophy of the Hippocampus in Depression



Normal

Depression

Bremner JD, et al. Am J Psychiatry. 2000;157(1):115-118.

Reprinted with permission from JD Bremner.

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## Persistent Cognitive Deficits in MDD

- Direct relationship between reduced gray matter volume in hippocampus, R frontal, L cingulate gyrus and cognitive deficits in remitted depressed patients<sup>1,2</sup>
- MDD may be a risk factor for AD and greater cognitive deficits in dementia and age related cognitive deficits in general<sup>3,4</sup>
- 2-3% drop in memory performance for each of the previous 4 depressive episodes in 8229 French pts<sup>5</sup>

<sup>1</sup>Vasic et al, J Affect Dis 2008 (109) 107; <sup>2</sup>Yuan et al, Biol Psychiatry 2008 (64)6 541;

<sup>3</sup>Cannon-Spoor et al, Am J Geriatr Psychiatry 2005 (13)4 312;

<sup>4</sup>Gualtieri Prog Neuropsychopharm Biol Psychiatry 32(4):962;

<sup>5</sup>Gorwood et al, Am J of Psychiatry 2008; 165(6) 731.

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### Residual Symptoms: Fatigue

- Fatigue was found to be a prodromal symptom of MDD<sup>1</sup>
- Individuals with a history of unexplained fatigue are at a markedly increased risk for new onset major depression (RR:28.4, 95% CI: 11.7-68.0)<sup>2</sup>
- Fatigue is one of the 9 symptoms of MDD
- Fatigue and lack of energy typically improve with antidepressant treatment, but perhaps more slowly than other symptoms<sup>3</sup>

<sup>1</sup>Fava GA et al; J Affect Disor 1990; 19:149-152; <sup>2</sup>Addington AM et al; Psychoml Med 2001; 31:1037-1044; Fava M J Clin Psych, in press;

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### Fatigue and Related Symptoms in MDD

- Tiredness: 73%<sup>1</sup>
- Fatigue or loss of energy: 94%<sup>2</sup>
- Reduced energy: 97%<sup>3</sup>
- Impaired concentration: 84%<sup>3</sup>
- Hypersomnia: 10%–16%<sup>4</sup>

1. Tylee et al. Int Clin Psychopharmacol 1999;14:139-151. 2. Maurice-Tyson et al. Br J Gen Pract 1998;48:1245-1246. 3. Baker et al. Comp Psychiatry 1971;12:354-65. 4. Horwath et al. J Affect Disord 1992;26:117-25. Reynolds and Kupfer. Sleep 1987;10:199-215.

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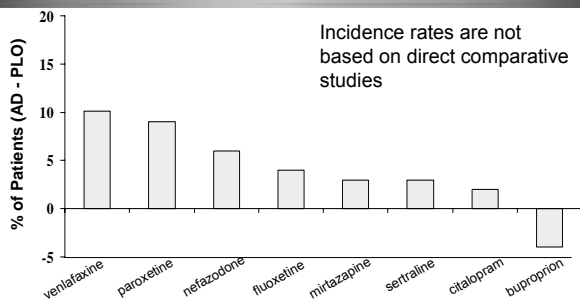
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### Incidence of Asthenia/Fatigue During Antidepressant Management



PDR 2001: Incidence on Active (AD) – Incidence on Placebo (PLO);

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### Targeted Treatment of Fatigue, Hypersomnia, and Cognitive Deficits

- Bupropion
- Stimulants
- Thyroid hormone
- Modafinil
- Dopamine agonists

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### Targeted Rx of Residual Sadness, Guilt, Suicidality

- Lithium
- Second generation antipsychotics (SGAs)
- Antidepressant augmentation

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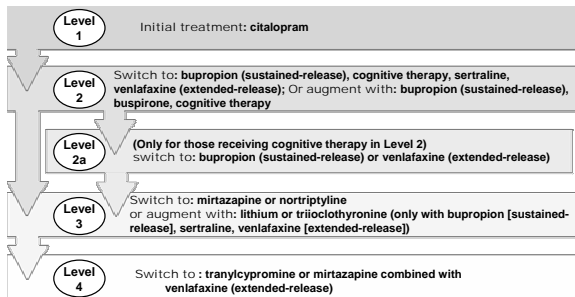
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### Treatment Algorithm Snapshot STAR\*D Algorithm



Rush AJ et al. (2003), Am J Psychiatry 160(2):237

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## Limitations of STAR\*D

### Benefits

- Largest sequential study in resistant depression
- Assesses rate of response with previous failures
- Uses stricter criteria of remission rather than response
- Uses "real world population"

### Limitations

- No Placebo
- Partial randomization
- Limited augmentation strategies
- Does not reflect clinical practice

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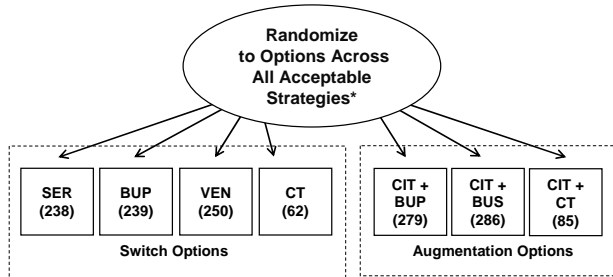
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## Level 2



\*If strategy group is not acceptable to the patient, then he/she is randomized to treatment options within remaining acceptable treatment strategies. If all treatment strategies are rejected, then patient enters naturalistic follow-up; SER = sertraline; VEN = venlafaxine XR; CT = cognitive therapy; CIT = citalopram; BUS = buspirone; Rush AJ et al. (2004), *Control Clin Trials* 25(1):119-142

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## Bupropion

### Bupropion SR (100 mg to 150 mg qd or bid)

- Advantages
  - Well tolerated in combination with various serotonergic antidepressants
  - May be synergistic in pharmacodynamic properties
  - May help SSRI-induced sexual dysfunction
- Disadvantages
  - No placebo controlled trials
  - Irritability, anxiety, tremor, seizure threshold consequences
  - Some SSRIs inhibit the metabolism of hydroxy bupropion

This information concerns a use that has not been FDA approved

Ashton AK, Rosen RC. *J Clin Psychiatry*. 1998;59:112.  
 Bodkin JA, et al. *J Clin Psychiatry*. 1997;58:137.  
 DeBattista C, et al. *J Clin Psychopharmacol*. 2003;23:27.

Labbate LA, et al. *Ann Clin Psychiatry*. 1997;9:241.  
 Marshall RD, Liebowitz MR. *J Clin Psychopharmacol*. 1996;16:80.  
 Spier SA. *Depress Anxiety*. 1998;7:73.

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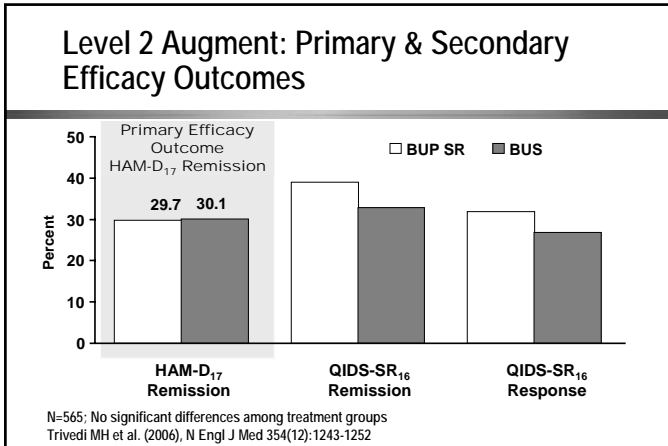
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### Lithium Carbonate

- Lithium
  - ≥50 trials, most positive
  - May enhance presynaptic release of 5HT
  - May work with many agents
  - Levels of .4 to .6 often effective
  - Some achieve rapid response
  - Not well studied with newer drugs
  - Low therapeutic index
  - Requires monitoring of levels, thyroid, renal

This information concerns a use that has not been FDA approved  
 Bauer M, et al. *Can J Psychiatry*. 2003;48:440.

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### Thyroid Supplements

- ≥25 studies, most positive
- May enhance NE transmission
- May help with energy and weight
- Well tolerated
- May work less well in men
- TFT monitoring required
- Bone demineralization possible

This information concerns a use that has not been FDA approved  
 Joffe RT, Sokolov ST. *Int J Neuropsychopharmacol*. 2000;3:143.

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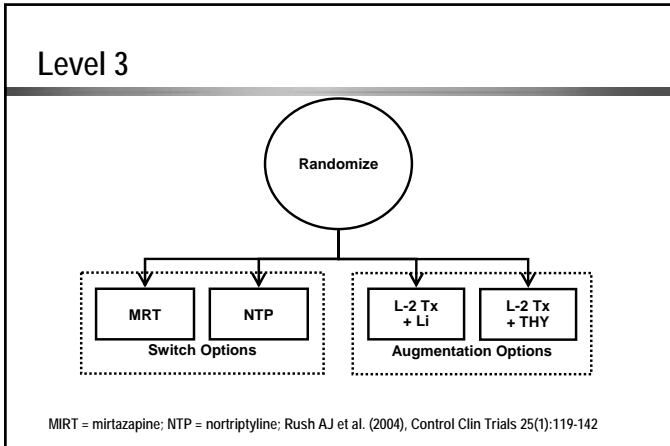
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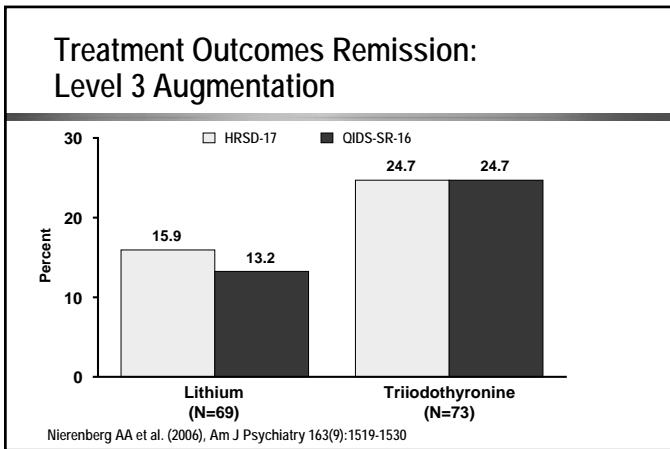
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### Augmentation of SSRIs: Mirtazapine

- Double-blind trial of 26 patients with 30 mg mirtazapine
  - 64% response vs 20% on placebo
  - May rapidly improve sleep, speed response
  - Disadvantages include sedation and weight gain

This information concerns a use that has not been FDA approved  
Carpenter LL, et al. Biol Psychiatry. 2002;51:183.

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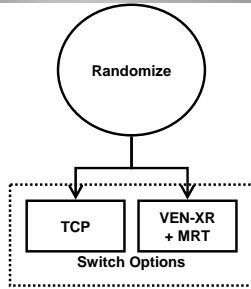
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Level 4



TCP = tranylcypromine; Rush AJ et al. (2004), Contol Clin Trials 25(1):119-142

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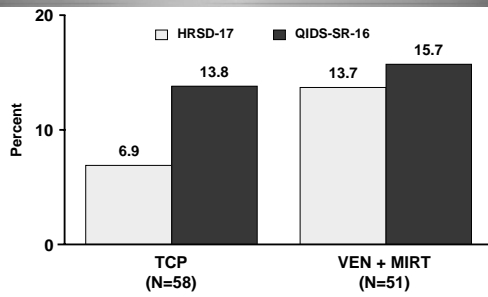
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Treatment Outcomes Remission:Level 4



McGrath PJ et al. (2006), Am J Psychiatry 163(9):1531-1541

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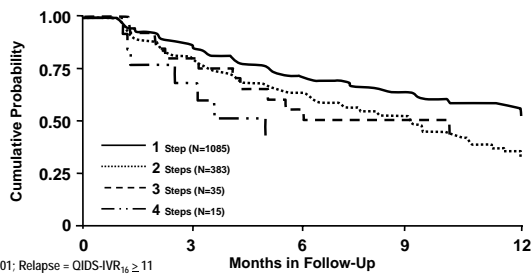
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Relapse in Follow-Up for Patients Remitting With Different Numbers of Acute Treatment Steps



p<0.0001; Relapse = QIDS-IVR<sub>16</sub> ≥ 11  
 Rush AJ, et al. Am J Psychiatry. 2006;163:1905-1917.  
 Reprinted with permission from the American Journal of Psychiatry, (Copyright 2006), American Psychiatric Association.

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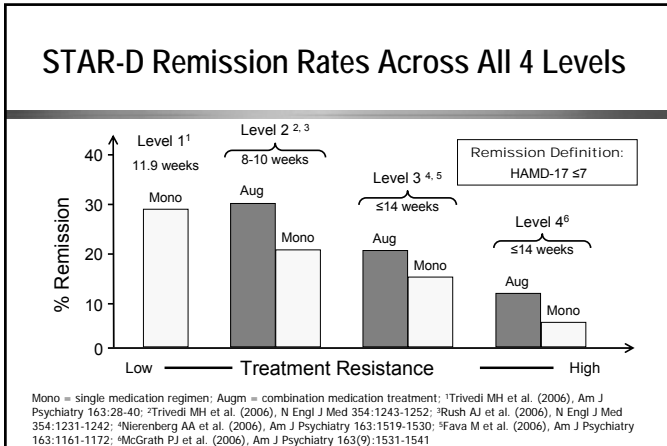
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### Atypical Antipsychotic Augmentation of Antidepressants

- Double blind data of olanzapine, aripiprazole, quetiapine, augmentation in MDD have been completed
- Atypicals may speed response, improve sleep, agitation, and overall depression
- Risks include metabolic and neurological side effects

Kennedy SH, Lam RW. *Bipolar Disord.* 2003;5:S36.  
 Papakostas GI, et al. *J Clin Psychiatry.* 2004;65:217.  
 Shelton RC. *J Clin Psychiatry.* 1999;60:S37.

Some of these therapeutic strategies may reflect uses that are not FDA approved.

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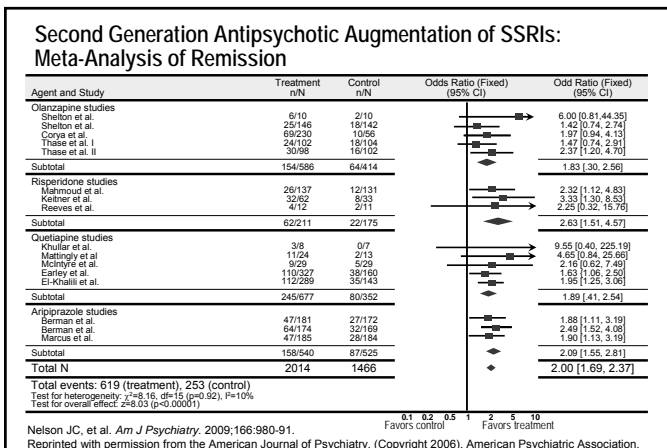
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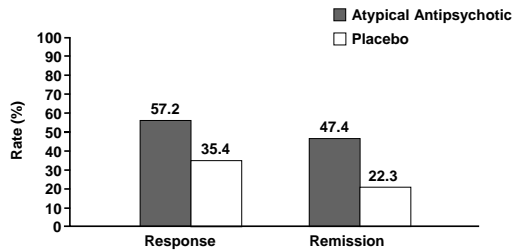
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### Atypical Antipsychotic Augmentation: A Meta-Analysis Response & Remission Rates



10 RCTs, N=1,500; Papakostas GI et al. (2007), J Clin Psychiatry 68(6):826-831

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### Olanzapine/Fluoxetine Combination for Treatment-Resistant Nonpsychotic MDD

**2 Pooled, 8-Week, Double-Blind, N=605**

- Study 1: no significant differences
- Study 2: OFC > OLZ and FLX
- Pooled: OFC > OLZ and FLX

Thase ME et al. (2007), J Clin Psychiatry 68(2):224-236

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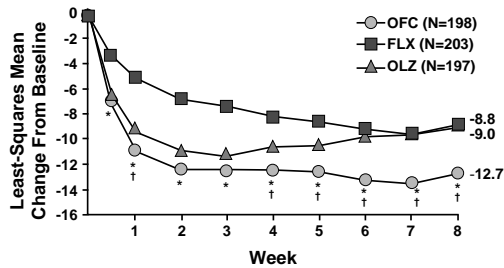
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### OFC for Treatment-Resistant MDD MADRS Change: 2 Pooled Studies



\*p<0.05 OFC vs. FLX; †p<0.05 OFC vs. OLZ  
Thase ME, Corya SA, Osuntokun O, et al, *The Journal of Clinical Psychiatry*, 2007;68:224-236. Copyright 2007 Physicians Postgraduate Press. Reprinted by permission.

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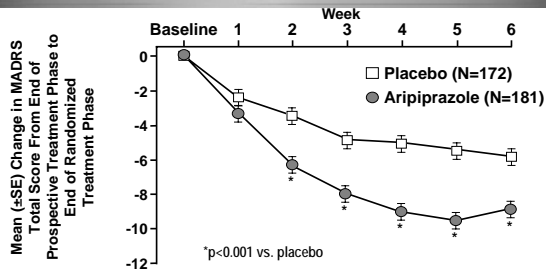
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### Adjunctive Aripiprazole for Incomplete Responders In MDD: MADRS Mean Change



Berman Rm, Marcus RN, Swanink R, et al. *The Journal of Clinical Psychiatry*. 2007;68:843-853. Copyright 2007, Physicians Postgraduate Press. Reprinted by permission.

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### Adjunctive Aripiprazole for Incomplete Responders in MDD: Remission Rates

Week	Aripiprazole* (n=181) Remission (%)	Placebo† (n=172) Remission (%)	P value
1	3.4	1.8	NS
2	10.5	5.8	NS
3	18.8	8.7	<0.05
4	22.7	11.0	<0.05
5	26.0	14.0	<0.05
6	26.0	15.7	<0.01

\*In the aripiprazole group, 1 patient discontinued prior to undergoing any efficacy assessment; †In the placebo group, 4 participants discontinued prior to undergoing any efficacy assessment.  
Berman RM et al. *J Clin Psychiatry*. 2007;68(6):843-853.

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### Augmentation for Resistant MDD: Dopamine Agonists

- Amphetamines\*
  - Role in medically ill and geriatric patients
  - No double blind studies
  - Dependence may be a problem
- Pramipexole\*
  - May augment SSRIs in unipolar
  - May augment mood stabilizers in bipolar depression
  - Associated with hallucinations
- Ropinirole\*
  - 72 patient Stanford-Duke study
  - Doses to 12 mg/day for 8 weeks
  - May help with sexual dysfunction and cognition
  - Nausea, somnolence, insomnia most common AE

\* This information concerns a use that has not been FDA approved

DeBattista C, et al. *Am J Psychiatry*. 1997;154:1625.  
Goldberg JF, et al. *Am J Psychiatry*. 2004;156:798.

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### Adjunctive Ropinirole Response Rates

	Responders	Nonresponders
• HamD 21	25(44.6%)	31(55.4%)
• MADRS	30(53.6%)	26 (46.4%)
• CGI	35(62.5%)	21 (37.5%)

(DeBattista et al, NCDEU Annual Meeting, 2008)

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### Modafinil as Adjunct Therapy for MDD

- Modafinil is a non-amphetamine, schedule IV agent approved for improving wakefulness in several sleep disorders
- The mechanism of modafinil is unknown but does act on DA transporters in the hypothalamus
- Modafinil improves wakefulness in patients with narcolepsy,<sup>4</sup> idiopathic hypersomnia,<sup>5</sup> obstructive sleep apnea,<sup>6</sup> Parkinson's disease<sup>7</sup>
- Modafinil improves fatigue in patients with multiple sclerosis<sup>8</sup>

<sup>1</sup>Nierenberg AA, et al. *J Clin Psychiatry*. 1999.  
<sup>2</sup>Judd LL, et al. *J Affect Disord*. 1998.  
<sup>3</sup>Paykel ES, et al. *Psychological Med*. 1995.  
<sup>4</sup>US Modafinil Study Group. *Ann Neurol*. 1998.

<sup>5</sup>Bastuji H, Jouvet M. *Prog Neuropsychopharmacol Biol Psychiatry*.1988  
<sup>6</sup>Pack AI, et al. *Am J Respir Crit Care Med*. 2001  
<sup>7</sup>Adler CH, et al. *Mov Disord*. 2003  
<sup>8</sup>Rammohan KW, et al. *J Neurol Neurosurg Psychiatry*. 2002

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### Modafinil Reduces Fatigue in Patients With MDD

- Fatigue and sleep problems are common residual symptoms despite adequate antidepressant therapy
- Patients who were partial responder to a 6-week treatment of antidepressant were randomized to adjunctive modafinil (n=69) or placebo (n=67) for 6 weeks
- Modafinil compared to placebo, improved fatigue\* from baseline at week 2 (p<0.05) and sleepiness<sup>1</sup> from baseline at week 1 (p<0.01)
- At week 6, the differences were not statistically significant

\*As measured by Fatigue Severity Scale  
<sup>1</sup>As measured by Epworth Sleepiness Scale  
 DeBattista C, et al. *J Clin Psychiatry*. 2003;64:1057-64.

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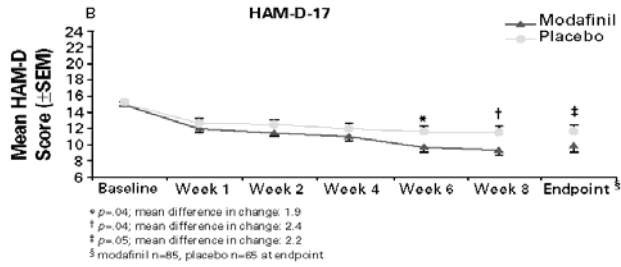
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### Modafinil Significantly Improves Mood (HAM-D 17-Item) in Severely Depressed Patient Subgroup



Fava M, et al. Poster presented at: ACNP. 2003.

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### Lamotrigine Augmentation

- Mixed evidence of useful in bipolar depression as monotherapy
- Useful in maintenance treatment of bipolar disorder
- Useless in acute mania
- May speed up antidepressant response in patients treated with paroxetine at 200 mg/d
  - However, no effect overall in HDRS

This information concerns a use that has not been FDA approved

Calabrese JR, et al. *Am J Psychiatry*. 1999;156:1019.  
 Normann C, et al. *J Clin Psychiatry*. 2002;63:337.

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### Adjunctive Steroid Agonists/Antagonists

- Hydrocortisone 15 mg results in rapid improvement in MDD in patients without psychosis but not patients with psychosis
- Adjunctive mifepristone patients with psychotic depression
  - Mixed or inclusive results
  - Several positive and negative controlled trials in psychotic major depression
  - May help psychosis and cognition more than depression
- Steroid agonists can contribute to psychiatric symptoms. The long term safety of glucocorticoid antagonists are not established.

This information concerns a use that has not been FDA approved

DeBattista C, et al. *Am J Psychiatry*. 2000;157:1334  
 DeBattista et al. *Biological Psychiatry*. 2006;13(12) 1343.

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### Estrogen Augmentation of Antidepressants

- Estrogen may augment TCAs
- Estrogen monotherapy helps MDD in resistant premenopausal women
- Estrogen HRT helps fluoxetine response in postmenopausal women
- Premenopausal women nonresponders to 6 weeks of fluoxetine not significantly more likely to respond when estradiol 10 mg added for 4 weeks
- 0.1 mg of estradiol patch speed response to sertraline in post-menopausal women

This information concerns a use that has not been FDA approved

Klaiber EL, et al. *Arch Gen Psychiatry*. 1979;36:550.  
Raspog Et al. *J Psych Res*. 2006  
Prange AJ Jr, et al. *Lancet*. 1972;2:999.  
Schneider LS, et al. *Am J Geriatr Psychiatry*. 1997;5:97.

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### OTC Potential Augmentors

- Folate/methylfolate
- Sam E
- Omega 3
- Tyrosine NE precursors
- Tryptophan/5HTP serotonin precursors

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### Psychotherapy Augmentation

- CBT augmentation as effective as medication augmentation
- CBT combined with nefazodone works significantly better than nefazodone or CBT alone
- Psychotherapy may be protective against relapse and well-tolerated
- Psychotherapy is poorly covered by third party payers, may be expensive, and takes time to be effective

Keller MB, et al. *N Engl J Med*. 2000;342:1462.  
Paykel ES, et al. *Arch Gen Psychiatry*. 1999;56:829.

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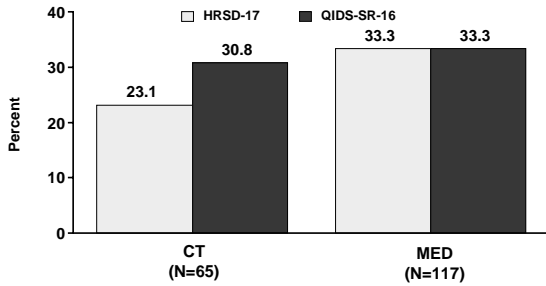
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### STAR\*D Tx Outcomes: Remission Rates CT vs Medication Augmentation



MED = medication augmentation; Thase ME et al. (2007), Am J Psychiatry 164(5):739-752

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### Summary

- Residual symptoms of depression are common
- Persistent fatigue, cognitive dysfunction, and sleep disturbance have important implications for the long-term functioning of recovered depressed patients
- Adjunctive medications and/or psychotherapy are often needed to treat residual symptoms

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A CE-Accredited Session/Seminar Session to be Covered During the 2009 American College of Clinical Pharmacy Annual Meeting

**OPTIMIZING PHARMACOTHERAPY**  
*in Depressed Patients with Residual Symptoms*

# Monitoring of Efficacy and Potential Adverse Effects in Augmentation Approaches

Shannon J Drayton, Pharm.D., BCPP  
*South Carolina College of Pharmacy  
Medical University of South Carolina, Institute of Psychiatry*

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## Efficacy

- What does the sequenced treatment alternatives to relieve depression study (STAR\*D) tell us
- What is measurement-based care (MBC)
- Realities of MBC

Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR\*D: implications for clinical practice. *Am J Psych* 2006;163:28-40.

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## Measurement-Based Care (MBC)

- Patient Health Questionnaire-9 (PHQ-9)
- Quick Inventory of Depressive Symptomatology (QIDS)
- Beck Depression Inventory (BDI)
- Hamilton Rating Scale for Depression (HAM-D)
- Montgomery Asberg Depression Rating Scale (MADRS)

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### Augmentation and Monitoring

- STAR\*D
  - Lithium
  - Liothyronine (T<sub>3</sub>)
  - Bupropion
  - Buspirone
  - Mirtazapine
- Second Generation Antipsychotics (SGA's)
  - Aripiprazole\*
  - Fluoxetine/Olanzapine combination\*
  - Quetiapine
  - Risperidone
  - Ziprasidone

\*FDA approved

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### Lithium

- Efficacy
  - Lithium levels 0.4 – 0.8 mEq/L
  - STAR\*D mean blood level: 0.6 mEq/L
- Adverse Effects
  - Lower levels/doses = increase tolerability
  - Upon initiation: GI, sedation, cognitive blunting
  - Long term: fine tremor, weight gain, polyuria/polydipsia, hypothyroidism, leucocytosis
  - ECG
  - Toxicity

Nierenberg AA, Fava M, Trivedi MH, et al. A comparison of lithium and T (3) augmentation following two failed medication treatments for depression: a STAR\*D report. Am J Psych 2006;163:1519-30.

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### Liothyronine (T<sub>3</sub>)

- Adverse Effects
  - Arrhythmia (6%)
  - Tachycardia (3%)
  - Cardiopulmonary arrest (2%)
  - Hypotension (2%)
  - Myocardial infarction (2%)
- Monitor
  - Thyroid function test
  - Bone demineralization

Drug Information Handbook for Psychiatry, Fuller MA, Sajatovic M, editors. Hudson, OH, Lexi-Comp, 2007.  
Nierenberg AA, Fava M, Trivedi MH, et al. A comparison of lithium and T (3) augmentation following two failed medication treatments for depression: a STAR\*D report. Am J Psych 2006;163:1519-30.

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**Bupropion**

- Adverse Effects
  - Insomnia
  - Weight loss
  - Tremor
  - Irritability
  - Increase seizure risk with doses >450mg per day
  - Drug interactions
    - Paroxetine and fluoxetine

Drug Information Handbook for Psychiatry, Fuller MA, Sajatovic M, editors. Hudson, OH, Lexi-Comp, 2007.

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**Buspirone**

- Adverse Effects
  - Dizziness
  - Headache
  - Nervousness
  - Light headedness
  - Excitement

Drug Information Handbook for Psychiatry, Fuller MA, Sajatovic M, editors. Hudson, OH, Lexi-Comp, 2007.

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**Mirtazapine**

- Adverse Effects
  - Weight gain
  - Sedation (doses <15mg QHS)
- Monitor
  - Fasting lipid panel

Drug Information Handbook for Psychiatry, Fuller MA, Sajatovic M, editors. Hudson, OH, Lexi-Comp, 2007.

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**Second Generation Antipsychotics**

- Aripiprazole\*
- Fluoxetine/Olanzapine combination\*\*
- Quetiapine
- Risperidone
- Ziprasidone

\*FDA approved, adjunctive treatment for unipolar depression  
\*\*FDA approved, acute treatment of treatment-resistant depression

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**Second Generation Antipsychotics**

**Monitoring for Prevention of Cardiovascular Risks**

- Baseline
  - Personal and family history
  - Weight (BMI)
  - Waist circumference
  - Blood pressure
  - Fasting plasma glucose
  - Fasting lipid profile

The American Diabetes Association, American Psychiatric Association, American Association Of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27: 596-601.

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**Second Generation Antipsychotics**

**Monitoring for Prevention of Cardiovascular Risks**

- 4 and 8 weeks and quarterly
  - Weight (BMI)
- 12 weeks
  - Weight (BMI)
  - Blood pressure
  - Fasting plasma glucose
  - Fasting lipid profile
- Annually
  - Personal and family history
  - Waist circumference
  - Blood pressure

The American Diabetes Association, American Psychiatric Association, American Association Of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27: 596-601.

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**Second Generation Antipsychotics**

- Extrapyrimalidal Symptoms (EPS)
  - Dystonia
  - Parkinsonism
    - Simpson-Angus Scale (SAS)
  - Akathisia
    - Barnes Akathisia Rating Scale (BARS)
  - Tardive dsykinesia
    - Abnormal Involuntary Movement Scale (AIMS)

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**Aripiprazole**

- Adverse Effects
- 6-12 weeks
  - Akathisia
  - Fatigue
  - Nausea
  - Insomnia
  - Jittery feeling/restlessness
  - Tremor

FDA approved, adjunctive treatment for unipolar depression

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**Fluoxetine / Olanzapine Combination**

- Adverse Effects
- 8-12 weeks
  - Somnolence
  - Weight gain
  - Dry mouth
  - Increased appetite

FDA approved, acute treatment of treatment-resistant depression

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**Quetiapine**

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- Adverse Effects
- 4-8 weeks
  - Weight gain
  - Dry mouth
  - Somnolence/sedation
    - Decline after 1 week

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**Risperidone**

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- Adverse Effects
- 4-6 weeks
  - Somnolence
  - Dry mouth
  - Weight gain
  - Dizziness
  - Tremor
  - Constipation
  - Increased prolactin levels

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**Ziprasidone**

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- Adverse Effects
- 6-8 weeks
  - Sedation
  - Dry mouth
  - GI distress

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### Depression Increases the Risk for Development of Type 2 Diabetes

Objective: Systematic review examining the bi-directional prospective relationships between depression and type 2 diabetes.

Methods: Medline search for comparative prospective studies of depression and type 2 diabetes that excluded prevalent cases of depression (for diabetes predicting depression) or diabetes (for depression predicting diabetes) published from 1950 through 2007. Reviewers assessed the eligibility of each report by exposure/outcome measurement and study design.

Results:

- The RR for incident diabetes associated with baseline depression was 1.60 (1.37–1.88)
- Depression is associated with a 60% increased risk of type 2 diabetes
- Type 2 diabetes however is associated with only increased risk of depression by (15%)

Mezuk B, et al. Diabetes Care. 2008;31:2383-2390.

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### Association of Depression with Diabetes Complications

Objective: To examine the relationship between depression and diabetes complications in studies of type 1 and type 2 adult patients with diabetes.

Method: Meta-analysis of MEDLINE and PsycINFO published articles examining depression and diabetes complications in type 1 and type 2 diabetes samples published between 1975 and 1999.

Results:

- 27 studies (total combined N = 5374)
- Significant association between depression & complications of diabetes ( $p < .00001$ ,  $z = 5.94$ ).
- Depression was significantly associated with a variety of diabetes complications (diabetic retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction).

Conclusions: These findings demonstrate a significant and consistent association of diabetes complications and depressive symptoms. Prospective, longitudinal studies are needed to identify the pathways that mediate this association.

de Groot et al. Psychosom Med. 2001;63:619-630

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### Reasons for Increased CVD Mortality in Major Mental Disorders

- CVD & Depression are prototype for comorbidity
- Primary and secondary prevention limitations for mentally ill versus general population
  - Less likely to
    - Be screened/treated for dyslipidemia, hyperglycemia, hypertension
    - Receive angioplasty or CABG
    - Receive drug therapies of proven benefit (thrombolytics, aspirin, beta-blockers, ACE inhibitors) post-myocardial infarction
  - More likely to have premature mortality post-myocardial infarction

Newcomer JW, Hennekens CH. JAMA 2007; 298(15):1794-1796.  
Druss BG et al. Arch Gen Psychiatry. 2001;58:565-572.

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### Reasons for Increased CVD Mortality in Major Mental Disorders

- ↑ Modifiable health risk factors
  - ↑ Overweight and obesity
  - ↑ Lipid abnormalities (↑TC, ↑LDL-C, ↑TG, ↓HDL)
  - ↑ Hyperglycemia
  - ↑ Hypertension
  - ↑ Metabolic syndrome
  - ↑ Physical inactivity
  - ↑ Smoking (41%)
- ↓ Access to and/or utilization of medical care
- ↓ Adherence with therapies
- ↓ Economic capabilities

Newcomer JW, Hennekens CH. JAMA 2007; 298(15):1794-1796. Ziedonis, D. Nic Tob Res 2008;10:1-25.

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### Depression Increases Risks for Cardiac Morbidity and Mortality

Community Samples

Study	Outcome
Anda, 1993	RR = 1.5 for cardiac mortality, 12.4 – year follow-up (NHEFS)
Aromaa, 1994	RR = 3.4 for cardiac mortality, 6.6-year follow-up (Finland)
Everson, 1995	RR = 1.9 for cardiac mortality, 6-year follow-up (Kuopio IHD study)
Pratt, 1996	RR = 4.5 for MI (History of MDD in the ECA Study)
Hippisley-Cox, 1998	RR = 3.0 for onset of CHD in men but not women depressed in the past 10 years. Case control study.
Penninx, 1998	RR = 2.0 for cardiovascular events in recently depressed men (but not in women) > 70 years old. EPESE longitudinal study.
Fort, 1998	RR = 2.0 for onset of CHD and MI in men who had ever been clinically depressed in the 40 yrs since med. school.

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### Conclusions

- Monitor for
  - Efficacy using MBC
  - Adverse effects
- Improve outcomes
  - Response
  - Remission

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A CE-Approved Session/Seminar Sponsorship to be Granted During the 2009 American College of Clinical Pharmacy Annual Meeting

**OPTIMIZING PHARMACOTHERAPY**  
*in Depressed Patients with Residual Symptoms*

## Expanding the Role of Pharmacists in the Care of Patients with Depression

Patrick R. Finley, PharmD, BCPP  
*Professor of Clinical Pharmacy  
Psychopharmacology and Behavioral Health  
University of California at San Francisco  
Email: finleyp@pharmacy.ucsf.edu*

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### Management of Depression in Primary Care

- > 70% of all depressed pts treated in 1<sup>o</sup> care
- 77% of all antidepressant Rx written by PCP
- < 50% of depressed patients accurately diagnosed
- < 50% of depressed patients accurately treated

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### The Epidemiology of Major Depressive Disorder

Results of National Comorbidity Survey Replication

- Methods
  - Face-to-face household survey; N=9090
- Results
  - Lifetime prevalence of MDD = 16.2 %
  - 12 month prevalence = 6.6 %
  - 12 month  $\Psi$  comorbidity prevalence = 78.5 %
    - Note: 51% of depressed pts had *comorbid anxiety disorder*
  - Percent of depressed pts receiving tx = 51.6 %
  - Percent of *treated* depressed pts receiving adequate tx = 41.9 %
  - Percent of *all* depressed pts receiving adequate tx = 21.7 %

Kessler RC et al. *JAMA* 2003;289:3095-3105

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### Impact of Depression

- Home
  - ↑ risk of substance abuse, domestic abuse, and divorce
  - Offspring more likely to develop psychiatric illness (independent of genetic predisposition)
- Work
  - Depression is #1 cause of absenteeism & presenteeism
  - 10% of employees depressed during any 2 week period
  - Lost productivity = 4 hours per week per depressed employee
- Overall Health
  - Depression predisposes to many medical illnesses (see bar graph)
  - Depressed patients 3x more likely to stop *all* medications

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### Prevalence of Depression with Medical Illnesses\*

Medical Illness	Prevalence of Depression (%)
General Population	5%
CAD	30%
Diabetes	25%
Cancer	20%
Stroke	22%
Epilepsy	30%
Dementia	35%
Parkinsons	50%
HIV	25%

\* - Point prevalence; Mean of range cited when applicable  
Finley PR. *Rx Consultant* 2004;12:1-8.

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Why are treatment outcomes suboptimal ?

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### Management of Depression in Primary Care: Barriers

- PCP time limitations (<7 minutes per visit)
- Lack of PCP familiarity with antidepressant tx
  - Limited effectiveness of available treatments
- Lack of PCP comfort with managing mental illness
- Lack of patient education and counseling
- Limited access to mental health care
- Patient attitude
- Lack of social supports
- Stigma

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What can we do ?

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### Historic Interventions

- Enhanced screening
- Improved patient education
- Mailed reminders
- Telecare
- Web-based care
- Collaborative Care

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### HEDIS 1999: Effectiveness of Care Measures Antidepressant Medication Management

- Number of antidepressant prescriptions during first 3 months of treatment
- Number of antidepressant prescriptions during first 6 months of treatment
- Minimum of 3 visits with prescriber during first 12 weeks of treatment [note: does NOT include baseline visit]

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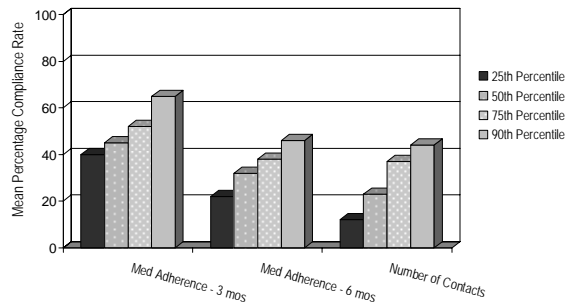
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### Medicaid Plans Accreditation 2005 Thresholds NCQA



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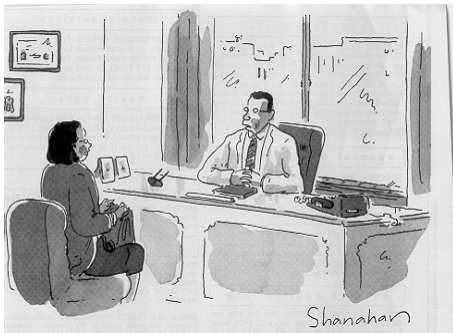
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'You can be rest assured, Mrs. Wilson, that your husband will receive the best care known to medical coverage.'

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Is there a role for pharmacists?

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### Expanding the Role of Pharmacists in the Care of Patients with Depression

#### Strengths

- The *most* accessible health professional
- Extensive training in medical model
- Extensive training in *discipline* of pharmacotherapy
- Extensive experience in patient education
- Cost-effective physician extender  
(e.g. – VA, Indian Health Service)
- Collaborative care protocols approved in 33 states
- MTM codes for pharmacists recently adopted as permanent (Medicare Part D)

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### Expanding the Role of Pharmacists in the Care of Patients with Depression

#### Weaknesses

- Reluctance to address mental health issues
- Lack of training in psychiatric interview
- Excessive workload
- Difficulty obtaining reimbursement

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## Pharmacists' Role in Depression Management

- Serve as source of medical information
  - Recommended websites: NAMI, DBSA, U Mass Hosp, naturalstandard.com
- Refer patients with suggestive symptoms to provider
- Give patients realistic expectations of antidepressants
  - Therapeutic effects *and* side effects
- Monitor and promote adherence with antidepressants
- Reinforce necessity of completing full course of treatment
- Communicate medication problems to providers
- Collaborative care management?

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*"Pharmacists continue to successfully expand their scope of practice. With the transition to the PharmD degree & automated dispensing, pharmacists are being trained to take a greater patient care role. ... Collaborative drug therapy is one of the best examples of how pharmacists work with physicians."*

Position Paper: Pharmacists Scope of Practice  
American College of Physicians & American Society of Internal Medicine  
*Annals of Internal Medicine* 2002; 136:79-85

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## Medication Alliance Clinic<sup>®</sup> *Optimizing Treatment Outcomes for Depressed Patients in Primary Care*

*University of California at San Francisco  
School of Pharmacy  
and  
Kaiser Permanente Medical Center  
San Rafael, California*

Investigators:  
Patrick Finley, Pharm.D. BCPP  
Heidi Rens, Pharm.D.  
Clifton Louie, DPA  
Lisa Bero, Ph.D.  
Joan Pont, M.D.  
Susan Gess, Pharm.D.  
Scott Bull, Pharm.D.

Finley PR et al. *Pharmacotherapy*. 2003;23:1175-1185.

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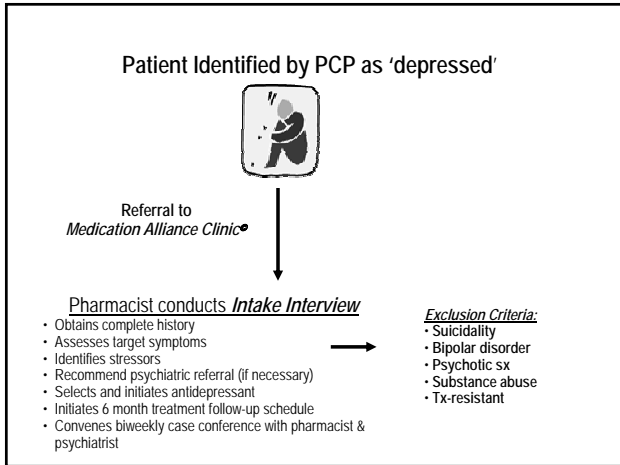
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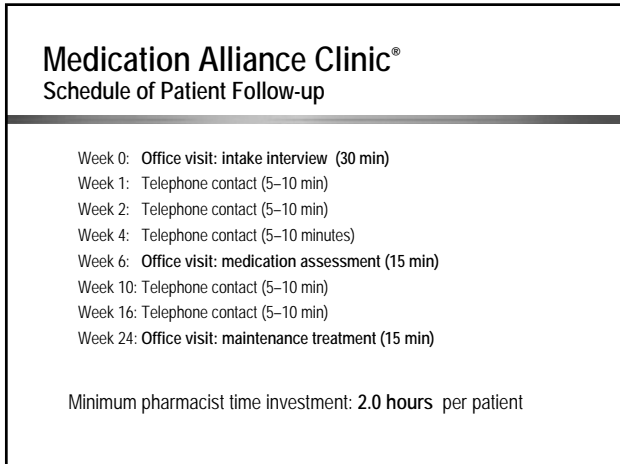
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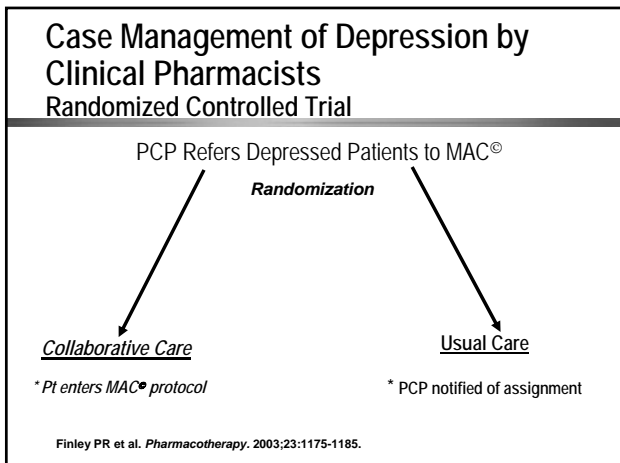
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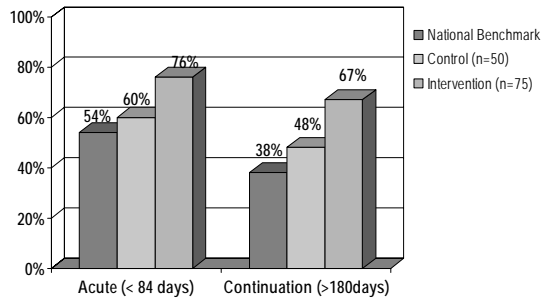
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### Medication Adherence Rates HEDIS specifications; Intent-to-treat analysis



Reproduced with permission. Finley PR et al. *Pharmacotherapy*. 2003;23:1175-1185.

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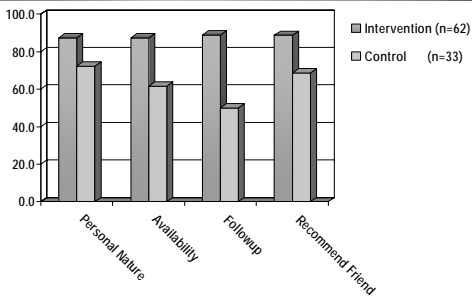
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### Patient Satisfaction Survey



[Chi square analysis of paired data; \*P < 0.05 for all measures]

Finley PR et al. *Pharmacotherapy*. 2003;23:1175-1185.

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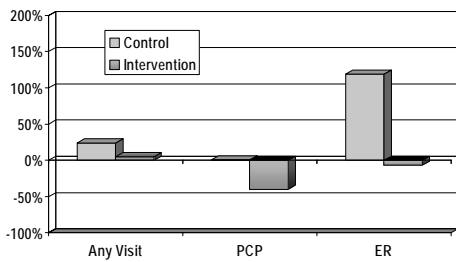
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### Change in Resource Utilization



Finley PR et al. *Pharmacotherapy*. 2003;23:1175-1185.

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### Change in Resource Utilization

- **Institutional Resources**
  - Resources = PharmD salary + 100% overhead [overhead accounts for benefits, space, charting etc]
  - Pharmacist time = 71 minutes / 6 month tx course [Avg 7.6 contacts/pt: 1.6 office visits, 6.0 phone calls]
  - \$ 75/hr X 1.2 hrs x 2 (overhead) = **\$ 180 per pt**
- **Total Resource Utilization**
  - Significant decrease in primary care visits [39% decline vs 1% increase with control; p=0.015]
  - No signif change in total resource utilization [p=0.48]

Finley PR et al. *Pharmacotherapy*. 2003;23:1175-1185.

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### Case Management of Depression by Pharmacists: Implementation Sites

- Kaiser Permanente
  - Northern California (10 sites)
  - Southern California (2 sites)
  - Oregon
- Others
  - UCSF Women's Health Center of Excellence
  - Veterans Administration (various)
  - Asheville, NC (Project ImPACT)

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### Clinical and Economic Outcomes of a Community-based, Pharmacist-focused Collaborative Care Program for Depression (ie, Project ImPACT: Depression)

Methods:

- Prospective, nonrandomized pilot project in Asheville, NC
- Employees with depressive symptoms enrolled in employer-sponsored care management program
- Pharmacists provided education, self-management tools, and provided treatment recommendation to providers
- Employees incentivized by waived Rx copays

DATA EMBARGOED PENDING PUBLICATION

Finley PR et al. (submitted for publication 9/09)

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**Project ImpACT: Depression Economic Analysis**

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**DATA EMBARGOED PENDING PUBLICATION**

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**Expanding the Role of Pharmacists in the Care of Patients With Depression**  
**Other Related Investigations & Descriptions**

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- **Jermain DM et al.** Psychopharmacy medication clinic in a managed care women's health setting. *AJHP* 1997; 54:2717-8.
- **Coleman EA et al.** Chronic care clinics: a randomized controlled trial of a new model of primary care for frail older adults. *J Am Geriatr Soc* 1999; 47:775-783.
- **Finley PR et al.** Impact of a collaborative pharmacy practice model on the treatment of depression in primary care clinic. *AJHP* 2002; 59:1518-1526.
- **Adler DA et al.** The impact of a pharmacist intervention on 6-month outcomes in depressed primary care patients. *Gen Hosp Psychiatry* 2004; 26:199-209
- **Capoccia KL et al.** Randomized trial of pharmacist interventions to improve depression care and outcomes in primary care. *AJHP* 2004; 61:364-372
- **Fortney JC et al.** Design and implementation of the telemedicine-enhanced antidepressant management study. *Gen Hosp Psychiatry* 2006; 28:18-26

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Future directions?

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**Expanding the Role of Pharmacists in the Care of Patients With Depression  
Unresolved Issues**

- Intensity of intervention
- Composition of multidisciplinary mix
- Improving exportability of models
- Cost-effectiveness of practical models
- Economic model

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**Expanding the Role of Pharmacists in the Care of Patients With Depression  
Who are the Stakeholders?**

- Patient
- Provider
- Institution
- Insurer
- Employer

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*“A cynic is a man who knows  
the price of everything  
and the value of nothing”*

**- Oscar Wilde**

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