

# case study

## *Expanded Indication for Clozapine*

Contributor

*Felix M Arellano*

Phone

+34 638 101 662

Email

*felix.arellano@spcorp.com*

### **ABSTRACT/STUDY OVERVIEW**

Clozapine (Clozaril®) is an atypical antipsychotic that was approved in 1989 for the treatment of schizophrenia. Due to concerns about agranulocytosis, use has been restricted to patients who failed other treatments, and availability of the branded product in the United States involves participation in a white blood cell monitoring program called the Clozaril National Registry (CNR), formerly known as the Clozaril Patient Monitoring System (CPMS). In 1997, Walker et al. published a retrospective, observational safety study using data derived from the Clozaril National Registry with follow-up information obtained from the Social Security Administration Death Master Files and the National Death Index. The authors investigated the relationship between clozapine use and mortality, including mortality due to agranulocytosis, pulmonary embolism, cardiac conduction disorders, and suicide. Clozapine exposure was categorized as current, recent, and past, and mortality was classified using ICD-9 codes. More than 67,000 patients were included in the analysis. Comparing current clozapine users to former users, the study documented some increases in mortality from some relatively rare conditions but also showed a significant reduction in suicides for current users compared to past users (rate ratio = 0.17, 95% CI = 0.10-0.30).

These findings were subsequently replicated in a large clinical trial, known as International Suicide Prevention Trial (InterSePT) in 1998. The multicenter, randomized trial compared olanzapine and clozapine use in 980 patients with schizophrenia or schizoaffective disorder. The trial evaluated suicidal behavior, including suicide attempts, hospitalizations to prevent suicides, and worsening suicidality based on the physician-rated Clinical Global Impression of Suicide Severity (CGI-SS). Compared to olanzapine, clozapine demonstrated significantly better outcomes in both suicide behavior (hazard ratio = 0.76, 95% CI = 0.58-0.97) and worsening of suicidality (hazard ratio = 0.78, 95% CI = 0.61-0.99). Because suicide is the primary cause of premature death in this patient population, beneficial treatment to reduce suicide risk was considered highly advantageous.

The manufacturer of Clozaril used both of these studies in its successful application to the FDA for an expanded indication for suicide prevention.

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### SUPPORT FOR DECISION-MAKING

What type of decision did the study support? How was the study used?

The observational study by Walker et al led to the development of the InterSepT trial. Information on both of these studies was submitted by the manufacturer to the FDA in its successful application for approval for a new indication in 2002. In addition to the established indication for treatment of resistant schizophrenia, Clozaril was approved for use in “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.”

Publication Reference(s).

- Walker A et al. Mortality in Current and Former Users of Clozapine. *Epidemiology* 1997; 8: 671-677.
- Meltzer HY et al. Clozapine treatment for suicidality in schizophrenia. International Suicide Prevention Trial [InterSePT], *Arch Gen Psych* 2003; 60: 82-91.
- Meltzer Hy, Baldessarini RJ. Reducing the risk for suicide in schizophrenia and affective disorders. *J Clin Psychiatry* 2003; 64: 1122-1129.
- Department of Health & Human Services. U.S Food and Drug Administration (FDA) Center for Drug Evaluation. FDA Approved Drug Products Label and Approval History. Accessed 25 March 2010 on [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2002/19758se1-047\\_Clozaril\\_lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/19758se1-047_Clozaril_lbl.pdf)

Were there any clinical trials that also addressed the same topic in the same population? If so, please provide reference (trial name and any key publications).

International Suicide Prevention Trial (InterSePT)

Meltzer HY et al. Clozapine treatment for suicidality in schizophrenia. International Suicide Prevention Trial [InterSePT], *Arch Gen Psych* 2003; 60: 82-91.

If there were trials conducted, did observational study have same/similar findings?

Yes

Although both studies measured different endpoints, as the randomized-controlled trial (RCT) was not powered to detect suicide deaths, both the observational study and RCT demonstrated the beneficial impact of Clozaril on various aspects of suicide.

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