Antidepressant/Tamoxifen Interaction

A preliminary report from a study conducted by Medco Health Solutions and presented at an American Society of Clinical Oncology meeting suggests that several antidepressants that inhibit cytochrome P450 (CYP) 2D6 reduce tamoxifen concentrations and may lead to cancer recurrence.

Methods: Nearly 1300 women with breast cancer and a new prescription for tamoxifen were identified from Medco medical and pharmacy claims. Rates of recurrent cancer over 2 years were compared between women taking tamoxifen alone (n=945) and those taking tamoxifen with a concurrent CYP2D6 inhibiting SSRI (n=353).

Results: Overall, women who took tamoxifen plus a CYP2D6 inhibitor (mean duration of concurrent treatment, 340 days) had a nearly 2-fold increase in breast cancer recurrence, compared with those who took tamoxifen alone (14% vs 7.5%; p<0.001). Concurrent users of one of the moderate/potent CYP2D6 inhibiting SSRIs (i.e., fluoxetine, paroxetine, sertraline) had the highest recurrence rate (16%). The rate of recurrence (9%) in women using a weaker inhibitor (i.e., citalopram, escitalopram, fluvoxamine) did not significantly differ from those receiving tamoxifen alone.

Clinical Implications: Because SSRIs with less potent CYP2D6 effects and antidepressants with no CYP2D6 effects are available, it seems reasonable to avoid use of fluoxetine, paroxetine, and sertraline in women taking tamoxifen.


Drug Trade Names: citalopram—Celexa; escitalopram—Lexapro; fluoxetine—Prozac; fluvoxamine—Luvox; paroxetine—Paxil; sertraline—Zoloft; tamoxifen—Nolvadex

Add-On Aripiprazole Reduced Weight

A small controlled trial showed that adding aripiprazole to olanzapine produced weight loss and other metabolic improvements in a group of overweight patients.

Methods: Adult outpatients (n=15; mean age, 49 years) with schizophrenia that was controlled with olanzapine (mean duration, 71 months) were eligible for study if they had a body mass
index (BMI) of ≥30 or had a BMI of >26 plus other risk factors (e.g., hypertension, lipid abnormalities, or increased fasting glucose). Participants were randomized to 4 weeks of double-blind placebo or 15 mg/day aripiprazole and then after a 2-week washout were crossed over to the alternate treatment. Weight, BMI, metabolic parameters, and schizophrenia symptoms were evaluated at baseline and at weeks 4, 6, and 10.

**Results:** During aripiprazole treatment, patients lost a mean of 3 lbs, compared with a gain of 2 lbs with placebo (p=0.003). The mean BMI of 33 decreased by half a point with aripiprazole and increased by a similar margin with placebo (-0.4 vs +0.3; p=0.003). Total, HDL, and LDL cholesterol were not significantly changed with aripiprazole, but triglycerides and very-low density (VLDL) cholesterol were significantly decreased from baseline (p≤0.01). Metabolic and weight changes were not the result of increased physical activity. Schizophrenia symptoms were unaffected by the addition of aripiprazole. Treatment was well tolerated with no significant blood pressure changes. Adverse effects included appetite changes, difficulty falling asleep, and tiredness and they affected nearly 30% of patients. It should be noted that although all patients were overweight or obese at baseline, it is not clear whether they had gained weight because of olanzapine treatment.

**Clinical Implications:** Adding aripiprazole to a stable olanzapine dose in overweight patients with schizophrenia appeared to be safe and effective at reducing weight and improving metabolic parameters that predict medical morbidity. Although the combination does not negatively affect schizophrenia symptoms, the cost of combined treatment may be prohibitive in some cases.

**Study Rating**—17 (100%): This study met all criteria for a randomized clinical trial.


**Drug Trade Names:** aripiprazole—*Abilify*; olanzapine—*Zyprexa*

*Reference Guide Item.

### Metformin for Clozapine Metabolic Effects

In a placebo-controlled trial, metformin was associated with weight loss and favorable metabolic effects in patients taking clozapine.

**Methods:** Study participants were 61 adults with schizophrenia, schizophreniform disorder, or bipolar disorder who had been treated with clozapine for ≥3 months (mean durations, 6.5–8 years). All had received information about its metabolic side effects and had been given diet and exercise recommendations. Patients were randomly assigned to receive 1000 mg/day metformin or placebo. Body weight was the primary outcome of the 14-week study, and 50% of the metformin group and 33% of the placebo group were obese at baseline.

**Results:** All 30 patients in the placebo group and 24 in the metformin group completed the study; 7 patients withdrew from treatment because of nonspecific side effects. After 14 weeks, patients in the metformin group, whose mean baseline weight was 181 lbs, had lost an average of 4 lbs. Weight was stable with placebo at about 170 lbs. Patients who took metformin also had a small average decreases in body mass index, HbA1c, and leptin levels, and a modest increase in HDL-cholesterol. Serum glucose decreased over time in both groups and did not differ significantly between them. Insulin levels were lower after treatment in the metformin group. No significant differences were observed in most blood lipid measurements and in blood pressure. The incidence of metabolic syndrome decreased in the metformin group (from 25% at baseline to 17% at 14 weeks) but remained stable in the placebo group.
Discussion: Because the patients represented a wide range of weight and metabolic status, the study treatment could be considered a mixed protocol of prevention and reversal of clozapine-induced metabolic dysfunction.

Study Rating*—17 (100%): This study met all criteria for a randomized clinical trial.


Drug Trade Names: clozapine—Clozaril; metformin—Glucophage

*Reference Guide Item.

Paroxetine and Male Fertility

In healthy men, 5 weeks of paroxetine (Paxil) treatment induced abnormal sperm DNA fragmentation as well as erectile changes and ejaculatory difficulties. The effects were transitory and most variables returned to or approached baseline levels 4 weeks after stopping paroxetine.

Background: Although SSRIs are known to have adverse effects on sexual function, little is known about SSRI effects on sperm quality and male fertility. A report of 2 men with decreased sperm concentration and motility that resolved after stopping the medication suggested that SSRIs may affect sperm transport rather than production. The present study evaluated the impact of an SSRI on standard semen parameters, sperm DNA integrity, endocrine and sexual function in healthy men. Paroxetine was chosen because it has been shown to produce the longest ejaculatory delay of the SSRIs and because of its relatively short half-life.

Methods: Healthy male volunteers (n=35) with normal semen parameters and no sexual dysfunction or Axis I psychiatric disorder were recruited for the study. Baseline semen samples were collected, and the men received 5 weeks of escalating-dose paroxetine treatment (10 mg/day in week 1; 20 mg/day in week 2; 30 mg/day in weeks 3 and 4; 20 mg/day in week 5). Semen analysis was performed at weeks 2 and 4 and again 1 month after paroxetine discontinuation.

Results: Paroxetine did not significantly affect semen parameters (i.e., volume, motility, concentration, morphology), and there were no changes in follicle-stimulating hormone, luteinizing hormone, or prolactin levels. Serum testosterone was significantly reduced from 844 ng/dL to 605 ng/dL with paroxetine but remained within the normal range. During paroxetine treatment 30–40% of men reported erectile dysfunction of varying degrees and 30–56% reported ejaculatory dysfunction. Sexual function approached or returned to baseline levels 4 weeks after paroxetine was stopped.

Abnormal DNA fragmentation, based on a cutoff value suggested to identify men with poor fertility, was present in 10% of the baseline sperm samples, compared with 50% of the samples after 4 weeks of paroxetine treatment. The odds ratio* for an abnormal result with paroxetine was 9.3.

Discussion: Although fertility was not directly addressed, the findings regarding DNA fragmentation strongly suggest paroxetine can impair male fertility. Future study should investigate the effects of other SSRIs and antidepressant classes on DNA fragmentation and the potential fertility issues.


*Reference Guide Item.
Atypicals Differ in Diabetes Risk

Most atypical antipsychotics are associated with no higher risk of diabetes than conventional agents, according to a large postmarketing study. The exceptions, olanzapine and clozapine, are associated with about a 2- to 3-fold increase in diabetes onset.

Methods: The study was based on electronic data from 3 U.S. health insurance plans covering more than 60 million subscribers. The analysis included 2 overlapping cohorts of adult patients, previously free of diabetes, who took any antipsychotic drug for 45 days or more between November 2002 and March 2005. The "standard cohort" comprised nearly 78,000 patients treated during this time. The "inception cohort" was a subset of about 56,000 patients who had no previous antipsychotic exposure for at least 3 months before starting the prescription. The investigators adjusted for numerous variables and accounted for antipsychotic drug switches.

About 10% of the patients used conventional antipsychotic drugs. Unlike many previous studies, the cohorts included large enough patient samples taking aripiprazole and ziprasidone to produce reliable estimates for these drugs. Patients had a mean age of 45 years, 60% were women, and 5% were obese.

Results: Compared with conventional agents in the standard cohort, the risk of diabetes was increased in patients taking clozapine (hazard ratio [HR],* 2.28; p=0.01) and olanzapine (HR, 1.77; p=0.001) and in those taking multiple agents (HR, 1.85; p=0.002). Relative risk estimates for these 2 drugs and for multi-drug regimens differed slightly in the inception cohort (see table).

<table>
<thead>
<tr>
<th>New Atypical Antipsychotic Use</th>
<th>Adjusted HR for Diabetes</th>
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</thead>
<tbody>
<tr>
<td>Risperidone</td>
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<tr>
<td>Aripiprazole</td>
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</tr>
<tr>
<td>Ziprasidone</td>
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</tr>
<tr>
<td>Quetiapine</td>
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<tr>
<td>Multiple atypical agents</td>
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<tr>
<td>Olanzapine</td>
<td>1.71</td>
</tr>
<tr>
<td>Clozapine</td>
<td>2.58</td>
</tr>
</tbody>
</table>

Discussion: Atypical antipsychotics are known to increase diabetes risk, but previous studies comparing individual drugs have had mixed results. In a recent consensus conference, the American Diabetes Association, the American Psychiatric Association, and other organizations concluded that clozapine and olanzapine increased the risk of diabetes. This panel could not reach a consensus on risperidone or quetiapine due to conflicting study results, and they stated that data on ziprasidone and aripiprazole were limited but they did not appear to be associated with diabetes. Results of the present study are consistent with the recommendations that came from the consensus panel. It is not likely that a study of this nature will be conducted again, since patients at high risk for diabetes should now be prescribed atypical agents not liable to increase their risk.


Drug Trade Names: aripiprazole—Abilify; clozapine—Clozaril, olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon

*Reference Guide Item.
Clonidine Improved Hyperarousal

A small controlled trial provided preliminary evidence that clonidine (Catapres) may improve hyperarousal symptoms in patients with borderline personality disorder and PTSD.

Methods: Adult inpatients (n=17; 1 male) with borderline personality disorder with or without comorbid PTSD were enrolled if they had been receiving stable psychotropic medication and exhibited prominent hyperarousal symptoms (i.e., sleep problems, irritability/anger, concentration difficulties, hypervigilance, exaggerated startle response). All received double-blind placebo and clonidine for 3 weeks each in a cross-over fashion separated by a 1-week washout. Clonidine was titrated over 1 week to 0.45 mg/day, continued for another week, and then tapered during week 3. Most patients had comorbid conditions including PTSD (n=12), eating disorders (n=9), and substance abuse (n=7). The clinician administered PTSD scale (CAPS-D) was used to measure a cluster of hyperarousal symptoms. Borderline personality symptoms were evaluated with the borderline symptom checklist (BSL), and the Symptom Checklist 90–Revised measured general psychopathology at baseline and after 2 weeks of each treatment.

Results: Five patients withdrew from the study, 3 after receiving placebo and 2 after receiving clonidine. Dropouts were not reported to be associated with adverse effects, which when present were generally mild and included xerostomia, orthostatic reactions, and mild edema. In the last observation carried forward analysis, clonidine produced an 18% reduction in hyperarousal symptom scores. The mean CAPS-D score was reduced from 28 to 18 with clonidine and to 23 with placebo (p=0.003) in the entire sample. Improvements in hyperarousal were 21% in the patients with comorbid PTSD and 13% in those without; this difference was not statistically significant (p=0.14), possibly because of the small sample size.

In the full sample, clonidine did not affect borderline personality symptoms, but patients with comorbid PTSD showed significant improvements on the self-destruction and self-perception items of the BSL (p<0.05). Similarly, general psychopathology scores did not significantly improve in the sample as a whole with clonidine treatment, although anxiety, rest items, and obsessive-compulsive symptoms improved significantly (p<0.02). During clonidine treatment patients reported decreased sleep onset latency (17 minutes) and that their sleep was slightly more restorative.

Discussion: This is the first controlled trial to show clonidine may reduce some symptoms of borderline personality disorder, perhaps particularly so in patients with comorbid PTSD, which has been reported to affect about half of patients. In light of the study’s limitations, including the small sample size and short treatment duration, the results must be viewed as preliminary.

Study Rating*—17 (100%): This study met all criteria for a randomized clinical trial. The checklist determines the presence or absence of the item, and it does not rate the quality of the item.

Smoking Cessation Aids and Suicidal Ideation

A postmarketing safety review of the smoking cessation aids varenicline (Chantix) and bupropion (Zyban, and others) has identified cases of suicidal ideation and suicidal behavior with treatment.1 Cases were reported in patients with and without a history of psychiatric symptoms. The FDA is now requiring a Boxed Warning about serious mental health events including behavioral changes, depressed mood, hostility, and suicidal thoughts.2
FDA reviewers identified 153 Adverse Event Reporting System (AERS) reports of suicidal adverse events from each agent’s approval date to November 2007: for varenicline (116 suicidal ideation; 37 suicides) and for bupropion (46 suicidal ideation; 29 suicides). The median time to event onset was <2 weeks after treatment initiation. In a similar proportion of cases with varenicline (35%) and bupropion (33%), symptoms resolved after discontinuation of the drug.

About 25% of the cases of suicidal ideation or behavior with varenicline occurred in patients with no history of psychiatric symptoms. A similar pattern was seen with bupropion: 32% of patients had no previous symptoms. With varenicline, 42% of patients who experienced suicidal ideation/behavior were receiving psychotropic medications in addition to the smoking cessation aid. A smaller percentage of bupropion-treated patients reported additional psychotropic use (see table). It should be noted that many of the AERS reports did not provide information on psychiatric history or concomitant medications.

For both drugs, a psychiatric history specific for depression was frequent: 58% with varenicline and 66% with bupropion. Depression was also frequently reported as a co-occurring condition at the time of the suicidal event: 50% and 70% with varenicline and bupropion, respectively.

### Psychiatric variables noted in AERS reports

<table>
<thead>
<tr>
<th></th>
<th>Varenicline</th>
<th>Bupropion</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Suicidal Ideation</td>
<td>Suicidal Behavior</td>
</tr>
<tr>
<td>Cases</td>
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</tr>
<tr>
<td>Psychiatric History</td>
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<tr>
<td>54%</td>
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</tr>
<tr>
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<td>30%</td>
</tr>
<tr>
<td>No Concomitant Psychiatric Meds</td>
<td>20%</td>
<td>24%</td>
</tr>
<tr>
<td>Unknown Concomitant Psychiatric Meds</td>
<td>38%</td>
<td>46%</td>
</tr>
</tbody>
</table>

Given the well-established health risks of smoking, healthcare providers should continue to assist patients with quitting smoking. However, because the AERS data suggest a possible association between suicidal events and varenicline and bupropion, patients should be closely monitored for neuropsychiatric symptoms. The review also evaluated transdermal nicotine products (e.g., Habitrol, Nicoderm, Nicoderm CQ, and Prostep), but no clear association was identified with suicidal ideation and/or behavior.


2FDA: boxed warning on serious mental health events to be required for Chantix and Zyban [FDA news release]; July 1, 2009; available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm170100.htm.
**Bipolar Disorder Guidelines: Depression**

The British Association for Psychopharmacology recently updated their guidelines for treatment of bipolar disorder. Last month their recommendations for acute mania were presented; now a summary of their key recommendations for treatment of depressive episodes is presented.

Treatment options for patients not already receiving long-term therapy include quetiapine, lamotrigine, and a combination of an antidepressant plus a mood stabilizer (i.e., lithium, valproate, atypical antipsychotic). Data suggest the combination is effective, but antidepressant monotherapy is not recommended because it can precipitate a manic switch. There is little evidence available for specific antidepressants with the exception of TCAs and venlafaxine, which seem to carry greater switching risk. Quetiapine may be particularly useful when a rapid treatment effect is needed. ECT should be considered for those with psychosis, those at risk of suicide, and during pregnancy. For mild symptoms, lithium or valproate monotherapy is an option. Adding a psychosocial treatment can shorten the duration of the episode.

When a patient experiences an acute episode of depression during long-term maintenance treatment, adequate dosages and serum levels should be confirmed, and treatment for the acute episode should be initiated. If symptoms persist, switching agents or augmentation can be considered. Antidepressants should be tapered and stopped when symptoms resolve. There are no specific recommendations for treatment-resistant bipolar depression.

The consensus group acknowledges that "guidelines are systematically derived statements that are aimed at helping individual patient and clinician decisions. The principal recommendations given here usually apply to the average patient" and may not be valid in all situations. In addition, they state that product licenses are designed mainly to limit the actions of manufacturers, not individual clinicians, and they acknowledge that some of the uses discussed are off-label.

Goodwin G for the Consensus Group of the British Association for Psychopharmacology: Evidence-based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology.* Published online March 27, 2009 at www.sagepub.co.uk; doi 10.1177/0269881109102919. From the British Association for Psychopharmacology, Cambridge, U.K.

**Drug Trade Names:** lamotrigine—*Lamictal*; quetiapine—*Seroquel*; valproate—*Depakene*; venlafaxine—*Effexor*

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**Olanzapine vs Ziprasidone**

In a head-to-head comparison, olanzapine and ziprasidone had similar efficacy in patients with recent onset schizophrenia or schizoaffective disorder. Weight gain and other laboratory abnormalities were more common with olanzapine, while ziprasidone produced more extrapyramidal symptoms (EPS).

**Methods:** Patients aged 18–40 years (n=74; 61 males) with at least moderate symptoms and a lifetime exposure to antipsychotics of <16 weeks were included. After screening and a washout of previous medications, subjects were randomized to either olanzapine or ziprasidone for 8 weeks. Olanzapine was flexibly dosed at 10, 15, or 20 mg/day (mean, 14 mg/day) and ziprasidone at 80, 120, or 160 mg/day (mean, 104 mg/day). Previous treatment with either agent was not an exclusion criteria, and 15 patients had previous exposure to olanzapine. The primary outcome measures were the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) Improvement and Severity scales. *

**Results:** PANSS improvements were similar in both groups at 8 weeks. Mean positive symptom scores decreased from 22 with olanzapine and 21 with ziprasidone to 15 in each group. Improvements on the negative subscales were similar. CGI Severity scores decreased from 5 to 4 in both groups, and CGI Improvement scores at 8 weeks were 3 in both groups. Clinical response, defined as a ≥20% decrease in PANSS score, was achieved by 61% of olanzapine-treated patients.
and 60% of ziprasidone-treated patients. Improvements in secondary measures of depression and quality of life also did not differ between groups.

Olanzapine was associated with significantly more weight gain than ziprasidone (15 lbs vs <1 lb; p<0.001); 65% of the olanzapine group gained >7% of their baseline weight, compared with 3% of the ziprasidone group (p<0.001). Olanzapine increased cholesterol, triglyceride, and transaminase levels, while ziprasidone reduced these values (p<0.05 for all comparisons). Fasting glucose and glycosolated hemoglobin did not differ between groups. Significantly more ziprasidone-treated patients required the addition of the anticholinergic biperiden for EPS (44% vs 20%; p<0.05). There were no between-group differences in adverse sexual effects, and no patient in either group showed ECG abnormalities.

**Discussion:** Olanzapine and ziprasidone appear to have comparable efficacy in recent-onset schizophrenia. The main difference between the agents seems to be the adverse effect profiles, with olanzapine producing metabolic effects and ziprasidone producing EPS, both of which were evident early in the course of treatment. The authors suggest the substantial weight gain with olanzapine may have resulted from the relatively high mean dose.


**Drug Trade Names:** biperiden (not available in the U.S.)—Akineton; olanzapine—Zyprexa; ziprasidone—Geodon

*Reference Guide Item.*

**Reference Guide**

**Clinical Global Impression (CGI) scales:** A CGI-improvement score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse. A CGI-severity score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

**Hazard Ratio:** A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that one group has half the risk of the other group.

**Odds Ratio:** A comparison of the probability of an event in two groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

**Study Rating:** A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists have been posted at www.alertpubs.com.