

# Patient/Dosing Clarity Document

**ZYPREXA** is indicated for both bipolar mania and schizophrenia. The **acute mania indication** was established in the spring of 2000 with clinical trials in patients with **manic OR mixed episodes**.

## ZYPREXA PCP Patient Types

Below are detailed descriptions of our current patients within the detail piece:

**Donna** (bipolar disorder, current episode mixed) exhibits the 4 core symptoms of mood swings, irritability, sleep disturbances and anxiety, as well as other symptoms including a lack of concentration, mood lability and increased energy, depressed mood, loss of interest, and agitation. It is important to note that all these symptoms are being experienced by Donna **at the same time, hence her mixed presentation**. These symptoms in many cases overlap or may be confused with depression; therefore, the patient may be initially misdiagnosed as a depressed patient. One means of accurately screening this patient for bipolar manic or mixed state is by utilizing the Mood Disorder Questionnaire (MDQ). It would also be very helpful for the physician to ask questions about Donna's psychiatric history, family history, and previous responses to antidepressant medication.

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), published by the American Psychiatric Association, includes descriptions of diagnostic criteria for psychiatric illnesses. These guidelines help physicians correctly and appropriately diagnose patients' illnesses.

Definition of patient in a mixed state: Concurrent major depression and mania for at least 1 week. Specifically, 5 of the 9 depressive symptoms, including at least one of the items marked with an asterisk (\*) -- *\*depressed mood* or *\*anhedonia (loss of interest or ability to experience pleasure)*, *weight loss/gain*, *sleep disturbance*, *psychomotor agitation/retardation*, *fatigue*, *guilt/worthlessness*, *inability to concentrate/indecisiveness*, *suicide ideation* -- must be present in combination with elevated/expansive or irritable mood, and the presence of 3 or more (4 if irritable only) of the following symptoms: *inflated self-esteem/grandiosity*, *decreased need for sleep*, *increased or pressured speech*, *flight of ideas/racing thoughts*, *distractibility*, *increased goal-directed activity*, *risk-taking behavior*. Anxiety and mood swings are often associated symptoms of the mixed episode patient.

**Mark** (bipolar disorder, current episode manic) is also experiencing the 4 core symptoms of irritability, anxiety, disrupted sleep, and mood swings; however, the mood swings and irritability may be more pronounced/severe than with Donna, and are accompanied by pressured speech, distractibility, and some impulsive behaviors. It is likely that Mark is brought to the office by his spouse or family member, since many times he does not feel he has a problem. Additionally, the elevated mood of a manic patient may be described as euphoric (unusually good, cheerful, or high). Although the person's mood may initially have an infectious quality for the uninvolved observer, those who know the person well recognize it as excessive. Additionally, many times this initial elevated mood increases in irritability as the episode continues, prior to the "crash" that the patient will eventually experience.

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## Overlapping of the 4 Core Symptoms

Misdiagnosis and confusion with unipolar depression is common partly due to the fact that the 4 core symptoms of irritability, mood swings, disrupted sleep and anxiety can be symptoms present in both major depression and mania. However, the causes of these symptoms may be different. For example, a depressed patient may suffer from insomnia or hypersomnia, both of which disrupt sleep patterns, whereas a manic patient's disruptions are caused by a decreased need for sleep.

## Dosing Guidelines for ZYPREXA

**Dosing ZYPREXA for a patient like Donna (bipolar mixed):** The dose range for this patient is 5 to 20 mg a day. Based on average dose results of our outpatient mania studies, the target dose for this patient is 10 mg a day. Depending on the customer's comfort level with ZYPREXA, the physician may start at 5 mg. If symptoms have not resolved, increase dose to 10 mg and re-evaluate. Hence: **"Start at 5 and move to 10."**

**Note: The goal of treatment is remission of symptoms and illness. If this is not achieved at the initial starting dose, it may be prudent to move the dose higher incrementally by 5 mg to the upper limit of the dose range (20 mg), monitoring for tolerability and safety.**

**Starting a patient at 10 mg:** Based on the patient presentation, the physician's clinical experience, and the current therapy, the patient may easily and safely be started at 10 mg (hence the point, **no required titration necessary**).

**2.5 mg as a starting dose for a patient like Donna:** The target dose for Donna is 10 mg based on clinical data available, and the initiation of ZYPREXA should generally be no lower than 5 mg. Clinical trial data on 2.5 mg are not available. Starting at 2.5 for a patient like Donna may produce poor efficacy results, and create the perception that the medication does not work.

**Dosing Zyprexa for a patient like Mark (bipolar manic):** The dose range for this patient is 10-20 mg a day. The goal of treatment is remission of symptoms, and if this is not achieved at the initial 10 mg dose, it may be prudent to move the dose higher incrementally by 5 mg to the upper limit of the dose range (20 mg), monitoring for tolerability and safety. Depending on Mark's degree of mania, he may need a higher dose than a patient like Donna.

## Patients Already on Antidepressant

At this time, the ZYPREXA label does not provide guidelines for dosing patients who are taking antidepressants. However, there is no reason to deviate from the above recommendations for a patient like Donna.

The opinion of some thought leaders is that, for patients already taking an antidepressant with some symptom improvement, ZYPREXA should be initiated at 5 mg. The goal of treatment is remission of symptoms, and if this is not achieved at the initial dose, it may be prudent to move the dose higher incrementally by 5 mg to the upper limit of the dose range (20 mg), monitoring for tolerability and safety.

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Some thought leaders also believe that if an antidepressant makes a patient worse or induces symptoms of mania (irritability, for example), the antidepressant should be discontinued, and ZYPREXA should then be initiated at the 10 mg/day dose to prevent any escalating manic symptoms.

Again, it is important to remember that the ZYPREXA label does not include these or any other guidelines for dosing patients who are taking antidepressants.

### **ZYPREXA as a First-line Treatment for Acute Mania Associated with Bipolar Disorder**

As you know, ZYPREXA is a psychotropic indicated for short-term treatment of acute manic episodes associated with Bipolar I Disorder. This indication was based on evidence of efficacy in patients with mixed or manic episodes with or without psychotic features. With this indication, ZYPREXA is an excellent treatment option for a broader range of patients. Other antipsychotic agents are just that: antipsychotics. They are indicated for treatment of schizophrenia but not for bipolar disorder. Because they have not established adequate efficacy in the treatment of mania and depression (to receive an FDA indication for this disorder), other antipsychotics are first-line treatments only for psychotic disorders.

ZYPREXA has demonstrated efficacy and safety in 2 registration and 5 other well-controlled clinical trials in patients with acute mania. Continuing trials aim to further establish efficacy in the treatment of bipolar depression and mania, as well as maintenance treatment. Some physicians use ZYPREXA as a maintenance treatment once it has proven effective in an individual patient. Currently, however, ZYPREXA is not indicated for maintenance treatment, bipolar depression, or treatment-resistant depression.

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