Duration of Untreated Psychosis and Duration of Untreated Illness: *New Vistas*

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ABSTRACT

The duration of untreated illness (DUI), defined as the interval between the onset of a psychiatric disorder and the administration of the first pharmacological treatment, has been increasingly investigated in the last decade as a predictor of outcome across different psychiatric conditions including schizophrenia and psychotic disorders (duration of untreated psychosis), and mood and anxiety disorders. Converging evidence indicates that a prolonged DUI may be viewed as a negative prognostic factor in schizophrenia and increasing data point toward a similar conclusion in mood and anxiety disorders. Through a Medline search, the present article highlights the role of the DUI in this group of psychiatric disorders, focusing on social and psychopathological determinants of the DUI, as well as the clinical consequences related to a longer DUI in terms of outcome. Hypotheses on neurobiological mechanisms underpinning outcome differences in relation to a prolonged DUI are provided and methodological limitations related to the assessment of the DUI in published studies and clinical practice discussed. Finally, given that DUI is supposed to be a potentially modifiable prognostic factor, intervention programs aimed to reduce this variable are briefly considered and discussed.

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FOCUS POINTS

- The duration of untreated illness (DUI) is defined as the interval between the onset of a psychiatric disorder and the administration of the first pharmacological treatment. When referred to a psychotic disorder, the DUI is indicated as duration of untreated psychosis (DUP).
- DUP has been intensively investigated as predictor of outcome with converging evidence indicating that the longer the psychosis remains untreated the worse is the outcome.
- Studies investigating the DUI and the way to reduce it are part of group of interventions which aim to the prevention of mental illness, to early diagnosis and early treatment as well as to the prevention of recurrences and chronicity.

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INTRODUCTION

The importance of an early pharmacological intervention in relation to a pathological onset may be variable according to the specific disorder. Even though it is generally believed that the earlier the administration of an effective treatment the better the outcome, there are pathologies (with the obvious exception of proper medical emergencies) for which the decision to procrastinate pharmacological treatment does not necessarily imply significant consequences in terms of outcome. The fields of early pharmacological interventions and duration of untreated illness (DUI) is, in this perspective, of great clinical interest in psychiatric practice in order to investigate the extent to which delays in beginning psychopharmacological treatments influence the clinical course, morbidity, and mortality of different disorders. Over the last two decades, the DUI (defined as the interval between the onset of a specific psychiatric disorder and the administration of the first pharmacological treatment) has been increasingly investigated as a predictor of clinical outcome and course across different conditions. Most published studies on this topic, however, have been focused on the prognostic role of the DUI in schizophrenia and psychotic disorders (duration of untreated psychosis [DUP]) and, only to a minor extent, in mood and anxiety disorders.

Different reasons encourage the investigation of causes and consequences of the DUI, mainly because it represents a modifiable parameter,[1-4] the reduction of which may positively influence the outcome and long-term course of related mental conditions.[5-7] In addition, a relationship of DUI to outcome may contribute to better elucidate the pathophysiology and the neurobiological modifications occurring with the progression of the illness. Nevertheless, approaching the field of the latency to treatments of mental disorders implies specific considerations which are inherent to the psychiatric field. On one hand, it is well established that psychiatric patients often wait for many years before beginning a proper pharmacological treatment, receiving a correct diagnosis, or even before consulting a clinician. This is certainly due, at least in part, to the secretiveness and social stigma that characterize many mental disorders,[8] as well as to the lack of insight which is characteristic of major psychoses (ie, schizophrenia and psychotic forms of bipolar disorder and major depressive disorder [MDD]).

Furthermore, other clinical factors such as poor premorbid function and mode of onset can influence the DUI.[6] If we focus on major psychoses, for example, large sample studies have recently reported in schizophrenia mean DUP values ranging from 8 weeks[9] to 48 weeks[10] in first-episode patients. These findings may look somehow surprising if we think that core symptoms of schizophrenia consist of hallucinations and delusions. In bipolar disorder mean DUI periods tend to be even longer, ranging from 5–10 years.[11-14] Actually, it is more difficult to provide reliable estimates of mean DUI in unipolar depression (MDD) and anxiety disorders given the greater heterogeneity of depressive and anxious subtypes as well as their reciprocal comorbidity compared to major psychoses.

Such variability in reported mean DUP/DUI values reflects an inherent complexity in providing reliable estimates for latency to treatments of psychiatric disorders, given that local factors within different mental health services influence the access and subsequent detection of many conditions. There are authors who believe that the DUP/DUI are only relevant measures of the early detection function and intervention services.[15] As a matter of fact, "help-seeking" and "referral" components have been explored within the DUP in first episode psychotics. It showed an interesting association between a longer "help-seeking" DUP and a diagnosis of schizophrenia spectrum disorders, an earlier age at onset, and poor-premorbid functioning; whereas a "longer referral" DUP was associated with an earlier age at onset and a first contact made with a non medical professional.[16] Therefore, both factors intimately related to the disorder as well as local care related aspects variably contribute to influence the latency to treatments in psychiatric disorders.

AIM AND METHODS

In order to provide an updated overview in relation to latency to treatments in psychotic, depressive, and anxiety disorders, relevant articles were located by searching MEDLINE. Keywords used included "duration of untreated illness (DUI)" and "duration of untreated psychosis (DUP)", the former and the latter respectively matched with the term anxiety disorders (ie, panic disorder, generalized anxiety disorder,

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obsessive-compulsive disorder, posttraumatic stress disorder, and social anxiety disorder), depressive disorders (ie, major depression, major depressive disorder and bipolar disorder), and schizophrenia/first episode psychosis. Epidemiological data related to mean DUI values in these disorders were identified and potential neurobiological mechanisms underpinning outcome differences in relation to a prolonged DUI considered as well as methodological limitations related to the assessment of the DUI. In addition, given that the DUI is a potentially modifiable prognostic factor, studies assessing intervention programs aimed to reduce this variable were briefly considered and discussed.

REASONS FOR INVESTIGATING THE LATENCY TO TREATMENTS

Investigating the latency to treatments in psychotic, depressive, and anxiety disorders is of great clinical interest for several reasons (Table). First, these conditions are highly prevalent and disabling. Second, they often tend to have onset in adolescence or early adulthood (if not in late childhood) and given that they frequently show a chronic course, they may accompany affected patients for a significant part of their life, influencing social and professional functioning. Finally, these disorders may frequently be undiagnosed/underdiagnosed and untreated/undertreated with dramatic consequences for this unserved/underserved population. In this perspective, the reduction of the DUI is part of a group of interventions which aim to prevent the illness,[17] to diagnose and treat early, as well as to prevent recurrences and chronicity that characterize the majority of disorders.

DUP AND SCHIZOPHRENIA

A preliminary issue related to the investigation of the DUP in this condition is the notion that schizophrenia tends to be a chronic neurodegerative disorder associated with cerebral volume deficits in a complex network of cortical and subcortical regions,[18] with studies showing that anatomical deficits become more severe after the first episode.[19-22] As a consequence, there may be an important therapeutic opportunity to ameliorate the long-term course by minimizing post-diagnosis neurodegenerative progression of the illness through a reduction of the DUP. In this regard, a systematic meta-analysis of 43 studies investigating the relationship between DUP and outcome in first-episode schizophrenics found that a prolonged DUP was associated with lower levels of symptomatic and functional recovery from the first episode and to the severity of negative symptoms, while there was no association between the DUP and the severity of positive and cognitive symptoms or brain morphology abnormalities.[6] The relationship of DUP to outcome was consistent across largely different follow up periods.

TABLE.
Clinical Characteristics of the Majority of Psychotic, Mood, and Anxiety Disorders and Related Interventions Including DUI/DUP

Clinical Characteristics	*Possible Interventions*
High prevalence and disability for affected patients and families	Prevention programs through educational and psychological interventions[82,87] • Universal Prevention: targets whole population group • Selective Prevention: targets subgroups of population on the basis of increased risk • Indicated Prevention: targets high risk persons having minimal symptoms
Common onset in early stages of life and often under-recognition in primary care services	Early recognition and diagnosis in primary care and psychiatric services
Often untreated or undertreated in the early stages of the illnesses due to: • Severity of different symptoms • Secretiveness of illness and social stigma • Cultural and parental attitudes • Access to local mental health services	Reduction of DUP/DUI and administration of pharmacological treatment through: • Early detection systems • Phase-specific treatment • Use of early intervention teams • Development of concerted international programs of early treatment interventions
High risk of recurrence, cyclicity of illness, and chronicity	Continuous therapies divided into specific treatment phases (acute, stabilization, maintenance)[41,42] on the basis of: • Evidence-based medicine treatment guidelines • Illness severity • Patient's clinical story

DUI=duration of untreated illness; DUP=duration of unteated psychosis.

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An 8 year prospective study conducted in first episode patients found that DUP was an independent predictor of prognosis in the medium to long term and that outcomes for psychopathological domains were significantly worse when DUP exceeded 3 months.[23] Subsequent studies confirmed the association between a longer DUP and a worse outcome of negative symptoms[3] as well as a poor influence on cognitive symptoms.[24] In addition, other studies with large samples indicating a worse outcome in schizophrenics with longer DUP in terms of more severe positive, negative, and cognitive symptoms have been recently reported.[9,10,25-27] In two previous studies by our group, an association between a longer DUP and a greater number of suicide attempters and a higher number of recurrences were found.[28,29]

In relation to neurobiological mechanisms, it has been hypothesized that the adverse effects on outcome associated with untreated psychosis may be biologically mediated. One toxicity model suggests that *N*-methyl-D-aspartic (NMDA) acid receptor hypofunctioning may induce psychosis and produce glutamatergically-medicated excitotoxic damage in neurons at the same time.[30,31] For the latter, NMDA receptor hypofunction would result in reduced activation of GABAergic inhibitory neurons, leading to an excitotoxic state.[31] Alternatively, prolonged stress, including stress resulting from untreated psychosis, may activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to greater glucocorticoid secretion which may contribute to neuronal damage.[32] However, the evidence for neurotoxicity stemming from untreated psychosis is still an object of debate and there is as yet little evidence of an effect of long DUP on brain morphology. Furthermore, the possibility of cognitive dysfunction being a neurotoxic consequence of delayed treatment with antipsychotic drugs has been advanced, but this is only a hypothesis given that cognitive impairment may begin prior to the onset of psychosis and is poorly affected by available antipsychotics.

Taken as a whole, hypotheses linking DUP to neurobiological abnormalities responsible for poor outcome in patients with schizophrenia need further investigation. The identification of differential cut-off values for DUP seems crucial in order to detect early neurochemical and neuroanatomical modifications occurring with the progression of the illness.

It is worthwhile to highlight that the term DUP merely refers to psychotic symptoms. In this perspective, negative symptoms (eg, blunted affect, anhedonia, avolition, etc.), which definitely represent a core dimension of schizophrenia but not of other psychoses, may be somehow underestimated and not adequately considered in the onset of the disorder when assessing DUP, particularly in cases of insidious onset with negative symptoms[33] within which DUP may be substantially longer.[34]

DUI AND MOOD DISORDERS

The hypothesis that not only schizophrenia and psychotic spectrum disorders but also depressive disorders tend to show anatomical deficits with the progression of the illness has been recently supported by a large meta-analysis conducted on 64 studies which reported that compared to healthy controls, depressed patients showed large volume reductions in frontal regions, particularly in the anterior cingulate and orbitofrontal cortex with smaller reductions in the prefrontal cortex. In addition, the hippocampus, putamen, and caudate nucleus showed moderate volume reductions.[35] As a consequence, the hypothesis that early effective antidepressant treatments may block and partially reverse the neurobiological modifications occurring with the progression of the untreated depressive episode may be advanced.

As already mentioned, it is more difficult to provide reliable estimates for mean DUI in the field of unipolar depression compared to psychotic disorders. A recent study by our group found a mean DUI of 47.8 months in a sample of 113 depressed patients.[36] However, untreated depressive episodes and disorders may range from a few weeks to several years.

In terms of outcome, previous studies reported that a longer DUI predicted persistence of depressive symptoms and chronicity.[37,38] More recently, two naturalistic studies suggested that a longer DUI may negatively influence the clinical course of MDD, and be associated with earlier age at onset, longer duration of illness, higher number of recurrences, and more frequent comorbidity with axis I disorders with onset later than MDD.[36,39] In this perspective, a recent study conducted on patients with unipolar depression showed that subjects with a long duration of an untreated episode had a longer time to attain a sus-

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tained response, indicating that antidepressant response is faster when the DUI is reduced.[40]

With respect to the investigation of the DUI in bipolar disorder, a preliminary methodological specification needs to be considered, given that some authors do not compute the DUI in relation to the administration of the first antidepressant but to the first mood-stabilizer. These currently include not only lithium and anticonvulsants but also atypical antipsychotics, and are considered the gold standard in the pharmacological treatment of bipolar disorder by major international treatment guidelines.[41,42] Nevertheless, bipolar disorder may frequently have a depressive onset and most patients may be treated with antidepressants in these conditions,[43] underscoring how clinical diagnosis of bipolar disorder is by far the most important prerequisite for adequate treatment and only subsequent follow up can often really differentiate bipolar from unipolar depression. This makes the assessment of the DUI more complicated.[13] One study reported that the majority of bipolar II and many bipolar I patients had been previously undiagnosed, and the remainder had a median 7.8 years delay from first episode to diagnosis. This finding confirms how, even in psychiatric settings, bipolar disorders may be undetected or recognized only after a long delay.[12]

With respect to possible consequences of a longer DUI in terms of treatment response and long-term outcome, a study by Goldberg and colleagues[11] reported that a delayed administration of mood stabilizer treatment in bipolar disorder was related to an increased risk of suicidal behavior, poorer social adjustment, and more frequent hospitalizations. In addition, a recent study reported that an early age at onset of bipolar disorder was associated with more severe clinical features and delayed treatment seeking.[44] More recently, a naturalistic study[45] conducted on a sample of 320 bipolar subjects, reported a mean DUI of 8.7 years and found that the group with a longer DUI showed a higher frequency of suicidal attempts, a higher number of suicidal attempters, and a longer duration of illness compared to patients with a shorter DUI.

With respect to the possible influence of the DUI on treatment response in bipolar patients, some studies found no difference between a short and a long latency to treatment on the final outcome of long-term treatments (lithium in particular).[46,47] In both bipolar and unipolar affective disorders, the existence of subgroups of patients with chronic illness and poorer outcome independent of treatment needs to be taken into account. Individual poor response to treatment and negative long term outcome may also be due to specific genetic charateristics (eg, polymorphic variants of serotonin transporter) and reducing the latency to treatments in these patients may produce limited effects.

Neurobiological hypotheses linking a longer DUI with negative outcome in mood disorders (particularly in depressive phases) have been put forward in light of a decreased neuroplasticity reported in depressed patients.[48,49] Structural and functional changes have been identified in depressed subjects in brain regions important for emotional regulation, including the hippocampus,[50,51] amygdala,[52,53] anterior cingulate,[54] and prefrontal cortex,[55,56] leading many researchers to hypothesize major depression as not only related to dysfunctioning of central nervous neurotransmitter systems, but also to impairments of neural plasticity.[57,58] Several studies have shown that impaired neuroplasticity can be reversed or even prevented by certain antidepressants.[59-63] In this perspective, it may be speculated that keeping a major depressive episode untreated may lead to impaired neuroplasticity,[64,65] which would be restored by the administration of an effective treatment.

DUI AND ANXIETY DISORDERS

The role of the DUI in anxiety disorders has been less investigated in comparison to psychotic and mood disorders. Nevertheless, anxiety disorders are very prevalent and burdensome conditions with frequent early onset. There has been increasing interest in preventing these illnesses, in particular by means of cognitive-behavioral interventions,[66] with great efforts in the field of posttraumatic stress disorder, with mixed results.[67-69] In this perspective, it needs to be remembered that interventions to reduce DUI in patients with significant risk factors or with soft symptoms may be seen as a form of selective or indicated prevention.

To date, studies specifically investigating the role of the DUI in anxiety disorders have been conducted in panic disorder, generalized anxiety disorder (GAD) and obsessive-compulsive disorder (OCD). Indeed, a study examining the cause and length of delays in reaching primary care and specialist services amongst patients

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with anxiety disorders indicated that patients with social phobia reported longer delays in reaching specialist care (>9 years) compared with patients with GAD or panic disorder.[70]

In a naturalistic study exploring the impact of the DUI on the outcome and treatment response of 96 outpatients with panic disorder who after receiving an 8 week antidepressant treatment were subdivided into two subgroups on the basis of a DUI <1 or >1 year, no differences with respect to treatment outcome were found. However, patients with a longer DUI had a higher frequency of comorbid depression with onset later than panic disorder, suggesting that longer DUI may be a predictor of the development of comorbid depression in panic disorder.[71]

In the field of GAD, a study analyzing the effect size of pharmacological treatments[72] found that in children and adolescents with GAD the effect size of selective serotonin reuptake inhibitors (SSRIs) was statistically significantly higher compared to adults with GAD. Of note, the authors hypothesized that this difference might be explained by a shorter duration of the illness (likely shorter DUI) in this population compared with the adult sample.

A subsequent study investigated the impact of the DUI on treatment response and clinical course in a sample of 100 subjects with GAD. Patients were treated with SSRIs or venlafaxine for 8 weeks in open conditions and then divided into two groups according to a DUI <1 or >1 year. Results showed that a shorter DUI computed with respect to the first antidepressant treatment (DUI-AD) was associated with a higher improvement after the pharmacologic treatment. In addition, patients with a longer DUI showed an earlier age at onset, a longer duration of illness, and a higher rate of comorbid psychiatric disorders with onset later than GAD. This suggests that a shorter DUI-AD may determine a better response to pharmacologic treatment in patients with GAD, and in general, a longer DUI may be associated to a worse clinical course.[73]

More recently, a naturalistic study evaluated the influence of the DUI on treatment response and remission in a sample of 66 patients with OCD treated with open pharmacological treatments for 12 weeks. It showed that a DUI <2 years was predictive of a higher rate of treatment response.[74]

Taken as a whole, reported studies do not allow any definitive conclusion to be drawn with regard to the relationship between the DUI and the clinical course and outcome in anxiety disorders, but should encourage further investigation. To date, neurobiological hypotheses relating a longer DUI with a worse outcome in terms of modifications of key brain structures in the generation of anxiety symptoms (eg, amygdala, hippocampus) with the progression of untreated anxiety disorders are of speculative nature. Nevertheless, psychosocial considerations, which may be valid not only in the field of anxiety disorders, have been put forward in order to explain possible consequences of a worse outcome associated to a longer DUI.[36,74] It can be hypothesized that chronic untreated anxiety might cause a higher number of sociodemographic consequences, such as greater medical burden, unpartnered or unemployed conditions, and/or socioeconomic disadvantages that would reduce the quality of life and negatively influence the long term course of the illness.

INTERVENTIONS TO REDUCE DUI/DUP

Given that the relationship between a longer DUI and a worse outcome has been particularly stressed in the field of schizophrenia and first episode psychosis, it is not surprising that the majority of interventions to reduce the latency to treatments have been implemented in this specific area. Early intervention has two main objectives: to prevent the onset of schizophrenia in people with prodromal symptoms and to provide effective treatment to schizophrenics in the early stages of the disorder, with the goal of reducing the severity of the illness.[75] In addition, there are at least three elements that distinguish early intervention in schizophrenia from standard care: early detection, phase-specific treatment, and the use of early intervention teams. It is worthwhile to highlight that early intervention services are now widespread in America, Europe, and Australia. Nevertheless, it is currently unclear how far the efficacy of these interventions is underpinned by evidence of clinical studies.

A systematic review performed by the Cochrane group, with the aim to evaluate the effects of early detection, phase-specific treatments and specialized early intervention teams in the treatment of people with prodromal symptoms or first episode psychosis, reported interesting results. A first important finding was that none of the reviewed studies adopted similar interventions and, therefore, they were analysed separately. Phase specific interventions were significantly different in terms of type of treatment (eg, people receiving low dose antipsychotics with or without psychotherapy) and

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they could be implemented with the presence of specialized teams. Taken as a whole, study results did not allow authors to draw any definitive conclusion, stressing how the significant international interest in early intervention still requires a concerted international program of research to address key unanswered questions and the use of a standardized model of interventions.[75,76]

More recently, a group analyzed the effects of reducing DUP through a comprehensive early detection (ED) system, based on public information campaigns and low-threshold-psychosis detecting teams, in a large sample of psychotic patients coming to their first pharmacological treatment compared to patients who could not benefit from the ED system. Of great clinical interest, the authors found that patients from the ED area had a significantly lower DUP, better clinical status, and milder negative symptoms at the start of treatment. In addition, after 2 years of follow up, once the pharmacological treatment had been initiated, there was a statistically significant difference in the positive, negative, cognitive, and depressive components in favor of the ED group.[3] In another study, after finding that a combination of easy access detection teams and massive information campaign reduced DUP (from 16 to 5 weeks) in first-episode schizophrenia, the authors reported an increase in DUP and baseline symptoms when these interventions were stopped.[77]

Literature studies investigating possible interventions to reduce the DUI in depressive and anxiety disorders are substantially lacking. In the field of mood disorders, however, there has been great attention in terms of prevention programs in different populations. In particular, prevention programs subdivided into universal, selective, and indicated prevention according to the presence of risk factors/soft symptoms, and represented by educational and psychological treatments, have been reviewed and were the object of meta-analyses with small but significant effect-sizes, particularly in the short-term.[17,78-84] Nevertheless, to date and to authors' knowledge, interventions specifically aimed to reduce DUI in these disorders have not been published and should be encouraged.

DISCUSSION

There are some methodological issues that need to be considered in relation to the investigation of DUI/DUP. The first is related to the lack of a valid definition of long- versus short-DUI in the different groups of disorders. Some authors consider the DUI as a categorical variable (eg, <1 or > 1 or 2 years) in relation to outcome whereas others consider it a continuous variable. Most studies in the field investigate the DUI focusing on first episode patients identified at first hospitalization excluding patients with milder symptoms who are identified and treated in the community. Other studies analyze the DUI retrospectively, investigating its relation to the subsequent course of the illness and/or to the outcome of an index episode (ie, duration of untreated episode). When analyzed retrospectively, however, a precise detection of the initial untreated illness may not be obtained, being subject to recall bias. Understandably, what patients identify as the onset of an episode may not necessarily correspond to what a clinician would identify as the proper onset of a specific disorder. In any case, demarcation points which validly identify long-DUI patients need to be factored into drug trial design in the future.

Other specific unanswered questions concern the presence of possible differences between first episode patients who will develop schizophrenia versus other non-schizophrenic psychotic patients (eg, those with substance induced psychosis) in relation to DUI and outcome. For any specific group of disorders, it should be investigated which symptoms and clinical aspects seem to be more influenced by a longer DUP (eg, cognitive, negative, or positive dimensions in the field of schizophrenia, as well as the development of comorbidity, treatment response, recurrence, and other long term variables in mood and anxiety disorders). The answer to this last question should actually rely on the identification of valid neurobiological correlates of DUI/DUP and on the definition of the period of time after which these eventually become significant. In addition, it should be investigated whether the administration of different forms of psychotherapy as first treatment within the DUI shows any difference in comparison with pharmacological therapies in terms of outcome. This is due to psychotherapy interventions already largely used in prevention programs[17] and since they are considered first line treatments in many depressive and anxiety disorders. Finally, other psychiatric fields such as substance use disorders, eating disorders, and some personality disorders (which, like psychotic, depressive, and anxiety disorders often present early onset, high disability levels, and chronic course) should be investigated in relation to the DUI as already done in terms of prevention programs.[85,86]

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CONCLUSION

The current body of evidence in the field of the DUI indicates this parameter as a predictor of outcome in particular in first episode psychoses and interventions to reduce DUP are already used as an object of research in the area. Further investigation is required in order to better define short versus long DUP, to understand neurobiological correlates of a longer DUP, as well as which groups of symptoms and other clinical aspects (eg, treatment response, number of recurrences) are more influenced by a longer DUP. The field of depressive and anxiety disorders has been less investigated with respect to the DUI and possible interventions to reduce it. This may seem difficult to justify given that these conditions have an even higher impact on patients and society compared to major psychoses in terms of prevalence, burden, and mental health expenses. Initial studies in these conditions would suggest that a longer DUI is associated to worse outcome. These associations, however, are frequently detected in a complex context of multiple associations where other clinical elements and confounding factors are often present. This makes it difficult to understand what actually came first and whether a specific correlation is part of a causal process or rather the result of a random association.

Even though in a half century of psychopharmacological history tremendous advances have been achieved with a substantial improvement in the prognosis and quality of life of psychiatric patients and families, several conditions still remain poorly treated and/or do not adequately respond to standard medications. In this perspective, we think that improving early detection and treatment along with the development of safer and more effective therapies will undoubtedly ameliorate the prognosis and burden of many psychiatric disorders. ***CNS***

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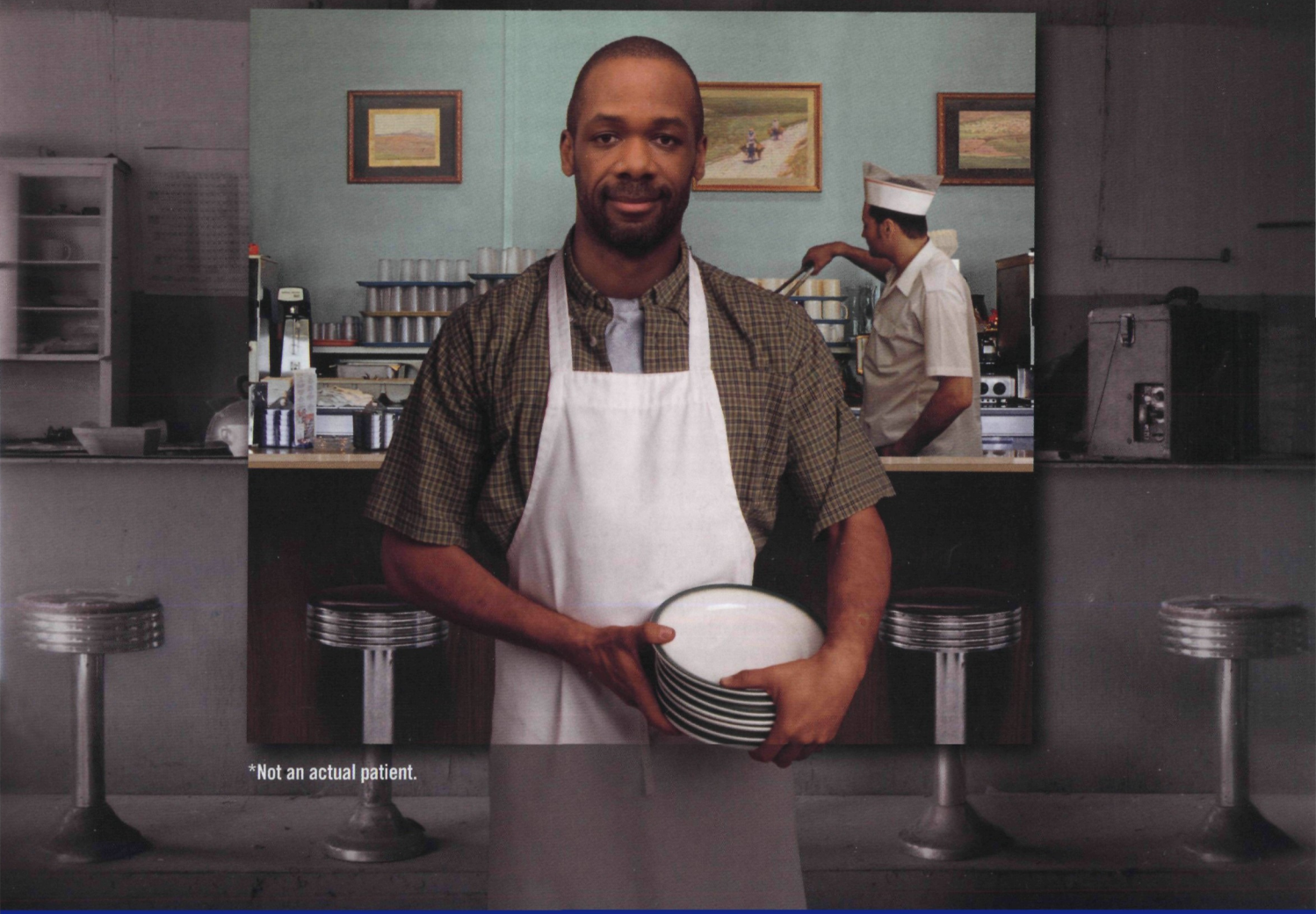
SEE ME FOR WHO I CAN BE

GREG, 35*
Diner Worker
Diagnosis: Schizophrenia



*Not an actual patient.

GEODON is indicated for schizophrenia. For full symptoms and diagnostic criteria, see the *DSM-IV-TR*® (2000).

Important Safety Information

Elderly patients with dementia-related psychosis treated with 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 certain other QT-prolonging drugs. GEODON has a greater capacity to prolong the QT_c 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. Hypokalemia may increase the risk of QT prolongation and arrhythmia.

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 short-term schizophrenia trials, the most commonly observed adverse events associated with GEODON at an incidence of ≥5% and at least twice the rate of placebo were somnolence and respiratory tract infection.

Please see brief summary of prescribing information on adjacent page.

For more information, please visit www.pfizerpro.com/GEODON

GEODON®
(ziprasidone HCl) **Capsules**

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GEODON® (ziprasidone HCl) Capsules

GEODON® (ziprasidone mesylate) injection for intramuscular use

BRIEF SUMMARY: See package insert for full prescribing information.

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS—Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death 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 (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. GEODON (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis (see WARNINGS).

INDICATIONS

GEODON is indicated for the treatment of schizophrenia, as monotherapy for the acute treatment of bipolar manic or mixed episodes, and as an adjunct to lithium or valproate for the maintenance treatment of bipolar disorder. GEODON intramuscular is indicated for acute agitation in schizophrenic patients.

DOSAGE AND ADMINISTRATION

Schizophrenia GEODON Capsules should be administered at an initial daily dose of 20 mg twice daily with food. In some patients, daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg twice daily. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state is achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, patients should ordinarily be observed for improvement for several weeks before upward dosage adjustment. Efficacy in schizophrenia was demonstrated in a dose range of 20 mg to 100 mg twice daily in short-term, placebo-controlled clinical trials. There were trends toward dose response within the range of 20 mg to 80 mg twice daily, but results were not consistent. An increase to a dose greater than 80 mg twice daily is not generally recommended. The safety of doses above 100 mg twice daily has not been systematically evaluated in clinical trials. *Maintenance Treatment*—While there is no body of evidence available to answer the question of how long a patient treated with ziprasidone should remain on it, a maintenance study in patients who had been symptomatically stable and then randomized to continue ziprasidone or switch to placebo demonstrated a delay in time to relapse for patients receiving GEODON. No additional benefit was demonstrated for doses above 20 mg twice daily. Patients should be periodically reassessed to determine the need for maintenance treatment. **Bipolar I Disorder** *Acute Treatment of Manic or Mixed Episodes*—Dose Selection: Oral ziprasidone should be administered at an initial daily dose of 40 mg twice daily with food. The dose may then be increased to 60 mg or 80 mg twice daily on the second day of treatment and subsequently adjusted on the basis of tolerance and efficacy within the range 40 mg to 80 mg twice daily. In the flexible-dose clinical trials, the mean daily dose administered was approximately 120 mg. *Maintenance Treatment* (as an adjunct to lithium or valproate)—Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40 mg to 80 mg twice daily with food. Patients should be periodically reassessed to determine the need for maintenance treatment. **Acute Treatment of Agitation in Schizophrenia** *Intramuscular Dosing*—The recommended dose is 10 mg to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every four hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than three consecutive days has not been studied. If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as possible. Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended. Ziprasidone intramuscular is intended for intramuscular use only and should not be administered intravenously. Intramuscular Preparation for Administration GEODON for Injection (ziprasidone mesylate) should only be administered by intramuscular injection and should not be administered intravenously. Single-dose vials require reconstitution prior to administration. Add 1.2 mL of Sterile Water for Injection to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20 mg ziprasidone. To administer a 10 mg dose, draw up 0.5 mL of the reconstituted solution. To administer a 20 mg dose, draw up 1.0 mL of the reconstituted solution. Any unused portion should be discarded. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. **Dosing in Special Populations** *Oral:* Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment. GEODON is not approved for use in children or adolescents. *Intramuscular:* Ziprasidone intramuscular has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function. Dosing adjustments are not required on the basis of gender or race.

CONTRAINDICATIONS

QT Prolongation Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus. Ziprasidone is also contraindicated with other drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning [see **WARNINGS**]. Ziprasidone is contraindicated in individuals with a known hypersensitivity to the product.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. GEODON is not approved for the treatment of dementia-related psychosis (see BOXED WARNING).

QT Prolongation and Risk of Sudden Death Ziprasidone use should be avoided in combination with other drugs that are known to prolong the QT_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see **CONTRAINDICATIONS**).

QT Prolongation in Clinical Trials A study directly comparing the QT/QT_c prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for ziprasidone ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of ziprasidone on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole

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200 mg twice daily). In placebo-controlled trials, oral ziprasidone increased the QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) patients who received GEODON and 1/440 (0.23%) patients who received placebo revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. **QT Prolongation and Torsade De Pointes** Some drugs that prolong the QT/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c prolongations may also increase risk, or increase it in susceptible individuals. Although torsade de pointes has not been observed in association with the use of ziprasidone in premarketing studies and experience is too limited to rule out an increased risk, there have been rare post-marketing reports (in the presence of multiple confounding factors) (see **ADVERSE REACTIONS**). A study evaluating the QT/QT_c prolonging effect of intramuscular ziprasidone, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of ziprasidone (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular ziprasidone is 50% higher than the recommended therapeutic dose. The mean change in QT_c from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT_c from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patients had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, ziprasidone's larger prolongation of QT_c length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval. **Electrolyte Disturbances May Increase The Risk of QT Prolongation** It is recommended that patients being considered for ziprasidone treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, ziprasidone should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Ziprasidone should be discontinued in patients who are found to have persistent QT_c measurements >500 msec. **Neuroleptic Malignant Syndrome (NMS)** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. **Tardive Dyskinesia** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. If signs and symptoms of tardive dyskinesia appear in a patient on ziprasidone, drug discontinuation should be considered. **Hyperglycemia and Diabetes Mellitus** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical anti-psychotics. 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. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia.

PRECAUTIONS

Leukopenia, Neutropenia, and Agranulocytosis In clinical trial and postmarketing experience, events of leukopenia/neutropenia and agranulocytosis (including fatal cases) have been reported temporally related to antipsychotic agents. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue GEODON at the first sign of decline in WBC in the absence of other causative factors. Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm3) should discontinue GEODON and have their WBC followed until recovery. **Rash** In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these reactions were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued. **Orthostatic Hypotension** Ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of the patients treated with ziprasidone. Ziprasidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). **Seizures** In clinical trials, seizures occurred in 0.4% of patients treated with ziprasidone. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. As with other antipsychotic drugs, ziprasidone should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. **Dysphagia** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and ziprasidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see **BOXED WARNING** and **Increased Mortality in Elderly Patients with Dementia-Related Psychosis in WARNINGS**). **Hyperprolactinemia** As with other drugs that antagonize dopamine D2 receptors, ziprasidone elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic

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administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Potential for Cognitive and Motor Impairment** Somnolence was a commonly reported adverse reaction in patients treated with ziprasidone. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of patients on ziprasidone compared to 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since ziprasidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that ziprasidone therapy does not affect them adversely. **Priapism** One case of priapism was reported in the premarketing database. **Body Temperature Regulation** Although not reported with ziprasidone in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. **Suicide** The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ziprasidone should be written for the smallest quantity of capsules consistent with good patient management in order to reduce overdose risk. **Patients With Concomitant Illnesses** Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses is limited. Ziprasidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT_c prolongation and orthostatic hypotension with ziprasidone, caution should be observed in cardiac patients (see **QT Prolongation and Risk of Sudden Death** in **WARNINGS** and **Orthostatic Hypotension in PRECAUTIONS**). **Information for Patients** To assure safe and effective use of GEODON, the information and instructions provided in the patient information should be discussed with patients. **Laboratory Tests** Patients being considered for ziprasidone treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be replaced before proceeding with treatment. Patients who are started on diuretics during Ziprasidone therapy need periodic monitoring of serum potassium and magnesium. Discontinue ziprasidone in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**).

DRUG INTERACTIONS

(1) Ziprasidone should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents. (4) Ziprasidone may antagonize the effects of levodopa and dopamine agonists. **Effect of Other Drugs on Ziprasidone** *Carbamazepine*, 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of ziprasidone. Ketoconazole, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and Cmax of ziprasidone by about 35-40%. *Cimetidine*, 800 mg qd for 2 days, did not affect ziprasidone pharmacokinetics. Co-administration of 30 mL of Maalox® did not affect ziprasidone pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. **Effect of Ziprasidone on Other Drugs** *In vitro* studies revealed little potential for ziprasidone to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and little potential for drug interactions with ziprasidone due to displacement. Ziprasidone 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. *In vivo* studies have revealed no effect of ziprasidone on the pharmacokinetics of estrogen or progesterone components. Ziprasidone 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the metabolism of *dextromethorphan*, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility Lifetime carcinogenicity studies were conducted with ziprasidone in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice, there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. Ziprasidone had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see **Hyperprolactinemia** in **PRECAUTIONS**). *Mutagenesis:* There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes. *Impairment of Fertility:* Ziprasidone increase time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m2 basis). The fertility of female rats was reduced.

USE IN SPECIFIC POPULATIONS

Pregnancy *Pregnancy Category C:* There are no adequate and well-controlled studies in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** The effect of ziprasidone on labor and delivery in humans is unknown. **Nursing Mothers** It is not known whether ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breastfeed. **Pediatric Use** The safety and effectiveness of ziprasidone in pediatric patients have not been established. **Geriatric Use** Of the total number of subjects in clinical studies of ziprasidone, 2.4 percent were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients.

ADVERSE REACTIONS

Adverse Findings Observed in Short-term, Placebo-Controlled Trials The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. **Adverse Events Associated With Discontinuation** *Schizophrenia:* Approximately 4.1% (29/702) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 2.2% (6/273) on placebo. The most common reaction associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients (see **PRECAUTIONS**). *Bipolar Mania:* Approximately 6.5% (18/279) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 3.7% (5/136) on placebo. The most common reactions associated with dropout in the ziprasidone-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these reactions among ziprasidone patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. **Adverse Events at an Incidence of ≥5% and at Least Twice the Rate of Placebo** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that

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occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: *Body as a Whole*—asthenia, accidental injury, chest pain. *Cardiovascular*—tachycardia. *Digestive*—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. *Nervous*—extrapyramidal symptoms, somnolence, akathisia, dizziness. *Respiratory*—respiratory tract infection, rhinitis, cough increased. *Skin and Appendages*—rash, fungal dermatitis. *Special Senses*—abnormal vision. Bipolar Mania: *Body as a Whole*—headache, asthenia, accidental injury. *Cardiovascular*—hypertension. *Digestive*—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. *Musculoskeletal*—myalgia. *Nervous*—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. *Respiratory*—pharyngitis, dyspnea. *Skin and Appendages*—fungal dermatitis. *Special Senses*—abnormal vision. **Dose Dependency** An analysis for dose response in the schizophrenia 4-study pool revealed an apparent relation of adverse reaction to dose for the following reactions: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. **Extrapyramidal Symptoms (EPS)** The incidence of reported EPS for ziprasidone patients in the short-term, placebo-controlled schizophrenia trials was 14% vs. 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo. **Dystonia** Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. Elevated risk of acute dystonia is observed in males and younger age groups. **Vital Sign Changes** Ziprasidone is associated with orthostatic hypotension (see **PRECAUTIONS**). **Weight Gain** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. Weight gain was reported as an adverse event in 0.4% of both ziprasidone and placebo patients. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain (>7% of body weight) in patients with low BMI (<23) compared to normal (23-27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a "low" baseline BMI, no mean change for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients who entered the program with a "high" BMI. **ECG Changes** Ziprasidone is associated with an increase in the QT_c interval (see **WARNINGS**). In the schizophrenia trials, ziprasidone was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. **Other Adverse Events Observed During the Premarketing Evaluation of Ziprasidone in Schizophrenia** Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare adverse events are those occurring in fewer than 1/1000 patients. *Body as a Whole*—Frequent: abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. *Cardiovascular System*—Frequent: tachycardia, hypertension, postural hypotension. Infrequent: bradycardia, angina pectoris, atrial fibrillation. Rare: first degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. *Digestive System*—Frequent: anorexia, vomiting. Infrequent rectal hemorrhage, dysphagia, tongue edema. Rare: gum hemorrhage, jaundice, fecal impaction, gamma glutamyl trans-peptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. *Endocrine*—Rare: hypothyroidism, hyperthyroidism, thyroiditis. *Hemic and Lymphatic System*—Infrequent: anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy. Rare: thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. *Metabolic and Nutritional Disorders*—Infrequent: thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia. Rare: BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. *Musculoskeletal System*—Frequent: myalgia. Infrequent: tenosynovitis. Rare: myopathy. *Nervous System*—Frequent: agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy. Infrequent: paralysis. Rare: myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. *Respiratory System*—Frequent: dyspnea Infrequent pneumonia, epistaxis. Rare: hemoptysis, laryngismus. *Skin and Appendages*—Infrequent: maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. *Special Senses*—Frequent: fungal dermatitis. Infrequent: conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia. Rare: eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. *Urogenital System*—Infrequent: impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria. Rare: gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Findings Observed in Trials of Intramuscular Ziprasidone** In these studies, the most commonly observed adverse reactions associated with the use of intramuscular ziprasidone (≥5%) and observed at a rate on intramuscular ziprasidone (in the higher dose groups) at least twice that of the lowest intramuscular ziprasidone group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence of ≥1% in Short-Term Fixed-Dose Intramuscular Trials** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of patients during acute therapy with intramuscular ziprasidone: *Body as a Whole*—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. *Cardiovascular*—postural hypotension, hypertension, bradycardia, vasodilation. *Digestive*—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. *Nervous*—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. *Respiratory*—rhinitis. *Skin and Appendages*—furunculosis, sweating. *Urogenital*—dysmenorrhea, priapism. **Other Events Observed During Post-marketing Use** Adverse reaction reports not listed above that have been received since market introduction include rare occurrences of the following—*Cardiac Disorders:* Tachycardia, torsade de pointes (in the presence of multiple confounding factors), (see **WARNINGS**); *Digestive System Disorders:* Swollen Tongue; *Reproductive System and Breast Disorders:* Galactorrhea, priapism; *Nervous System Disorders:* Facial Droop, neuroleptic malignant syndrome, serotonin syndrome (alone or in combination with serotonergic medicinal products), tardive dyskinesia; *Psychiatric Disorders:* Insomnia, mania/hypomania; *Skin and subcutaneous Tissue Disorders:* Allergic reaction (such as allergic dermatitis, angioedema, orofacial edema, urticaria), rash; *Urogenital System Disorders:* Enuresis, urinary incontinence; *Vascular Disorders:* Postural hypotension, syncope.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class Ziprasidone is not a controlled substance.

OVERDOSAGE

In premarketing trials in over 5400 patients, accidental or intentional overdosage of oral ziprasidone was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (200/95).

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