The impact of clozapine on hospital use: a systematic review and meta-analysis

Authors: Rachel Land [1]

Dan Siskind [2, 3]

Peter Mcardle [2, 3]

Steve Kisely [2, 3]

Karl Winckel [1, 4]

Samantha A Hollingworth [1 *]

Affiliations:

1. University of Queensland, School of Pharmacy, Woolloongabba, QLD, Australia
2. University of Queensland, School of Medicine, Herston, QLD, Australia
3. Metro South Addiction and Mental Health Services, Woolloongabba, QLD, Australia
4. Princess Alexandra Hospital, Pharmacy Department, Woolloongabba, QLD, Australia

*Corresponding Author:

Samantha A Hollingworth

School of Pharmacy

University of Queensland

20 Cornwall St

Woolloongabba QLD 4102

Email: s.hollingworth@uq.edu.au

Ph: 61 7 3346 1981

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Abstract

Objective

The objective of this study was to perform a systematic review and meta-analysis of studies reporting the impact of clozapine on hospital use in people with a psychotic illness.

Method

PubMed, EMBASE, PsycINFO and the Cochrane Schizophrenia Group Trials Register were systematically searched from inception to 12 October 2016. We included all trials and observational studies, except case-reports.

Results

37 studies were included. Clozapine significantly reduced the proportion of people hospitalised compared to control medicines (RR=0.74; 95%CI 0.69 to 0.80, P<0.001, 22 studies, n=44,718). There were significantly fewer bed days after clozapine treatment compared to before clozapine treatment in both controlled (MD=-34.41 days; 95%CI -68.22 to -0.60 days, P=0.046, n= 162) and uncontrolled studies (MD=-52.86 days; 95%CI -79.86 days to -25.86 days, P<0.001, n=2,917). Clozapine and control medicines had a similar time to rehospitalisation (-19.90 days; 95%CI -62.42 to 22.63 days, P=0.36).

Conclusion

Clozapine treatment reduced the number of people hospitalised and the number of bed days after treatment compared with before treatment. Clozapine has the potential to reduce acute hospital use among people with treatment refractory schizophrenia.

Key words**:** schizophrenia, psychotic disorders, clozapine, hospital use, meta-analysis

Summations

- Clozapine treatment is effective in reducing the proportion of people hospitalised and the number of bed days after treatment compared to before treatment.

Considerations

- The paucity of randomised controlled trial data limits the interpretation of the results.
- Given reductions in the average length of stay in recent years, older studies may not be generalisable to current clinical situations.

Introduction

Schizophrenia is a heterogeneous syndrome classified as one of the top 20 causes of disability by the World Health Organisation with a global prevalence of 7.2 per 1,000 persons (1, 2). The management of schizophrenia consists of non-pharmacological and pharmacological options. Non-pharmacological measures include somatic therapy and psychosocial interventions (3). Antipsychotics are the main pharmacological treatment option (4).

Antipsychotics do not benefit all, with 20% of people with first episode psychosis failing to respond to adequate trials of at least two different antipsychotics (5). This is termed treatment refractory schizophrenia (TRS), and estimates range from 20% - 33% among all people with schizophrenia (6). The second generation antipsychotic, clozapine, is the gold-standard treatment for TRS, with superior efficacy for positive symptoms (7) compared to first generation and non-clozapine second generation antipsychotics.

Clozapine is associated, however, with rare but potentially fatal (agranulocytosis, neutropenia, myocarditis, cardiomyopathy) and common troubling (metabolic syndrome, sedation, sialorrhea, constipation) adverse drug reactions (ADRs) (8). People prescribed clozapine require regular blood tests to prevent the life-threatening haematological events of agranulocytosis and neutropenia. Additional monitoring is also required to prevent cardiovascular events such as myocarditis and cardiomyopathy (9).

Clinical trials often test medicines in ideal circumstances, have short durations, recruit a homogenous, low risk set of subjects, and may have surrogate outcomes such as rating scales as endpoints. Hence their generalisability to 'real world' consumers can be limited. Hospital use can be a reliable endpoint to ascertain the real world effectiveness of antipsychotic treatment (10). This is because hospitalisation encompasses admission due to either treatment failure leading to psychosis, or due to adverse effects from treatment. A key goal in therapy for many people with schizophrenia is the avoidance of hospital admission. Hospital admissions are often associated with bad memories, stigma, increased cost to the patient and government, and disrupted social integration in people with schizophrenia (11). It is pertinent to ensure the 'real world' effectiveness of clozapine outweighs the potential harms.

Aim of the study

The aim of this study was to investigate the impact of clozapine on hospital use in people with a psychotic illness by conducting a systematic review and meta-analysis.

Materials and methods

Protocol and registration

The review was registered with PROSPERO (registration number: CRD42016038287), an international database of prospectively registered systematic reviews (12). We followed recommendations for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (13). Ethical approval was not required for this manuscript as all included intervention data had been previously published with ethical approval.

Eligibility criteria

We included all randomised controlled trials (RCTs) and observational studies, except case-reports, that reported hospital use in people who had a psychotic illness and were prescribed clozapine. We excluded studies if they had insufficient data or examined a diagnosis other than a psychotic illness. Published data in all languages were included and translated into English.

Search strategy

We searched PubMed, EMBASE, PsycINFO, and the Cochrane Schizophrenia Group Trials Register from inception to 12 October 2016. In the case of PubMed, we used the following terms: (clozapin* OR clozaril* OR denzapin* OR zaponex* OR clopine*) AND (schizophrenia OR schizoaffective OR psychosis OR psychotic) AND (hospital OR hospitalization OR hospitalisation OR rehospitalisation OR rehospitalization OR admission OR admitted OR bed OR inpatient).

Study selection

We included both randomised and non-randomised studies. We included controlled and uncontrolled studies that reported on hospital use in people with a psychotic illness who

were prescribed clozapine. One author (RL) screened all identified studies at the title and abstract level. Studies that met the inclusion criteria based on title and abstract, or that could not be excluded on the basis of information provided in the abstract were reviewed at full text level by two authors (RL and PM). We contacted the first authors if data were missing in the included studies.

Data collection process

One author (RL) extracted data which was checked by two authors (PM and DS). We resolved discrepancies at any stage of study selection, data extraction, and quality assessment by re-checking source studies. One author (DS) validated the extracted data. Three authors analysed the data (RL, DS and SK).

Data items

We extracted data on the following aspects: study design, study years, study duration, study setting, diagnostic tool, diagnoses, TRS definition, number of participants, gender distribution, reason for hospitalisation, mean (standard deviation [SD]) age, dose of clozapine, and control medicine(s). We also extracted the summary of findings, statistical analyses, funding, and conflicts of interest. We converted doses of clozapine and control medicines to chlorpromazine equivalents (14). They were used in separate meta-analyses to compare clozapine and control medicines in chlorpromazine dose equivalents in order to exclude any potential bias due to discrepancies between relative dosing of clozapine and control medicines.

Outcomes

The primary outcome was hospital use for any reason. This included the proportion of people hospitalised, change in number of bed days after clozapine or control medicine

compared to before, and time to rehospitalisation. If multiple time points were reported in a study, we used the data from the last time point.

Study quality

Study quality was assessed by two authors (RL and PM). We assessed the quality of the RCTs using the following criteria adapted from the Cochrane Collaboration guidelines (15): 1) adequate generation of allocation sequence; 2) blinding of allocation to conditions to participant and/or assessor; 3) adequate random sequence generation; 4) pre-specified primary outcome measures; 5) appropriate reporting on missing data; 6) use of intention to treat analysis; and 7) other sources of potential bias including pharmaceutical company funding.

We assessed the quality of the observational studies using the following criteria adapted from the Newcastle-Ottawa Scale (16): 1) selection of the study groups; 2) comparability of the groups; and 3) ascertainment of outcome.

Statistical analyses

We used Review Manager (Cochrane) version 5.3 for Mac and Comprehensive Meta-Analysis (Biostat) version 3.3 for the meta-analyses. We also used Win-Pepi (Brixton Health) for the cumulative forest plot. We reported the risk ratio (RR) for dichotomous data. We calculated the mean difference (MD) for continuous data.

We conducted sensitivity analyses for the study duration, study years, effect of dosage, use of first or second-generation antipsychotic control medicines, reason for hospital use, study quality and TRS diagnosis.

We assessed heterogeneity using the I^2 statistic, a measure that does not depend on the number of studies in the meta-analysis and hence has greater power to detect heterogeneity when the number of studies is small. It is calculated using the chi-squared statistic (Q) and its degrees of freedom (17). An estimate of 50% or greater indicates possible heterogeneity, and scores of 75-100% indicate considerable heterogeneity.

We used the random effects model for all the analyses, as we could not definitely exclude between-study variation, even in the absence of statistical heterogeneity, given the range of medicines under review. We tested for publication bias using Egger's regression asymmetry test where low P-values suggest publication bias.

Results

Study selection

We found 4,582 studies of interest in the initial search of the electronic databases, of which 3,380 titles and abstracts were screened. Of these, 276 were potentially relevant and were reviewed at full text level: 239 studies were excluded (Figure 1) and 37 studies were included in the systematic review. The sum of people in these 37 studies prescribed clozapine was 12,631 and 35,337 prescribed control medicines. We contacted the first author for two studies about missing data, but were unable to obtain the data.

Study characteristics

We included 37 studies in the meta-analysis (18-54): three randomised controlled trials and 34 observational studies (Table 1). Studies were published between 1990 and 2016. Studies reported data at time points ranging from 28 weeks to 364 weeks. Twenty-two studies provided data on the proportion of people hospitalised. There were 15 studies that reported the number of bed days using two different study types: two were controlled before-and-after treatment studies and 13 were uncontrolled before-and-after treatment studies. Five studies provided data on the time to rehospitalisation.

Two of the three RCTs were good quality (27, 35) and one was moderate quality (38) using the Cochrane Collaboration's assessment of bias tool. The method of randomisation was not stated in two studies (27, 35), with no description of the method of allocation concealment. In the third study (38), the method of allocation concealment was described as being "open". One study (35) reported double blinding, while the other two studies (27, 38) were open label. One study (35) blinded the outcome assessors to treatment status. The other two studies used structured questionnaires to assess outcome. Two studies used intention to treat analysis with a clear description of dropouts. Fewer people prescribed clozapine

dropped out compared to control medicines; this was significantly different in one study (38) but not different in the other (35).

Overall, out of the 34 observational studies included in the review, five (42, 46-48, 52) were considered good quality, 21 (18-23, 26, 28, 30, 31, 33, 34, 36, 39-41, 45, 50, 51, 53, 54) were considered moderate quality and eight (24, 25, 29, 32, 37, 43, 44, 49) were considered poor quality on the Newcastle-Ottawa scale. Studies were considered poor if they included less than 20 people prescribed clozapine or failed to provide any participant characteristics e.g. age, gender distribution, or dose. Most (n=32) of the 34 studies had a moderate risk of bias. Only three studies independently validated the diagnosis, nine stated a diagnosis but did not specify the diagnostic criteria, and the remaining 22 studies reported clinical diagnoses using the International Classification of Diseases (55) or the Diagnostic and Statistical Manual (56). Fifteen of the 34 studies were mirror studies, comparing clinical outcomes in a pre-treatment period and a post-clozapine treatment period. In the remaining studies, 12 had substantial differences in baseline characteristics. In all 34 studies, the effect of clozapine use on hospitalisation was assessed using patient records.

In studies where clozapine was compared to more than one control medicine, the number of participants in the clozapine group was divided proportionally to the number of participants in the control medicine group. This was done to avoid double counting clozapine participants.

Control medicines included first generation antipsychotics such as chlorpromazine, chlorprothixene, haloperidol, fluphenazine, flupentixol, levomepromazine perphenazine, thioridazine and zuclopenthixol. Second generation antipsychotics included amisulpride, aripiprazole, olanzapine, risperidone, quetiapine and ziprasidone (Table 1).

Twelve studies provided definitions of TRS, two of which adhered to the criteria outlined by Kane et al (1988)(57). One study explicitly excluded people with TRS (38). Two studies included diagnoses of schizophrenia or bipolar disorder (28, 29). One study explored the relationship between clozapine and hospital use in people with schizophrenia and concomitant alcohol use disorder (33).

The reasons for hospital use varied among studies: 24 studies defined hospital use for a psychiatric condition; one study defined hospital use for psychiatric and other conditions; two studies defined hospital use for any reason; and ten studies did not define the reason for hospital use (Table 1).

People prescribed clozapine were significantly younger than people prescribed control medicines (MD -1.33 years, 95% confidence interval [CI] -2.21 to -0.49 years, P=0.003, 18 studies, n=33,286). There was no difference in duration of illness for clozapine compared to control (MD=1.09 years; 95% CI -0.40 to 2.57 years, P=0.15, 5 studies, n=658). People prescribed clozapine were significantly younger at onset of illness than control (MD=-1.92 years; 95% CI -2.87 to -0.98 years, P<0.001, 6 studies, n=1,430). There was no difference in the mean daily dose in chlorpromazine equivalents in the clozapine group compared to the control group (MD=-93.63mg; 95% CI -204.20mg to 16.94mg, P=0.10, 7 studies, n=1,684).

Proportion of people hospitalised

From the 37 studies included, 22 studies reported the proportion of people hospitalised, the remaining 15 studies did not report on this data. 9,520 people were prescribed clozapine and 35,198 people were prescribed control medicines. Clozapine significantly reduced the proportion of people hospitalised compared to control medicines (RR=0.74; 95% CI 0.69 to 0.80, P<0.001, 22 studies, n=44,718). Both the RCTs (RR=0.62; 95% CI 0.41 to 0.94, P=0.03, 3

studies, n=369) and observational studies (RR=0.75; 95% CI 0.69 to 0.81, P<0.001, 19 studies, n=44,349) favoured clozapine with regards to hospitalisation (Figure 2). The heterogeneity for the RCTs was 0% and for the observational studies was 29%. The heterogeneity for comparisons among control medicines ranged from 0 to 42%.

When we examined studies using second-generation antipsychotics as the control medicine, clozapine significantly reduced the proportion of people hospitalised (RR=0.75; 95% CI 0.67 to 0.83, P<0.001, 13 studies, n=29,559). This result remained significant in sub-analyses by individual medicines: risperidone (RR=0.74; 95% CI 0.60 to 0.93, P=0.009, 12 studies, n=8,634); quetiapine (RR=0.60; 95% CI 0.45 to 0.79, P=0.0003, 4 studies, n=2,686); and olanzapine (RR=0.82; 95% CI 0.69 to 0.97, P=0.02, 8 studies, n=14,617) (Figure 2).

In studies using first-generation antipsychotics as the control medicine, clozapine significantly reduced the proportion of people hospitalised (RR=0.71; 95% CI 0.65 to 0.77, P<0.001, 13 studies, n=8,344). There was no difference in the proportion of people hospitalised when clozapine was compared to haloperidol (Figure 2).

There was no difference in the proportion of people hospitalised when we compared clozapine to antipsychotic depot treatment (first generation and second generation) (Figure 2). When we excluded studies reporting first generation depot antipsychotics, clozapine significantly reduced the proportion of people hospitalised compared to risperidone long-acting injection (RR=0.48; 95% CI 0.32 to 0.72, P=0.0004, 1 study, n=1,194). In a sensitivity analysis which removed an outlying study (52) comparing clozapine to perphenazine depot, clozapine significantly reduced the proportion of people hospitalised (RR=0.57; 95% CI 0.42 to 0.77, P=0.0002, 5 studies, n=1,505).

We performed a series of pre-specified sensitivity analyses on study characteristics. Clozapine, compared to control medicines, reduced the proportion of people hospitalised to a greater extent in study durations of less than one year (RR=0.68; 95% CI 0.59 to 0.78, P<0.001, 6 studies, n=24,391) compared to durations of more than one year (RR=0.78; 95% CI 0.71 to 0.85, P<0.001, 16 studies, n=20,327). We considered the years when the studies were conducted but three studies did not provide information (32, 33, 44). The proportion of people hospitalised was significantly lower for clozapine compared to control medicines in studies conducted before 2000 (RR=0.76, 95% CI 0.67 to 0.86, P<0.001, 10 studies, n=10,227) and studies conducted after 2000 (RR=0.77, 95% CI 0.71 to 0.84, P<0.001, 9 studies, n=33,642).

We explored the reasons for hospital use. When we excluded studies that did not state a psychiatric reason for hospital use, the proportion of people hospitalised remained significantly lower for clozapine than control (RR=0.75, 95% CI 0.70 to 0.82, P<0.001, 16 studies, n=43,674). Only one study (38) provided usable information on non-psychiatric hospitalisations, and found no difference between clozapine and control.

We investigated studies reporting the proportion of people hospitalised using chlorpromazine equivalent doses. There was no difference in the dose equivalents between clozapine and control medicines (MD=-53.53mg; 95% CI -145.66mg to -38.59mg, P=0.25, 7 studies, n=1,858).

When we considered people with only TRS, the proportion of people hospitalised was significantly lower for clozapine than control medicines (RR=0.59; 95% CI 0.45 to 0.78, P=0.002, 7 studies, n=2,381).

Pre- versus post-treatment bed days

Fifteen observational studies compared the number of bed days before and after treatment with medicines. Two (30, 49) were controlled observational studies with 70 people prescribed clozapine and 92 people prescribed control medicines. Thirteen (18, 20, 25, 26, 28, 29, 34, 37, 39-41, 43, 47) studies were uncontrolled observational studies with 2,917 people prescribed clozapine.

People prescribed clozapine, compared to control medicines, had significantly fewer bed days after treatment versus before (MD=-34.41 days; 95%CI -68.22 to -0.60 days, P=0.046, n= 162) (Figure 3). People prescribed clozapine had significantly fewer bed days after treatment compared to before treatment in 13 uncontrolled studies (MD=-52.86 days; 95%CI -79.86 days to -25.86 days, P<0.001, n=2,917) (Figure 4).

People who continued clozapine for more than two years had significantly fewer bed days after treatment versus before than those who discontinued clozapine within the two years (MD=-78.03 days; 95% CI -118.68 days to -37.8 days, P<0.001, 3 studies). We examined study duration in a sensitivity analysis. There was 3-fold difference in the number of bed days before treatment versus after treatment for durations of less than one year (MD=-24.0 days; 95% CI -32.4 days to -15.7 days, P<0.001, 6 studies) compared to more than one year (MD=-84.23 days; 95% CI -133.08 days to -35.37 days, P=0.001, 7 studies). One study specifically included children and adolescents (34). When we excluded it, clozapine still significantly reduced the number of bed days after treatment compared to before treatment (MD=-52.09 days; 95% CI -79.29 days to -24.88, P<0.001, 12 studies).

Time to rehospitalisation

Five observational studies reported the time to rehospitalisation (n=243 clozapine; n=1,169 control medicines). There was no difference between clozapine and control medicines in time to rehospitalisation (MD=-19.90 days; 95 CI -62.42 days to 22.63 days, P=0.36, 5 studies, n=1,412). A sub-analysis of control medicines revealed no difference between clozapine and individual control medicines in the time to rehospitalisation. The heterogeneity was 86%.

In the one study that reported a study duration of less than one year, people treated with clozapine had a significantly increased time to rehospitalisation compared to combined controls (risperidone, olanzapine, haloperidol decanoate, and fluphenazine decanoate) (MD=36.86 days; 95% CI 1.02 days to 72.70 days, P=0.04, 1 study, n=412). In four studies with durations of more than one year, however, there was no difference in the time to rehospitalisation among treatments (MD=-48.72 days; 95% CI -107.50 days to 10.06 days, P=0.10, 4 studies, n=1,000).

All five studies reported a psychiatric condition as the reason for hospital use. People prescribed clozapine were on significantly lower chlorpromazine equivalent doses than control medicines (MD=-147.66mg; 95% CI -288.59mg to -6.74mg, P=0.04, 3 studies, n=1,192). In the one study with only people with TRS, there was no difference to the time to rehospitalisation (MD=-78.30 days; 95% CI -186.58 days to 29.99 days, P=0.16, 1 study, n=96). In the four studies with an unknown TRS population, there was no difference to the time to rehospitalisation (MD=-12.43 days; 95% CI -57.53 days to 32.67 days, P=0.59, 4 studies, n=1,316).

Publication bias

We were only able to test for publication bias for two outcomes: the proportion of people hospitalized and bed days before and after clozapine. Using Egger's regression asymmetry test, there was no evidence of publication bias for either hospitalisation (intercept = -0.05 (95% CI -0.30 to 0.20, p= 0.807) or bed days (intercept = -0.06, 95% CI -2.88 to 2.79, p=0.96).

Discussion

To our knowledge, this study is the first systematic review and meta-analysis to specifically investigate the impact of clozapine on hospital use in people with a psychotic illness. We included 37 studies with 47,968 participants.

Clozapine was superior to control medicines in reducing the proportion of people hospitalised. This finding was consistent across study types including RCTs and observational studies. Clozapine was superior to risperidone, quetiapine and olanzapine in reducing the proportion of people hospitalised. Clozapine treatment was not different to depot treatment and haloperidol in reducing the proportion of people hospitalised. This was likely due to the smaller number of studies rather than a real difference (Figure 2). When we excluded first generation depot antipsychotics in a sensitivity analysis, however, clozapine was superior to risperidone long-acting injection in reducing the proportion of people hospitalised. Clozapine was superior to control medicines in reducing the proportion of people with TRS who were hospitalised.

Clozapine was superior in both controlled and uncontrolled before-and-after studies in reducing the number of bed days after starting treatment compared to before treatment. People who continued clozapine, compared to those who discontinued, had fewer bed days after treatment versus before treatment.

Clozapine's effectiveness in reducing hospitalisations may be due in part to the need for ongoing regular haematological monitoring. This monitoring process usually entails monthly blood tests and clinic appointments (58), and may be greater than monitoring for other anti-psychotics. It is possible that this greater ongoing monitoring and contact with clinical services for people on clozapine may allow earlier detection of mental state deterioration and appropriate interventions to avert hospitalisations.

Clozapine had no effect, compared to control medicines, on the time to rehospitalisation. Clozapine's lack of effect may be explained by subsequent re-titrations (if required) in people prescribed clozapine. They are often admitted to hospital if they have missed three days or more of dosing (retitration) for the purpose of slowly starting clozapine with careful monitoring of blood pressure, heart rate, and other outcomes. It is possible that a subgroup of people on clozapine had incomplete response. Agid et al 2011 (5) noted that 25% of people with TRS had inadequate response to clozapine. As such this sub-group may have been more likely to be rehospitalised.

The majority of studies were observational studies, as such incomplete adherence may have been responsible for a failure to show any effect on time to rehospitalisation and hospitalisation rates compared with antipsychotic depot treatment (first generation and second generation) (Figure 2).

Limitations

There were several limitations of this review. Many of the studies were of various observational study designs and therefore lacked standardised methodologies. Eight observational studies were deemed to be poor quality but a sensitivity analysis excluding these studies made no difference to the results. Observational studies have inherent

limitations such as difficulty controlling for confounding variables and a high risk of bias. Despite these limitations, observational studies can provide valuable information about the effectiveness, rather than efficacy, of medicines. It is likely that the people prescribed clozapine had a more severe psychotic illness than those prescribed control medicines. This confounding may have made clozapine seem less effective at reducing hospital use than it really is. Despite the different study types, RCTs and observational studies revealed consistent results in the meta-analyses.

Some analyses showed substantial heterogeneity. Although we explored this aspect with sensitivity analyses and used a random effects model throughout to incorporate heterogeneity into our analyses, our results should still be treated with caution. In particular, the results for the outcome of time to rehospitalisation have a non-normal distribution.

A major limitation was the lack of dose information. People prescribed clozapine were on lower chlorpromazine equivalent doses compared to control medicines in the seven studies that provided information. It is possible that the lower doses of clozapine may have underestimated the effectiveness of clozapine. No studies reported serum levels of clozapine.

Some studies did not define the reason for hospital use. It is important to cautiously interpret the results of hospital use. People may be admitted to hospital for reasons other than schizophrenia and not necessarily because they are experiencing a relapse or medicine failure. However, a sensitivity analysis of studies with a psychiatric reason for hospital use showed that the proportion of people hospitalised remained significantly lower for clozapine than control. The lack of published data on the frequency of hospital use for medical rather

than psychiatric reasons limits the opportunity to determine this cohort's general health. People on clozapine may have poorer general health due to it's side effect profile or other lifestyle factors (4), though they may also have better general health given epidemiological studies show clozapine reduces overall mortality (59).

Most studies were published before 2005. Since that time, the average hospital duration has decreased (60) and so clozapine may no longer reduce bed days to the same extent. However, a sensitivity analysis of the time at which the study was conducted did not alter the results.

In conclusion, our findings have highlighted the superior benefit of clozapine treatment versus control medicines in reducing the proportion of people hospitalised and the bed days after treatment compared with before treatment.

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