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Second Generation Atypical Antipsychotic (SGA) Mood Stabilizers: Geodon

- General
  - Generic name is ziprasidone.
  - Introduced in US in 2000; released in Sweden in 1998.
- Evidence
  - FDA-approval
    - Mania and mixed episodes in adults 2004
    - Adults with schizophrenia
      - Many studies
      - Zyprexa vs Geodon in a 28-week double-blind study in 277 patients with schizophrenia
        - Zyprexa was more effective
        - Geodon demonstrated less weight gain and less lipid profile difficulties
        - Health Canada (equivalent of FDA) approval for the treatment of schizophrenia and related psychotic disorders in 2008
  - Adults
    - General
      - May be useful in other mood and anxiety disorders.
    - Bipolar depression
      - Two negative studies in bipolar depression (Lombardo et al, 2009)
      - Sachs et al, 2011: Geodon add-on in bipolar I depression did not demonstrate efficacy; side effects:
        - Somnolence 22.4% vs. 4.8% placebo
        - Sedation 14.3% vs. 4.8%
        - Fatigue 12.9% vs. 4.1%
        - Dizziness 12.9% vs. 6.1%
        - Headache 11.6% vs. 9.5%
        - Insomnia 11.6% vs. 6.8%
        - Nausea 10.9% vs. 5.4%
        - Anxiety 6.1% vs. 0.7%
        - Restless muscles 6.4% vs. 1.4%
        - Restlessness 5.4% vs. 1.4%
    - Mania
      - Geodon augmentation of lithium or Depakote in acute mania; Sachs et al, 2012
        - Well tolerated but not more effective than placebo
      - Two three-week placebo-controlled RCTs in adults with mania:
        - 46-50% response rate with Geodon (average dose 136 mg/day)
        - 29-35% response rate with placebo
    - Treatment-resistant depression
      - JCP, 2007: randomized, open-label, treatment-resistant depression (response rate to 6 weeks Zoloft was 13.5%), Zoloft continuation alone vs. Zoloft plus Geodon 80 mg/day vs. Zoloft plus Geodon 160 mg/day
        - Response rates:
          - Zoloft: 10%
          - Zoloft plus Geodon 80 mg: 19%
          - Zoloft plus Geodon 160 mg: 32%
        - Remission rates:
          - Zoloft: 5%
          - Zoloft plus Geodon 80 mg: 5%
          - Zoloft plus Geodon 160 mg: 21%
        - Side effects when Geodon added to Zoloft
          - Insomnia 32-36.4% vs. 5% Zoloft alone
          - Agitation 26.3% vs. 0 Zoloft alone
          - Lassitude 23-26.3% vs. 0 Zoloft alone
          - Sleepiness 16-23% vs. 10% Zoloft alone
          - Tremor 10.5-23% vs. 5% Zoloft alone
          - Dizziness 18-21% vs. 0 Zoloft alone

        - Dry mouth 9-21% vs. 0 Zoloft alone
        - Nausea 4.5-21% vs. 0 Zoloft alone
        - Muscle restlessness/discomfort 4.5-21% vs. 0 Zoloft alone
        - Abnormal vision 4.5-21% vs. 0 Zoloft alone
        - Headache 16-18% vs. 5% Zoloft alone
        - Constipation 5.3-13.6% vs. 0 Zoloft alone
        - Abnormal thinking 10% vs. 0 Zoloft alone
    - Dunner, 2006: 8 week, RCT, Zoloft alone vs. Zoloft plus Geodon 80 mg/day vs Zoloft plus 160 mg/day—efficacy increased with Geodon and then Geodon at a higher dose, but improvement was not statistically significant
    - Papakostas et al: 20 patients, open-label: effective

- Schizophrenia
    - 52-week maintenance study of Geodon in schizophrenia:
        - 65% relapse-free with Geodon
        - 30% with placebo (Arato, 2002).

- Youths
    - Schizophrenia
        - Findling, et al, 2013: treatment in adolescent schizophrenia
            - 6-wk, double-blind, placebo-controlled, randomized trial (RCT) of Geodon followed by 26-week open label extension (OLE)
            - 70 international sites, 25 of which were in the US
            - RCT phase had 286 adolescents 13-17
            - Target range 120-160 mg if 45 kg or more vs. 60-80 mg if less than 45 kg
            - OLE phase had 221 adolescents
            - Results
                - No significant differences
            - Side effects
                - Somnolence 19.7%
                - Extrapyramidal symptoms 11.4%
                - Nausea 9.8%
                - Dizziness
                - Fatigue
                - Headache
                - Tremor
                - Weight and BMI did not increase
                - Increase in QTc by 5.1 mg, but no adverse cardiac events
            - Study terminated (primarily the OLE phase) due to lack of efficacy
        - Sikich, 2006: open-label treatment of early onset (8-19 yo) schizophrenia, schizophreniform, and schioaffective disorder over one year; 40 youths, 20-220 mg (average 118 mg);
            - 13 of 40 completed one year in the study
                - Generally positive results
                - Of those who dropped out, 9 developed mania or hypomania (either unrelated or related to Geodon treatment)
    - Mania (OR schizophrenia)
        - Findling et al, 2013
            - 4-wk, double-blind, placebo-controlled, randomized trial (RCT) of Geodon for manic or mixed episodes in bipolar I disorder followed by 6 month open label extension (OLE)
            - 36 sites in the US
            - Geodon was superior to placebo
            - Side effects
                - Sedation 32.9%
                - Somnolence 24.8%
                - Headache 22.1%
                - Fatigue 15.4%
                - Nausea 14.1%
                - No abnormal weight gain
        - Adolescent Mania
            - Geodon > placebo

- DelBello et al, 2006; youth with mania or schizophrenia, open label, dose-ranging safety and tolerability study, 3-week, 51 youth; side effects:

	Low dose (80 mg)	High dose (160)
Somnolence/sedation	48%	68%
Nausea	22%	28.6%
Headache	13%	25%
Vomiting	13%	18%

  - Bipolar maintenance
    - Barnett, 2004: effective (at 40-80 mg) in 4 youths with symptoms of mania and depression
  - Agitation
    - Intramuscular Geodon tolerable and effective in 59 youth hospitalized for acute agitation
      - 37% with bipolar disorder
      - 20% with major depression
      - 20% with mood disorder not otherwise specified
      - 20% with psychotic disorder
  - Psychosis, unspecified
    - Psychosocial improvements seen in open-label Geodon treatment (DelBello et al, 2006)
  - Irritability in autism spectrum disorders
    - Malone et al, 2007, 6-wk prospective, open-label study, 12 subjects, 12-18 yo, 20-160 mg/day
      - 75% response rate
      - no significant weight gain
      - QTc increased an avg of 14.7 msec; none > 448 msec
    - McDougle et al, 2002, retrospective case series, 6-24 weeks, 12 subjects, 8-20 yo, 20-120 mg/day
      - 50% response rate
      - no significant weight gain

- Some of the side effects/risks include:
  - sedation (14%)
  - headache
  - dizziness
  - nausea, stomach upset
  - constipation
  - weight loss; not associated with weight gain (but 2 pounds weight gain over 1 year of use in one study)
  - no incidents of tardive dyskinesia as of yet
  - rare: restless muscles, muscle spasms
  - some cases of hyperglycemia and hyperglycemia/diabetes-related risks.
  - ECG changes
    - in 4-5% of patients, mild to moderate prolongation of the QTc interval which increases the risk of an arrythymia names torsades de pointes which increases the risk of dangerous/potentially lethal heart rhythms
    - must follow ECG's
    - the amount of variability in QTc due to Geodon is ½-1/3 that of normal variation in ECG
    - rare occurrence of QTc prolongation over 500 ms but no torsdaes de pointes was seen in over 4500 patients treated with Geodon for 1733 patient-years.
  - recent (2015) allergic reaction:
    - "FDA is warning that the antipsychotic drug ziprasidone (marketed under the brand name, Geodon, and its generics) is associated with a rare but serious skin reaction that can progress to affect other parts of the body. A new warning has been added to the Geodon drug label to describe the serious condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). See the FDA Drug Safety Communication for a Data Summary and additional information. DRESS may start as a rash that

can spread to all parts of the body. It can include fever, swollen lymph nodes, and inflammation of organs such as the liver, kidney, lungs, heart, or pancreas. DRESS also causes a higher-than-normal number of a particular type of white blood cell called eosinophils in the blood. DRESS can lead to death."

        -
    - to date, not associated with congenital anomalies.
- Pharmacodynamics
    - Blocks D2/3, 5HT2a/2c/1d/7 receptors, is an agonist at 5HT1a receptors, and has norepinephrine and serotonin reuptake inhibition (equivalent to that of amitriptyline).
    - Enhances the release of dopamine in the dorsolateral prefrontal cortex.
    - Lower doses are more activating. May be more tolerable if start at 40 mg twice a day and quickly increase to 60-160 mg twice-a-day.
    - Effective dose range 40-160 mg/D; comes in capsules (20 mg, 40 mg, 60 mg, 80 mg)
    - Metabolized by aldehyde oxidase and 3A4 and 1A2
    - Half-life is 5-7 hours; time to peak 3-5 hours (but see below)
    - Levels change dramatically with diet—take it consistently with food or take it consistently without food
        - Food, especially high fat:
            - Peak 4.5 hours
            - Increased peak level
            - Increased systemic exposure
            - Decreased half-life (metabolized quicker)
        - Without food
            - Peak is 3.6 hours
    - Take with food (500 calories or more)

Ziprasidone (Marketed as Geodon and Generics): Drug Safety Communication - Rare But Potentially Fatal Skin Reactions

ISSUE: FDA is warning that the antipsychotic drug ziprasidone (marketed under the brand name, Geodon, and its generics) is associated with a rare but serious skin reaction that can progress to affect other parts of the body. A new warning has been added to the Geodon drug label to describe the serious condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). See the FDA Drug Safety Communication for a Data Summary and additional information.

DRESS may start as a rash that can spread to all parts of the body. It can include fever, swollen lymph nodes, and inflammation of organs such as the liver, kidney, lungs, heart, or pancreas. DRESS also causes a higher-than-normal number of a particular type of white blood cell called eosinophils in the blood. DRESS can lead to death.

BACKGROUND: Ziprasidone is an atypical antipsychotic drug used to treat schizophrenia and bipolar I disorder.

FDA reviewed information from six patients in whom the signs and symptoms of DRESS appeared between 11 and 30 days after ziprasidone treatment was started. None of these patients died (see Data Summary in the Drug Safety Communication). Based on this information, FDA required the manufacturer of Geodon to add a new warning for DRESS to the Warnings and Precautions section of the drug labels for the capsule, oral suspension, and injection formulations.

RECOMMENDATION: Patients who have a fever with a rash and/or swollen lymph glands should seek urgent medical care. Health care professionals should immediately stop treatment with ziprasidone if DRESS is suspected.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

- Complete and submit the report Online: www.fda.gov/MedWatch/report.htm
- Download form or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

Ziprasidone Less Effective for Bipolar Patients With Elevated BMI

By: M. ALEXANDER OTTO, Clinical Psychiatry News Digital Network

05/17/11

Major Finding: Patients with body mass indexes below 28.8 kg/m^2 were about twice as likely to respond to ziprasidone or to go into remission than were their counterparts with higher BMIs.

Data Source: Pooled analysis of data from 267 patients with acute mania.

Disclosures: The study was funded by ziprasidone's maker, Pfizer. Dr. McIntyre is a consultant to and speaker for the company. His coauthors on the paper are both Pfizer employees.

HONOLULU – The antipsychotic ziprasidone does not appear to work as well in patients with bipolar disorder who are either obese or hyperglycemic, according to a study funded by the drug's maker, Pfizer.

Among 267 acutely manic patients on ziprasidone (Geodon) monotherapy for 2-3 weeks, those with body mass indexes below 28.8 kg/m^2 were about twice as likely to respond to ziprasidone or go into remission during treatment than were those with BMIs above 28.8 kg/m^2, which roughly defines the border between being overweight and obese.

Among other findings, 52% of patients below that cut-off responded to treatment; for those above it, the response rate was 37%.

Meanwhile, patients with randomly tested blood glucose levels below 140 mg/dL were more than three times more likely to go into remission and more than five times more likely to respond to treatment than were those with blood glucose levels at or above 140 mg/dL, a level rarely reached in people with normal glucose metabolism.

More than half of patients with randomly tested glucose levels below 140 mg/dL – but only 16% of patients who tested at or above that level – responded to treatment.

Obese and hyperglycemic patients also showed less improvement on Global Assessment of Functioning scores. The findings all were statistically significant.

"Patients with bipolar disorder who have elevated blood glucose and/or elevated BMI do not respond as well to ziprasidone treatment of acute mania" and "may have a lower probability of responding" to antipsychotics in general, said lead author Dr. Roger S. McIntyre, associate professor of psychiatry and pharmacology at the University of Toronto.

Obese patients might need higher-than-typical doses to overcome greater body mass, but that's "not clear at this point. You can increase the drug dose all you want; it may not make any difference," said Dr. McIntyre, who also is head of the mood disorders psychopharmacology unit at University Health Network in Toronto.

In any case, he said the findings offer another good reason to encourage patients to lose

weight, and also argue for using antipsychotics such as ziprasidone that are less likely than others to cause weight gain, since excess weight now appears to diminish the effects of antipsychotics.

The problem with hyperglycemia might be related to insulin dysregulation; there's emerging consensus "that insulin dysregulation manifesting as hyperglycemia might be neurotoxic," Dr. McIntyre noted.

He and his colleagues pooled data from previous Pfizer studies to gauge the effects of BMI on response. "It's intuitive if you have an [elevated] BMI, that the psychopharmacotherapies you are taking would have different distributions and different concentrations, [but] it's almost never been studied," Dr. McIntyre said.

Based on the results, the research community needs to rethink the effect of BMI on response, he said. "It's an important way to stratify data."

The patients in the study were at least moderately manic, with baseline Mania Rating Scale scores of 14 or greater. Remission was defined by a score dropped below 10 by the study's end; response was defined by a greater than 50% score reduction.

A Retrospective Naturalistic Study of Ziprasidone for Irritability in Youth with Autism Spectrum Disorder
Kelli Dominick, Logan K Wink, Christopher J McDougle, Craig A Erickson
Journal of Child and Adolescent Psychopharmacology 2015, 25 (5): 397-401
OBJECTIVE: The purpose of this study was to assess the impact of ziprasidone monoantipsychotic treatment targeting irritability in a naturalistic outpatient autism spectrum disorder (ASD) clinical setting.
METHODS: We examined the use of ziprasidone, predominantly in combination with other psychotropic agents, targeting irritability in 42 youth with ASD in a large ASD-specific treatment database. Mean age at start of treatment, treatment duration, final dose, body mass index (BMI), BMI Z score, and Clinical Global Impressions-Improvement Scale (CGI-I) score at final visit were determined, and changes with treatment were analyzed using paired t tests. Cardiac corrected QT (QTc) interval data were extracted from electrocardiograms when available.
RESULTS: Mean age at start of treatment was 11.8 years. And final mean dose of ziprasidone was 98.7mg/day or 1.7mg/kg/day. Seventeen (40%) participants were considered treatment responders based on the CGI-I. No changes in QTc (although only examined in nine participants), weight, BMI, or other vital signs were noted, with ziprasidone use. The rate of treatment response was less than what has been reported for the two atypical antipsychotics, risperidone and aripiprazole, approved by the Food and Drug Administration (FDA) for the treatment of irritability in autistic disorder. The response rate with ziprasidone may be more consistent with response rates for other atypical antipsychotics, although none of these agents has been studied in larger-scale double-blind, placebo-controlled trials. The lower rate of response to ziprasidone in this open-label trial is likely influenced by the treatment-refractory nature of the population studied.
CONCLUSIONS: The weight neutrality of ziprasidone appears favorable compared with other second generation antipsychotics in this population. The response rate to ziprasidone targeting irritability may be lower than response rates associated with FDA-approved agents for this indication. Overall, ziprasidone use appeared well tolerated in youth with ASD.