

# Clozapine may be more effective than olanzapine for reducing suicidal behaviour in people with schizophrenia at high risk

Meltzer HY, Alphs L, Green AI *et al.* Clozapine treatment for suicidality in schizophrenia. *International Suicide Prevention Trial (InterSePT)*. *Arch Gen Psychiatry* 2003, Jan; **60**:82–91.

**QUESTION:** Compared with olanzapine, how effective is clozapine for preventing suicidal behaviour among people with schizophrenia or schizoaffective disorder?

## Design

Randomised open label trial with masked outcome raters.

## Setting

67 centres in 11 countries (Argentina, Canada, Chile, Croatia, Czech Republic, France, Hungary, Italy, South Africa, United Kingdom, United States); March 1998 - February 2001.

## Participants

980 people aged 16–65 years with schizophrenia (62%) or schizoaffective disorder (38%) considered at high risk for suicide based on current suicidal ideation, suicide attempts, or preventive hospitalisation within 3 years. Mean age 37 years; 39% women; 71% white; 27% treatment refractory.

## Intervention

Participants were randomised to receive olanzapine or clozapine daily. The mean daily doses of olanzapine and clozapine prescribed were 16.6 mg and 274.2 mg, respectively. Doses were adjusted and additional treatments were provided by unmasked clinicians. All participants were seen weekly for 6 months and biweekly for an additional 18 months. Suicidal behaviour was assessed at each visit.

## Main outcome measures

The main outcomes were reported suicide attempts, hospitalisations to prevent suicide, and ratings of “much worsening of suicidality” from baseline (assessors blind to treatment allocation).

## Main results

There was less suicidal behaviour in the clozapine group compared with olanzapine (hazard ratio 0.76, 95% CI 0.58 to 0.97,  $P=0.03$ , see table). People receiving clozapine had a reduced 2-year event rate (olanzapine 32.2% *v* clozapine 24.0%; 95% CI of the difference 0.02 to 0.14; NNT=13) and delay in time to event. The overall annual rate for attempted suicides (including suicide deaths) was 7.2% (8.7% for olanzapine and 5.8% for clozapine). There were few deaths due to suicide during the 2-year study period (5 people in the clozapine group *v* 3 with olanzapine,  $P=0.73$ ).

## Conclusions

Clozapine prevented suicidal behaviour more effectively than olanzapine among people with schizophrenia or schizoaffective disorder at high risk of suicide.

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*Suicidal behaviour in high risk people with schizophrenia or schizoaffective disorder treated with clozapine or olanzapine*

	Clozapine %(n=490)	Olanzapine %(n=490)
Attempted suicide	7.7	13.8
Suicide ideation	26.1	32.1
Hospitalised to prevent suicide	16.7	21.8
Rescue interventions to prevent suicide	24.1	31.6
“Much worsening from baseline” rating	24.5	32.9
Required concomitant antidepressant treatment	49.1	55.1
Required concomitant anxiolytics or soporifics	60.2	69.4

Note: All  $P \leq 0.05$ .

## COMMENTARY

The risk of suicide in schizophrenia is similar to that in mood disorders, and is much higher than in the general population. The risk of suicidal behaviour is therefore an important problem, complicating clinical care in schizophrenia. Meltzer *et al* describe a pivotal study of treating suicidal behaviour in schizophrenia and schizoaffective disorder. This is the first randomised controlled trial to suggest the superiority of clozapine over another atypical antipsychotic (olanzapine) for this indication. The study supports a number of previous uncontrolled observations.

Selecting olanzapine as the comparator treatment was somewhat ambitious given that this drug has some antidepressant effects. Furthermore, several studies have found that olanzapine and clozapine have comparable antipsychotic efficacy. The finding that clozapine is superior to olanzapine in this context is therefore even more remarkable.

Doses were based on clinical judgment. While the mean olanzapine dose was close to that used in the United States for schizophrenia, the clozapine dose was relatively low. The authors hypothesise that the low clozapine dose was because most patients were not treatment refractory. The mechanism of effectiveness of this low dose may be separate from that implicated in the general antipsychotic activity of clozapine (which typically requires higher doses).

It is important to note that antidepressants were prescribed concomitantly with olanzapine (55.1%) and clozapine (49.1%). The difference in concomitant antidepressant prescriptions was statistically significant. From a clinical standpoint, it is perhaps more important to realise that neither of the two antipsychotics alone had sufficient antidepressant or anti-suicidal effect. Instead, about half of the participants required antidepressant supplementation. Clinicians may be interested in an analysis investigating the effect of diagnosis (schizophrenia versus schizoaffective disorder) on this concomitant antidepressant use.

Overall, this is a landmark study that will influence clinical practice for years to come. The risk of suicide is a major cause of hospitalisation for people with schizophrenia or schizoaffective disorder. The other major cause of hospitalisation is risk of violence. Aggression against self (suicidal behaviour) and aggression against others have a number of common underlying neurobiological mechanisms. Clozapine is a relatively specific treatment for both conditions. An analysis of any measure of aggression or hostility in Meltzer’s database would be interesting.

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