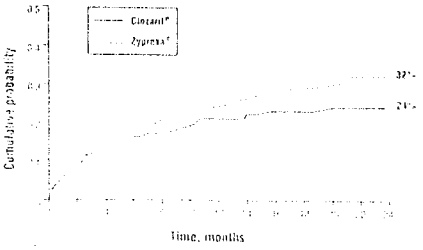
Kaplan-Meier Estimates of Cumulative Probability of a Significant Suicide Attempt or Hospitalization to Prevent Suicide.



ments for schizophrenia, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. *(See WARNINGS.)*

The effectiveness of CLOZARIL in a treatment-resistant schizophrenic population was demonstrated in a 6-week study comparing CLOZARIL and chlorpromazine. Patients meeting DSM-III criteria for schizophrenia and having a mean BPRS total score of 61 were demonstrated to be treatment resistant by history and by open, prospective treatment with haloperidol before entering into the double-blind phase of the study. The superiority of CLOZARIL to chlorpromazine was documented in statistical analyses employing both categorical and continuous measures of treatment effect.

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated.

Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorders

CLOZARIL is indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state. Suicidal behavior refers to actions by a patient that puts him/herself at risk for death.

The effectiveness of CLOZARIL in reducing the risk of recurrent suicidal behavior was demonstrated over a 2-year treatment period in the InterSePT Trial *(see Clinical Trial Data under CLINICAL PHARMACOLOGY)*. Therefore, CLOZARIL treatment to reduce the risk of suicidal behavior should be continued for at least 2 years *(see DOSAGE AND ADMINISTRATION)*.

The prescriber should be aware that a majority of patients in both treatment groups in InterSePT received other treatments as well to reduce suicide risk, such as antidepressants and other medications, hospitalization, and/or psychotherapy. The contributions of these additional measures are unknown.

CONTRAINDICATIONS

CLOZARIL® (clozapine) is contraindicated in patients with a previous hypersensitivity to clozapine or any other component of this drug, in patients with myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, or a history of CLOZARIL-induced agranulocytosis or severe granulocytopenia. As with more typical antipsychotic drugs, CLOZARIL is contraindicated in severe central nervous system depression or comatose states from any cause.

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WARNINGS

General

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS TREATED WITH ATYPICAL ANTIPSYCHOTIC DRUGS ARE AT AN INCREASED RISK OF DEATH COMPARED TO PLACEBO. CLOZARIL® (clozapine) IS NOT APPROVED FOR THE TREATMENT OF PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS *(SEE BOXED WARNING)*.

AGRANULOCYTOSIS

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT *(SEE FOLLOWING)*, CLOZARIL® (clozapine) SHOULD BE RESERVED FOR USE IN THE FOLLOWING INDICATIONS: 1) FOR TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD DRUG TREATMENT FOR SCHIZOPHRENIA, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL® (clozapine); IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST 2 TRIALS, EACH WITH A DIFFERENT STANDARD DRUG PRODUCT FOR SCHIZOPHRENIA, AT AN ADEQUATE DOSE, AND FOR [illegible] DURATION OF [illegible] SUICIDAL BEHAVIOR IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER WHO ARE JUDGED TO BE AT RISK OF RE-EXPERIENCING SUICIDAL BEHAVIOR. CLOZARIL® (clozapine) IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM THAT ENSURES MONITORING OF WHITE BLOOD CELL (WBC) COUNT AND ABSOLUTE NEUTROPHIL COUNT (ANC) ACCORDING TO THE SCHEDULE DESCRIBED BELOW PRIOR TO DELIVERY OF THE NEXT SUPPLY OF MEDICATION.

AS DESCRIBED IN TABLE 1, PATIENTS WHO ARE BEING TREATED WITH CLOZARIL® (clozapine) MUST HAVE A BASELINE WBC COUNT AND ANC BEFORE INITIATION OF TREATMENT, AND A WBC COUNT AND ANC EVERY WEEK FOR THE FIRST 6 MONTHS. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ANC (WBC ≥3500/mm³ and ANC ≥2000/mm³) HAVE BEEN MAINTAINED DURING THE FIRST 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNTS AND ANC CAN BE MONITORED EVERY 2 WEEKS FOR THE NEXT 6 MONTHS. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ANC (WBC≥3500/mm³ and ANC ≥2000/mm³) HAVE BEEN MAINTAINED DURING THE SECOND 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNT AND ANC CAN BE MONITORED EVERY 4 WEEKS.

WHEN TREATMENT WITH CLOZARIL® (clozapine) IS DISCONTINUED (REGARDLESS OF THE REASON), WBC COUNT AND ANC MUST BE MONITORED WEEKLY FOR AT LEAST 4 WEEKS FROM THE DAY OF DISCONTINUATION OR UNTIL WBC ≥3500/mm³ AND ANC ≥2000/mm³.

Agranulocytosis

Background

Agranulocytosis, defined as an ANC of less than 500/mm³, has been estimated to occur in association with CLOZARIL® (clozapine) use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1,743 patients exposed to CLOZARIL® (clozapine) during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. Agranulocytosis could prove fatal if not detected early and therapy interrupted. Of the 149 cases of agranulocytosis reported worldwide in association with CLOZARIL® (clozapine) use as of December 31, 1989, 32% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL® (clozapine)-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. In the U.S., under a weekly WBC count monitoring system with CLOZARIL® (clozapine), there have been 585 cases of agranulocytosis as of August 21, 1997; 19 were fatal (3%). During this period 150,409 patients received CLOZARIL® (clozapine). A hematologic risk analysis was conducted based upon the available information in the Clozaril® National Registry (CNR) for U.S. patients. Based upon a cut-off date of April 30, 1995, the incidence rates of agranulocytosis based upon a weekly monitoring schedule, rose steeply during the first two months of therapy, peaking in the third month. Among CLOZARIL® (clozapine) patients who continued the drug beyond the third month, the weekly incidence of agranulocytosis fell to a substantial degree. After 6 months, the weekly incidence of agranulocytosis declines still further, however, it never reaches zero. It should be noted that any type of reduction in the frequency of monitoring WBC counts may result in an increased incidence of agranulocytosis.

Risk Factors

Experience from clinical development, as well as from examples in the medical literature, suggest that patients who have developed agranulocytosis during CLOZARIL® (clozapine) therapy are at increased risk of subsequent episodes of agranulocytosis. Analysis of WBC count data from the Clozaril® National Registry also suggests that patients who have an initial episode of moderate leukopenia (3000/mm³ >WBC ≥2000/mm³) are at an increased risk of subsequent episodes of agranulocytosis. Except for bone marrow suppression during initial CLOZARIL® (clozapine) therapy, there are no other established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL® (clozapine) use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during domestic development of CLOZARIL® (clozapine). Most of the U.S. cases of agranulocytosis occurred within 4-10 weeks of exposure but neither dose nor duration is a reliable predictor of this problem. Agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL® (clozapine), although this has not been definitely demonstrated.

WBC Count and ANC Monitoring Schedule

Table 1 provides a summary of the frequency of monitoring that should occur based on various stages of therapy (e.g., initiation of therapy) or results from WBC count and ANC monitoring tests (e.g., moderate leukopenia). The text that follows should be consulted for additional details regarding the treatment of patients under the various conditions (e.g., severe leukopenia).

Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection occurring at any time during CLOZARIL® (clozapine) therapy. Such patients should have a WBC count and ANC performed promptly.

[See [illegible] at bottom of [illegible] page]

Consult Table 1 above [illegible] who experience decre[illegible] point during treatme[illegible] carefully monitored f[illegible] toms suggestive of in[illegible]

Non-rechallengeable

If the total WBC cou[illegible] below 1000/mm³, be[illegible] sidered to ascertai[illegible] should not be recha[illegible] Protective isolation [illegible] if granulopoiesis is d[illegible] dence of infection de[illegible] priate cultures perf[illegible] regimen instituted.

Patients discontinued from CLOZARIL® (clozapine) therapy due to significant granulopoietic suppression have been found to develop agranulocytosis upon rechallenge, often with a shorter latency on re-exposure. To reduce the chances of rechallenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL® (clozapine) therapy, a single, national master file (i.e., Non-rechallengeable Database) is maintained confidentially.

Treatment of Rechallengeable Patients

Patients may be rechallenged with CLOZARIL® (clozapine) if their WBC count does not fall below 2000/mm³ and the ANC does not fall below 1000/mm³. However, analysis of data from the Clozaril® National Registry suggests that patients who have an initial episode of moderate leukopenia (3000/mm³ >WBC≥2000/mm³) have up to a 12-fold increased risk of having a subsequent episode of agranulocytosis when rechallenged compared to the full cohort of patients treated with CLOZARIL® (clozapine). Although CLOZARIL® (clozapine) therapy may be resumed if no symptoms of infection develop, and when the WBC count rises above 3500/mm³ and the ANC rises above 2000/mm³, prescribers are strongly advised to consider whether the benefit of continuing CLOZARIL® (clozapine) treatment outweighs the increased risk of agranulocytosis.

Analyses of the Clozaril® National Registry have shown an increased risk of having a subsequent episode of granulopoietic suppression up to a year after recovery from the initial episode. Therefore, as noted in Table 1 above, patients must undergo weekly WBC count and ANC monitoring for one year following recovery from an episode of moderate leukopenia and/or moderate granulocytopenia regardless of when the episode develops. If acceptable WBC counts and ANC (WBC ≥3500/mm³ and ANC ≥2000/mm³) have been maintained during the year of weekly monitoring, WBC counts can be monitored every 2 weeks for the next 6 months. If acceptable WBC counts and ANC (WBC ≥3500/mm³ and ANC ≥2000/mm³) continue to be maintained during the 6 months of every 2 week monitoring, WBC counts can be monitored every 4 weeks thereafter, ad infinitum.

Interruptions in Therapy

Figure 2 provides instructions regarding reinitiating therapy and subsequently the frequency of WBC count and ANC monitoring after a period of interruption.

[See figure 2 at top of page 2187]

Eosinophilia

In clinical trials, 1% of patients developed eosinophilia, which, in rare cases, can be substantial. If a differential count reveals a total eosinophil count above 4000/mm³, CLOZARIL therapy should be interrupted until the eosinophil count falls below 3000/mm³.

Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1,743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Myocarditis

Post-marketing surveillance data from four countries that employ hematological monitoring of clozapine-treated patients revealed: 30 reports of myocarditis with 17 fatalities in 205,493 U.S. patients (August 2001); 7 reports of myocarditis with 1 fatality in 15,600 Canadian patients (April 2001); 30 reports of myocarditis with 8 fatalities in 24,108 U.K. patients (August 2001); 15 reports of myocarditis with 5 fatalities in 8,000 Australian patients (March 1999). These reports represent an incidence of 5.0, 16.3, 43.2, and 96.6 cases/100,000 patient-years, respectively. The number of fatalities represent an incidence of 2.8, 2.3, 11.5, and 32.2 cases/100,000 patient-years, respectively.

The overall incidence rate of myocarditis in patients with schizophrenia treated with antipsychotic agents is unknown. However, for the established market economies (WHO), the incidence of myocarditis is 0.3 cases/100,000 patient-years and the fatality rate is 0.2 cases/100,000 patient-years. Therefore, the rate of myocarditis in

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clozapine-treated patients appears to be 17-322 times greater than the general population and is associated with an increased risk of fatal myocarditis that is 14-161 times greater than the general population.

The total reports of myocarditis for these four countries was 82 of which 51 (62%) occurred within the first month of clozapine treatment, 25 (31%) occurred after the first month of therapy and 6 (7%) were unknown. The median duration of treatment was 3 weeks. Of 5 patients rechallenged with clozapine, 3 had a recurrence of myocarditis. Of the 82 reports, 31 (38%) were fatal and 25 patients who died had evidence of myocarditis at autopsy. These data also suggest that the incidence of fatal myocarditis may be highest during the first month of therapy.

Therefore, the possibility of myocarditis should be considered in patients receiving CLOZARIL who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or electrocardiographic findings such as ST-T wave abnormalities or arrhythmias. It is not known whether eosinophilia is a reliable predictor of myocarditis. Tachycardia, which has been associated with CLOZARIL treatment, has also been noted as a presenting sign in patients with myocarditis. Therefore, tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis.

Prompt discontinuation of CLOZARIL treatment is warranted upon suspicion of myocarditis. Patients with clozapine-related myocarditis should not be rechallenged with CLOZARIL.

Other Adverse Cardiovascular and Respiratory Effects

Orthostatic hypotension with or without syncope can occur with CLOZARIL treatment and may represent a continuing patients), collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation and may even occur on first dose. In one report, initial doses as low as 12.5 mg were associated with collapse and respiratory arrest. When restarting patients who have had even a brief interval off CLOZARIL, i.e., 2 days or more since the last dose, it is recommended that treatment be reinitiated with one-half of a 25-mg tablet (12.5 mg) once or twice daily. *(See DOSAGE AND ADMINISTRATION.)*

Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even CLOZARIL by itself. Although it has not been established that there is an interaction between CLOZARIL and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function.

A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with

tion, arrhythmias and sudden death. In addition, there have been post-marketing reports of congestive heart failure, pericarditis, and pericardial effusions. Causality assessment was difficult in many of these cases because of serious pre-existing cardiac disease and plausible alternative causes. Rare instances of sudden death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to anti-psychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular and/or pulmonary disease, and the recommendation for gradual titration of dose should be carefully observed.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including CLOZARIL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

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. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

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.

There have been several reported cases of NMS in patients receiving CLOZARIL alone or in combination with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated 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 treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine-blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. A few cases of tardive dyskinesia have been reported in patients on CLOZARIL who had been previously treated with other antipsychotic agents, so that a causal relationship cannot be established. There have been no reports of tardive dyskinesia directly attributable to CLOZARIL alone. Nevertheless, it cannot be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

Table 1

Frequency of Monitoring Based on Stage of Therapy or Results from WBC Count and ANC Monitoring Tests

Situation	Hematological Values for Monitoring	Frequency of WBC and ANC Monitoring
Initiation of Therapy	WBC ≥3500/mm³ ANC ≥2000/mm³ Note: Do not initiate in patients with 1) history of myeloproliferative disorder or 2) CLOZARIL® (clozapine)-induced agranulocytosis or granulocytopenia	Weekly for 6 months
6 Months – 12 Months of Therapy	All results for WBC ≥3500/mm³ and ANC ≥2000/mm³	Every 2 weeks for 6 months
12 Months of Therapy	All results for WBC ≥3500/mm³ and ANC ≥2000/mm³	Every 4 weeks ad infinitum
Immature Forms Present	N/A	Repeat WBC and ANC
Discontinuation of Therapy	N/A	Weekly for at least 4 weeks from day of discontinuation or until WBC ≥3500/mm³ and ANC >2000/mm³
Substantial Drop in WBC or ANC	Single Drop or Cumulative Drop within 3 Weeks of WBC ≥3000/mm³ or ANC ≥1500/mm³	1. Repeat WBC and ANC 2. If repeat values are 3000/mm³ ≤WBC ≤3500/mm³ and ANC <2000/mm³, then monitor twice weekly
Mild Leukopenia - - - - - - - - - - - - Mild Granulocytopenia	3500/mm³ >WBC ≥3000/mm³ and/or 2000/mm³ >ANC ≥1500/mm³	Twice weekly until WBC >3500/mm³ and ANC >2000/mm³ then return to previous monitoring frequency
Moderate Leukopenia - - - - - - - - - - - - Moderate Granulocytopenia	3000/mm³ >WBC ≥2000/mm³ and/or 1500/mm³ >ANC ≥1000/mm³	1. Interrupt therapy 2. Daily until WBC >3000/mm³ and ANC 1500/mm³ 3. Twice weekly until WBC >3500/mm³ and ANC >2000/mm³ 4. May rechallenge when WBC >3500/mm³ and ANC >2000/mm³ 5. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks ad infinitum
Severe Leukopenia - - - - - - - - - - - - Severe Granulocytopenia	WBC <2000/mm³ and/or ANC <1000/mm³	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: • Daily until WBC >3000/mm³ and ANC >1500/mm³ • Twice weekly until WBC >3500/mm³ and ANC >2000/mm³ • Weekly after WBC >3500/mm³
Agranulocytosis	ANC ≤500/mm³	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: • Daily until WBC >3000/mm³ and ANC 1500/mm³ • Twice weekly until WBC >3500/mm³ and ANC >2000/mm³ • Weekly after WBC >3500/mm³

* WBC = white blood cell count; ANC = absolute neutrophil count

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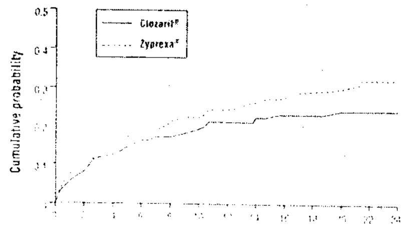

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AS DESCRIBED IN TABLE 1, PATIENTS WHO ARE BEING TREATED WITH CLOZARIL® (clozapine) MUST HAVE A BASELINE WBC COUNT AND ANC BEFORE INITIATION OF TREATMENT, AND A WBC COUNT AND ANC EVERY WEEK FOR THE FIRST 6 MONTHS. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ANC (WBC ≥3500/mm³ and ANC ≥2000/mm³) HAVE BEEN MAINTAINED DURING THE FIRST 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNTS AND ANC CAN BE MONITORED EVERY 2 WEEKS FOR THE NEXT 6 MONTHS. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ANC (WBC≥3500/mm³ and ANC ≥2000/mm³) HAVE BEEN MAINTAINED DURING THE SECOND 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNT AND ANC CAN BE MONITORED EVERY 4 WEEKS.

WHEN TREATMENT WITH CLOZARIL® (clozapine) IS DISCONTINUED (REGARDLESS OF THE REASON), WBC COUNT AND ANC MUST BE MONITORED WEEKLY FOR AT LEAST 4 WEEKS FROM THE DAY OF DISCONTINUATION OR UNTIL WBC ≥3500/mm³ AND ANC ≥2000/mm³.

Agranulocytosis

Background

Agranulocytosis, defined as an ANC of less than 500/mm³, has been estimated to occur in association with CLOZARIL® (clozapine) use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1,743 patients exposed to CLOZARIL® (clozapine) during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. Agranulocytosis could prove fatal if not detected early and therapy interrupted. Of the 149 cases of agranulocytosis reported world wide in association with CLOZARIL® (clozapine) use as of December 31, 1989, 32% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL® (clozapine)-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. In the U.S., under a weekly WBC count monitoring system with CLOZARIL® (clozapine), there have been 585 cases of agranulocytosis as of August 21, 1997; 19 were fatal (3%). During this period 150,409 patients received CLOZARIL® (clozapine). A hematologic risk analysis was conducted based upon the available information in the Clozaril® National Registry (CNR) for U.S. patients. Based upon a cut-off date of April 30, 1995, the incidence rates of agranulocytosis based upon a weekly monitoring schedule, rose steeply during the first two months of therapy, peaking in the third month. Among CLOZARIL® (clozapine) patients who continued the drug beyond the third month, the weekly incidence of agranulocytosis fell to a substantial degree. After 6 months, the weekly incidence of agranulocytosis declines still further, however, it never reaches zero. It should be noted that any type of reduction in the frequency of monitoring WBC counts may result in an increased incidence of agranulocytosis.

Risk Factors

Experience from clinical development, as well as from examples in the medical literature, suggest that patients who have developed agranulocytosis during CLOZARIL® (clozapine) therapy are at increased risk of subsequent episodes of agranulocytosis. Analysis of WBC count data from the Clozaril® National Registry also suggests that patients who have an initial episode of moderate leukopenia (3000/mm³ >WBC ≥2000/mm³) are at an increased risk of subsequent episodes of agranulocytosis. Except for bone marrow suppression during initial CLOZARIL® (clozapine) therapy, there are no other established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL® (clozapine) use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during domestic development of CLOZARIL® (clozapine). Most of the U.S. cases of agranulocytosis occurred within 4-10 weeks of exposure but neither dose nor duration is a reliable predictor of this problem. Agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL® (clozapine), although this has not been definitely demonstrated.

WBC Count and ANC Monitoring Schedule

Table 1 provides a summary of the frequency of monitoring that should occur based on various stages of therapy (e.g., initiation of therapy) or results from WBC count and ANC monitoring tests (e.g., moderate leukopenia). The text that follows should be consulted for additional details regarding the treatment of patients under the various conditions (e.g., severe leukopenia).

Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection occurring at any time during CLOZARIL® (clozapine) therapy. Such patients should have a WBC count and ANC performed promptly.

[See table 1 at bottom of next page]

Consult Table 1 above to determine how to monitor patients who experience decrements in WBC count and ANC at any point during treatment. Additionally, patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection.

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Non-rechallengeable Patients

If the total WBC count falls below 2000/mm³ or the ANC falls below 1000/mm³, bone marrow aspiration should be considered to ascertain granulopoietic status and patients should not be rechallenged with CLOZARIL® (clozapine). Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients discontinued from CLOZARIL® (clozapine) therapy due to significant granulopoietic suppression have been found to develop agranulocytosis upon rechallenge, often with a shorter latency on re-exposure. To reduce the chances of rechallenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL® (clozapine) therapy, a single, national master file (i.e., Non-rechallengeable Database) is maintained confidentially.

Treatment of Rechallengeable Patients

Patients may be rechallenged with CLOZARIL® (clozapine) if their WBC count does not fall below 2000/mm³ and the ANC does not fall below 1000/mm³. However, analysis of data from the Clozaril® National Registry suggests that patients who have an initial episode of moderate leukopenia (3000/mm³ >WBC≥2000/mm³) have up to a 12-fold increased risk of having a subsequent episode of agranulocytosis when rechallenged compared to the full cohort of patients treated with CLOZARIL® (clozapine). Although CLOZARIL® (clozapine) therapy may be resumed if no symptoms of infection develop, and when the WBC count rises above 3500/mm³ and the ANC rises above 2000/mm³, prescribers are strongly advised to consider whether the benefit of continuing CLOZARIL® (clozapine) treatment outweighs the increased risk of agranulocytosis.

Analyses of the Clozaril® National Registry have shown an increased risk of having a subsequent episode of granulopoietic suppression up to a year after recovery from the initial episode. Therefore, as noted in Table 1 above, patients must undergo weekly WBC count and ANC monitoring for one year following recovery from an episode of moderate leukopenia and/or moderate granulocytopenia regardless of when the episode develops. If acceptable WBC counts and ANC (WBC ≥3500/mm³ and ANC ≥2000/mm³) have been maintained during the year of weekly monitoring, WBC counts can be monitored every 2 weeks for the next 6 months. If acceptable WBC counts and ANC (WBC ≥3500/mm³ and ANC ≥2000/mm³) continue to be maintained during the 6 months of every 2 week monitoring, WBC counts can be monitored every 4 weeks thereafter, ad infinitum.

Interruptions in Therapy

Figure 2 provides instructions regarding reinitiating therapy and subsequently the frequency of WBC count and ANC monitoring after a period of interruption.

[See figure 2 at top of page 2187]

Eosinophilia

In clinical trials, 1% of patients developed eosinophilia, which, in rare cases, can be substantial. If a differential count reveals a total eosinophil count above 4000/mm³, CLOZARIL therapy should be interrupted until the eosinophil count falls below 3000/mm³.

Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1,743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Myocarditis

Post-marketing surveillance data from four countries that employ hematological monitoring of clozapine-treated patients revealed: 30 reports of myocarditis with 17 fatalities in 205,493 U.S. patients (August 2001); 7 reports of myocarditis with 1 fatality in 15,600 Canadian patients (April 2001); 30 reports of myocarditis with 8 fatalities in 24,108 U.K. patients (August 2001); 15 reports of myocarditis with 5 fatalities in 8,000 Australian patients (March 1999). These reports represent an incidence of 5.0, 16.3, 43.2, and 96.6 cases/100,000 patient-years, respectively. The number of fatalities represent an incidence of 2.8, 2.3, 11.5, and 32.2 cases/100,000 patient-years, respectively.

The overall incidence rate of myocarditis in patients with schizophrenia treated with antipsychotic agents is unknown. However, for the established market economies (WHO), the incidence of myocarditis is 0.3 cases/100,000 patient-years and the fatality rate is 0.2 cases/100,000 patient-years. Therefore, the rate of myocarditis in

Continued on next page

clozapine-treated patients appears to be 17-322 times greater than the general population and is associated with an increased risk of fatal myocarditis that is 14-161 times greater than the general population.

The total reports of myocarditis for these four countries was 82 of which 51 (62%) occurred within the first month of clozapine treatment, 25 (31%) occurred after the first month of therapy and 6 (7%) were unknown. The median duration of treatment was 3 weeks. Of 5 patients rechallenged with clozapine, 3 had a recurrence of myocarditis. Of the 82 reports, 31 (38%) were fatal and 25 patients who died had evidence of myocarditis at autopsy. These data also suggest that the incidence of fatal myocarditis may be highest during the first month of therapy.

Therefore, the possibility of myocarditis should be considered in patients receiving CLOZARIL who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or electrocardiographic findings such as ST-T wave abnormalities or arrhythmias. It is not known whether eosinophilia is a reliable predictor of myocarditis. Tachycardia, which has been associated with CLOZARIL treatment, has also been noted as a presenting sign in patients with myocarditis. Therefore, tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis.

Prompt discontinuation of CLOZARIL treatment is warranted upon suspicion of myocarditis. Patients with clozapine-related myocarditis should not be rechallenged with CLOZARIL.

Other Adverse Cardiovascular and Respiratory Effects

Orthostatic hypotension with or without syncope can occur with CLOZARIL treatment and may represent a continuing patients), collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation and may even occur on first dose. In one report, initial doses as low as 12.5 mg were associated with collapse and respiratory arrest. When restarting patients who have had even a brief interval off CLOZARIL, i.e., 2 days or more since the last dose, it is recommended that treatment be reinitiated with one-half of a 25-mg tablet (12.5 mg) once or twice daily. *(See DOSAGE AND ADMINISTRATION.)*

Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even CLOZARIL by itself. Although it has not been established that there is an interaction between CLOZARIL and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function.

A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with diac events, including ischemic changes, myocardial infarction, arrhythmias and sudden death. In addition, there have been post-marketing reports of congestive heart failure, pericarditis, and pericardial effusions. Causality assessment was difficult in many of these cases because of serious pre-existing cardiac disease and plausible alternative causes. Rare instances of sudden death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to anti-psychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular and/or pulmonary disease, and the recommendation for gradual titration of dose should be carefully observed.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including CLOZARIL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

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. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

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.

There have been several reported cases of NMS in patients receiving CLOZARIL alone or in combination with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated 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 treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine-blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. A few cases of tardive dyskinesia have been reported in patients on CLOZARIL who had been previously treated with other antipsychotic agents, so that a causal relationship cannot be established. There have been no reports of tardive dyskinesia directly attributable to CLOZARIL alone. Nevertheless, it cannot be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

Table 1
Frequency of Monitoring Based on Stage of Therapy or Results from WBC Count and ANC Monitoring Tests

Situation	Hematological Values for Monitoring	Frequency of WBC and ANC Monitoring
Initiation of Therapy	WBC ≥3500/mm³ ANC ≥2000/mm³ Note: Do not initiate in patients with 1) history of myeloproliferative disorder or 2) CLOZARIL® (clozapine)-induced agranulocytosis or granulocytopenia	Weekly for 6 months
6 Months – 12 Months of Therapy	All results for WBC ≥3500/mm³ and ANC ≥2000/mm³	Every 2 weeks for 6 months
12 Months of Therapy	All results for WBC ≥3500/mm³ and ANC ≥2000/mm³	Every 4 weeks ad infinitum
Immature Forms Present	N/A	Repeat WBC and ANC
Discontinuation of Therapy	N/A	Weekly for at least 4 weeks from day of discontinuation or until WBC ≥3500/mm³ and ANC >2000/mm³
Substantial Drop in WBC or ANC	Single Drop or Cumulative Drop within 3 Weeks of WBC ≥3000/mm³ or ANC ≥1500/mm³	1. Repeat WBC and ANC 2. If repeat values are 3000/mm³ ≤WBC ≤3500/mm³ and ANC ≤2000/mm³, then monitor twice weekly
Mild Leukopenia - - - - - - - - - - - - Mild Granulocytopenia	3500/mm³ >WBC ≥3000/mm³ and/or 2000/mm³ >ANC ≥1500/mm³	Twice weekly until WBC >3500/mm³ and ANC >2000/mm³ then return to previous monitoring frequency
Moderate Leukopenia - - - - - - - - - - - - Moderate Granulocytopenia	3000/mm³ >WBC ≥2000/mm³ and/or 1500/mm³ >ANC ≥1000/mm³	1. Interrupt therapy 2. Daily until WBC >3000/mm³ and ANC 1500/mm³ 3. Twice weekly until WBC >3500/mm³ and ANC >2000/mm³ 4. May rechallenge when WBC >3500/mm³ and ANC >2000/mm³ 5. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks ad infinitum
Severe Leukopenia - - - - - - - - - - - - Severe Granulocytopenia	WBC <2000/mm³ and/or ANC <1000/mm³	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: • Daily until WBC >3000/mm³ and ANC >1500/mm³ • Twice weekly until WBC >3500/mm³ and ANC >2000/mm³ • Weekly after WBC >3500/mm³
Agranulocytosis	ANC ≤500/mm³	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: • Daily until WBC >3000/mm³ and ANC 1500/mm³ • Twice weekly until WBC >3500/mm³ and ANC >2000/mm³ • Weekly after WBC >3500/mm³

* WBC = white blood cell count; ANC = absolute neutrophil count

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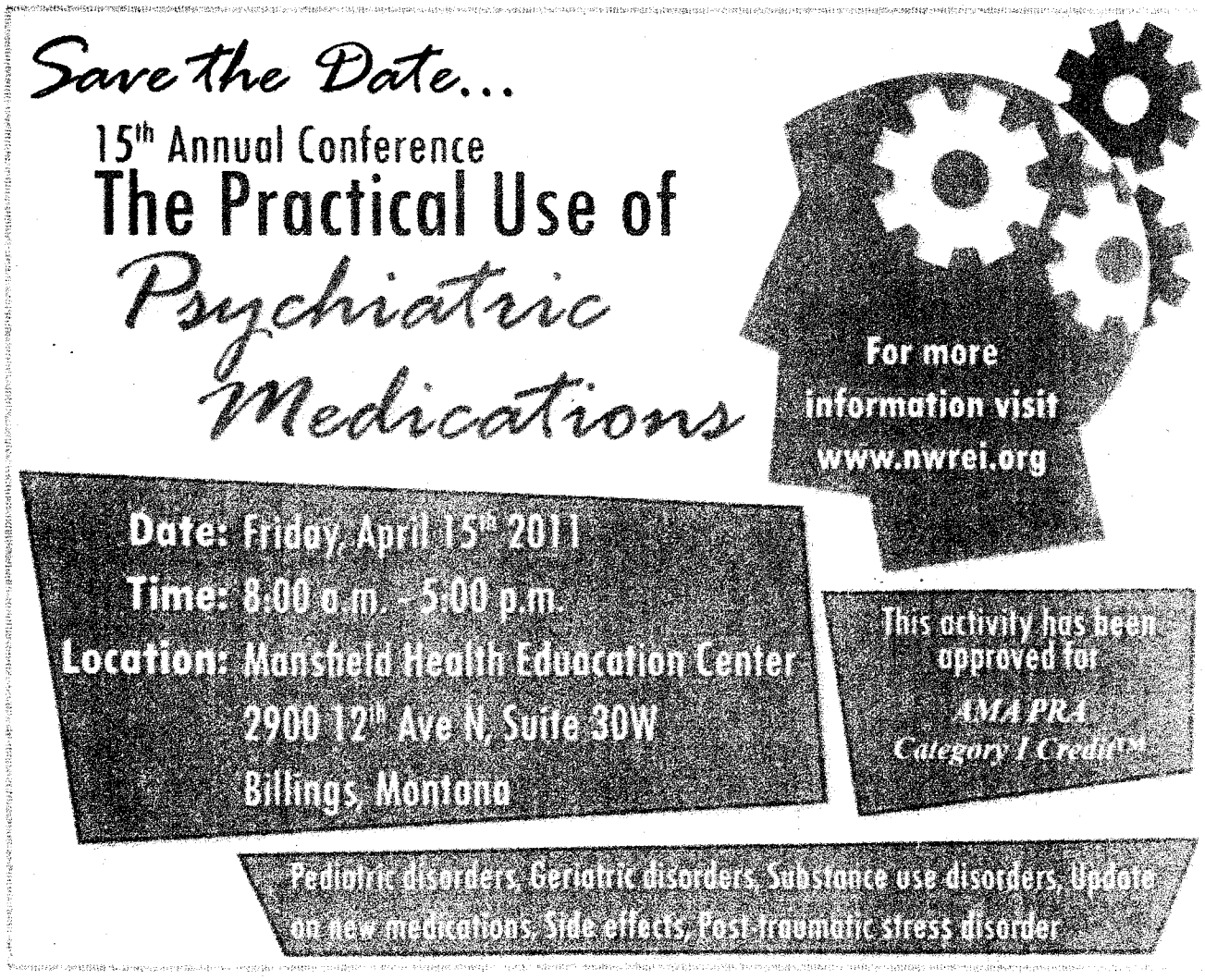

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