

# Real-world clinical and cost-effectiveness of community clozapine initiation: mirror cohort study

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## Background

Clozapine is the only drug licensed for treatment-resistant schizophrenia (TRS) but the real-world clinical and cost-effectiveness of community initiation of clozapine is unclear.

## Aims

The aim was to assess the feasibility and cost-effectiveness of community initiation of clozapine.

## Method

This was a naturalistic study of community patients recommended for clozapine treatment.

## Results

Of 158 patients recommended for clozapine treatment, 88 (56%) patients agreed to clozapine initiation and, of these, 58 (66%) were successfully established on clozapine. The success rate for community initiation was 65.4%; which was not significantly different from that for in-patient initiation (58.82%,  $\chi^2(1,88) = 0.47$ ,  $P = 0.49$ ). Following clozapine initiation, there was a significant reduction in median out-patient visits over 1 year (from 24.00 (interquartile range (IQR) = 14.00–41.00) to 13.00 visits (IQR = 5.00–24.00),  $P < 0.001$ ), and 2 years (from 47.50 visits (IQR = 24.75–71.00) to 22.00 (IQR = 11.00–42.00),  $P < 0.001$ ), and a 74.71% decrease in psychiatric hospital bed days

( $z = -2.50$ ,  $P = 0.01$ ). Service-use costs decreased (1 year: –£963/patient ( $P < 0.001$ ); 2 years: –£1598.10/patient ( $P < 0.001$ ). Subanalyses for community-only initiation also showed significant cost reductions (1 year: –£827.40/patient ( $P < 0.001$ ); 2 year: –£1668.50/patient ( $P < 0.001$ ) relative to costs prior to starting clozapine. Relative to before initiation, symptom severity was improved in patients taking clozapine at discharge (median Positive and Negative Syndrome Scale total score: initial visit: 80 (IQR = 71.00–104.00); discharge visit 50.5 (IQR = 44.75–75.00),  $P < 0.001$ ) and at 2 year follow-up (Health of Nation Outcome Scales total score median initial visit: 13.00 (IQR = 9.00–15.00); 2 year follow-up: 8.00 (IQR = 3.00–13.00),  $P = 0.023$ ).

## Conclusions

These findings indicate that community initiation of clozapine is feasible and is associated with significant reductions in costs, service use and symptom severity.

## Keywords

Psychotic disorders; out-patient treatment; schizophrenia; real word service use; mirror study.

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Treatment-resistant schizophrenia (TRS) is defined as an inadequate clinical response to sequential treatment with at least two different antipsychotics at adequate dose, duration and adherence.<sup>1</sup> It occurs in approximately a third of patients diagnosed with schizophrenia.<sup>2</sup> TRS is associated with higher symptom severity<sup>3</sup> and 3–11 times higher healthcare costs than treatment-responsive schizophrenia.<sup>4</sup> Clozapine is the only drug licensed for TRS<sup>7</sup> and is the recommended first-line treatment for TRS in clinical guidelines in most countries.<sup>5–7</sup> Approximately 50% of patients with TRS achieve an adequate response to clozapine in clinical trials.<sup>8</sup>

## Clozapine – real-world clinical use

Clozapine's clinical and cost-effectiveness has been investigated in real-world hospital settings by mirror studies examining data before and after clozapine initiation. These studies have demonstrated significant cost reductions after clozapine initiation, ranging between £3800 and £10 000 per patient per year, but have almost all been studies about in-patients.<sup>7,9,10</sup> It is thought that a large portion of this saving is the result of a reduction in hospital admissions after clozapine initiation.<sup>4</sup> Lower frequencies of hospital admissions correlate with reports of a better quality of life in people with schizophrenia.<sup>11</sup>

Despite this, clozapine is underused in many settings and there are also long delays in clozapine initiation once TRS is detected.<sup>12–14</sup> A number of barriers to initiating clozapine use have been identified, including lack of experience and/or resources to assess TRS and to

initiate and monitor clozapine during the dose titration.<sup>15–17</sup> A further barrier and potential source of delay is that clozapine is often only initiated in hospital, which some patients may find unattractive.<sup>18</sup> Indeed, surveys have found that a third of psychiatrists in the UK did not know that clozapine could be initiated in the community<sup>19</sup> and that two-thirds of psychiatrists had no recent experience of initiating clozapine.<sup>17</sup>

The treatment review and assistance team (TREAT) was established as a service model to provide expertise and additional clinical resources to assess and treat patients with TRS in South London, UK (see Beck et al (2014) for a full description<sup>20</sup>). This includes community initiation of clozapine where indicated or arranging in-patient admission for clozapine initiation where community initiation is not possible.<sup>20</sup> However, it remains to be established if this approach is feasible or cost-effective in clinical practice. Here, we investigate the feasibility and cost-effectiveness of the TREAT service,<sup>20</sup> relating to both community and in-patient titrations of clozapine. Given concerns that clozapine initiation in the community is not feasible or cost-effective,<sup>21,22</sup> we also conducted subanalyses restricted to patients who commenced clozapine in the community.

## Method

### Setting

The TREAT service covers the South London boroughs of Southwark, Lambeth and Croydon (as of 2018, a population of

1 028 519<sup>23</sup>). Patients referred to the TREAT service undergo an initial assessment to determine if they meet treatment-resistant criteria (see Supplementary Appendix 1 available at <https://doi.org/10.1192/bjp.2022.47>) and to identify the appropriate treatment. Although clozapine is the only licensed drug for TRS, in some circumstances clozapine may not be the most appropriate treatment, for example because of the presence of contra-indications or where there is a history of prior unsuccessful treatment with clozapine.<sup>6,24</sup> Where clozapine is indicated, the TREAT service offers patients a trial of clozapine through out-patient initiation, which involves the patient attending out-patient clinic appointments for dose titration and side-effect monitoring. However, in some circumstances standard out-patient initiation may not be feasible, for example because the patient is unable to attend out-patient clinic appointments reliably (see Beck et al for a description of contra-indications,<sup>20</sup> breakdown in Supplementary Table 1). In these circumstances, community initiation is offered through domiciliary visits conducted by a separate home treatment team (HTT), to manage the clozapine dosing and side-effect monitoring at the patient's home, in collaboration with the TREAT team. In this study, community titration refers to either out-patient or HTT titrations. Where community initiation through either the out-patient or HTT routes is not feasible, for example because the patient requires close monitoring because of the severity of their mental illness and/or comorbidities, patients are offered an admission to hospital for clozapine initiation. No patients switched from community to in-patient titration (or vice-versa).

This study was conducted as part of an audit approved by the Lambeth Directorate of South London and Maudsley NHS Trust. The NHS Act (2006) makes provision for the collection of patient data for the purposes of clinical audit.

## Study design

All data were routinely collected clinical data, retrospectively extracted from electronic health records. The sample consisted of patients previously referred to TREAT for assessment from three London Boroughs. Inclusion in the service use analyses required that patients were:

- assessed by TREAT from 1 December 2011 to 31 December 2017;
- TREAT recommended clozapine as the primary treatment option;
- service-use data were available for the 1- and 2-years periods directly prior to (pre-) and following (post-) clozapine titration, defined as at least 6 months of healthcare records for each of the 4 years of interest.

Exclusion criteria were: patients who had received clozapine at any point in the 2 years prior to TREAT assessment, and (for mirror analyses) patients who stopped clozapine within the first year after initiation.

Patients could be referred to the service with troubling psychotic symptoms that were not responding to existing treatment. As a result of the naturalistic and observational design of the study, no symptoms cut-offs were utilised and it is possible referring clinicians referred the most severe patients directly for admission, which could influence the generalisability of findings.

The cost-effectiveness and clinical effectiveness of clozapine treatment was assessed using a mirror study design. This design compares data for each patient for a specified time period after clozapine initiation to data over the same length of time immediately prior to the intervention, thus patients act as their own control (Supplementary Figure 1). In this study we conducted mirror analyses over 1-year and 2-year mirror periods.

## Data extraction

The following data were extracted from clinical records: the number of patients for whom clozapine treatment was recommended by TREAT;<sup>7,25</sup> who consented to clozapine initiation; who commenced clozapine; and who completed clozapine titration in community or in-patient settings. Completion of titration was defined as achieving a daily dose of at least 300 mg or target trough plasma levels of at least 0.35 mg/L, in line with guidelines,<sup>25</sup> or achieving a lower target dose where this was explicitly stated in the records for a specified clinical reason, for example intolerance of side-effects.

For each patient meeting study inclusion criteria, the following service-use data were extracted: number of out-patient care-coordinator/nurse, psychiatric doctor, occupational therapy and psychology visits; number of HTT visits; and number of days in hospital. Numbers of other visits (for example phlebotomy) were also recorded (Supplementary Table 2). Cost estimates for mental health service use were calculated using UK estimates for unit healthcare costs and cost data from South London and Maudsley NHS Foundation Trust (SLaM) (Supplementary Appendix 2).

Ratings of symptom severity and functioning, conducted by TREAT and community clinicians, were extracted from assessment records. These scales included the Positive and Negative Syndrome Scale (PANSS)<sup>26</sup> and the Health of Nation Outcome Scales (HoNOS).<sup>27</sup> PANSS ratings reflect the severity of schizophrenia symptoms and were collected at the initial assessment by the TREAT team and again at discharge after clozapine titration. HoNOS scores provide a broader measure of overall mental health symptom severity, additional mental and physical health problems and functional status and are routinely collected in SLaM clinical records. HoNOS scores were extracted for the closest date to pre-clozapine baseline (before initiation), discharge from titration service, 1- and 2-year follow-up after clozapine initiation.

## Statistical analysis

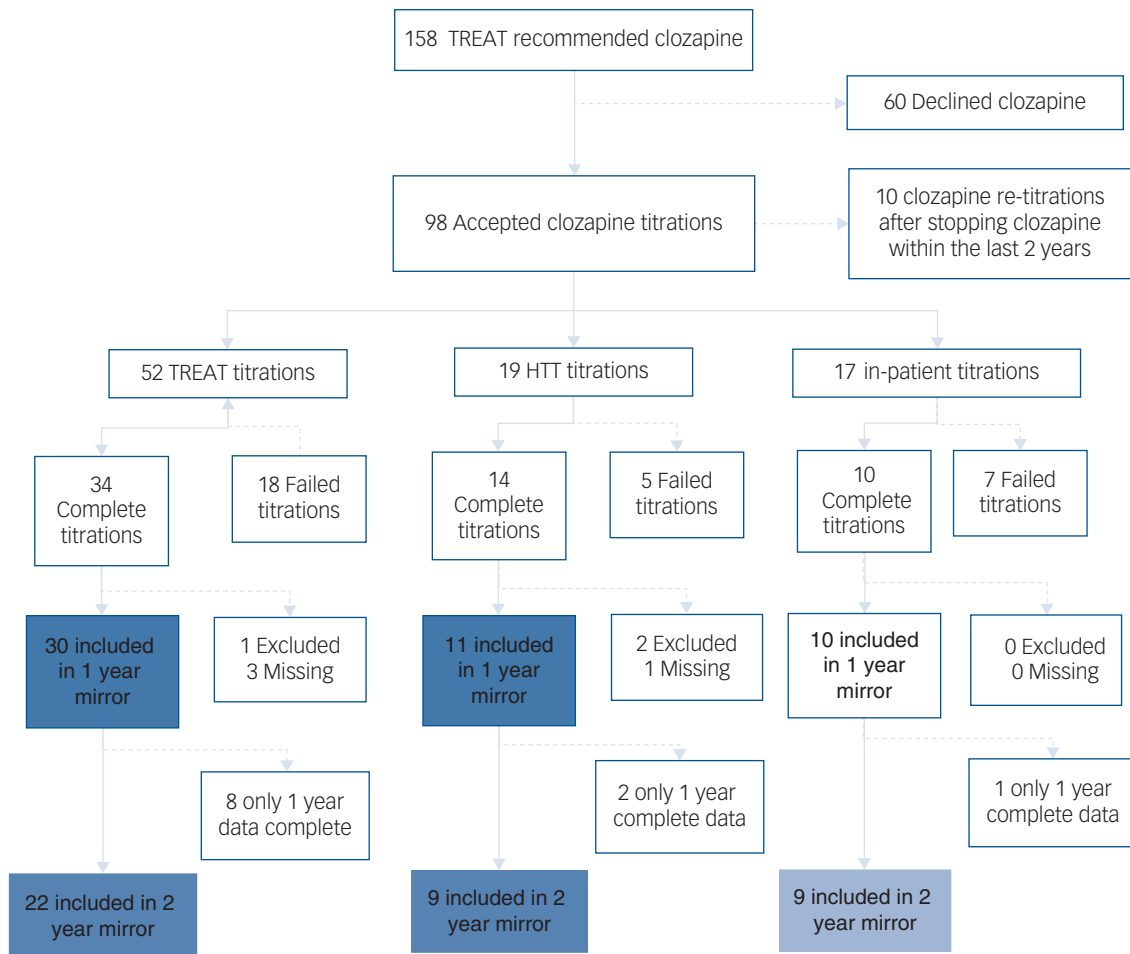
All data were tested for normality of distribution using Kolmogorov–Smirnov tests. Feasibility data including success of titration, titration service and length of titration were compared using  $\chi^2$ - and Mann–Whitney *U*-tests where appropriate. Service-use data and associated cost in the 1- and 2-years pre- and post-clozapine initiation were compared using the Wilcoxon signed-rank test, reported with *z* approximation. Effect sizes for the Wilcoxon signed-rank tests were calculated via the formula:

$$r = z/\sqrt{N}$$

where *r* is the effect size, *z* is the *z*-value and *N* the observation number.

Mean percentage change comparing 1- and 2-years pre- and post-clozapine initiation was also calculated for service-use data. Across service-use data analyses, out-patient clinical contact was defined as the sum of all out-patient care-coordinator, nursing, psychologist and psychiatric doctors' visits. Wilcoxon signed-rank tests were used to compare PANSS scores before clozapine initiation and at discharge. As there were multiple follow-up time points, Friedman's and *post hoc* Wilcoxon signed ranks tests were used to assess change in HoNOS scores before clozapine initiation and at discharge and 1- and 2-year follow-up.

Secondary analyses restricted to the subsample of patients who received community titration were also conducted to explore effects in this subgroup. Analyses were performed using SPSS software (v26.0, Chicago, Illinois), and significance defined as *P* < 0.05.



**Fig. 1** Sample breakdown of clozapine titrations across the three services: out-patient (treatment review and assistance team (TREAT)), home treatment teams (HTT) and in-patient.

## Results

### Feasibility of community clozapine

The TREAT service recommended clozapine for 158 patients over the sample period. Figure 1 summarises their flow through the study. Ten of these patients (6.3%), had previously received clozapine in the 2 years prior to their TREAT referral so were excluded from the mirror analyses. In 60 (38%) patients where clozapine was recommended, the patient declined clozapine initiation or did not start for another reason. Reasons for not initiating clozapine included: patient declined blood monitoring ( $n = 11$ ); patient declined other aspects of clozapine monitoring (such as blood pressure) measures during initiation ( $n = 7$ ); patient declined because of side-effect profile ( $n = 12$ ); patient family or life situation prevented them attending for monitoring or admission ( $n = 4$ ); patient chose to commence/continue with an antipsychotic other than clozapine ( $n = 3$ ) and patient died before titration ( $n = 1$ ). Some patients cited more than one of the reasons for not commencing titration, and 26 patients did not provide a reason for declining clozapine. Clozapine treatment was initiated in 88 (55.7%) patients out of the 158 for whom it was recommended.

The mean age at referral to the TREAT service of patients for whom clozapine was recommended was 41 years old (s.d. = 12.41) and, for those who completed a clozapine titration, it was 39 years old (s.d. = 12.5) years old, with a range from 18 to 61 years. For

those titrated on to clozapine, 41.17% ( $n = 21$ ) of the sample identified as White, 33.33% ( $n = 17$ ) identified as Black and 7.84% ( $n = 4$ ) identified as Asian. An ICD<sup>28</sup> F20.0 diagnosis of paranoid schizophrenia was the most common diagnosis (80.39% of patients) (Supplementary Table 3).

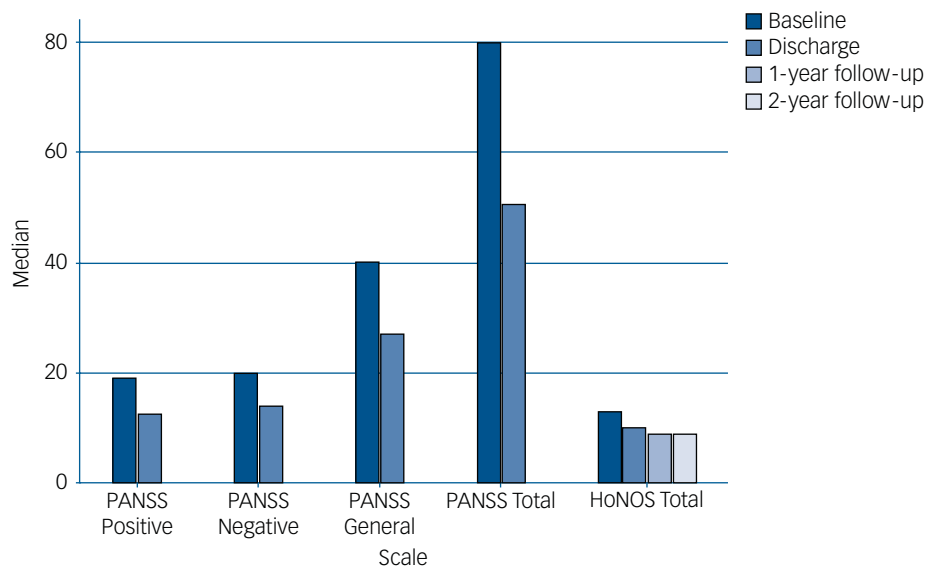
Of those who initiated clozapine, 58 (66%) successfully completed clozapine titration, and 48 (83%) of these were completed in the community. Table 1 summarises the success rates by location. There is no indication of difference between success rate of clozapine titration in community and in-patient settings ( $\chi^2 (1,88) = 0.47, P = 0.49$ ). However, it should be noted this study was not powered to test non-inferiority. A further study is needed to test this, guided by the effects we report here. The median length of titration was significantly different between in-patient and community settings ( $U = 72.00, P = 0.003$ ), with community titration taking on average 11 days longer (Table 1). The median time with TREAT for the sample was 305 (interquartile range (IQR) = 203–408.5) days before the evaluation of outcome and discharge.

### Symptom and function change following clozapine titration

PANSS scores were available at the initial TREAT assessment before clozapine initiation in 43 patients and at discharge from the TREAT service on clozapine in 34 patients. Figure 2 shows the symptom severity ratings at baseline and discharge. At discharge, symptom severity was significantly improved compared with at the initial

	Median length of titration, days	IQR	Successful titration		Failed titration	
			<i>n</i>	%	<i>n</i>	%
In-patient	21	16–31	10	58.8	7	41.2
Community	32	26–50	48	67.6	23	32.4
TREAT (out-patient)	38	24–70	34	65.4	18	34.6
Home treatment team	29	26–37	14	73.7	5	26.3

IQR, interquartile range; TREAT, treatment review and assistance team.



**Fig. 2** Graph showing the median change in scores at four time points for Positive and Negative Syndrome Scale (PANSS) and the Health of Nation Outcome Scales (HoNOS) assessments.

There is a significant reduction for PANSS scores from first assessment before clozapine and at discharge from TREAT while on clozapine ( $P < 0.001$ ). There is a significant reduction in HoNOS total score from before clozapine over 2 years after titration ( $P = 0.023$ ).

assessment. This reduction was observed for PANSS positive, negative, general, and total scores (Supplementary Table 4). A similar reduction was also seen in the subsample of 29 community titrations who had initial and discharge PANSS scores recorded (Supplementary Table 4).

### HoNOS – longitudinal symptoms and functional change

HoNOS scores were available in 41 patients at the initial visit; 35 patients at discharge from TREAT; 40 patients at 1 year and 24 patients at 2 years (shown in Fig. 2).

Friedman's test showed a significant reduction in HoNOS score across the follow-up 2-year period ( $\chi^2(3) = 9.57, P = 0.023$ ). *Post hoc* tests show a significant reduction from baseline to both the 1-year ( $z = 2.19, P = 0.028$ ) and 2-year follow-up ( $z = -3.43, P = 0.001$ ) time points (Supplementary Table 4).

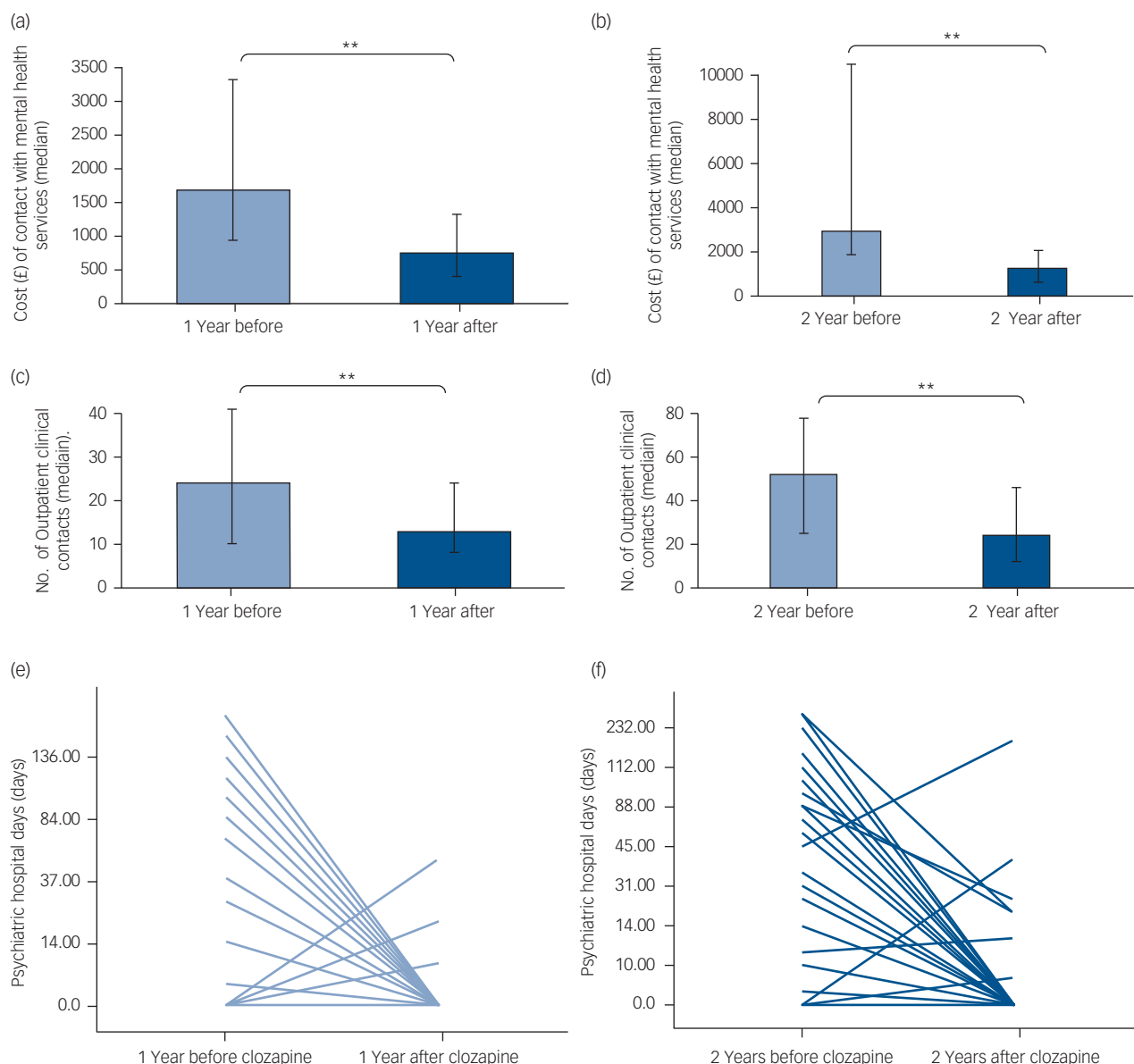
The subanalysis restricted to community titrations showed a significant reduction in HoNOS score over the total follow-up ( $\chi^2(3) = 8.53, P = 0.036$ ). Similar to the analysis in the whole sample, there was a significant reduction in HoNOS scores in the community titration sample from baseline to 1- and 2-year follow-up with a median change of 3.0 points ( $z = -1.95, P = 0.05$ ) and 4.0 points ( $z = -2.96, P = 0.003$ ), respectively.

### Service use and healthcare costs: 1 year and 2 years prior and following initiation of clozapine

Of the 58 patients who completed clozapine titration, 51 (87.9% of successful titrations) had electronic health records showing continuation

on clozapine for at least 1 year and were included in the 1-year mirror analyses (Fig. 1). This sample included 41 (70.7% of successful titrations) patients who underwent clozapine initiation in the community (30 by TREAT and 11 by the HTT) and 10 who underwent in-patient initiation. Of the seven patients who completed titration but were excluded from the 1-year mirror analysis, four had incomplete data-sets (three patients moved out of the area and one patient died in the year following discharge) and a further three patients discontinued clozapine during the first year of treatment (two because of side-effects, one because of poor adherence) (Fig. 1). Of the sample of 51 included in the 1-year mirror analyses, data were available for 40 patients for inclusion in the 2-year mirror analyses.

Supplementary Table 5 summarises the mental healthcare service use and costs. All service-use data were non-normally distributed (all Kolmogorov–Smirnov  $P$ -values  $< 0.0001$ ). In the first year after clozapine initiation there was a significant reduction in the number of days spent in a psychiatric hospital bed ( $z = -2.48, P = 0.01, r = 0.35$ ) with a mean decrease of 19.45 (s.d. = 7.70) hospital bed days, equating to a 94% reduction relative to the year prior to clozapine initiation (see Fig. 3(e) and 3(f)). There was also a significant median (IQR) reduction of 11 (9.00–23.00) out-patient clinical contacts equating to a 45.8% reduction over the 1-year period ( $z = -3.84, P < 0.001, r = 0.54$ ) (Supplementary Table 5, Fig. 3(c)). A similar reduction was seen over 2 years after clozapine initiation, where there was a 74.71% mean decrease in days in psychiatric hospital bed ( $z = -2.50, P = 0.01, r = 0.41$ ) and a 53.7% median decrease in out-patient clinical contacts ( $z = -3.72,$



**Fig. 3** Service-use data showing a significant decrease in clinical contacts and healthcare costs in the 1 and 2 years after clozapine initiation compared with the 1 and 2 years prior to clozapine. Error bars represent 95% CI. (a) Median total cost of contact with mental health services shows a significant reduction from the 1 year before to the 1 year after clozapine initiation (\*\* $P < 0.001$ ). (b) Median total cost of contact with mental health services shows a significant reduction from the 2 years before to the 2 years after clozapine initiation (\*\* $P < 0.001$ ). (c) Median number of out-patient clinical contacts including psychiatrist, care-coordinators, nurses and psychologist visits, shows a significant reduction from the 1 year before to the 1 year after clozapine initiation (\*\* $P < 0.001$ ). (d) Median number of out-patient clinical contacts including psychiatrist, care-coordinators, nurses and psychologist visits, shows a significant reduction in the 2 years before to the 2 years after clozapine initiation (\*\* $P < 0.001$ ). (e) Patient-level change in number of days spent in psychiatric hospital 1 year before and 1 year after clozapine titration, showing a significant reduction ( $P = 0.01$ ). (f) Patient-level change in number of days spent in psychiatric hospital in the 2 years before and 2 years after clozapine initiation, showing a significant reduction ( $P = 0.01$ ).

$P < 0.001$ ,  $r = 0.60$ ) compared to in the 2 years before clozapine initiation (Supplementary Table 5, Fig. 3(d)).

The number of occupational therapy, psychology (individual and group) and HTT visits in the 1- and 2-years post-TREAT clozapine initiation, were not significantly different from the corresponding periods prior to clozapine initiation (all  $P > 0.05$ ) (Supplementary Table 5).

Overall, total costs of contact with mental health services significantly reduced post-clozapine initiation by a median of £963 per patient over 1 year ( $z = -3.79$ ,  $P < 0.001$ , effect size  $r = 0.54$ ), and by a median of £1598.10 per patient over 2 years ( $z = 3.57$ ,  $P < 0.001$ ,  $r = 0.59$ ) (Fig. 3(a) and 3(b)).

### Service use and healthcare costs following community titration of clozapine

There were 41 patients who had community titrations with data for the 1-year comparison and 31 patients for the 2-year comparison. There was a significant reduction in days spent in psychiatric hospital ( $z = -2.60$ ,  $P = 0.009$ ,  $r = 0.41$ ) and in out-patient clinical contacts (median reduction: 45.2%;  $z = -3.111$ ,  $P = 0.002$ ,  $r = 0.486$ ) in the 2-year post-clozapine initiation relative to the 2 years preceding clozapine (see Supplementary Table 5).

A significant reduction of 50% (median percentage change) could also be seen for out-patient clinical contact during the

1 year after clozapine initiation compared with the 1 year before initiation ( $z = -3.11$ ,  $P = 0.002$ ,  $r = 0.49$ ; Supplementary Table 5). There were also significantly fewer days spent in psychiatric hospital ( $z = -2.67$ ,  $P = 0.008$ ,  $r = 0.50$ ) (Supplementary Figure 2). However, similar to the results for the whole sample, HTT, psychology one to one, occupational therapy and social support did not reach significance (Supplementary Table 5).

The total cost of contact with services reduced post-clozapine initiation by £827.40/patient (median) over 1 year ( $z = -3.78$ ,  $P = 0.02$ ,  $r = 0.59$ ), and by £1686.50/patient (median) over 2 years ( $z = -3.30$ ,  $P = 0.01$ ,  $r = 0.61$ ; Supplementary Figure 2).

## Discussion

### Main findings

Our main findings are that clozapine initiation had a 68% success rate in community settings and was associated with significant improvements in symptoms, reductions in service use and cost savings. On average, community titration was associated with substantial (38.7–94%) decreases across psychiatric service use and mental healthcare cost savings of £827.40 per patient over 1 year and £1686.50 per patient over 2 years.

The significant reductions in the PANSS (over an average 1-year period) and HoNOS (over average 3-year period) scores with clozapine treatment extend clinical trial findings that clozapine improves clinical outcomes in people with TRS to show this in a naturalistic setting.<sup>8</sup> The 1- and 2-year follow-up HoNOS data indicates that these improvements in broader mental and physical health and functioning are maintained over time. This suggests that not only are patients using mental health services less within the 2 years after clozapine initiation, but that their clinical presentation and daily functioning also improved over the same period.

### Comparison with findings from other studies

Previous studies have reported mean reductions in hospital bed stays of between 5.09 to 120 days and mean cost reductions of £7300 to ~£10 188, reductions in healthcare costs up to 2 years after starting clozapine.<sup>9,10,29–34</sup> However, these studies have only included patients who initiated clozapine in hospital, whereas our study focused on patients in the community, most of whom received community clozapine initiation. This difference likely explains much of the disparity between the larger cost savings previously reported in hospital settings in comparison with those reported in the present analysis<sup>9,10,33,34</sup> because of the costs associated with hospital admission prior to clozapine initiation. Cost savings after clozapine initiation should also be considered against the costs associated with hospital admission for the purpose of initiating clozapine (in-patient titration, approximately £11 697, Supplementary Appendices 3–5), in patients where it could be initiated in the community at lower cost (out-patient titration, approximately £1180.10, Supplementary Appendices 3–5). Unfortunately, we do not have the individual granular-level data for each patient to calculate exact costs. However, future works in this area may wish to focus on the titration period, that was omitted in this design, including assessing actual service cost and safety data.

To our knowledge, there have been two previous studies on community clozapine titration, both conducted over two decades ago.<sup>22,35</sup> The study by Luchins et al (1998), conducted in USA, found an average 15.9 hospital bed day reduction in the year after clozapine initiation,<sup>22</sup> whereas the other study, conducted in Italy found a reduction of 49 days.<sup>35</sup> Our finding of an average 19.7 bed day reduction in the 1-year post community clozapine initiation compared with the year pre-clozapine thus extends prior findings to

show reductions in a UK setting as well. Both prior studies found cost increases in the year following clozapine initiation. This contrasts with our finding of a cost saving over the 1-year post-community clozapine initiation of £827.40. It should be noted that we did not include medication costs in our study, in contrast to the other studies. However, the average cost for 1 year's supply of clozapine is £430.18 for a dose of 300 mg/day,<sup>36</sup> which does not offset the savings found in our study during the first year after a community titration. Two important differences between the studies are the healthcare setting (Italy/USA versus UK) and year of study, both of which could factor into medication and service-use costs and could explain this cost difference. Additionally, clozapine is now generic and the costs, relative to other antipsychotics, are much lower than they were when the earlier studies were conducted. Our study thus extends the finding of these prior studies to a different healthcare setting and indicates that, in this setting and with current costs, community clozapine initiation is associated with cost savings.

### Interpretation

The reduction of service use and cost that we observed is partly driven by a decrease in hospital days following titration of clozapine. Meltzer et al, also reported that the majority of cost savings resulted from reduced cost of hospital admissions.<sup>33</sup> Our study found a 94% reduction in psychiatric hospital bed days in the first year after clozapine and a 75% reduction in the 2 years following initiation of clozapine. However, the reduction in hospital days in our community sample of 20 days is a less marked reduction than the 78-day reduction reported in a meta-analysis of studies of the effect of clozapine initiation in a hospital setting over 2-year follow-up.<sup>32</sup> This could be because of the selection of patients who were already hospital in-patients in the previous studies and the relatively low number of patients in our sample with hospital admissions before TREAT involvement.

The difference in length of titration from 32 days in a community setting to 21 days in an in-patient setting was to be expected given the difference in community and in-patient titration protocols.<sup>25</sup> A slower titration is used in the community relative to in-patient settings to reduce the risk of side-effects in the community. This requires the visits to be spread out over a longer period and may have had some influence on titration success rates in the different settings. The additional length of contact that is needed should be considered when assessing the resources available to implement community titrations of clozapine.

In 38% of patients where clozapine was indicated, the patient did not commence clozapine. Reasons for declining clozapine included the side-effect profile and requirements for blood monitoring and an increased frequency of engagement. This highlights that clozapine is not acceptable to all patients, and the need for an alternative to clozapine with more favourable side-effect profiles and that do not require blood monitoring.<sup>24,37</sup> Our analysis only included patients who continued to take clozapine for at least 1 year. The impact on symptoms and healthcare use would likely be lower in an intention-to-treat analysis. However, only three patients stopped clozapine within the first year, indicating differences are unlikely to be large. Nevertheless, it would be useful for future studies to investigate this. It would also be useful for future studies to further investigate the factors influencing acceptability of clozapine further.

### Strengths and limitations

Strengths of this study include the mirror design, which includes all eligible patients and is therefore likely to be more representative of clinical practice than samples in randomised controlled trials.

Additionally, the mirror design incorporated an extended length of follow-up to establish longer-term outcomes. The within-subject analyses increase statistical power and mitigate potential sources of bias that may occur because of between-subject or between-group differences.

It is important to consider that the allocation to community or in-patient titration was not random when considering the comparisons between titration success rates, service cost etc between settings. The patients receiving in-patient titration likely had more complicated conditions than those receiving community titration. Unfortunately, we were unable to find data from studies that use a comparable definition of titration to enable comparison with our success rates. Differences in patient characteristics for each titration route also mean that the costs of clozapine initiation for each route cannot be directly compared.




One potential limitation is that a proportion (17%) of the sample had a diagnosis of an affective psychotic or delusional disorder rather than schizophrenia (Supplementary Table 3). Although this may better reflect the case-loads of real-world mental health clinics as efficacy of clozapine for these disorders is not established this may have resulted in underestimation of the effects of clozapine on symptomatic and functional outcome and health service use and costs. As a result of the clinical nature of the study, raters were not masked to treatment, which could have added bias into symptom ratings, although it is unlikely to affect service use and costs. Our study does not compare the cost of out-patient, HTT and in-patient clozapine initiation routes. As the route for clozapine initiation is selected by the TREAT team according to the patient's needs there are likely systematic differences.

Another consideration is that a general reduction in psychiatric service provision over time could have contributed to observed effects. However, total expenditure on psychiatric services<sup>38</sup> increased over the time period and there was no reorganisation of services that would have reduced services for patients with psychotic disorders, indicating that this is unlikely to explain our findings. An additional possible limitation is the lack of a comparator antipsychotic to clozapine. Engagement with TREAT and having specialist support may have improved outcomes for patients, regardless of the antipsychotic prescribed. Although we did not assess non-psychiatric healthcare use, previous studies have indicated that this is not a major driver of societal costs in schizophrenia<sup>4</sup> and our study also did not assess other costs to society or carer costs, such as lost employment, and housing costs. However, exclusion of these additional costs may have led to underestimation of the savings associated with clozapine initiation.

## Implications

Our findings indicate that community assessment and initiation of clozapine is feasible, and associated with significant improvements in symptoms, reductions in psychiatric healthcare use and costs. This supports the broader implementation of community services dedicated to identifying individuals with TRS and initiation of clozapine treatment, including in the community.

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First received 11 Oct 2021, final revision 15 Feb 2022, accepted 16 Feb 2022

## Supplementary material

To view supplementary material for this article, please visit <https://doi.org/10.1192/bjp.2022.47>

## Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request. Due to clinical nature of the data and need for privacy of participants, data is not publicly available. Clinicians or others wishing to establish similar services are welcome to contact the authors for the service protocol.

## Author contributions

O.D.H., P.M., D.T., R.R., J.M., F.G., T.R.M., contributed to the conceptualisation, research and provided advice and support throughout the project. K.Be. and F.B. contributed to the early stages, design and implementation of the project. E.B., K.Br., F.B. and A.B. completed data screening, collection and had input on analysis. T.P., S.K., K.Be., S.J., E.D., M.R. and L.D. provided advice and input for clinical matters. P.M. provided advice and input regarding economic analysis. E.B. authored this paper with input from T.P., under the supervision of O.D.H. and A.E. All authors read, revised and approved the final manuscript.

## Funding

This work was supported by grants to O.D.H. from The Maudsley Charity (grant no. 666) and Medical Research Council-UK (no. MC\_U120097115).

## Declaration of interest

O.D.H. is a part-time employee of H. Lundbeck A/S and has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organised by Angellini, Autifony, Biogen, Boehringer-Ingelheim, Eli Lilly, Heptares, Global Medical Education, Invicro, Janssen, Lundbeck, Neurocrine, Otsuka, Sunovion, Rand, Recordati, Roche and Viatrix/Mylan. Neither O.D.H. or his family have holdings/a financial stake in any pharmaceutical company. O.D.H. has a patent for the use of dopaminergic imaging.

R.A.M. has received honoraria from Otsuka pharmaceutical for educational talks. R.A.M. is funded by a clinical lectureship from the National Institute of Health Research. F.B. became an employee at COMPASS Pathways plc after the completion of this work. This work is unrelated to COMPASS Pathways plc. S.J. has received honoraria for educational talks given for Sunovion, and his employer, King's College London, has received honoraria for educational talks he has given for Lundbeck. D.T. reports grants from Janssen and Recordati, personal fees from Janssen, Mylan, Recordati and Sunovion and stock in Saladax and Psychiatric Genetic Testing. Other Authors have not declared any conflicts of interest.

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