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Editor:
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Highlights...

Our top lead looks at results from an exciting new study of short term tamoxifen treatment for mania. This protein kinase C inhibitor appears to reduce manic symptoms in hard to treat bipolar I patients. Long-term use is not recommended due to potentially severe side effects, but this short-term trial suggests that further investigation of anti-PKC agents with a superior safety profile might prove fruitful.

Inside

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BIPOLAR DISORDER

Short-term tamoxifen treatment improves manic symptoms in bipolar patients

Tamoxifen has been shown to reduce manic symptoms in hard-to-treat patients with bipolar I disorder. In a 3-week clinical trial, investigators at a psychiatric unit of a university medical center in Izmir, Turkey, found that tamoxifen significantly reduced manic symptoms compared with placebo, and reduced positive and general subscale scores on the Positive and Negative Syndrome Scale (PANSS) in bipolar patients with psychotic features. The study is the first randomized, double-blind, placebo-controlled trial with adequate statistical power to investigate the antimanic effects tamoxifen.

Tamoxifen, a drug that is widely used for treating and preventing breast cancer in high-risk patients, has been hypothesized to alter manic behavior by inhibiting protein kinase C (PKC). This enzyme is present throughout the body's organs and tissues, serving a major role in second-messenger systems responsible for intracellular signaling. Disrupting PKC function results in inhibition of manic behaviors in animal models, and produces effects

TAMOXIFEN, *continued on page 4*

précis

- In a small, short-term clinical trial, the widely-used anti-cancer drug tamoxifen significantly reduced manic symptoms in treatment-resistant bipolar patients
- The trial enrolled 66 patients (ages 18-60 years) with DSM-IV bipolar I disorder in a current manic or mixed state, who were randomized to tamoxifen (N=35) or placebo (N=31) for 3 weeks under double-blind conditions
- Tamoxifen may alter manic behavior by inhibiting protein kinase C (PKC), producing mood-stabilizing effects similar to lithium and divalproex; the findings merit further investigation of anti-PKC activity as a potential target in the development of new mood-stabilizing or antimanic agents

ADVERSE EVENTS

SSRIs linked to nongastrointestinal bleeding in coumarin users

A study published in the *Archives of Internal Medicine* concluded that SSRI use is associated with an increased risk of hospitalization due to major nongastrointestinal bleeding, but not because of gastrointestinal bleeding, in users of coumarin anticoagulants.

Coumarin anticoagulants are used effectively to manage thromboembolic diseases. However, the drugs have a narrow therapeutic range and are sensitive to interactions with other drugs. Some of these interactions can increase the risk of major bleeding, the main adverse effect of coumarin anticoagulant therapy.

SSRIs, *continued on page 6*

précis

- Researchers identified 1,848 users of coumarins who were hospitalized with abnormal bleeding and matched each one with up to four control subjects
- They determined the risk of hospitalization because of abnormal bleeding associated with concurrent use of SSRIs or nonsteroidal anti-inflammatory drugs (NSAIDs)
- SSRI users were at an increased risk for hospitalization due to nongastrointestinal tract bleeding. Users of NSAIDS were at a similar increased risk for nongastrointestinal bleeding, as well as a higher risk for gastrointestinal bleeding

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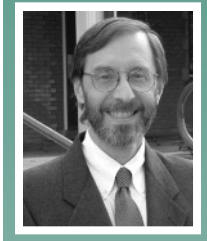

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DRUG-DRUG INTERACTIONS

Possible tardive dyskinesia with aripiprazole and duloxetine

By Y.W. Francis Lam, Pharm.D., FCCP

Tardive dyskinesia is a common side effect associated with long-term use of typical antipsychotic agents. The risk is reported to be lower with the use of atypical antipsychotics, including the third-generation antipsychotic aripiprazole (Abilify).

The following case described a patient who had aripiprazole added as augmentation therapy to duloxetine (Cymbalta) for management of treatment-resistant depression, and who later developed tardive dyskinesia.[1]

CLINICAL REPORT

A 46-year-old female patient presented to the psychiatric clinic with a history of mood lability, possible premenstrual dysphoric disorder, and recurrent major depressive disorder. She had no other psychiatric history, but there was a family history of alcohol dependence and anxiety disorder. At the time of the clinic visit, her chief complaints included sad and irritable mood, increased guilt, poor concentration, low levels of interest and enjoyment, passive suicidal ideation, visual illusions, and increased sleeping episodes.

The patient had previously been treated with fluoxetine (Prozac), and was currently receiving duloxetine for her depression. She was also taking hydrocodone (Vicodin) on an as needed basis for trigeminal neuralgia and tolterodine (Detrol) for urinary incontinence. She had had only lmited benefit from the duloxetine regimen, although she did not report any adverse drug reactions associated its use.

A decision was made to initiate a trial of low-dose augmentation therapy with an atypical antipsychotic. An initial attempt with ziprasidone (Geodon) 40 mg daily was discontinued after two weeks because of side effects, including akathisia. Aripiprazole was then started at a dose of 5 mg per day and titrated gradually up to 15 mg daily.

After the addition of aripiprazole, the patient reported gradual but consistent clinical improvement in her depressive symptoms, and she remained in remission for about 15 months on concurrent duloxetine and aripiprazole. Other than a mild weight gain of about 9 pounds, she had no other side effects. A work up for metabolic syndrome was negative.

The patient then developed involuntary lateral jaw movements, primarily on the left side, at a frequency of two to three movements every few minutes. She had no history of dentition problems or pre-existing nervous or motor tics that could explain the abnormal movements. She scored 9 of 42 on the Abnormal Involuntary Movement Scale (AIMS), and was diagnosed with new onset oromandibular tardive dyskinesia. Aripiprazole regimen was tapered and discontinued. Eight months later, the patient's lateral jaw movements were completely resolved.

Discussion

This patient had no pre-existing causes of abnormal movements and was not taking any other drug that could induce tardive dyskinesia. The case replicates previous a report of tardive dyskinesia occurring with the use of aripiprazole in managing a treatment-resistant depressed patient.[2] The dosage regimens used in previous reports of aripiprazole-induced tardive dyskinesia were similar to those used for the patient in this case.

The aripiprazole dose in this case was not excessive. However, duloxetine exerts

BOTTOM LINE

Even though the atypical antipsychotics are reported to have a low incidence of extrapyramidal side effects and tardive dyskinesia, clinicians need to be aware of the potential for these sequelae, and careful adjustment of dose with close monitoring for emergent side effects is prudent.

mild inhibitory effects on CYP2D6, which mediates the elimination of aripiprazole. This pharmacokinetic effect could have resulted in elevated aripiprazole concentrations. ■

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WHAT'S NEW IN RESEARCH

D-cycloserine augmentation of behavioral therapy for OCD

précis

- First trial to compare antidepressant switch alone to a switch plus cognitive behavioral therapy in adolescent non-responders to SSRI treatment for major depression
- Patients randomized to 1 of 4 conditions: venlafaxine alone, venlafaxine plus CBT, a different SSRI alone, or a different SSRI plus CBT
- More patients receiving CBT reach adequate clinical response, but no significant difference between SSRI or venlafaxine treatment; venlafaxine associated with more cardiovascular adverse events

In a double-blind, randomized, placebo-controlled pilot trial, Sabine Wilhelm and colleagues reported promising results which they believe could lead to the use of the N-methyl-D-aspartic acid (NMDA) receptor agonist D-cycloserine as an augmentation of behavior therapy for obsessive-compulsive disorder (OCD). The study authors write that although treatment strategies for OCD have improved in recent years, the success rate of treatment remains relatively low and research combining medication with behavior therapy has yielded modest results. Only two previously reported studies have investigated augmentation of behavior therapy with D-cycloserine for OCD (Storch et al. and Kushner et al.), with inconsistent results. Wilhelm and colleagues conclude that although it is "premature" to recommend D-cycloserine for routine clinical use (it is not FDA approved for this indication), future studies should be undertaken to confirm that this drug may accelerate and potentiate behavior therapy for OCD.

Subjects and study design

Intent-to-treat analyses include data for 23 patients (mean age 40 ±13.4) with a primary DSM-IV diagnosis of OCD. Patients had the following comorbid diagnoses: major depression (3), social phobia (3), specific phobia (3), dysthymia (2), generalized anxiety disorder (2), anxiety disorder not otherwise specified (1) and panic disorder with agoraphobia (1). Sixteen patients were taking a stable dose of a psychotropic medication. The D-cycloserine and placebo treatment groups did not differ significantly with regard to age, comorbid diagnoses or medication, pre-treatment Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores (26.5 ±5.0 and 25.5 ±4.2, respectively,) or Beck Depression Inventory-II (BDI-II) scores (15.5 ±12.7 and 10.9 ±8.3, respectively).

Following randomization [D-cycloserine 100 mg (N=10) or placebo (N=13)] and pre-treatment assessments, patients participated in a psychoeducational planning session, including the creation of an individualized exposure hierarchy. For 5 weeks, the patients reported to the clinic twice each week, arriving one hour prior to behavior therapy sessions to take their medication in the presence of a therapist. Each patient underwent 10 sessions total of behavior therapy, an abbreviated version of a well-validated treatment protocol (Kozak and Foa), which emphasizes exposure and response prevention, without formal cognitive restructuring.

Results

The patients' response was followed over the course of the study, with assessments at mid-treatment (after session 5), post-treatment (after session 10) and at 1 month follow-up. For OCD symptoms, there was a significant main effect of time ($p<0.001$) and a time-by-condition interaction ($p=0.02$), but the main effect for condition did not reach significance. However, follow-up t tests found that the D-cycloserine group had significantly lower Y-BOCS scores at mid-treatment than the placebo group ($p=0.009$), with a large effect size ($d=1.17$). There were no significant group differences at post-treatment or at 1-month follow-up, which the authors suggest may have been due to limited power.

For depressive symptoms, general linear models found a main effect of time ($p<0.001$) and a significant time-by-condition interaction ($p=0.004$). No significant main effect for condition was found. Follow-up tests indicated significantly fewer depressive symptoms in the D-cycloserine group at post-treatment ($p=0.04$), but no significant group differences at mid-treatment or 1-month follow-up.

Contrast with related studies

The authors discussed how their findings differ from those of the two earlier studies of D-cycloserine augmentation of behavior therapy for OCD, by Storch et al. (2007) and Kushner et al. (2007). While the present study found that D-cycloserine appeared to "accelerate and potentiate" behavior therapy, Storch et al. found no significant benefit of augmentation at any time over the course of treatment. Wilhelm and colleagues describe a few methodological differences that might account for this discrepancy. For example, some research suggests that there may be a narrow therapeutic range of D-cycloserine when used to enhance learning, such that a high dose could have an attenuated effect on fear extinction compared with a lower dose. Consistent with this, Storch et al. used a dose of 250 mg, compared with this study's 100 mg dose. Also, this study differed from Storch et al. with regard to the timing of the D-cycloserine dose (Storch et al. administered D-cycloserine 4 hours before behavior therapy, compared with this study's 1 hour) and the number of behavior therapy sessions and frequency of D-cycloserine administration (12 weeks total in Storch et al., compared with 5 weeks total in this study).

Regarding differences from Kushner et al., Wilhelm and colleagues write that Kushner et al. included only subjective

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fear ratings at mid-treatment, whereas this study employed "the gold standard" rating scale in OCD, the Y-BOCS. An inspection of all studies on the effects of D-cycloserine augmentation of behavior therapy for OCD suggests that effects are most powerful early in treatment (even in Storch et al., there was a non-significant tendency favoring D-cycloserine at week 6) and that the differences with placebo tend to decrease over time. The authors suggest that future research include more assessment points to precisely determine when group differences occur.

The authors write that it is also informative to compare this study with findings from previous studies of non-D-cycloserine-augmented behavior therapy for OCD. In Foa et al. after 30 hours of behavior therapy, patients showed a 55% decrease in OCD symptom severity on the Y-BOCS, compared with a 52% decrease at mid-treatment (5 hours of exposure) in this study and a 62% decrease at post-treatment (10 hours of exposure). The authors believe this underscores D-cycloserine's "significant potential" as an augmentation strategy.

Clinical implications

The authors believe their study has important clinical implications in light of high dropout rates for behavioral treatments of OCD and the considerable costs of prolonged treatment. In patients who experience significant anxiety during prolonged exposure treatment, an augmented treatment that reduces anxiety faster could have an impact. Future large-scale studies should investigate this possibility, write Wilhelm et al. The authors believe it is of note that they also found positive effects on depression in this study. They suggest that future research should investigate whether D-cycloserine accelerates or increases the modification of dysfunctional beliefs, "which might point to a mechanism of change of relevance to both OCD and depression." ■

Wilhelm A, Buhlmann U, Tolin D, et al.: Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. *Am J Psychiatry* In Advance 2008; published online ahead of print, February 1; AiA:1-7. E-mail: Wilhelm@psych.mgh.harvard.edu.

TAMOXIFEN

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similar to those of mood-stabilizing drugs such as divalproex and lithium. In nonhuman primates, high PKC activity in the prefrontal cortex is associated with impairment of working memory. Pretreatment of monkeys and rats with lithium or valproate and chelerythrine, a PKC inhibitor, blocks such impairment.

These preclinical findings suggest that excessive PKC activation can disturb prefrontal cortical regulation of behavior and may contribute to the impaired judgment, distractibility, impulsivity, and disorganized thinking characteristic of patients with bipolar disorder, particularly during manic episodes.

Psychostimulants, which can trigger manic episodes in susceptible individuals, have also been shown to activate PKC. According to Aysegül Yildiz, M.D., principal investigator of the current study, and colleagues, "antiestrogenic activity might decrease PKC activity indirectly, whereas estrogens, which increase PKC activity in the brain, may exacerbate mania and increase risk of post-partum episodes of BPD [bipolar disorder]." These findings suggest that PKC signaling in the brain represents "a highly plausible target for mood-stabilizing drugs."

Study details

The study was designed as a 3-week single-site clinical trial that enrolled 66 patients (18 to 60 years) with DSM-IV bipolar I disorder in a current episode of mania or mixed state. The mean ages at the time of randomization were 29 years in the tamoxifen group and 36 years in the placebo group. Most of the patients had been refractory to previous treatment and had been referred for the study by their physicians. Baseline scores on the Young Mania Rating Scale (YMRS) were high, with an average score of 38 and ratings as high as 49. Approximately 67% of the participants had psychotic features.

For safety reasons, all subjects were hospitalized during the entire trial due to the severity of their illness. Several unique aspects of the study included the presence of one close family member who remained in the hospital with each patient for the duration of the trial, individual choice of diet, and the availability of extra recreational activities. This "enriched environment" was provided to limit the number of study drop outs.

Participants were randomized to tamoxifen (N=35) or placebo (N=31) for 3 weeks under double-blind conditions. Dosing was started at 20 mg b.i.d. and titrated in 10-mg daily increments to a maximum dose of 30 mg/day in 2 divided doses for all subjects. Oral lorazepam up to 5 mg/day was allowed during the trial. Risperidone was used as a rescue medication for subjects with agitation and other symptoms not controlled by the study medications.

The primary outcome measure was weekly change in YMRS scores; secondary measures included weekly changes in scores on the CGI-Mania, the 17-item Hamilton Depression Rating Scale (HAMD-17), and the PANSS for psychotic symptoms. At the end of the trial, only patients with a score of ≤3 on the Clinical Global Impression-Bipolar Version Severity of Mania scale (CGI-Mania) or a ≥50% reduction in YMRS scores were allowed to be discharged.

Results

Based on intent-to-treat analyses, there were statistically significant differences between tamoxifen-treated patients, who experienced an average weekly decrease of 5.8 ±0.6 on the YMRS, compared with placebo-treated patients, whose ratings increased marginally by 1.5 ±0.7 ($p<0.001$). Tamoxifen was also shown to be superior to placebo on all individual items of the YMRS. As anticipated, retention rates were relatively high in both groups: 83% in the tamoxifen group and 68% in the placebo group.

One of the key findings of the study was the worsening of manic symptoms in the placebo group, with only 5% of placebo patients showing 50% or more improvement on the YMRS. The outcome is unusual in view of the extra personal attention that all patients received during the trial, and contrasts with findings of other short-term clinical trials in mania. In earlier mania trials of similar duration conducted at multiple study sites, placebo response rates averaged approximately 23%, compared with 11% in comparable single-site trials. Yildiz and colleagues suggest that these poor placebo response

rates may be attributed to treatment-resistant patients who are generally enrolled in single-site rather than multi-site clinical trials, where local differences in patient characteristics or circumstances may influence outcome. Another factor that may have contributed to the worsening symptoms in the placebo group was that the "enriched environment" may have resulted in over-stimulation in some of these patients, particularly as they were not receiving any medication.

PANSS total scores, which can reflect both manic and psychotic symptoms, indicated greater improvement with tamoxifen vs. a slight worsening of symptoms with placebo ($p<0.001$). Similar trends were shown in positive and general subscale scores, with the tamoxifen group showing greater improvements than the placebo group ($p<0.001$). However, there were low scores in both groups on the negative subscales, and minimal change with either treatment. Some improvements in depression scores were found in tamoxifen-treated subjects compared with placebo, but these differences were not statistically significant.

Mixed-model analyses showed no significant effects on the different responses between groups when taking into account baseline mania and depression ratings, current age, age at onset, and sex.

Two attempted suicides occurred during the study: one in the tamoxifen group on day 18 and the other in the placebo group on day 13. Although neither of these patients was in a mixed episode or experiencing depression, their suicidal ideation was closely associated with delusions. Side effects were otherwise mild to moderate and low in both groups, and included worsening of acne, headache, dry skin, urticaria, flushing and loss of appetite in the tamoxifen group, and eczematous rash, excessive sweating and headache in the placebo group. Aside from similar, minor weight loss in both groups, there were no other remarkable changes in vital signs or laboratory values in either group.

Clinical implications

One major limitation of short-term trials investigating innovative treatments for mania is that efficacy may be demonstrated through symptom improvement compared with placebo, write Yildiz and colleagues. However, such short-term outcomes are often brief, and symptom improvement may not necessarily extend to clinically significant functional recovery over several months or longer.

In an editorial accompanying the Yildiz et al. study, Mauricio Tohen, M.D., writes that the most notable aspect of this trial and others that preceded it (e.g., Zarate et al., 2007) is "the scientific rationale that led to its development (namely, identifying molecular targets as a key to developing improved therapeutics)." These studies provide further support for future investigations of agents having central anti-PKC activity.

The decision to select tamoxifen as an antimanic agent for these studies was

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Commentary

Novel treatment for mania

By Aysegül Yildiz, M.D.

Bipolar (manic-depressive) disorder affects millions of ordinary people around the world (more than 1/100), as well as many well-known and highly gifted artists, writers, musicians, and scientists. This prevalent, complex and hard-to-treat illness leads to extreme and erratic shifts of mood, thinking, and behavior, with a very high risk of suicide. Currently available treatments for the disorder include lithium and some drugs developed for the treatment of epilepsy or schizophrenia. Most of these have been known for many years. Their benefits are substantial, but typically far from curative, and innovation in the treatment of the disorder has been very slow in coming.

Based on laboratory research into the actions of lithium and antimanic anticonvulsant drugs, scientists at the National Institute of Mental Health (NIMH), led by Husseini Manji, M.D., discovered that an important brain enzyme (*protein kinase C* or "PKC") was inhibited by both lithium and the antimanic-anticonvulsant drug valproate. This protein is important in chemical systems that support communication among nerve cells in the brain. Tamoxifen is a selective estrogen receptor modulator, widely used in the prophylactic treatment of breast cancer. It is also the only known centrally active PKC inhibitor available for human use.

Recently, two scientifically rigorous, placebo-controlled, randomized trials of tamoxifen in mania have been carried out. The first study, with 66 bipolar manic patients, supported by the Stanley Medical Research Institute and conducted by Aysegül Yildiz, M.D. and her colleagues at Dokuz Eylül University, Izmir, Turkey, was reported initially at the Congress of the European College of Neuropsychopharmacology in Paris in September, 2006. The second study, with 16 patients, was reported by Carlos Zarate, M.D., and his NIMH colleagues, including Dr. Manji, in the journal *Bipolar Disorders* in September, 2007.

A full report of the study led by Dr. Yildiz appears in the March, 2008 issue of the *Archives of General Psychiatry*. Both trials, which were carried out independently, indicate that this novel drug is at least as effective as any currently clinically used treatment for mania. The findings strongly encourage development of other agents with similar effects on brain chemistry. Tamoxifen represents not only the first truly innovative treatment for mania to appear in recent years, but a rare example of how basic neuroscience can lead to the rational prediction of a novel treatment principle in a still-mysterious, but common and often disabling or lethal disease.

Although, effective and quite safe for short-term treatment of mania, long-term use is not recommended due to potential side effects such as transient thrombocytopenia, leukopenia, hot flushes, vaginal bleeding, vaginal discharge, peripheral edema, menstrual irregularities, hepatotoxicity, and retinopathy, which are all related to the drug's estrogen-blocking properties. Development of new central nervous system-penetrant protein kinase C inhibitors with a superior safety and tolerability profile that would be suitable for long-term use is the most challenging task for future research. Identification of biomarkers within the brain or peripheral blood cells indicative of bipolar disorder and/or responders to certain treatment options is another exciting research track to pursue.

Aysegül Yildiz, M.D., is Associate Professor of Psychiatry at Dokuz Eylül University, Izmir, Turkey.

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based on data from previous preclinical and clinical trials that investigated selected molecular targets, an approach which represents a first in the development of drugs for bipolar disorder. However, whether tamoxifen per se will have a role in the treatment of bipolar disorder is unclear, writes Tohen, as its antiestrogen effects will likely present safety challenges, especially when used over long periods.

Nevertheless, the findings of this trial are encouraging and merit further investigation in the development of new anti-PKC compounds as mood stabilizers, in particular those that can inhibit PCK activity in the brain without influencing estrogen signaling elsewhere in the body. ■

Study supported by a research grant to Dr. Yildiz from the Stanley Medical Research Institute.

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SSRIs

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"In several population-based studies, a further increase in the risk of major bleeding in users of coumarin anticoagulants has been convincingly demonstrated for other drugs that increase the risk of major bleeding such as nonsteroidal anti-inflammatory drugs (NSAIDS), aspirin, and glucocorticoids," the authors, led by Tom Schalekamp, PharmD, Ph.D., wrote. Use of selective serotonin reuptake inhibitors (SSRIs) has also been associated with an increased risk of upper gastrointestinal tract bleeding and with abnormal major bleeding in general.

"These findings suggest a pharmacodynamic interaction between SSRIs and coumarin anticoagulants," write the authors. For the SSRIs fluoxetine and fluvoxamine, a pharmacokinetic effect might have had a contributing role because both drugs are inhibitors of CYP2C9, the primary metabolizing enzyme of the more active (S)-enantiomers of coumarins. However, a recent population-based control study did not find an association between SSRI use and an increased risk of hospitalization due to upper gastrointestinal bleeding in users of warfarin sodium.

The present study examines the association between concurrent use of SSRIs and coumarin anticoagulants with major bleeding, conducted as a population-based case-control study in a cohort of users of the coumarin anticoagulants acenocoumarol and phenprocoumon.

Study methodology

The study used data from the PHARMO Record Linkage System from the Pharmo Institute, Utrecht, the Netherlands. Drug prescription and hospitalization data were used, culled from a database of 2 million community-dwelling residents. The cohort included new users of one of the coumarin anticoagulants who were 18 years or older, who received a first prescription for a coumarin between January 1, 1991 and December 31, 2004, and who did not have a history of hospital admission due to major bleeding.

All cases in the study were first hospitalizations because of abnormal bleeding while being treated with a coumarin. For each case patient, up to four nonhospitalized control subjects were randomly selected from the database. Control subjects were matched with case patients for gender, age (±5 years), coumarin anticoagulant used (acenocoumarol or phenprocoumon), time since initiation of coumarin therapy (±90 days from dispensing date), and geographic region.

"The clinical impact of our finding is that we should take the pharmacodynamic interaction between coumarins and SSRIs more seriously than we used to do."

Tom Schalekamp, PharmD, Ph.D.

SSRIs analyzed were citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, and sertraline. Study authors also assessed whether the use of nortriptyline or mirtazapine, frequently prescribed antidepressants without a significant affinity for the serotonin transporter, was associated with abnormal bleeding.

Study authors defined as confounding co-medications the current use of nonsteroidal anti-inflammatory drugs (NSAIDs), anti-platelet agents, glucocorticoids, gastroprotective agents, established inhibitors of coumarin metabolism, inducers of coumarin metabolism, and antibiotics.

Study authors identified 70,201 patients who were treated with a coumarin. Within this cohort, they identified 2403 cases of first bleeding requiring hospitalization. In this cohort, 555 patients could not be matched to control subjects, leaving 1848 patients, who were then matched with 5818 control subjects. Mean patient age was 72.7, and there were more men than women. Almost 90% of the patients used acenocoumarol.

Study results

Gastrointestinal bleeding occurred in 605 patients, and nongastrointestinal bleeding occurred in 1243 patients. "The most frequently occurring category was upper gastrointestinal bleeding (29%), followed by intracranial bleeding (17.2%)," write the authors. Other sites of bleeding were the nose (8.7%), the uterus (7.1%), and the urinary tract (6.2%). The category of "other" represented 25% of bleeding events.

SSRI users were at a significantly increased risk of hospitalization due to nongastrointestinal bleeding, but not because of gastrointestinal bleeding. For the non-SSRIs nortriptyline and mirtazapine, no increased risk for major bleeding was found. NSAID use was associated with a higher risk of gastrointestinal bleeding.

A separate analysis of intracranial bleeding showed no significantly increased risk for users of SSRIs or NSAIDS. Separate analyses of the individ-

ual SSRIs used resulted in no different estimates for gastrointestinal and nongastrointestinal bleeding.

Sensitivity analysis did not change the overall results of the study. Changes between the last dispensing date of a coumarin and the index date, ranging from 180 days to 30 days, did not alter the results. "Only if the maximum time between the last dispensing date of the coumarin and the index date was reduced to 30 days was significance lost for the association with SSRIs (P=.08)," the authors wrote.

Clinical significance

Study authors found a substantially increased risk of nongastrointestinal bleeding in current SSRI and coumarin users. The SSRIs' different effects on gastrointestinal and nongastrointestinal bleeding among coumarin users was unexpected, the authors write.

"We were not surprised at the result that SSRIs increase the bleeding risk of coumarins, but it was somewhat surprising that the risk of gastrointestinal bleedings was not increased, but only the risk of nongastrointestinal bleeding," lead author Schalekamp told *The Update*. Schalekamp is with the Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University (Netherlands).

The authors write that SSRI use seems to be associated with an increased risk of nongastrointestinal bleeding to the same extent as use of NSAIDs. For gastrointestinal bleeding, NSAIDS are associated with a markedly increased risk, while the SSRIs present no risk at all.

In coumarin users with upper gastrointestinal bleeding, lesions have been identified in as many as 70% of patients. An association between NSAID use and an increased bleeding risk in coumarin users has been convincingly demonstrated in several population-based observational studies, the authors write.

If SSRI use is associated with increased upper gastrointestinal bleeding in coumarin users, it is likely due to decreased platelet aggregation, which has been demonstrated for all SSRIs in patients with depression and in healthy control subjects, rather than a gastrointestinal toxic reaction. Previous studies suggest that SSRIs precipitate bleeding in patients with hemostatic defects or in patients who are taking drugs that can cause gastrointestinal injury, such as NSAIDs.

Several studies have found a synergistic effect causing increased risk of upper gastrointestinal bleeding with concurrent use of SSRIs and NSAIDs. Apart from the effect of NSAIDs on the gastrointestinal tract, the synergism could be due to the different anti-platelet effects of SSRIs and NSAIDs, with SSRIs reducing platelet serotonin levels and NSAIDs reducing thromboxane synthesis by inhibiting cyclooxygenase 1. This synergism does not exist for SSRIs and coumarins. Any effect of SSRIs on pre-existing lesions in the gastrointestinal tract is offset by the stronger anticoagulant effect of the coumarins.

In this study of coumarin users, the risk of nongastrointestinal bleeding was due to inhibition of platelet aggregation, not any potential damaging effect on gastric mucosa, making the risk for SSRIs and NSAIDs similar. For intracranial bleeding, the results of the study suggest a similar increased risk with NSAIDs and SSRIs.

The study suggests that there is no increased risk for gastrointestinal or nongastrointestinal bleeding with nortriptyline and mirtazapine therapy, although the numbers were too small for a reliable analysis. Because of the pharmacodynamic nature of the effect of SSRIs on bleeding risk in coumarin users, the authors believe the study's results also apply to warfarin sodium. The percentages of the most frequently occurring bleeding events in the present study are comparable to results from two clinical trials involving warfarin sodium and ximelagatran. In the warfarin study, 34% of bleeding events were gastrointestinal and 18% were intracranial, compared to 32.9% and 17.2% in the present study.

According to the authors, the results of this study indicate that the advantages of prescribing SSRIs for coumarin users must be carefully weighed against the adverse effect of an increased bleeding risk.

"The clinical impact of our finding is that we should take the pharmacodynamic interaction between coumarins and SSRIs more seriously than we used to do," said Schalekamp.

Because of the study's limitations, the authors cannot advise against the concurrent use of coumarin anticoagulants and SSRIs, but recommend intensified monitoring of these SSRI users. "More research is needed before we can fully advise against combined use of an SSRI and a coumarin," Schalekamp told *The Update*. "One observational study is indicative, not decisive."

It would be reasonable to consider an alternative to SSRIs when antidepressant therapy is necessary for a user of a coumarin. Other studies have found no increased bleeding risk for tricyclic antidepressants, said Schalekamp. The study's lead author does, however, believe more research is needed for mirtazapine, because the drug could affect platelet aggregation by blocking the 5-HT2A receptor.

In conclusion, the results of the study strongly suggest that SSRI use is associated with an increased risk of hospitalization due to nongastrointestinal bleeding. ■

Schalekamp T, Klungel OH, Souverein PC, et al.: Increased bleeding risk with concurrent use of selective serotonin reuptake inhibitors and coumarins. *Arch Intern Med* 2008; 168 (2):180-185. E-mail: t.schalekamp@pharm.uu.nl.

NEWS NOTES

Metformin attenuates olanzapine-induced weight gain

In a study designed to assess the efficacy of metformin (Glucophage) in preventing olanzapine-induced weight gain in drug-naïve first-episode schizophrenia patients, 40 patients were randomized to 12 weeks of treatment with olanzapine (Zyprexa) 15 mg/day plus metformin 750 mg/day (N=20) or olanzapine 15 mg/day plus placebo (N=20). Weight, body mass index, waist circumference, and waist-to-hip ratio levels increased less in the group taking metformin relative to the placebo group. Also, patients taking placebo saw a significant increase at weeks 8 and 12 in insulin and insulin resistance index values, compared to unchanged levels in the metformin group. Significantly fewer metformin-treated patients increased their baseline weight by > 7%, the cutoff for clinically significant weight gain. [*Am J Psychiatry* 2008; 165:352-358]

Antidepressant dose requirements in pregnancy

In a study examining the dose requirements and level-to-dose (L/D) ratios of antidepressant drugs in pregnant and post-par-

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NEWS NOTES

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tum women, the authors write that theirs is one of few published trials to examine the disposition of individual antidepressant drugs across pregnancy. The investigators examined 11 cases of pregnant women with major depressive disorder taking citalopram (Celexa) (N=3), escitalopram (Lexapro) (N=2), and sertraline (Zoloft) (N=6). In 4/5 of women taking citalopram or escitalopram and 5/6 women taking sertraline, the L/D ratios decreased between 20 weeks gestation and delivery, reflecting an increased drug metabolism. By 12 weeks postpartum the L/D ratios were similar to those at 20 weeks. Replicating and extending earlier data with other antidepressants, these findings suggest that dose requirements often increase during the second half of pregnancy. [*J Clin Psychiatry* online ahead of print, March 11, 2008: e1-e7.]

Switch to quetiapine reduces EPS in schizophrenia

The findings of an open-label randomized study appear to support a switch to quetiapine (Seroquel) for the management of preexisting neuroleptic-induced extrapyramidal side effects (EPS) in patients with schizophrenia. The authors write that while clinicians often use an antipsychotic switch to manage EPS, they are guided by little empirical evidence. In this trial, 22 patients with schizophrenia meeting clinical criteria for tardive dyskinesia or coexisting parkinsonism were either switched from their current antipsychotic to quetiapine (N=13) (target dosage 400-800 mg/d) or maintained on their current stable dose of antipsychotic medication (N=9). The investigators observed significant reductions in parkinsonism ($p<0.001$), akathisia ($p=0.02$) and dyskinesia ($p<0.05$) in the quetiapine group. In subjects remaining on current treatment, the investigators observed an increase in rigidity ($p<0.05$). Of note, patients switched to quetiapine from another second-generation antipsychotic showed a greater reduction in akathisia than other patients. [*J Clin Psychopharmacol* 2008; 28:69-73]

CASE REPORT

Drug-induced liver disease with citalopram

Patient: Female, 56 years old

Medications: Citalopram (Celexa)

Comment: A 56-year-old woman presented with weakness, asthenia, weight loss and jaundice. She was taking citalopram (Celexa) 20 mg/day for three weeks. She reported no alcohol or drug use and no blood transfusions. She had no history of liver disease. A physical exam revealed a mild hepatomegaly without signs of chronic liver disease. Abdominal ultrasound suggested an acute hepatitis. Because the etiology of the acute liver injury was unclear, a biopsy was performed. Histology was consistent with a drug-induced liver injury with subacute liver dystrophy and liver cell necrosis. Treatment with citalopram was stopped and within three weeks serum liver function tests were completely normal.

Discussion: There are many reports about antidepressants and hepatotoxicity, write the authors, who cite another recent report (Lopez-Torres et al, 2004) describing a case linked with citalopram. However, there are no special warnings related to hepatotoxicity in the prescribing information for citalopram. Although they believe that it is premature to recommend regular monitoring of liver function in patients treated with citalopram, they believe physicians should keep the possibility of hepatotoxicity in mind when prescribing this SSRI. ■

Neumann H, Csepregi A, Evert M, et al.: Drug-induced liver disease related to citalopram. *J Clin Pyschopharmacol* 2008; 28(2):254-255.

From the FDA

✓ Approval: Aripiprazole for adolescent bipolar disorder

On Feb. 27, the FDA approved a supplemental New Drug Application for the atypical antipsychotic aripiprazole (Abilify) for the acute treatment of manic and mixed episodes associated with bipolar I disorder, with or without psychotic features, in pediatric patients aged 10-to-17-years old. The FDA approved aripiprazole for acute and maintenance treatment of bipolar I disorder in adults in September 2004 and March 2005. The current approval is based on results from a 4-week double-blind, placebo-controlled study that showed significant improvement with aripiprazole compared to placebo on the Young-Mania Rating Scale (YMRS). Aripiprazole is the first dopamine partial agonist approved for a pediatric population suffering from bipolar I disorder. [www.otsuka-global.com]

✓ Approval: Desvenlafaxine (Pristiq) for adult MDD

On February 29, the FDA approved the serotonin-norepinephrine reuptake inhibitor (SNRI) desvenlafaxine (Pristiq) to treat major depressive disorder in adults. Pristiq was approved as a once-daily 50-mg dose following four 8-week randomized, double-blind, placebo-controlled, fixed-dose studies in adult outpatients with major depressive disorder. The most commonly observed adverse reactions include nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety and specific male sexual function disorders. FDA approval was subject to several post-marketing commitments, including a new long-term maintenance study, a sexual dysfunction study, pediatric studies, a study exploring lower doses, and an additional non-clinical toxicity study. Wyeth Pharmaceuticals expects the drug to be available in the second quarter of 2008. [www.wyeth.com]