ORIGINAL RESEARCH

Comorbidity with Axis I Anxiety Disorders in Remitted Psychotic Patients 1 Year After Hospitalization

CASE REPORTS

Williams Syndrome: A Genetic Deletion Disorder Presenting Clues to the Biology of Sociability and Clinical Challenges of Hypersociability
S.I. Deutsch, R.B. Rosse, and B.L. Schwartz

Somnambulism Induced by Quetiapine: Two Case Reports and a Review of the Literature
Z.H. Hafeez and C.M. Kalinowski

Unexpected Reduction in Migraine and Psychogenic Headaches Following rTMS Treatment for Major Depression: A Report of Two Cases
J.P. O’Reardon, J.F. Fontecha, M.A. Cristancho, and S. Newman

NEW CLINICAL COLUMN SERIES

BRAIN REGIONS OF INTEREST

The Ventral Striatum as an Interface Between the Limbic and Motor Systems
H.J. Groenewegen

IN SESSION

Insight into the Sequenced Treatment Alternatives to Relieve Depression Study
A. Nierenberg

COMMUNIQUE

Gamma Hydroxy Butyric Acid and Sodium Oxybate Used to Treat Posttraumatic Stress Disorder
The voices in his head are back.
I can't bear to see him like this.

He was doing so well on his own.
This will ruin everything.
It could send him back to the hospital.

We're fighting to get things back under control.
But we need help now.

For resources to help you help your patients with schizophrenia, visit www.ToolsForTheFight.com
The labeling for ZYPREXA includes a boxed warning:

- Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo.
- ZYPREXA is not approved for the treatment of elderly patients with dementia-related psychosis.

ZYPREXA is approved for the treatment of schizophrenia, acute bipolar mania, and for maintenance treatment in bipolar disorder.

For Important Safety Information, including boxed warning, see adjacent page and accompanying Brief Summary of Prescribing Information.
Important Safety Information for ZYPREXA® (Olanzapine)

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ZYPREXA is not approved for the treatment of elderly patients with dementia-related psychosis.

Cerebrovascular adverse events (CVAE), including stroke, in elderly patients with dementia—Cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, were reported in patients in trials of ZYPREXA in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of CVAE in patients treated with ZYPREXA compared to patients treated with placebo. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and diabetes mellitus—Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including ZYPREXA. All patients taking atypicals should be monitored for symptoms of hyperglycemia. Persons with diabetes who are started on atypicals should be monitored regularly for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing.

Neuroleptic malignant syndrome (NMS)—As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Medication dispensing and prescribing errors have occurred between ZYPREXA® (olanzapine) and Zyrtec® (cetirizine HCl). These errors could result in unnecessary adverse events or potential relapse in patients suffering from schizophrenia or bipolar disorder. To reduce the potential for dispensing errors, please write ZYPREXA clearly.

The most common treatment-emergent adverse event associated with ZYPREXA (vs placebo) in 6-week acute-phase schizophrenia trials was somnolence (26% vs 15%). Other common events were dizziness (11% vs 4%), weight gain (6% vs 1%), personality disorder (COSTART term for nonaggressive objectionable behavior; 8% vs 4%), constipation (9% vs 3%), akathisia (5% vs 1%), and postural hypotension (5% vs 2%).

The most common treatment-emergent adverse event associated with ZYPREXA (vs placebo) in 3- and 4-week bipolar mania trials was somnolence (35% vs 13%). Other common events were dry mouth (22% vs 7%), dizziness (18% vs 6%), asthenia (15% vs 6%), constipation (11% vs 5%), dyspepsia (11% vs 5%), increased appetite (6% vs 3%), and tremor (6% vs 3%).

For complete safety profile, see the full Prescribing Information.

ZYPREXA is a registered trademark of Eli Lilly and Company.

Zyrtec is a registered trademark of UCB, SA.
In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients (3.3%) was significantly greater than placebo-treated patients (1.6%).

In 5 placebo-controlled studies in elderly patients with dementia-related psychosis treated with olanzapine, the incidence of extrapyramidal events was significantly greater than placebo only with the 2 higher doses of olanzapine than with placebo. The incidence of akathisia events (spontaneously reported COSTART terms akathisia and hyperkinesia) showed a statistically significant greater adverse events incidence with the 2 higher doses of olanzapine than with placebo. The incidence between any dose of oral olanzapine (5±2.5, 10±2.5, or 15±2.5 mg/d) and placebo for parkinsonism was 0.5% for each dose in olanzapine-treated patients and 5% in placebo-treated patients. In placebo-controlled oral olanzapine trials (olanzapine vs placebo: schizophrenia, 5% vs 6%; bipolar mania (24-36 week trials), 2% vs 3%; diabetes type II, 1% vs 4%).

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Olanzapine-induced changes that tended to normalize while olanzapine treatment was continued. Among 2500 patients in oral olanzapine, the incidence of extrapyramidal events was significantly greater than placebo only with the 2 higher doses of olanzapine than with placebo. The incidence of akathisia events (spontaneously reported COSTART terms akathisia and hyperkinesia) showed a statistically significant greater adverse events incidence with the 2 higher doses of olanzapine than with placebo. The incidence between any dose of oral olanzapine (5±2.5, 10±2.5, or 15±2.5 mg/d) and placebo for parkinsonism was 0.5% for each dose in olanzapine-treated patients and 5% in placebo-treated patients. In placebo-controlled oral olanzapine trials (olanzapine vs placebo: schizophrenia, 5% vs 6%; bipolar mania (24-36 week trials), 2% vs 3%; diabetes type II, 1% vs 4%).

Hypersalivation—Excessive salivation has been associated with olanzapine use. In 5 placebo-controlled studies in elderly patients with dementia-related psychosis treated with olanzapine, the incidence of extrapyramidal events was significantly greater than placebo only with the 2 higher doses of olanzapine than with placebo. The incidence of akathisia events (spontaneously reported COSTART terms akathisia and hyperkinesia) showed a statistically significant greater adverse events incidence with the 2 higher doses of olanzapine than with placebo. The incidence between any dose of oral olanzapine (5±2.5, 10±2.5, or 15±2.5 mg/d) and placebo for parkinsonism was 0.5% for each dose in olanzapine-treated patients and 5% in placebo-treated patients. In placebo-controlled oral olanzapine trials (olanzapine vs placebo: schizophrenia, 5% vs 6%; bipolar mania (24-36 week trials), 2% vs 3%; diabetes type II, 1% vs 4%).

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Highest dose of oral olanzapine (15±2.5 mg/d) in controlled clinical trials of intramuscular olanzapine for 5 weeks; there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales incidence or spontaneous patient reported adverse events.

Other Adverse Events—Dose-related adverse events were assessed using data from this same clinical trial involving 5 fixed oral dosage ranges (5±2.5, 10±2.5, or 15±2.5 mg/d) compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

In an 8-week, randomized, double-blind study in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder comparing fixed doses of 10, 20, and 40 mg/d, statistically significant differences were seen between doses for the following: baseline to endpoint weight gain, 10 vs 40 mg/d; incidence of treatment-emergent prolactin elevations ≥24.2 ng/mL (female) or ≥18.7 ng/mL (male), 10 vs 40 mg/d and 20 vs 40 mg/d; fatigue, 10 vs 40 mg/d and 20 vs 40 mg/d; and diziness, 20 vs 40 mg/d.

Vital Signs Changes—Olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia or clinical tachycardia (see PRECAUTIONS).

Weight Gain—its placebo-controlled 6-week schizophrenia studies, weight gain was reported in 5.2% of olanzapine patients (average 2.9-kg gain) compared to 3.6% of placebo patients (average 0.4-kg loss), 29% of olanzapine patients gained ≥7% of their baseline weight, compared to 3% of placebo patients. During continuation therapy (226 median days of exposure), 45.6% of patients met the criteria for having gained ≥7% of their baseline weight. Average gain during long-term therapy was 5.4 kg.

Laboratory Changes—Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT and increases in serum prolactin and CPK (see PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine in the premarketing database.

In clinical trials among olanzapine-treated patients with baseline random triglyceride levels of <150 mg/dL (N=669), 0.5% experienced triglyceride levels of ≥500 mg/dL, anytime during the trials. In those trials, olanzapine-treated patients (N=1198) had a mean triglyceride increase of 20 mg/dL, from a mean baseline of 175 mg/dL. In placebo-controlled trials, olanzapine-treated patients with baseline random cholesterol levels of <200 mg/dL (N=1034) experienced cholesterol levels of ≥240 mg/dL anytime during the trials, those more often than placebo-treated patients (N=80; 3.6% vs 2.2%, respectively). In these same trials, olanzapine-treated patients (N=528) had a mean increase of 0.6% in cholesterol from a mean baseline of 200 mg/dL, which was significantly different compared to placebo-treated patients (N=1415) with a mean decrease of 4.6 mg/dL from a mean baseline of 203 mg/dL.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in incidence of potentially important changes in ECG parameters, including ST, Tc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

Other Adverse Events Observed During Clinical Trials—The following treatment-emergent events were reported with oral olanzapine at multiple doses ≥ mg/d in clinical trials (8661 patients, 1165 patient-years of exposure). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. Frequent events occurred in ≥1% of patients; infrequent events occurred in 1/100 to 1/1000 patients; rare events occurred in <1/1000 patients; clinical trials involving 3 fixed oral dosage ranges (5±2.5,10±2.5, or 15±2.5 mg/d) compared with placebo. In controlled clinical trials of intramuscular olanzapine for injection, there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales incidence or spontaneously reported adverse events.

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Alzheimer's Disease Summit
Translating Research Advances Into Clinical Practice

Save the Date:
Saturday, May 3, 2008 • The Park Hyatt • Washington, DC
8:00 a.m. – 7:00 p.m.

Program Chairs:
Jeffrey L. Cummings, MD, and Pierre N. Tariot, MD

Program Sessions include:

• Advances in Clinical Assessment
• Advances in Neuroimaging and Biomarkers
• Current Alzheimer Therapy: Best Practices
• The Future of Alzheimer Therapeutics
• Panel Discussion including Russell Katz, MD, Director of Neurology Products, FDA

For complete ADS program and registration information, please visit www.adsummit2008.com

CNS Spectr 12:12

Published online by Cambridge University Press
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Suicide: The possibility of a

**WARNINGS**

- **Prolactin**
  - Elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used in combination with other drug treatments.
  - Aspiration pneumonia has been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients. Therefore, it is important to use caution when using antipsychotic drugs in elderly patients who are at risk for aspiration pneumonia.

- **Seizures**
  - In clinical trials, seizures occurred in 0.4% of GEODON patients. There were no reports of seizures in placebo patients. The relationship of seizures to GEODON treatment is unknown.

**ADVERSE REACTIONS**

**Frequent**
- Nausea
- Vomiting
- Diarrhea
- Dyspepsia
- Abdominal pain
- Constipation

**Infrequent**
- Dry mouth
- Nausea
- Diaphoresis
- Tachycardia
- Orthostatic hypotension

**Rare**
- Dizziness
- Anxiety
- Insomnia
- Somnolence
- Akathisia
- Agitation
- Extrapyramidal symptoms
- Hypertonia
- Cogwheel rigidity
- Paresthesia
- Personality disorder
- Psychosis
- Speech disorder
- Respiratory—rhinitis
- Skin and Appendages—pruritus
- Urogenital System—dysuria, cystitis, male impotence, abnormal ejaculation, penile erections, priapism

**Extraordinary Symptoms (EPS)**
- Incoordination, akathisia, chorea, dystonia, muscle stiffness, muscle spasm, myoclonus, rigidity
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**Dysmenorrhea**
- The incidence of dysmenorrhea was higher in patients treated with GEODON compared to placebo.

**Impairment of Fertility**
- GEODON increased the incidence of tumors in male and female rats. Increases in serum prolactin were noted in both male and female rats.

**Drug Interaction**
- GEODON is metabolized primarily by the liver. Therefore, it is important to use caution when using antipsychotic drugs in patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular.

**Adverse Reactions at an Increasing Rate**
- Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs have an increased risk of death compared to placebo. The risk of death was increased in patients treated with antipsychotic drugs compared to placebo in two large controlled trials and one post-marketing study. The risk appeared to be particularly elevated in elderly females who had severe cardiovascular disease and other risk factors.

**Pregnancy**
- There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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- Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs have an increased risk of death compared to placebo. The risk of death was increased in patients treated with antipsychotic drugs compared to placebo in two large controlled trials and one post-marketing study. The risk appeared to be particularly elevated in elderly females who had severe cardiovascular disease and other risk factors.

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Control acute agitation with

GEODON®
for Injection (ziprasidone mesylate)

In schizophrenia...

Rapid control* with low EPS1-4

- Low incidence of movement disorders1-4
- Smooth transition, with continued improvement, from IM to oral therapy3,4
- May be used concomitantly with benzodiazepines2,3,5

*In 2 pivotal studies vs control, significance was achieved at the 2-hour primary end point (10 mg study) and at the 4-hour primary end point (20 mg study).

GEODON for Injection is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with GEODON is appropriate and who need intramuscular antipsychotic medication for rapid control of the agitation.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON is not approved for the treatment of patients with dementia-related psychosis.

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with other QT-prolonging drugs. GEODON has a greater capacity to prolong the QT interval than several antipsychotics. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. In many cases this would lead to the conclusion that other drugs should be tried first.

As with all antipsychotic medications, a rare and potentially fatal condition known as neuroleptic malignant syndrome (NMS) has been reported with GEODON. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation, treatment, and monitoring are recommended.

Prescribing should be consistent with the need to minimize tardive dyskinesia (TD), a potentially irreversible dose- and duration-dependent syndrome. If signs and symptoms appear, discontinuation should be considered since TD may remit partially or completely.

Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Precautions include the risk of rash, orthostatic hypotension, and seizures.

In fixed-dose, pivotal studies, the most commonly observed adverse events associated with the use of GEODON for Injection (incidence ≥5%) and observed at a rate in the higher GEODON dose groups (10 mg, 20 mg) of at least twice that of the lowest GEODON dose group (2 mg control) were somnolence (20%), headache (13%), and nausea (12%).

Please see brief summary of prescribing information on adjacent page.
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We think they'll be great together. At Vanda, we're using pharmacogenetics to match promising molecules to the right patients. So selecting the right medicine will be easier, thanks to our more personal approach. To learn more, visit www.vandapharma.com.

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