

PSYCHIATRY DRUG ALERTS

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Sustained Antidepressant Use Reduces Suicide Risk

In patients with depressive disorders suicide risk is high but appears to decline with continuing antidepressant treatment.

Methods: Data on filled antidepressant prescriptions, psychiatric diagnosis, and suicides were collected from databases in Denmark from 1995 to 2000. Adults discharged from hospital-based care with a diagnosis of depressive disorder comprised the study cohort of >31,000 patients. Suicide rates were calculated from a cause of death registry for patients taking SSRIs, SNRIs, and older antidepressants based on the number of prescriptions filled.

Results: After discharge 16% of patients did not fill an antidepressant prescription. Among those who did, 93% purchased antidepressants more than once. Nearly one third of the patients were prescribed SSRIs only, 12% were prescribed SNRIs, and 13% received older antidepressants (e.g., TCAs, MAOIs). The remaining patients were treated with agents from 2 or more antidepressant classes.

As expected, the rate of suicide in the study cohort was higher than what has been reported in the general population: 310 patients died by suicide over the 6-year study period. After adjustment for confounding factors, patients who filled only 1 antidepressant prescription had a significantly higher rate of suicide than those who filled none (risk ratio, 1.13), regardless of the type of antidepressant. The rate was significantly decreased among patients who filled ≥ 2 prescriptions, compared with none (risk ratio, 0.35) or only 1 (risk ratio, 0.31). The rate continued to decline with each successive filled prescription, also irrespective of antidepressant class.

Sondergard L, Garcia Lopez A, Andersen P, Kessing L: Continued antidepressant treatment and suicide in patients with depressive disorder. *Archives of Suicide Research* 2007;11(2):163-175. From University Hospital of Copenhagen, Denmark. **Funded by the Lundbeck Foundation; and other sources.**

Context of Antidepressant Warning

Because the FDA has ordered antidepressant manufacturers to expand the black-box warning on suicide risk to include young adults aged 18-24 years, a recent editorial cautions clinicians not to overlook the "real killer," untreated depression, whose risks "dwarf" those of antidepressant treatment.* The newest recommendation resulted from a meta-analysis of 100,000 patients of

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all ages enrolled in 372 randomized trials during the past 2 decades. The results, which showed a statistically significant effect on suicidal behavior and ideation in children and a 55% increase in patients age 18 to 24 ($p=ns$), were presented at a December 2006 FDA advisory committee meeting. No increase in risk was found in adults overall, and a beneficial effect was found in patients age 65 and older. Only 8 suicide deaths occurred in study participants: 5 in nearly 40,000 patients taking the investigational drug, 2 in about 27,000 placebo-treated patients, and 1 in nearly 15,000 taking an active comparator.

The FDA's warning may confuse clinicians and patients and could do more harm than good by discouraging the pharmacologic treatment of depression. Despite its strengths, the analysis was restricted to patients treated for psychiatric disorders and does not adequately account for confounding by indication (i.e., the possibility that suicidality is caused by the disease rather than the treatment). Studies of antidepressant use for nonpsychiatric or nonbehavioral indications were included in a secondary analysis. The lack of a suicidal effect in these studies of other indications suggests depression plays a key role in suicidality and that antidepressants themselves do not cause suicidal symptoms to appear. The FDA's analysis of antidepressant trials did not include any efficacy data, making it impossible to calculate the risk–benefit ratio of treatment. Lifetime risk of suicide in patients with depression ranges from 2.2% to 15%. In contrast, the risk of suicide in patients taking investigational antidepressants during short-term trials was 0.01%.

Clinicians have long known that during the first few weeks of antidepressant treatment, when core symptoms of depression have not yet lifted, some patients become "activated" making them more likely to act on pre-existing suicidal impulses. Patients starting antidepressant therapy should be warned of this risk and followed very closely during the first 4–6 weeks of treatment.

*Friedman R, Leon A: Expanding the black box—depression, antidepressants, and the risk of suicide [editorial]. *NEJM*. Published online 5/7/2007; DOI 10.1056/NEJMp078015. Accessed May 9, 2007. From Weill Cornell Medical College, New York, N.Y.

Tamoxifen for Bipolar Mania

A controlled trial was undertaken to evaluate the effects of the selective protein kinase C inhibitor tamoxifen on manic symptoms in bipolar disorder.

Background: Protein kinase C enzymes regulate pre- and post-synaptic neurotransmission, and patients with bipolar disorder have been shown to have elevated levels of protein kinase C. Both lithium and valproate decrease the level. Animal studies have shown that protein kinase C inhibitors improve manic-like symptoms, suggesting they may be useful in bipolar disorder.

Methods: Participants were 16 patients (mean age 35 years; 2 females) with bipolar disorder and a Young Mania Rating Scale (YMRS) score of ≥ 14 . All were experiencing a manic or mixed episode with or without psychotic features. The mean duration of illness was 16 years and the current episode duration was about 1 month. Treatment-naïve subjects were excluded from the study as were those with a QTc interval >480 ms because tamoxifen has been reported to prolong the QT interval. After a 2–7 day screening period and medication washout, patients were randomized to receive 20–140 mg/day tamoxifen or placebo for 3 weeks. Concomitant lorazepam was permitted for the first 10 days. The primary outcome measure was the YMRS and response was defined as a $\geq 50\%$ decrease in score.

Results: Patients treated with tamoxifen showed a mean 18-point decrease in YMRS score at 3 weeks (from a baseline score of 30; $p<0.05$ compared with placebo). The mean score increased by 5 points in those who received placebo. Of the 8 patients randomized to each group, 5 (63%) in the tamoxifen group met response criteria, compared with 1 (13%) in the placebo group. A final YMRS score of ≤ 7 was achieved by 2 of the tamoxifen-treated patients. Improvement with tamoxifen was evident by day 5. Treatment did not significantly affect depression rating scale scores, suggesting that improvement in mania was not associated with worsened depression.

No serious adverse effects were reported and only loss of appetite occurred significantly more often with active treatment. No patient withdrew from the study because of QTc prolongation.

Discussion: In addition to protein kinase C inhibition, tamoxifen has anti-estrogenic effects and is currently approved for prevention and treatment of breast cancer. While the results suggest that protein kinase C inhibition has antimanic effects, the study was small and needs to be replicated in larger patient groups.

Zarate C, Singh J, Carlson P, Quiroz J, et al: Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study. *Bipolar Disorders* 2007;9 (September):561–570. From the NIMH; and the Department of Health and Human Services, Bethesda, Md. **Funded by the NIMH; and the Department of Health and Human Services.**

Drug Trade Names: lorazepam—*Ativan*; tamoxifen—*Nolvadex*; valproate—*Depakene*

Donepezil and Memory in Bipolar Disorder

In a case series, treatment with donepezil improved memory in patients with bipolar II disorder. Patients with bipolar I appeared to worsen with donepezil.

Fifty-eight patients treated at a single practice were offered a trial of donepezil after reporting memory problems. The patients' bipolar symptoms had been stabilized with lamotrigine (n=55), oxcarbazepine (n=32), lithium (n=32), and aripiprazole (n=27). Adjunctive donepezil was started at 5 mg/day and increased if needed to 10 mg/day. Most patients (n=43) had bipolar II disorder; 7 had bipolar I, and 8 had bipolar disorder not otherwise specified (NOS). The Clinical Global Impression-Improvement (CGI-I) Scale was used to evaluate changes in memory.

Of the 58 patients, 39 (67%) experienced memory improvement with donepezil. The mean CGI-I score was 1.8; a CGI-I score of 2 corresponds with a rating of "much improved." Thirty-five of these patients had been diagnosed with bipolar II disorder. Among the 7 patients with bipolar I disorder, 5 discontinued donepezil: 4 because of clinical worsening (e.g., mild agitation, racing thoughts, rapid cycling and irritability, hypomania) and 1 for adverse effects. Neither of the 2 patients with bipolar I disorder who continued donepezil experienced improvement. Clinical worsening was apparent in 2 of 8 patients (25%) with bipolar NOS, and 4 showed improved memory.

Several patients who had improved stopped donepezil and within 3–4 weeks lost the memory improvements. In each patient memory again improved when donepezil was restarted.

Kelly T: Is donepezil useful for improving cognitive dysfunction in bipolar disorder? *Journal of Affective Disorders In Press*. Available online September 10, 2007; DOI 10.1016/j.jad.2007.07.027. From Fort Collins, Colo. **The study was conducted with no external funding; and the author declared no conflicts of interest.**

Drug Trade Names: aripiprazole—*Abilify*; donepezil—*Aricept*; lamotrigine—*Lamictal*; lithium—*Cytomel*; oxcarbazepine—*Trileptal*

Efficacy of Dual-Mechanism Antidepressants

In patients with unipolar major depression, dual-mechanism antidepressants were found to have a very small advantage over SSRIs.

Methods: Data from published randomized controlled trials, psychiatry meeting abstracts, public and industry clinical trial registries, and unpublished manufacturers studies were included in a meta-analysis. All studies measured outcomes using the Hamilton Rating Scale for Depression or the Montgomery-Asberg Depression Rating Scale and reported response ($\geq 50\%$ improvement). The analysis included 93 trials in more than 17,000 patients randomly assigned to treatment with a dual-mechanism agent (i.e., duloxetine, mianserin, milnacipran, mirtazapine, moclobemide, or venlafaxine) or an SSRI.

Results: The pooled response rate was 64% for dual-mechanism antidepressants and 60% for SSRIs ($p=0.003$). Although the difference was statistically significant, the clinical significance is

uncertain. The number needed to treat (NNT)* with a dual-mechanism agent was 24, which is well above the NNT of 10 proposed as the cutoff for significance.

No serotonergic-noradrenergic drug appeared to be more effective than the others, despite differences in their mechanisms of action. Mirtazapine and mianserin increase serotonergic and noradrenergic neurotransmission and moclobemide acts via monoamine oxidase inhibition. Results did not differ between industry-sponsored studies and those with other funding sources, but >75% of the studies were funded by the manufacturer of a dual-mechanism agent.

Papakostas G, Thase M, Fava M, Nelson J, et al: Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. *Biological Psychiatry*. Published online June 22, 2007; DOI 10.1016/j.biopsych.2007.03.027. From Massachusetts General Hospital, Boston; and other institutions. **Funded by the NIMH.**

*NNT indicates the number of patients that need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the value, the less effective the treatment.

Drug Trade Names: duloxetine—*Cymbalta*; mianserin (not available in the U.S.)—*Bolvidon, Norval, Tolvan*; milnacipran (not available in the U.S.)—*Ixel*; mirtazapine—*Remeron*; moclobemide (not available in the U.S.)—*Aurorix, Manerix*; venlafaxine—*Effexor*

Treating Anxiety in Older Patients

A meta-analysis has found pharmacotherapy to be more effective than behavioral treatment in older patients with anxiety.

Methods: Controlled and uncontrolled studies of interventions for anxiety were identified by literature search. Included in the meta-analysis were 32 published studies (2484 patients) that had a mean patient age ≥ 60 years. Nineteen studies investigated pharmacotherapy, 12 used behavioral therapies, and 1 included both treatments.

Results: Both pharmacotherapy and behavioral therapy produced large improvements in anxiety (effect size, 0.8; 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect) and moderate improvements in depressive symptoms (effect size, 0.6). In an analysis of change within intervention groups, treatment effects for anxiety symptoms were stronger in pharmacological studies (effect size, 1.76) than in behavioral studies (effect size, 0.81). The reduction in depressive symptoms did not differ by intervention. Although pharmacotherapy was expected to be associated with more adverse effects, the percentage of patients dropping out of treatment did not differ between the pharmacotherapy (22%) and behaviorally-treated groups (27%). In the controlled studies, older age appeared to predict better response.

Benzodiazepines, SSRIs, TCAs, and other drugs were evaluated separately, as were CBT and other behavioral interventions. SSRIs were found to be significantly more effective than CBT and other behavioral interventions ($p < 0.001$). Benzodiazepines were significantly more effective than other behavioral interventions ($p < 0.001$) but not CBT.

Discussion: The evidence suggests that both pharmacotherapy and behavioral treatment reduce anxiety in older patients. Pharmacotherapy appears to produce greater improvements overall, but comorbid conditions and other factors can limit drug therapy in these patients. CBT was not significantly less effective than benzodiazepines, suggesting that it may be a good option in patients who can not tolerate medication.

Pinquart M, Duberstein P: Treatment of anxiety disorders in older adults: a meta-analytic comparison of behavioral and pharmacological interventions. *American Journal of Geriatric Psychiatry* 2007;15 (August):639–651. From Friedrich Schiller University, Jena, Germany; and University of Rochester Medical Center, Rochester, N.Y.

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*An...