



Depression Dilemmas in Primary Care: Appropriate Uses of Antidepressants and Alternatives

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May 18, 2006

Treating Depression is Important

Many studies have shown that depression is

- **Risk factor for many medical illnesses** (hypertension, stroke, e.g.) and
- Worsens prognosis in other illnesses: diabetes, breast cancer survival

Hjerl K et al, Depression as a prognostic factor for breast cancer mortality. *Psychosomatics* 2003 Jan/Fe: 44:24-30.

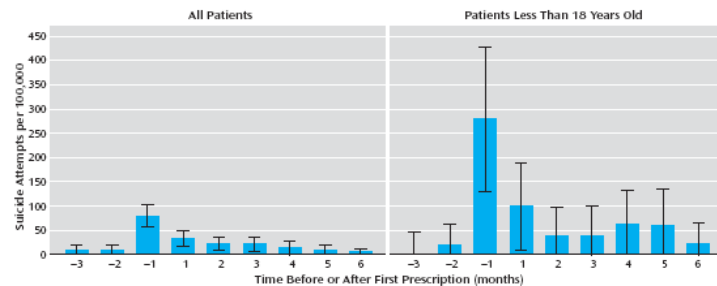
ENRICHD Study

- Looked at 4000 people with depression and heart disease
- Initially treated everyone with psychotherapy
- An antidepressant was added to some patients
- Those who were still depressed who did not receive an antidepressant did worse medically
- Those who got both were 40% less likely to have a repeat MI

Joynt KE, O'Connor CM: Lessons from SADHART, ENRICHED, and other trials. *Psychosom Med* 67 (Suppl 1):S63;2005.

Antidepressants Reduce Suicide Rates

FIGURE 4. Rates of Suicide Attempts During the 3 Months Before and the 6 Months After initial Antidepressant Prescription^a



^a Bars indicate 95% confidence intervals.

Simon GE et al. Suicide risk during antidepressant treatment. *Am J Psychiatry* 2006 (January) 163:41-7.

Rebecca

- 32 year-old female
- Married 15 years with three children
- “I’m moody. One minute I’m on top of the world and the next I’m angry.” “The littlest things will set me off.”
- Sleeps “as much as possible.”
- Over-eats and craves carbohydrates
- No interest in sex—a problem for marriage

Rebecca

- Started having mood problems as a teen. “Would get sad and want to be alone.”
- Also had bouts of rebellious behavior—dropped out of high school.
- Did some self-mutilating behavior
- Two summers ago only slept a couple of hours at night because she didn’t need to sleep more

Rebecca

- Started antidepressants about ten years ago. Tried a tricyclic, Celexa, Wellbutrin, Effexor. Found that they would work for a while then stopped working.
- About three months ago stopped her antidepressant because she was “really moody,” and cried all the time.
- Afraid of physically hurting someone

Rebecca

- Denies ever hearing or seeing things, but admits that “we used to live in a house where I thought the landlord had put video cameras.”
- Family history--Dad described as “an abusive alcoholic.” One brother has had problems with the law.

Rebecca

- Diagnosis: Bipolar II Disorder
- Treatment Plan: Start Lamotrigine 25 mgs daily for two weeks, then 50 mgs daily for two weeks
- Return in four weeks

Rebecca

Four weeks later returned taking 50 mgs daily of Lamotrigine to report:

- Feeling like “my old self”
- More relaxed
- Able to cope with minor irritations
- No side effects
- No signs of mania or depression

Rebecca

- Typical of many patients who may respond initially to antidepressants, then get worse
- History including irritability, self-injurious behavior, “moodiness,” bouts of over-activity
- Low-level psychotic symptoms
- Family history of mood disturbance, substance abuse, violent or criminal behavior

Bipolar Spectrum

- Ratio of bipolar disorders to depression initially thought to represent <1:10
 - Using expanded criteria including
 - Euphoric or irritable mood or over-activity
 - DSM-IV criteria for hypomania
 - Functional impairment
- Incidence increases to 1:3

Angst et al. Clin Approaches in Bipolar Disorder 2002.

The Bipolar Spectrum

- **Bipolar I: Must have had a manic episode**
Most also have depressive episodes
- The majority of patients fall on the “bipolar spectrum” including
- **Bipolar II--Major Depression and intermittent hypomania**
- **Mixed states**
- **Mood lability** (rapid shifts between states) often diagnosed as borderline personality disorder

DSM Criteria for Mania

A distinct period of **elevated, expansive or irritable mood** lasting at least a week (4 days for hypomania)

And three of the following:

1. Inflated self esteem

“Have there been times when you thought you were much smarter, more creative or important than you usually think?”

2. Decreased need for sleep

“Have there been times when you didn’t sleep much and felt fine, like you didn’t need to sleep? Or have you stayed up all night when you didn’t have to?”

DSM Criteria for Mania

3. *More talkative than usual*

“Have people commented to you that you are much more talkative or you couldn’t seem to stop talking?”

4. *Flight of ideas*

Does it seem sometimes that your thoughts are going really fast?

5. *Distractibility*

“Are there times when you can’t keep your mind on something because so many other thoughts keep popping in your head?”

DSM Criteria for Mania

6. *Increase in goal-directed activity*

“Do you have times when you feel that you have much more energy than usual and you get involved in doing a lot of new or different things?”

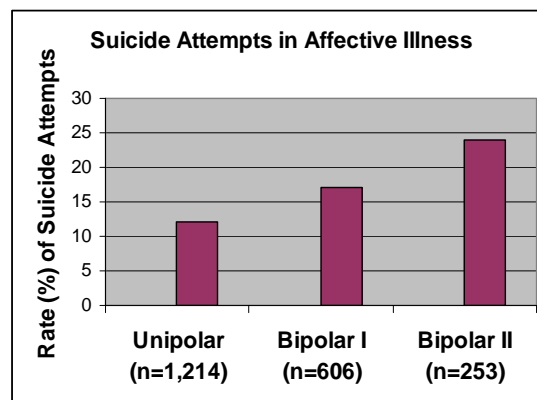
7. *Excessive involvement in pleasurable activities that are potentially risky or dangerous*

“Have there been times when you did risky things like driving your car recklessly, going on spending sprees, or having sex with people you barely knew?”

Clues to Bipolar Illness

- Mood problems in childhood or early teens
- Family history of bipolar illness, substance abuse, suicide, volatile behavior
- Any history of psychotic symptoms-paranoia, strange thinking, voices
- History of substance abuse
- “Borderline Symptoms”
- Marital instability
- Suicide attempts
- Reckless behavior
- Rage episodes
- Episodes of hypersexuality or promiscuity

Bipolar II Patients Have Increased Suicide Risk



Rihmer et al. Psychiatry Clin North Am 1999.

Underdiagnosis of Bipolar Disorder=Increased Suicide Risk

- The rate of suicide attempts is nearly double that for unipolar depression.

Rihmer et al. *Psychiatry Clinics of North America*. 1999

- Without treatment, bipolar disorder is associated with a 25-fold increase in the likelihood of suicide.

Angst F et al. Mortality of patients with mood disorders: follow-up over 34-38 years. *J Affect Disord* 68 (2-3):167-181.

The Bipolar Spectrum

Identification of bipolarity in patients with depression is important since treatment with antidepressants can increase their morbidity, especially if used without a mood stabilizer.

APA Guidelines for Bipolar Depression

- Antidepressant **monotherapy is not recommended** in bipolar depression.
- Antidepressants, if used, should only be given **in conjunction with a mood stabilizer**.

Antidepressants are Risky in Bipolar Patients

- Mood stabilizers often **do not protect** Bipolar I and II patients treated with an antidepressant **even while being maintained on a mood stabilizer**
- **Only 23% of bipolar patients experience a sustained antidepressant response after one year**

Leverich GS et al. Risk of switch *Am J Psychiatry* 2006 Feb; 163:232-9

Antidepressants are Risky in Bipolar Patients

- **Venlafaxine (Effexor)**
 - Twice the switch rate of Sertraline (Zoloft)
 - Three-times the rate of Bupropion (Wellbutrin)
- **Bipolar I switch to mania more often than Bipolar II**

Leverich GS et al. Risk of switch *Am J Psychiatry* 2006 Feb; 163:232-9.

APA Guidelines for Bipolar Depression

First line treatment of bipolar depression

- **Lithium Carbonate** (It along with clozapine is the only drug with an indication for reducing suicidality.)
- **Lamotrigine (Lamictal)**

Practice Guideline for the Treatment of Patients With Bipolar Disorder (Revision) *Am J Psychiatry* 159:4, 2002.
Cipriani A, et al. Lithium in the prevention of suicidal behavior. *Am J Psychiatry*. 2005 Oct;162(10):1805-19.

Atypical Antipsychotics

- Only FDA-approved treatment for bipolar depression is **Symbyax (Olanzapine-Fluoxetine)**.
- Recent data suggest that **Quetiapine (Seroquel)** at doses of 300 to 600 mgs daily is effective for bipolar depression.

Calabrese et al. (2005) *Am J Psychiatry* 162 97 0:1351-1360.

Mixed States

For **mixed states** the following have FDA approval

- Divalproex (Depakote)
- Carbamazepine (Tegretol/ Equetro)
- All second-generation antipsychotics
Risperidone (Risperdal), Olanzapine (Zyprexa), Ziprasidone (Geodon), Aripiprazole (Abilify)

Antidepressants in Bipolar Depression

- May have efficacy when used emergently, but there is **no evidence of efficacy when used for maintenance therapy**.
- There are risks of mania and worsening of illness in some bipolar patients.

Fredrick K. Goodwin, MD
George Washington University School of Medicine

Antidepressants in Bipolar Depression

- Generally should be reserved for **severe cases of acute bipolar depression** and not used routinely in mild to moderate cases.
- **Discontinue within 1 to 2 months** of recovery from depression; maintain them only in patients who repeatedly relapse soon after discontinuation (about 20%).

Fredrick K. Goodwin, MD
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Using Antidepressants in Children

Helen



Helen

I'm starting to feel nothing

I'm starting to go weak

I'm falling into complete darkness

I'm starting to die slowly

Helen

I've stopped eating, sleeping

I don't want to go to sleep anymore

Because, I don't want to see my dreams anymore

My dreams are nothing about happiness

Helen

If I shut everyone out of my life
I won't get hurt anymore
I don't have to feel anymore pain
I want to be left alone forever

Helen

No one cares about what I'm going through
They all just want me to die
So they don't have to worry about me anymore
So that everyone can be happy

Helen

16-year-old female experiencing her second episode of major depression with

- Loss of appetite and energy
- Hopelessness
- Guilt
- Nightmares and insomnia
- Preoccupation with death

Helen

- Can't concentrate in school
- Has been cutting
- Denies voices, but admits that it feels like people are watching her
- Afraid

Helen

- Had her first episode at age 13 and was treated briefly with Remeron. Gained weight and became more agitated after the depression lifted.
- Had voices and an “imaginary friend”
- Mother is on disability for bipolar illness
- Witnessed domestic violence as a child

Helen

- Tried Remeron again, but was too sedated
- Got into a “fist fight” with her mother
- Started to have uncontrollable anger

WHAT WOULD YOU DO?

Helen

- **Lithium carbonate (Lithobid)**
300 mgs twice daily and increased to one in the a.m. and two at night.
- Achieved a blood level of 0.7 mEq/L

Helen

- Helen rapidly improved. Only side effects were increased thirst and more frequent urination. Neither were a problem for her.
- The anger stopped and then the depression.
- Continued in school and kept her job
- Still doing well

Antidepressants in Children

- FDA: “Antidepressants increase suicidal thoughts and actions in some children and teenagers.”
- All antidepressants –**including Atomoxetine (Strattera)** carry a black box warning.
- Pooled data of 24 different studies of children and adolescents with depression or other illnesses. No child committed suicide, but some became suicidal. **On placebo, 2 out of 100 became suicidal compared to 4 out of every 100 on antidepressants.**

Antidepressants seem to reduce completed suicides

Conversely, another large study showed that from 1990 to 2000, the number of completed suicide in teens decreased inversely and significantly with the increase in antidepressant prescriptions.

Olson M et al. Relationship between antidepressant medication treatment and suicide in adolescents.
Arch Gen Psychiatry 2003 Oct; 60:978-82.

Prozac

- **Fluoxetine is the only SSRI with published data showing benefit over placebo** in children and adolescents with major depression although others are frequently used(1997).
- It required 12 weeks to have its full effect. Thirteen previous studies showed no efficacy of SSRIs.
- Fluoxetine is the only medication approved by the FDA for pediatric depression.

Prozac + Psychotherapy = Better Outcomes

439 teens with major depression at 12 weeks:

71% responded to Fluoxetine plus CBT

61% to Fluoxetine alone

43% to CBT alone

35% to placebo

- **Combination treatment reduced suicidal ideation far more than it increased suicide-related events.**
- **However, Fluoxetine treatment doubled the risk of harm-related events (aggression against others and deliberate, non-suicidal self-harm).**

Treatment for Adolescent with Depression Study (TADS) Team. JAMA 2004 Aug 18; 292:807-20.

When Using Antidepressants in Kids

- Use antidepressants **only for moderate to severe depressive disorder**.
- Follow FDA guidelines for monitoring and discontinue and refer if condition worsens.
- Be aware that Fluoxetine is the only antidepressant approved for kids. If you choose another agent, explain why to parents.

When Using Antidepressants in Kids

- Be aware that it may require 6 to 8 weeks for the medication to work.
- Screen for risk factors for bipolar depression. If highly suspect, do not start with an antidepressant.
 - Get a consult
 - Consider Lithium, Lamotrigine, Olanzapine+Fluoxetine, or Quetiapine

Four Drug Alternatives for Bipolar Depression

- Lamotrigine
- Lithium carbonate
- Quetiapine
- Fluoxetine/Olanzapine

Lamictal (Lamotrigine)

- First-line treatment for bipolar depression
- More effective for depression than mania
- Well tolerated: little weight gain and sedation
- Risk of skin rash comparable to Tegretol and many antibiotics

Lamictal (Lamotrigine)

- Depakote doubles the blood level so half the dose
- FDA Approval for bipolar maintenance therapy and seizures
- Useful in combination with lithium and/or atypical antipsychotics, especially in bipolar I
- Useful adjunct for treatment-resistant depression

Lithium Carbonate

- You can't treat bipolar illness unless you know how to use Lithium—there is a lot to know.
- Renal excretion—diuretic properties, thyroid suppression, effects on skin, etc.
- Works for all phases of mood disturbance and is first-line for treatment-refractory depression.

Lithium Carbonate

- May be best for “classic” mania. Depakote may be better for mixed, rapid-cycling.
- May be more effective for mania than depression (mix it with Lamotrigine).
- **Patients maintained on Lithium are seven times less likely to kill themselves.**

Cipriani A, et al. *Am J Psychiatry*. 2005 Oct;162(10):1805-19.

Seroquel (Quetiapine)

- Probably soon to be approved for bipolar depression
- Atypical antipsychotic
- Helpful for both manic and depressive symptoms
- Useful as augmenting strategy for treatment-resistant depression

Seroquel (Quetiapine)

- Commonly under-dosed—need 300 to 600 mgs daily
- Can combine with other mood stabilizers but not atypicals
- Monitor for weight gain, lipid abnormalities and hyperglycemia
- Sedating
- Expensive

Symbyax (Olanzapine/Fluoxetine)

- Zyprexa + Prozac
- Only drug currently FDA-approved for bipolar depression
- Wonderful short-term tolerability
- Difficult long-term because of weight-gain and dyslipidemia
- Expensive

Non-Drug Alternatives

Electroconvulsive Therapy (ECT)

- Remains as effective as any known treatment for major depression.
- May be preferable for patients with psychotic bipolar depression and pregnant patients.

Non-Drug Alternatives

Light therapy

- Improved mood often within 2 to 3 days after initiation
- Requires 10,000 lux, an 18" X 12" surface area
(home light is about 100 lux) twice daily
- Side effects are mild—nausea, headache
- Effective for non-seasonal depression

Golden RN et al: The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry* 162:656, 2005.

Non-Drug Alternatives

Exercise

- One study found exercise comparable to Sertraline in 50-year-olds with major depression and more lasting benefit
- Overall, more research is needed to prove effectiveness

Babyak. Psychosom. Med. 62[5]:633-38, 2000.

Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomized controlled trials. *BMJ* 2001 Mar 31;322(7289):763-7.

Non-Drug Alternatives

Omega-3 Fatty Acids

- Major depression is less common in populations that consume 0.5 to 1.0 g/day of omega-3 polyunsaturated fatty acids (found in seafood)
- Omega-3 supplements are being studied for bipolar illness, post-partum depression, major depressive illness

Peet M and Horrobin DF. *Arch Gen Psychiatry* 2002 Oct; 59:913-9.

Non-Drug Alternatives

Psychotherapy

- Especially for patients with life-circumstance problems,
- Adolescents (CBT), and
- Vascular depression (problem-solving therapy)

Resources

- Essential Psychopharmacology, The Prescriber's Guide- Stephen Stahl, MD
- Practice Guideline for the Treatment of Patients with Bipolar Disorder (Revision) Supplement to the American Journal of Psychiatry
- For phototherapy resources:
www.normanrosenthal.com/links
- American Psychiatric Association
www.psych.org