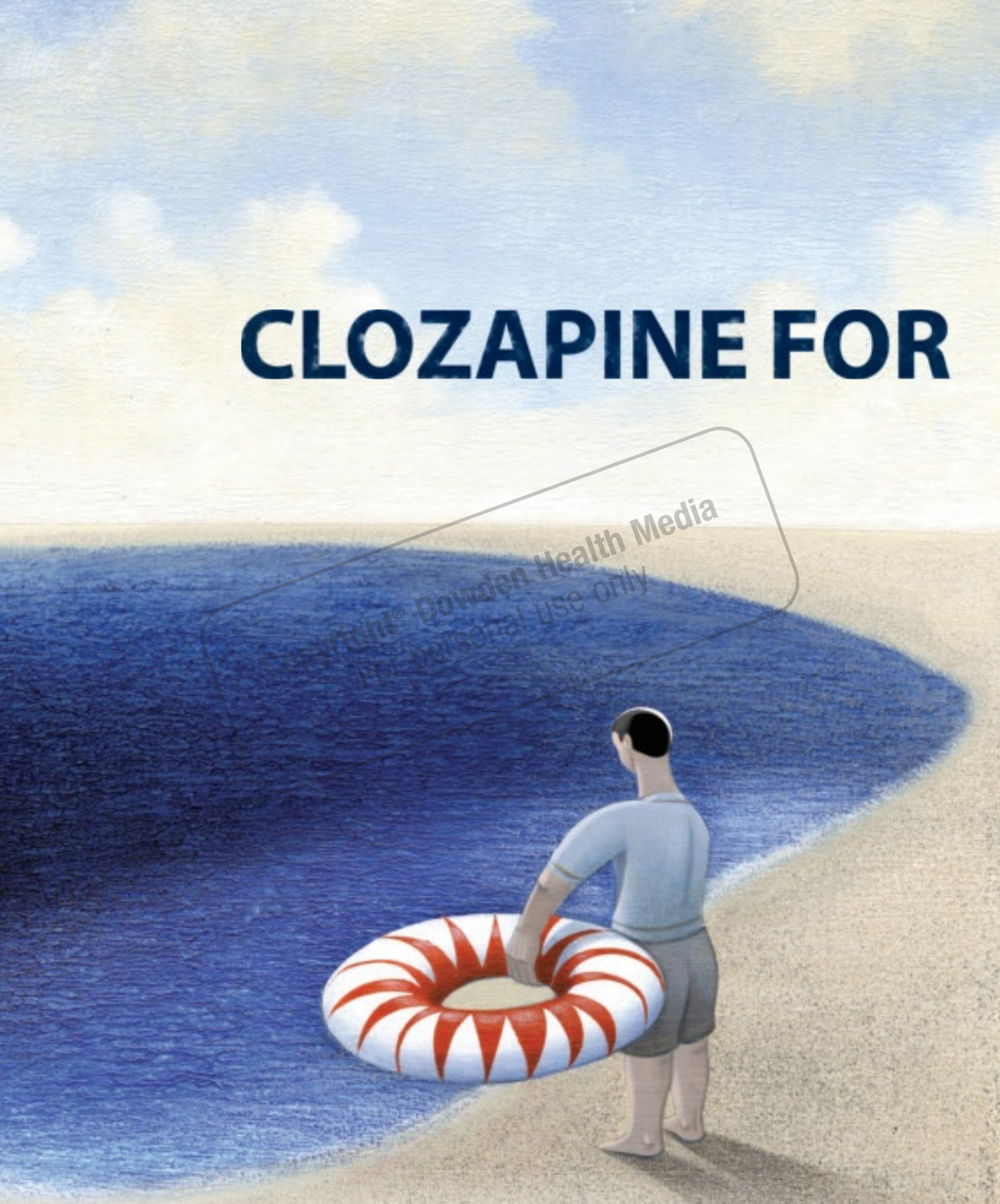
CLOZAPINE FOR



Clozapine, despite its side effect burden, may be the most effective and have the lowest mortality risk among all available antipsychotics

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When clozapine may be right for your patient, and how to initiate therapy

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SCHIZOPHRENIA

Life-threatening or life-saving treatment?

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Researchers in Finland surprised psychiatrists this year by announcing that clozapine "seems to be associated with a substantially lower mortality than any other antipsychotic."[1] This finding also surprised the researchers, who expected their 11-year study to link long-term use of second-generation ("atypical") antipsychotics with increased mortality in patients with schizophrenia. Instead they found longer lives in patients who used antipsychotics (and particularly clozapine), compared with no antipsychotic use.

This study's findings do not change clozapine's association with potentially fatal agranulocytosis as well as weight gain, metabolic abnormalities, and other adverse effects. Clozapine also is difficult to administer (*Box 1, page 58*),[2] and patients must be enrolled in FDA-mandated registries (see *Related Resources, page 63*). These obstacles might discourage you from offering clozapine to patients who could benefit from it (*Box 2, page 59*).[3-5]

Why bother considering clozapine? Because recent data on decreased mortality, decreased suicidality, and control of aggressive behavior make clozapine a compelling choice for many patients. Careful attention to clozapine's adverse effect profile is necessary, but you can manage these risks with appropriate monitoring.

Potential for longer life?

The population-based, cohort study from Finland demonstrated that—contrary to popular belief—the introduction of atypical antipsychotics during the 1990s did not adversely affect mortality of patients with schizophrenia, at least in Finland.[1]

Researchers used nationwide case registers from 1996 to 2006 to

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Clozapine update

Clinical Point

Frequent visits for blood monitoring can be used to foster patient engagement with treatment and promote a therapeutic alliance

Box 1

How to meet FDA mandates for administering clozapine

Because of clozapine's risk for leukopenia and agranulocytosis, frequent white blood cell count (WBC) monitoring is required. The risk of drug-induced blood dyscrasias has been shown to decrease over time, however, from 0.70/1,000 patient-years in the second 6 months of treatment to 0.39/1,000 patient-years after the first year.[2]

To start clozapine treatment, FDA guidelines require that the patient's WBC must be at least 3,500 mm^3, *and* the absolute neutrophil count (ANC) must be at least 2,000 mm^3. For the first 6 months, patients receiving clozapine must have a weekly blood test for WBC and ANC.

The dispensing pharmacist must see the blood work result prior to releasing the drug to the patient. The blood draw date must be within the previous 7 days for the pharmacist to dispense a 1-week supply of clozapine.

Decreased monitoring over time. After 6 months of continuous therapy with clozapine without any interruptions because of a low WBC and/or ANC—defined as WBC <3,000 mm^3 and/or ANC <1,500 mm^3 or increased monitoring (when WBC <3,500 mm^3 and/or ANC <2,000 mm^3)—the patient's blood monitoring may be done every 14 days and a 2-week supply of clozapine can be dispensed.

After 12 months of continuous clozapine therapy—6 months of continuous weekly monitoring, then 6 months of continuous biweekly monitoring—without any interruptions or increased monitoring, the patient may have blood monitoring done every 4 weeks and can receive a 4-week supply of clozapine.

One advantage of these monitoring requirements is that the increased frequency of visits can be used to foster greater patient engagement with treatment and promote a therapeutic alliance. Peer-led clozapine support groups, available in some communities, can facilitate adherence to monitoring requirements.

compare cause-specific mortality in 66,881 patients vs Finland's population (5.2 million) and to link these data with antipsychotic use. In those 11 years, the utilization rate for atypical antipsychotics increased from 13% to 64% of all antipsychotic treatments. Concurrently, the 25-year gap in life expectancy that existed between patients with schizophrenia and the general population narrowed to 22.5 years.

This study made specific drug comparisons and used perphenazine as the reference drug. The lowest risk for mortality was observed with clozapine, which showed a 26% relative advantage compared with perphenazine. Clozapine's advantage was statistically significant when compared with all other antipsychotics tested.

The authors suggested provocatively that restrictions on clozapine use as a second- or third-line agent should be reassessed. A few caveats, however, might affect how one interprets this study or applies its findings to clinical practice:

- The main comparisons were for patients receiving outpatient antipsychotic monotherapy. No information was available about antipsychotics used during in-hospital treatment.
- Only the most frequently used atypical antipsychotics (clozapine, olanzapine, oral risperidone, and quetiapine) or the most frequently prescribed first-generation antipsychotics (oral perphenazine, thioridazine, and oral haloperidol) were assessed individually.
- Data about patients' marital status, diagnoses of substance abuse, socioeconomic status, and other social variables were not available.
- Not all antipsychotics were available throughout the study (quetiapine was the newest and available for the shortest time).
- The study population consisted of patients of all ages, including those under 20 and over 70 years of age. Although the number of deaths and mortality rates increased with age, causes of mortality may differ when younger and older persons are compared. A data supplement to the study—available at www.thelancet.com—contains information about odds ratios by age and other factors.

Perhaps the study's most valuable (and

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Box 2

Clozapine's indications, dosing, and use in clinical practice

Clozapine was approved in the United States in 1989 for severely ill patients with schizophrenia who had not responded adequately to standard drug treatment. In 2002 it received an indication for 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.

Off-label, clozapine has been commonly used for refractory bipolar disorder. Since 1998, it has been available in generic formulations and in a proprietary orally-disintegrating tablet formulation.

Dosing. The recommended target clozapine dosage is 300 to 450 mg/d. If an adequate response is not achieved, obtaining a plasma level might be helpful.[3] Plasma levels ≥350 ng/mL constitute an optimal clozapine trial.

Not a 'last resort.' American Psychiatric Association treatment guidelines for schizophrenia state: "Because of clozapine's superior efficacy, a trial of clozapine should be considered for a patient with a clinically inadequate response to antipsychotic treatment or for a patient with suicidal ideation or behavior. Besides clozapine, there are limited options for the many patients who have severe and significant residual symptoms even after antipsychotic monotherapy has been optimized, and none have proven benefits."[4]

As additional evidence accumulates—including benefits regarding mortality and aggression—clozapine's advantages support its clinical use earlier than as a "last resort." In institutional settings, clozapine use has increased with the availability of additional data, such as from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).

In New York State Office of Mental Health hospitals, clozapine use increased from 20.6% of prescriptions in 2005 to 24.9% in 2007, compared with the other CATIE medications (olanzapine, quetiapine, risperidone, ziprasidone) and haloperidol.[5] Whether clozapine use will increase in outpatient settings remains to be seen.

Clinical Point

The recommended target clozapine dosage is 300 to 450 mg/d; a plasma level ≥350 ng/mL constitutes an optimal trial

reassuring) finding was that long-term antipsychotic treatment of patients with schizophrenia is associated with lower mortality when compared with no antipsychotic treatment.

Recommendation. Consider clozapine earlier than as a "last resort" in the disease course of patients with schizophrenia. At the very least, routinely present clozapine to patients and their families as a possible treatment option.

Antiaggressive properties

Case series and retrospective studies have provided insights into clozapine's antiaggressive properties, but the strongest evidence comes from a 12-week, double-blind, randomized trial that specifically enrolled patients with violent behavior.[6] Clozapine, olanzapine, and haloperidol were directly compared in the treatment of assaults and other aggressive behaviors by physically assaultive inpatients with schizophrenia and schizoaffective disorder:

- The Modified Overt Aggression Scale (MOAS) physical aggression score measured the number and severity of assaults.
- The Positive and Negative Syndrome Scale (PANSS) was used to assess psychiatric symptoms.

Clozapine was shown to be more effective than olanzapine and olanzapine was more effective than haloperidol in reducing the number and severity of physical assaults and in reducing overall aggression. Clozapine's antiaggressive property was specific and not related to the PANSS outcomes or sedation.

Recommendation. Offer clozapine as an option for patients with schizophrenia or schizoaffective disorder and persistent aggressive behavior. Another antipsychotic might not be "good enough."

Reduced risk of suicidality

The International Suicide Prevention Trial (InterSePT) was a multicenter, randomized, 2-year clinical study that compared the risk

Clinical Point

Offer clozapine as an option for patients with persistent aggressive behavior; another antipsychotic might not be 'good enough'

Table

Common adverse effects of clozapine

Adverse effect	Frequency*
Hypersalivation	31% to 48%
Drowsiness/ sedation/ somnolence	39% to 46%
Weight increase	31%
Tachycardia	25%
Dizziness/vertigo	19% to 27%
Constipation	14% to 25%
Seizures	5% (can be higher with doses approaching 900 mg/d); slow titration needed

*Pooled data from clinical trials reporting percentage of patients taking clozapine who experienced adverse effects
Source: Prescribing information for Clozaril® brand clozapine tablets. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/Clozaril.pdf. Accessed October 27, 2009

for suicidal behavior in patients treated with clozapine vs olanzapine.[7] Enrolled were 980 patients with schizophrenia or schizoaffective disorder who were considered at high risk for suicide because of past suicide attempts or current suicidal ideation. Approximately one-quarter had not responded adequately to previous treatment.

All patients were seen weekly for 6 months, then biweekly for 18 months. The weekly or biweekly contact required to monitor for clozapine-associated agranulocytosis was matched with a similar visit schedule for olanzapine-treated patients, during which clinicians obtained vital signs. Primary endpoints included suicide attempts (including death), hospitalization to prevent suicide, and a rating of "much worsening of suicidality" from baseline. Blinded raters, including an independent suicide monitoring board, determined when patients achieved endpoint criteria.

Patients receiving clozapine showed significantly less suicidal behavior than those treated with olanzapine (a 24% relative advantage in the hazard ratio for suicide attempts or hospitalizations to prevent suicide). Fewer patients in the clozapine group:

- attempted suicide (34 vs 55)
- required hospitalization (82 vs 107) or rescue interventions to prevent suicide (118 vs 155)
- required concomitant treatment with antidepressants (221 vs 258) or anxiolytics/soporifics (301 vs 331).

The number needed to treat (NNT) to prevent 1 additional suicide attempt or 1 hospitalization to prevent suicide was 13 in favor of clozapine vs olanzapine. This means that for every 13 at-risk patients treated with clozapine instead of olanzapine, 1 suicide attempt or 1 hospitalization to prevent suicide would be prevented. (For more information about NNT, see ***Related Resources, page 63***.)

More deaths from suicide occurred in the clozapine group than the olanzapine group, but the numbers were small (5 vs 3) and the difference between clozapine and olanzapine on this outcome was not statistically significant ($P = .73$).

Recommendation. Clozapine is a first-line treatment for patients with schizophrenia or schizoaffective disorder who exhibit suicidal behavior. This is reflected in the drug's product labeling.

Superior symptom management

CATIE findings. Phase 2 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) showed clozapine to be more effective than other atypical antipsychotics, as measured by time to all-cause discontinuation.[8] Patients in this phase of CATIE had discontinued another atypical antipsychotic in phase 1, principally because of lack of adequate efficacy. In phase 2, they were re-randomized to receive open-label clozapine or double-blinded risperidone, olanzapine, or quetiapine.

Only 90 patients were included in the time-to-discontinuation analysis, yet the greater amount of time that patients remained on clozapine (median 10.5 months) compared with quetiapine (median 3.3 months) or risperidone (median 2.8 months) was statistically significant. Time to discontinuation because of inadequate therapeutic effect also was significantly

longer for clozapine than for olanzapine, quetiapine, or risperidone.

The NNT for the outcome of all-cause discontinuation for clozapine was 4 compared with risperidone and 3 compared with quetiapine. This means for every 4 or 3 patients randomly assigned to clozapine instead of risperidone or quetiapine, respectively, 1 additional patient successfully completed the CATIE trial on the original phase 2 medication.[9] The NNT for clozapine vs olanzapine was 7, indicating a respectable effect size difference that might have been statistically significant if the sample size had been larger.

Meta-analyses support CATIE results. Clozapine's greater efficacy (and effectiveness) compared with other antipsychotics as demonstrated in CATIE is supported by 2 meta-analyses:

- A systematic review of clinical trials between January 1953 and May 2002 found clozapine's effect size in reducing symptoms for patients with schizophrenia was greater than that of any other antipsychotic.[10]
- In a similar but more recent meta-analysis of 150 double-blind, mostly short-term studies totaling 21,533 participants, clozapine showed the largest effect size when atypical antipsychotics were compared with first-generation antipsychotics.[11]

Finally, a meta-analysis of data from randomized trials comparing ≥2 atypical antipsychotics (78 studies; 13,558 total participants)[12] demonstrates the importance of providing therapeutic dosing of clozapine. Most of the studies used low clozapine dosages (such as <210 mg/d), rather than the recommended 300 to 450 mg/d. In these comparisons, clozapine did not show greater efficacy than other atypical antipsychotics except for zotepine or risperidone (the latter when clozapine was dosed at >400 mg/d).

Caveats about clozapine

First-episode schizophrenia. Clozapine has been shown to be more effective than chlorpromazine in terms of time to remission and maintenance of remission for treatment-naïve patients with first-episode schizophrenia.[13] Even so, most clinicians probably would not consider clozapine as a first-line treatment for an uncomplicated first-episode patient because of concerns

Clinical Point

Most clinicians probably would not consider clozapine as first-line treatment for an uncomplicated first episode of schizophrenia

about agranulocytosis. When genetic testing becomes available to determine individual risk for agranulocytosis, perhaps clozapine will be used earlier in the disease course.[14]

Titration and monitoring. Slow and careful titration of clozapine is necessary, making it less than ideal if rapid control of acute psychotic symptoms is required. In terms of monitoring for adverse effects, clozapine's product information carries "black box" warnings about the risk of agranulocytosis, seizures, myocarditis, orthostatic hypotension, and increased mortality in elderly patients with dementia-related psychosis. Common side effects include hypersalivation, excessive sedation, weight gain/metabolic abnormalities, tachycardia, dizziness, and constipation (***Table, page 60***).

The patient's ethnicity may influence the risk of adverse effects, as observed in the study examining clozapine's antiaggressive effect;[6] African-American patients receiving antipsychotics—and particularly clozapine—may be more likely to develop metabolic abnormalities than patients in other ethnic groups.[15] Carefully monitor all patients receiving clozapine for metabolic adverse effects, and be prepared to institute remediative psychosocial, lifestyle, and adjunctive medication interventions, such as statins.[16]

Myocarditis may be difficult to diagnose, and commonly used tests have limited sensitivity. A symptom questionnaire—such as described by Annamraju et al[17]—may help with earlier recognition of this potentially fatal complication, particularly during the first weeks of clozapine treatment.

Clinical Point

African-American patients receiving clozapine may be more likely to develop metabolic abnormalities than other ethnic groups

Adjunctive treatments. Patients with a low baseline white blood cell count (WBC) and/or absolute neutrophil count (ANC) may benefit from adjunctive lithium treatment to increase their WBC, as demonstrated in case reports.[18]

When no other alternatives were clinically feasible, chronic treatment with granulocyte colony-stimulating factor (filgrastim) has been used successfully for some patients whose clozapine course was interrupted because of a low WBC and/or ANC.[19]

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Bottom Line

Despite clozapine's perceived dangerousness, recent data on decreased mortality, decreased suicidality, and control of aggressive behavior make this antipsychotic a compelling choice for many patients with schizophrenia. Careful attention to clozapine's adverse effects is necessary, but risks such as agranulocytosis, metabolic abnormalities, and myocarditis can be managed with appropriate monitoring.

Related Resources

- Clozapine product information (as revised July 2009): www.pharma.us.novartis.com/product/pi/pdf/Clozaril.pdf.
- Citrome L. Compelling or irrelevant? Using number needed to treat can help decide. Acta Psychiatr Scand. 2008;117(6):412-419.

Clozapine registries (by manufacturer):

- Teva: www.clozapineregistry.com.
- Clozaril: www.clozarilcare.com.
- Caraco: www.caracoclozapine.com.
- FazaClo: www.fazacloregistry.com.
- Mylan: www.mylan-clozapine.com.

Drug Brand Names

Chlorpromazine • Thorazine
Clozapine • Clozaril, FazaClo
Filgrastim • Neupogen
Haloperidol • Haldol
Lithium • Lithobid, others
Olanzapine • Zyprexa
Perphenazine • Trilafon
Quetiapine • Seroquel
Risperidone • Risperdal
Thioridazine • Mellaril
Ziprasidone • Geodon

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