Ziprasidone-Associated DRESS

The FDA has issued a warning regarding the potential for ziprasidone (Geodon) to cause Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). This rare but serious and potentially fatal skin reaction may begin as a rash that can spread to all parts of the body. The rash is accompanied by an elevated eosinophil level. Other symptoms may include fever, swollen lymph nodes, and inflammation of major organs (e.g., heart, liver, lungs, kidneys, pancreas). Patients who experience these symptoms while taking ziprasidone should seek medical attention and stop taking ziprasidone immediately.

This warning is a result of an FDA review of 6 cases of DRESS associated with ziprasidone. In these patients, symptoms appeared between 11 and 30 days after ziprasidone was started. The FDA will now require the manufacturer to add a warning about DRESS to the ziprasidone prescribing information.


Antidepressants and Platelet Count

In patients with depression, treatment with venlafaxine or mirtazapine was associated with increased platelet counts. Mean platelet volume, a marker for platelet reactivity, was unaffected.

**Background:** High platelet counts are an independent long-term predictor of coronary heart disease and are associated with increased platelet reactivity. Depression is associated with increases in platelet counts and mean platelet volumes, but studies of antidepressants’ platelet effects have had conflicting results, with changes in both directions reported for SSRIs. Studies of other antidepressant drug categories have been rare.

**Methods:** Study participants, 62 adult inpatients (mean age, 52 years; 43 women) with unipolar major depression, received treatment with randomly assigned, flexibly-dosed venlafaxine or mirtazapine. Patients were free of acute or chronic inflammatory disorders and were withdrawn...
from other medication for ≥6 days prior to randomization. Mean drug dosages were about 200 mg/day for venlafaxine and 45 mg/day for mirtazapine. In all patients, platelet counts were assessed at baseline and after 4 weeks of treatment. In addition, mean platelet volume was assessed at the same time points in 26 venlafaxine-treated and 15 mirtazapine-treated patients.

**Results:** Both groups showed a response to treatment, with average Hamilton Rating Scale for Depression (HAM-D) scores decreasing from 23 to 10 with venlafaxine and from 22 to 8 with mirtazapine (p<0.0001 for both). Platelet counts were significantly correlated with mean platelet volume and showed a significant increase from baseline in the mirtazapine group (p=0.046) and a modest, nonsignificant increase with venlafaxine. Mean platelet volume changed numerically, but not with statistical significance, and in opposite directions, increasing slightly with venlafaxine and decreasing with mirtazapine.

<table>
<thead>
<tr>
<th></th>
<th>Baseline PLC</th>
<th>Endpoint PLC</th>
<th>Significance</th>
<th>Baseline MPV</th>
<th>Endpoint MPV</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>279</td>
<td>290</td>
<td>n.s.</td>
<td>8.16</td>
<td>8.23</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>256</td>
<td>271</td>
<td>p=0.046</td>
<td>8.16</td>
<td>8.11</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

**Discussion:** The present study results suggest that both venlafaxine and mirtazapine increase platelet counts. While the increases are numerically small, they may be large enough to cause concern about bleeding on a population basis.


**Atypical Antipsychotic Augmentation in OCD**

Limited evidence supports the cautious use of risperidone and aripiprazole to augment SSRI therapy in refractory obsessive-compulsive disorder, according to a systematic review and meta-analysis.

**Background:** The U.K. National Institute of Clinical and Health Excellence (NICE) guideline for OCD recommends atypical antipsychotics as 1 of several augmentation options for patients with resistant disease. However, the guideline is not clear on how to use these agents in terms of dose or duration and is based on older evidence. The present analysis was undertaken to update the evidence base for atypical antipsychotic use in resistant OCD.

**Methods:** A systematic review identified all double-blind, placebo-controlled, randomized studies that investigated the use of an atypical for adults with OCD. For inclusion, studies were required to use an intent-to-treat analysis and to use the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) as the primary outcome measure. Study participants had been required to have persistent OCD symptoms (Y-BOCS score, ≥16) after at least 1 adequate trial of an SSRI or clomipramine. Patients remained on their SSRI during randomized treatment and received an atypical antipsychotic or placebo for at least 4 weeks.

**Results:** A total of 14 studies, which included 493 participants (242 who received an antipsychotic), were identified. Most studies had small sample sizes (16–80 participants), and none had long-term follow-up (durations, 6–16 weeks). Overall, the atypicals produced an average 2-point Y-BOCS reduction, equivalent to a 10% reduction in the total score (effect size,* 0.40).
Analysis of individual agents found olanzapine (2 studies; n=35) and quetiapine (5 studies; n=89) were not superior to placebo as augmentation. Risperidone was evaluated in 77 patients from 5 studies. Analysis of these studies showed a nearly 4-point greater improvement in Y-BOCS score with risperidone than with placebo (p<0.001), with a pooled effect size of 0.53. A single risperidone study that used a low fixed dose of 0.5 mg showed a larger effect size than those that used moderate doses. Aripiprazole was evaluated in 2 studies with 79 patients (n=41 receiving aripiprazole). Results showed that aripiprazole was associated with a 6.3-point difference from placebo in Y-BOCS score and an effect size of 1.11.

Discussion: Both risperidone and aripiprazole appear to be effective as short-term augmentation strategies in resistant OCD. The efficacy of longer treatment is unclear as study durations were short and no additional improvement was seen after 4 weeks of treatment.

Study Rating*—17 (100%): This study met all criteria for a systematic review/meta-analysis.


Drug Trade Names: aripiprazole—Abilify; clomipramine—Anafranil; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal

*See Reference Guide.

Quetiapine in Borderline Personality Disorder

In a small, manufacturer-sponsored, randomized trial, low-dose quetiapine (Seroquel) was superior to placebo in reducing the overall severity of borderline personality disorder symptoms. Moderate-dose quetiapine was not as effective or as well tolerated.

Background: Quetiapine is currently FDA approved for treatment of schizophrenia and bipolar disorder. Results of open-label studies suggest the drug may improve borderline symptoms such as impulsivity and self-harm.

Methods: Patients aged 18–45 years with mood and relationship problems were recruited from referrals and the community. Study participants were required to meet DSM-IV diagnostic criteria, to have a score of ≥9 on the Zanarini Rating Scale for Borderline Personality Disorder, and to be free of depression, an anxiety disorder, obsessive-compulsive disorder, and a history of psychosis. Participants (n=95) were randomly assigned to double-blind treatment with placebo, low-dose quetiapine (150 mg/day), or moderate-dose quetiapine (300 mg/day). In both active-treatment groups, quetiapine was started at 50 mg/day and then increased after the first week to 150 mg/day; in the moderate-dose group, the drug was increased to 300 mg/day after 4 weeks. Change from baseline on the clinician-rated Zanarini scale was the primary outcome measure of the 8-week trial.

Results: Two-thirds of patients completed the trial; there were no significant differences between the groups in dropout rates. Patients in all 3 groups showed improvement as evidenced by decreased Zanarini scores. Low-dose quetiapine was associated with statistically significant improvement compared with placebo (effect size,* 0.79; p=0.03), while the higher dose was not (effect size, 0.41; p=ns). The mean score decreased by 1.22 points per week with low-dose quetiapine, 1 point with the moderate dose, and by 0.75 points with placebo. Response criteria (≥50% decrease in Zanarini Scale score) were met by 82% of the low-dose quetiapine group, 67% of the moderate-dose group, and 62% of the placebo group. For some secondary endpoints, both dosages of quetiapine were statistically superior to placebo: the self-rated Zanarini total score, the Borderline Evaluation of Severity Over Time total score, several subscales of these instruments, and the Modified Overt Aggression Scale score. Neither dose improved
impulsivity more than placebo, but the higher dose of quetiapine had a significantly larger effect on mania. Risk of adverse effects—sedation, change in appetite, and dry mouth—was greater with moderate-dose than low-dose quetiapine (p≤0.02 for all).

Discussion: Several psychotherapeutic options have been developed for the treatment of borderline personality disorder, and while pharmacotherapy is being investigated, there are no FDA-approved medications for the disorder. However, similarities between affective instability in borderline personality disorder and mood shifts in bipolar disorder suggested that a drug effective in bipolar disorder, such as quetiapine, might also be useful in borderline personality disorder. The present study results provide preliminary support for the efficacy of quetiapine but require replication.

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

Vilazodone in MDD

In a manufacturer-sponsored, multicenter, placebo-controlled trial, patients who received treatment with vilazodone (Viibryd) experienced rapid and significant improvement in depressive symptoms and moderate improvement in anxiety.

Methods: Study participants were 518 adults, aged 18–70 years (54% female), who met DSM-IV-TR criteria for major depressive disorder (MDD), with the current episode duration of 8 weeks to 12 months. Following a 1–4 week drug-free screening period, patients with a Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥26 were randomly assigned to 8 weeks of double-blind treatment with either vilazodone, titrated over 2 weeks to 40 mg/day, or placebo. At study end, patients underwent a 1-week double-blind taper. Most comorbid psychiatric disorders were grounds for exclusion, but patients with secondary generalized anxiety disorder, social anxiety disorder, and/or specific phobias were allowed to participate. Patients whose symptoms had been unresponsive to ≥2 previous antidepressant trials were also excluded. The primary outcome was change in MADRS score. Changes in Clinical Global Impression–Severity* (CGI-S) and Improvement* (CGI-I) scales and the Hamilton Anxiety Rating Scale (HAM-A) were secondary outcomes. Sustained response was defined as a MADRS score of ≤12 for 2 consecutive study visits. Remission was not evaluated as a study outcome. (See next story in this issue.)

Results: At baseline, patients had at least moderate depression, indicated by a mean MADRS score of 31 in both treatment groups. Mean duration of the current episode was 7 months in the vilazodone group and 6 months in the placebo group. Vilazodone was significantly superior to placebo beginning at week 2, and the between-group difference in MADRS scores increased over time. At 8 weeks, the intent-to-treat analysis* showed mean scores had decreased by 11 and 16 points (to 20 and 15) in the placebo and vilazodone groups, respectively (p<0.00001; effect size,* 0.54). Secondary outcomes also significantly favored vilazodone. Effect sizes for vilazodone on the HAM-A and CGI-I were 0.39 and 0.43, respectively. Final CGI-S scores were 2.5 with vilazodone and 3.2 with placebo. Sustained response occurred in 27% of the vilazodone group, compared with 17% of the placebo group (p=0.004).

Several adverse effects were more common with vilazodone than with placebo: diarrhea (83% vs. 26%), nausea (63% vs. 21%), dizziness (18% vs. 7%), and insomnia (15% vs. 3%). Most occurrences were mild and transient. No serious treatment-related adverse events were
The incidence of sexual dysfunction, a concern with SSRI treatment, was low in both groups, but significantly more men receiving active treatment experienced erectile dysfunction (5% vs. 1%) and delayed ejaculation (2% vs. 0%). There were no differences between the groups in dropout rates; 83% of patients completed the study.

**Discussion:** A mean 2-point difference in MADRS score versus placebo has been considered the threshold for clinical relevance. The 5-point difference found in the present study indicates that vilazodone is an effective treatment option for MDD. Anxiety affects up to 50% of patients with MDD, so the improvement observed in this study is encouraging; however, anxiety levels in the present sample were low, which may have affected the strength of improvement.

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

**Vilazodone and Depression Remission**

According to a post-hoc analysis of data from a phase IV clinical trial, vilazodone (Viibryd) treatment results in remission of depression and/or anxiety in 18–49% of treated patients. The agent has SSRI properties and is posited to have additional antidepressant and anti-anxiety efficacy due to its partial 5-HT1A agonist activity.

**Background:** The superiority of vilazodone over placebo has been demonstrated in several clinical trials of major depression. However, remission of depression should be the goal of treatment and this outcome has not been evaluated prospectively to date. The present study uses data from a previously completed multicenter trial (see previous story in this issue) in order to evaluate remission of depression and comorbid anxiety in patients with major depression.

**Methods:** Study participants were adults with major depressive disorder who received 8 weeks of randomly assigned 40 mg/day vilazodone or placebo. (See previous story for details.) The Montgomery-Asberg Depression Rating Scale (MADRS) was the primary outcome measure, with remission defined as a score of ≤10, and total remission as a score of ≤5. Anxiety was measured with the Hamilton Anxiety Rating Scale (HAM-A), with remission defined as a score of ≤7. Overall response was defined as a Clinical Global Impression–Severity* score of 1.

**Results:** At 8 weeks, the patients who received vilazodone demonstrated significantly greater improvement in depression and anxiety than those in the placebo group. Vilazodone was significantly superior to placebo for all response and remission outcomes, with numbers needed to treat* (NNT) ranging from 6 to 11. (See table.) The between-group differences in response and remission were evident by treatment week 6.

<table>
<thead>
<tr>
<th>Response and remission rates at the end of 8 weeks of treatment</th>
<th>Placebo</th>
<th>Vilazodone</th>
<th>Odds Ratio*</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADRS Response</td>
<td>33%</td>
<td>51%</td>
<td>2.0</td>
<td>6</td>
</tr>
<tr>
<td>MADRS Remission</td>
<td>22%</td>
<td>34%</td>
<td>1.8</td>
<td>9</td>
</tr>
<tr>
<td>MADRS Complete Remission</td>
<td>8%</td>
<td>18%</td>
<td>2.4</td>
<td>11</td>
</tr>
<tr>
<td>HAM-A Remission</td>
<td>35%</td>
<td>49%</td>
<td>1.8</td>
<td>8</td>
</tr>
<tr>
<td>Both MADRS and HAM-A Remission</td>
<td>20%</td>
<td>32%</td>
<td>1.8</td>
<td>9</td>
</tr>
<tr>
<td>CGI-S Remission</td>
<td>12%</td>
<td>24%</td>
<td>2.4</td>
<td>8</td>
</tr>
</tbody>
</table>

*See Reference Guide.
Discussion: Remission of depression/anxiety may require prolonged therapy, and a longer treatment duration may have resulted in higher remission rates than were found in this study. It should be noted that previous research has linked early depression response to better long-term outcomes.

Citrome L, Gomoll C, Tang X,NUnez R,et al: Evaluating the efficacy of vilazodone in achieving remission in patients with major depressive disorder: post-hoc analyses of a phase IV trial. *International Clinical Psychopharmacology* 2014; doi 10.1097/yic.000000000000056. From New York Medical College, Valhalla; and Forest Research Institute, Jersey City, NJ. Funded by Forest Research Institute, Inc. All 5 study authors disclosed financial relationships with commercial sources, including Forest Labs (manufacturer of *Viibryd*) or Forest Research Institute.

*See Reference Guide.

Sertraline-Associated Maculopathy

Within 2 weeks of starting treatment with sertraline (*Zoloft*), a 23-year-old man presented with worsening bilateral blurred vision and metamorphopsia, a type of distorted vision in which a grid of straight lines appears wavy and parts of the grid may appear blank.\(^1\) The patient had no previous ocular issues or family history of eye disease. Intraocular pressure was normal, but dilated fundal examination showed Bull’s-eye-type maculopathy similar in appearance to that which occurs in chloroquine toxicity. Optical coherence tomography showed intermittent outer segment defects and thickening of the retinal pigment epithelium. Sertraline was discontinued. At 1-month follow-up, the patient reported some visual improvement.

Most adverse effects of sertraline and other SSRIs are well documented; however, the incidence of adverse ocular effects appears to be unknown. Reports of SSRI-associated adverse ocular effects including mydriasis, increased intraocular pressure, glaucoma, and oculogyric crisis, are anecdotal and few in number. There appears to be only 1 previous report of maculopathy developing in association with sertraline treatment. The previous patient was a 58-year-old woman in whom symptoms developed within 4 months of starting treatment.\(^2\)

\(^1\)Ewe S, Abell R, Vote B: Bilateral maculopathy associated with sertraline. *Australasian Psychiatry* 2014; doi 10.1177/1039856214556327. From Tasmanian Eye Institute, Australia. The authors declared no conflicts of interest.


Antidepressant-Induced Jitteriness

"Jitteriness/anxiety syndrome" occurred with newly prescribed antidepressants in 7% of a sample of prospectively evaluated patients.\(^1\) Risk appeared to be greatest among patients with a first-degree relative with a mood-disorder diagnosis.

Background: Research suggests that in patients newly started on antidepressant therapy, jitteriness/anxiety may be a reflection of antidepressant-related activation, which has been associated with suicidal thoughts and behavior.\(^2\)\(^-\)\(^3\) The present study was undertaken to investigate the incidence of "jitteriness/anxiety syndrome" and to examine factors predictive of its development.

Methods: The study population comprised 301 patients (mean age, 45 years; 70% women) who received a new prescription for an antidepressant and had then taken the drug for ≥1 month. The antidepressants were prescribed for mood disorders including major depressive disorder in half of the patients. Other frequent indications were pain disorder (19%) and panic disorder (11%). Two-thirds of patients received a prescription for SSRIs, 20% for TCAs, and the remaining small proportion for SNRIs. One-third of patients were also given a prescription for benzodiazepines. "Jitteriness/anxiety syndrome" was defined as the new onset during the first month of treatment of ≥1 symptom listed in the FDA’s 2004 warning on antidepressant-related activation syndrome: anxiety; agitation; panic attacks; insomnia; irritability; hostility; aggressiveness; impulsivity; akathisia; and hypomania or mania. "Jitteriness/anxiety syndrome" was judged by the attending physician based on the presence of the specified symptoms.
Results: A total of 21 patients (7%) experienced onset of ≥1 symptom of jitteriness/anxiety; 6 patients experienced 2 symptoms, and 3 patients experienced 3 symptoms. Symptoms usually began within 1 week of starting treatment and were treated in about half of patients by stopping the antidepressant; nearly all patients improved. Insomnia was the most common symptom (43% of patients), followed by irritability (33%), anxiety/agitation (24%), and panic attacks (14%). No patient showed hostility or mania. In this study, 1 patient had onset of suicidal ideation, but none showed self-harm or attempted suicide.

In a multivariate analysis, a family history of mood disorder was associated with a 10-fold increase in risk of jitteriness/anxiety (odds ratio,* 10.2). Risk was increased 3- to 4-fold in patients with major depressive disorder. Risk was not associated with age, antidepressant class, or use of benzodiazepines.

Discussion: Results of previous research have suggested that young patients are more liable to develop behavioral activation associated with antidepressant treatment, and that risk is increased with the use of paroxetine. The present study may have had too few young patients to identify young age as a risk factor. There was no difference in risk between patients taking paroxetine or sertraline, the 2 most commonly prescribed drugs.

1 Harada T, Inada K, Yamada K, Sakamoto K, et al: A prospective naturalistic study of antidepressant-induced jitteriness/anxiety syndrome. Neuropsychiatric Disease and Treatment 2014;10;2115–2121. From Tokyo Women’s Medical University School of Medicine, Japan. Funded by the Japan Society for the Promotion of Science. All study authors disclosed financial relationships with com mercial sources.


Drug Trade Names: paroxetine—Paxil; sertraline—Zoloft

*See Reference Guide.

Antidepressant Augmentation and Obesity

In a phase II clinical trial, the investigational nicotinic acetylcholine receptor partial agonist CP-601,927 was not superior to placebo as antidepressant augmentation therapy. However, a post-hoc analysis showed that obesity and high leptin levels may have influenced treatment outcomes.

Methods: Study subjects were nonsmoking patients with major depressive disorder who had been receiving SSRI treatment for the current episode for ≥8 weeks before study entry and had an inadequate response, defined as a <50% reduction in severity. At baseline screening, participants were required to have a 17-item Hamilton Rating Scale for Depression (HAM-D) score of ≥18. All patients received 8 weeks of open-label SSRI treatment, with the SSRI selected on the basis of clinical history. Those whose depression continued to be nonresponsive were randomly assigned to receive either CP-601,927 or placebo. The primary study endpoint was change in the Montgomery-Asberg Depression Rating Scale (MADRS) score from baseline to the end of 6 weeks of double-blind treatment. Change in HAM-D score was a secondary outcome measure.

Results: The study was terminated early after an interim futility analysis. At that time, the trial had accrued 123 patients, of its target enrollment of 198 patients. There was no difference between CP-601,927 and placebo in MADRS change or in most of the secondary endpoints. However, post-hoc analyses conducted to evaluate the effect of body mass index (BMI) and of various biomarkers in plasma found that CP-601,927 may have been superior to placebo in the 85 patients with a BMI of ≤35 (p=0.068). Patients with lower BMI also had better responses to the test drug as measured with the HAM-D (p=0.031) and the Clinical
Global Impression–Improvement scale (p=0.03). Of several biomarkers tested, only leptin influenced treatment response. CP-601,927 was superior to placebo in patients with leptin levels below the median (p=0.055), and placebo was superior in those with higher levels (p=0.0055).

Discussion: The post-hoc analysis suggests that obesity and leptin levels may have adversely affected signal detection in this study. Previous research has shown higher BMI to be associated with negative treatment outcomes in depression, and obesity may delay patients’ response to open-label SSRIs, thus creating an artificially large placebo effect in the present study. Levels of leptin, a hormone secreted by adipose tissue, are elevated in obesity and recent research has also found a connection between leptin deficiency and poor antidepressant response. Finally, variability in antidepressant response may be related to the amount of adipose tissue present in obese subjects into which highly lipophilic drugs may distribute. Increased amounts of this tissue may lead to lower drug plasma concentrations and a need for increased drug exposure.

Although, in this study, CP-601,927 was not superior to placebo as an adjunctive antidepressant, further investigation of the effects and the feasibility of obesity on antidepressant response appear to be warranted.


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Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A 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.

Clinical Global Impression–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A 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.

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance and large effect sizes do not ensure treatment efficacy.

Intent-to-Treat: An analysis based on initial treatment intent, not on the treatment actually administered or completed. In an ITT analysis, everyone begins treatment is included regardless of treatment completion. ITT analyses are done to avoid the effects of crossover, drop-out, and other factors that could alter the results or inflate the magnitude of effects.

Number Needed to Treat (NNT): Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio >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.

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