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1 **A retrospective study of intramuscular clozapine prescription for treatment initiation**  
2 **and maintenance in treatment-resistant psychosis**

3  
4 Casetta Cecilia<sup>1,2</sup>, Oloyede Ebenezer<sup>1,2</sup>, Whiskey Eromona<sup>2</sup>, Taylor David Michael<sup>2</sup>, Gaughran  
5 Fiona<sup>1,2</sup>, Shergill Sukhi<sup>1,2</sup>, Onwumere Juliana<sup>2,3</sup>, Segev Aviv<sup>1,4</sup>, Dzahini Olubanke<sup>2</sup>, Legge Sophie<sup>5</sup>,  
6 MacCabe James Hunter<sup>1,2</sup>

7  
8 Affiliations:

9 <sup>1</sup>King's College London, Department of Psychosis Studies, Institute of Psychiatry, Psychology &  
10 Neuroscience

11 <sup>2</sup>South London and Maudsley NHS Foundation Trust, London

12 <sup>3</sup>King's College London, Department of Psychology, Institute of Psychiatry, Psychology &  
13 Neuroscience

14 <sup>4</sup>Sackler faculty of medicine, Tel Aviv University, Tel Aviv, Israel

15 <sup>5</sup>Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and  
16 Clinical Neurosciences, School of Medicine, Cardiff University, UK

17  
18 Corresponding author:

19 *Cecilia Casetta, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 16*  
20 *De Crespigny Park, Camberwell, London SE5 8AB, United Kingdom.*

21  
22 **ABSTRACT**

23  
24 Background: Clozapine is uniquely effective in treatment-resistant psychosis but remains  
25 underutilised, partly due to psychotic symptoms leading to non-adherence to oral medication. An  
26 intramuscular (IM) formulation is available in the UK but outcomes remain unexplored.

27  
28 Aims: This was a retrospective clinical effectiveness study of IM clozapine prescription for treatment  
29 initiation and maintenance in treatment-resistant psychosis over a 3-year period.

30  
31 Methods: Successful initiation of oral clozapine after IM prescription was the primary outcome.  
32 Secondary outcomes included all-cause clozapine discontinuation two years following initiation, and  
33 one year after discharge. Discontinuation rates were compared with a cohort only prescribed oral  
34 clozapine. Propensity scores were used to address confounding-by-indication.

35  
36 Results: Among 39 patients prescribed IM clozapine, 19 received at least one injection, while 20  
37 accepted oral when given an enforced choice between oral and IM clozapine. Thirty-six (92%)

38 successfully initiated oral clozapine after IM prescription; 3 never transitioned to oral. Eight  
39 discontinued oral clozapine during the two-year follow-up, versus 83/162 in the comparator group  
40 (discontinuation rates of 24% and 50% respectively). Discontinuation rates at one-year post-  
41 discharge were 21%, compared to 44% in the comparison group. IM clozapine prescription was  
42 associated with a non-significantly lower hazard of discontinuation two-years after initiation and one-  
43 year after discharge (HR0.39,95%CI 0.14–1.06; HR0.37,95%CI 0.11-1.24). The only reported  
44 adverse event specific to the IM formulation was injection site pain and swelling.

45  
46 Conclusions: IM clozapine prescription allowed transition to oral maintenance in a cohort initially  
47 non-adherent. Discontinuation rates were similar to patients only prescribed oral clozapine and  
48 comparable to existing literature.

## 51 INTRODUCTION

52  
53 Clozapine has been considered the gold-standard for treatment-resistant psychotic disorders since  
54 the 1980s (1). It demonstrates a 50 to 75% response rate among those who fail to achieve remission  
55 with conventional first- or second-generation antipsychotics (2). Clozapine is associated with better  
56 long-term outcomes than other antipsychotics or no treatment, including lower long-term all-cause  
57 mortality rates (3), reduced violent offending (4) and readmission rates (5). Despite superior efficacy,  
58 clozapine remains significantly underutilized and its initiation is often substantially delayed. The  
59 Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study reported that only 14 to 50%  
60 of eligible patients were treated with clozapine (6). Furthermore, data from the United Kingdom (UK)  
61 shows that clozapine initiation is typically delayed by approximately 4 years (7).

62  
63 One common problem occurs when treatment-resistant patients are not able to accept clozapine or  
64 associated blood tests due to symptoms of acute psychosis, including impaired insight and  
65 delusional beliefs. Although the Mental Health Act (MHA) in England and Wales gives the legal  
66 authority to administer involuntary drug treatment and ancillary investigations, including blood tests  
67 to support clozapine use (Mental Health Act. Nottingham: CQC; 2008), most patients who require  
68 but are non-adherent to antipsychotics are prescribed long-acting injections, due to the practical  
69 difficulties of enforcing oral treatment. However, since clozapine is not available as a long acting  
70 injection, an unwillingness to take the oral form of clozapine has hitherto precluded clozapine  
71 treatment. While compulsory administration of medication is not uncommon in psychiatric care, this  
72 is rarely employed with clozapine treatment, with only a few facilities worldwide reporting the use of  
73 nasogastric (8) and intramuscular (IM) clozapine (9,10,11,12,13).

74

75 In this study, we present our 3-year experience with short acting IM clozapine in the South London  
76 and Maudsley Hospital (SLaM) Foundation Trust.

77

78

## 79 **METHODS**

80

### 81 *Study design*

82

83 Observational data from SLaM were collected to follow-up a cohort of patients prescribed IM  
84 clozapine as a short-term strategy to initiate oral clozapine. Our aim was to evaluate its potential  
85 value in initiating and maintaining clozapine in patients initially reluctant to take oral clozapine.  
86 Transition from IM prescription to oral clozapine was the primary outcome. The secondary outcome  
87 was all-cause clozapine discontinuation, a widely used outcome measure in observational studies.  
88 Post-discharge discontinuation rates were investigated in order to assess long-term adherence to  
89 oral medication outside a hospital setting where concordance cannot be prompted and supervised  
90 by healthcare professionals. Finally, we compared all-cause clozapine discontinuation rates with  
91 those of a comparison group of patients started and maintained on oral clozapine, without IM  
92 prescription, while detained under the MHA in SLaM. This analysis was conducted to investigate  
93 whether addressing an initial reluctance to accept clozapine treatment by prescribing the IM  
94 formulation will lead to long-term compliance at rates similar to or different from patients who  
95 accepted oral clozapine from initiation.

96

### 97 *IM clozapine*

98

99 The IM clozapine used in this study is manufactured by Apotheek A15® (formerly Brocacef®) in the  
100 Netherlands and was approved by the Drugs and Therapeutics Committee of SLaM NHS Foundation  
101 Trust in 2016. Owing to the need for daily administration, and the large volume that must be injected  
102 to achieve maintenance doses of clozapine, IM clozapine is not suitable as a long-term treatment.  
103 Although there is no upper limit, the protocol suggests not exceeding 14 days of injections;  
104 nonetheless previous data report safe use of IM clozapine for up to 96 days (9). Therefore, the  
105 SLaM protocol (see Supplementary material 1) allows for IM clozapine as a short-term intervention  
106 to initiate or re-initiate clozapine treatment in patients who refuse oral medication, with a view to  
107 converting to oral clozapine once compliance is achieved. The decision to prescribe IM clozapine is  
108 undertaken on an individual basis and our local protocol states that it must be agreed by a  
109 multidisciplinary team, Director of Pharmacy and a second opinion doctor appointed by the Care  
110 Quality Commission under the provisions of the MHA, 1983. The final decision is driven by a  
111 comprehensive assessment, which includes extensive information gathered from various sources

112 such as family discussions, capacity assessments and best interest meetings. The latter aims to  
113 reach a decision in the best interest of a patient who is assessed to lack capacity for the decision in  
114 question.

115

116 Once IM clozapine is prescribed, the choice of oral clozapine must be offered at every administration,  
117 and the injection is only administered as a last resort when oral clozapine is refused. The strength  
118 of IM clozapine is 25mg/ml and each ampoule contains 5ml (125mg). Current recommendations,  
119 based on clozapine pharmacokinetics, assume oral bioavailability of clozapine to be approximately  
120 50% of the IM formulation (14). As the injection of larger volumes can be painful, it is suggested that  
121 the maximum volume that can be injected into each site is 4ml (100mg), which gives approximately  
122 equivalent bioavailability as 200mg oral clozapine. For doses greater than 100mg daily, the dose  
123 may be divided and administered into two sites based on individual preference. To minimise the  
124 number of injections, once daily dosing is preferred.

125

#### 126 *IM clozapine cohort*

127

128 All individuals prescribed IM clozapine between 1<sup>st</sup> June 2016 and 7<sup>th</sup> March 2019 in an inpatient  
129 care setting within SLAM were included in the study. They all lacked capacity to treatment. Each  
130 patient prescribed IM clozapine was added to a register and linked to electronic medical notes and  
131 pharmacy dispensing records. Patients were followed-up with regard to concordance to oral  
132 clozapine treatment until clozapine discontinuation or two years after IM clozapine prescription or  
133 31<sup>st</sup> July 2019, when the data collection ended, whichever occurred sooner. Time to all-cause post-  
134 discharge discontinuation was defined as the time from the date of discharge until the date oral  
135 clozapine was stopped, one year of treatment or end of data collection (31<sup>st</sup> July 2019), whichever  
136 occurred sooner. Treatment discontinuation was defined as a discontinuation for longer than seven  
137 consecutive days, even if clozapine was later re-initiated.

138

139 Patient demographics and clinical data such as the duration of illness, prior use of clozapine and the  
140 date of clozapine initiation, discharge and transition from IM to oral clozapine were collected from  
141 electronic medical records. Global clinical severity was rated retrospectively at IM clozapine  
142 prescription using the Clinical Global Impression Improvement scale (CGI-I) by manual analysis of  
143 patients notes in the electronic medical records by an experienced psychiatrist (CC). Further data  
144 included clozapine injection date(s) and dose(s), and use of restraints. Reasons for clozapine  
145 discontinuation where applicable were obtained from descriptive medical records. Patients who were  
146 discharged from SLAM were followed up through their registered pharmacies responsible for  
147 clozapine supply. A questionnaire was sent to respective pharmacists asking whether the patient  
148 under their care remained on clozapine treatment and, if not, the date and reason for discontinuation.

149

150 *Comparison group: historical cohort*

151

152 The comparison group included patients with a diagnosis of a treatment-resistant psychotic disorder  
153 (ICD-10: F20–F29) aged between 18 and 65 years old initiated on oral clozapine in a SLaM facility  
154 in routine clinical practice between 1<sup>st</sup> January 2007 and 31<sup>st</sup> December 2011. We selected patients  
155 who were initiated on clozapine while detained under the MHA (Section 2, Section 3 or Section  
156 47/49) to represent compulsory treatment in the historical cohort. These data were collected as part  
157 of a previous study investigating reasons for clozapine discontinuation (15) from the Clinical Records  
158 Interactive Search (CRIS) system, an anonymized case register derived from SLaM electronic case  
159 records. Follow-up with regard to continuing clozapine was carried on until clozapine discontinuation  
160 or 2 years after clozapine initiation, whichever occurred sooner. Post-discharge follow-up was  
161 continued from the date of discharge until the date clozapine was stopped or one year of treatment,  
162 whichever occurred sooner. Global clinical severity was rated retrospectively at clozapine  
163 prescription using the CGI-I by manual analysis of the electronic medical records. No information on  
164 the use of restraints was available for the historical cohort.

165

166 *Adverse events*

167

168 All SLaM patient records were scrutinized for documented adverse events (including when they first  
169 occurred in relation to the initiation date). Adverse events were defined as any unfavourable and  
170 unintended sign, symptom or disease noted on the electronic records, which occurred during use of  
171 IM clozapine or within 3 days from administration, that are not recorded by the manufacturer's  
172 summary product characteristics (<https://www.medicines.org.uk/emc/product/4411/smpc>).

173

174 *Statistical methods*

175

176 Statistical analysis was carried out using Stata, version 15 (16). The percentage of patients who  
177 successfully initiated oral clozapine after IM prescription was calculated. Kaplan-Meier survival  
178 curves were used to estimate and graph the time to clozapine discontinuation from IM or oral  
179 clozapine prescription in both the IM cohort and the comparison group respectively. Patients were  
180 followed from the date of first IM clozapine prescription and were censored after 2 years follow up  
181 or 31<sup>st</sup> July 2019, whichever occurred sooner. All cause discontinuation of oral clozapine was  
182 calculated, and all patients who were prescribed IM clozapine were included, whether or not they  
183 received the drug intramuscularly. After checking proportional hazard assumptions, a Cox regression  
184 was employed to model the association between IM clozapine prescription and clozapine  
185 discontinuation. Propensity scores were used in order to address the issue of confounding-by-

186 indication and a fully adjusted Cox analysis was carried out with the propensity score included as a  
187 covariate. Propensity scores indicate the probability of being prescribed IM clozapine based on  
188 patient characteristics (age, gender, diagnosis, length of illness, CGI at clozapine prescription) and  
189 were calculated using logistic regression.

190

191 A separate survival analysis was set up to model post-discharge clozapine discontinuation rates,  
192 which were graphed using a Kaplan-Meier survival curve in both the IM and comparison group, with  
193 T0 at the date of discharge. Patients were censored after one-year follow up or 31<sup>st</sup> July 2019,  
194 whichever occurred sooner. The discontinuation rates in the two groups were analysed using a Cox  
195 regression model adjusted for propensity scores, which were included in the analysis as a covariate.

196

197 Post hoc analysis using Kaplan-Meier survival curves was conducted to evaluate differences in  
198 discontinuation rates after IM prescription between the subgroup of patients who were prescribed  
199 and administered IM clozapine and those who had it prescribed but not administered. Post-hoc Cox  
200 regression analysis was conducted to calculate the hazard of clozapine discontinuation in the two  
201 sub-groups.

202

### 203 *Ethical standards*

204

205 This clinical effectiveness study was approved by the Drugs and Therapeutics Committee (DTC) of  
206 the South London and Maudsley NHS Foundation Trust, the locally designated approval committee  
207 for all non-interventional prescribing outcome audits. The local SLaM protocol for the use of IM  
208 clozapine was approved by DTC.

209

210 Ethical approval for the use of CRIS as a research dataset was given by Oxfordshire Research  
211 Ethics Committee C (08/H0606/71). The service-user led CRIS oversight committee granted  
212 permission for the use of a previously identified anonymised cohort of patients commencing oral  
213 clozapine to provide the comparison group data. Informed consent was not required as CRIS is an  
214 anonymized case register.

215

216

## 217 **RESULTS**

218

### 219 *Patient Characteristics: IM clozapine cohort*

220

221 Data were available for 39 inpatients with a treatment-resistant psychotic disorder who had been  
222 prescribed IM clozapine. Of these, 19 (49%) were administered at least one injection (median 2,

223 range 1 – 56), while 20 (51%) preferred to receive oral clozapine when offered the enforced choice  
224 between oral and IM administration. Of the patients who received more than one injection, 7 (50%)  
225 were administered consecutively and 7 (50%) received IM intermittently with oral clozapine. 32  
226 patients (82% of our sample) had previously taken clozapine. Cohort characteristics are presented  
227 in Table 1. Table 2 summarises characteristics of IM clozapine administrations in our sample.

228

229 Among the 19 patients who received IM clozapine, the median maximum daily IM dose was 75 mg  
230 (range 6.25 – 200mg), equivalent to 150mg of oral clozapine. Most patients (n=16, 84%) received  
231 the injection(s) during the titration period; either from the first dose (n=11, 58%) or after refusing later  
232 doses (n=5, 26%). Manual restraints by nursing staff were used in nine patients (47%) with a median  
233 of zero and a mean of two restraints per patient (0 restraints: 10 patients; 1 restraint: 5 patients; >1  
234 restraint: 4 patients). No mechanical restraints were used. The most common adverse event  
235 associated with IM formulation was swelling at the injection site, which occurred in the three patients  
236 who had more than 29 injections (16%). Other side effects reported in the patients' notes were  
237 drowsiness in two patients (10%), urinary incontinence (one patient, 5%) and neutropenia (1 patient,  
238 5%). No side effects associated with physical restraints were reported in the electronic notes,  
239 although psychological consequences were not explicitly investigated.

240

#### 241 *Patient Characteristics: Historical cohort*

242

243 The comparison group included 162 patients who started oral clozapine while admitted to a SLam  
244 hospital under the MHA. They all fulfilled the criteria for a treatment-resistant psychotic disorder, and  
245 their characteristics are summarized in Table 1.

246

#### 247 *Transition from IM to oral clozapine and discontinuation rates*

248

249 In total, 36 patients (92%) eventually started oral clozapine after being prescribed the IM formulation.  
250 Among those who received at least one injection, 16 (84%) were later switched to oral. The  
251 remaining three either continued to refuse oral clozapine despite IM administrations or discontinued  
252 IM clozapine due to adverse effects (neutropenia, recurrent pneumonia). The median number of  
253 days of injection before transition to oral was 2 (range 1-47).

254

255 In the IM cohort, median follow-up was 694 (IQR 481 – 720) days from IM prescription date and 296  
256 (IQR 0 – 365) days from discharge date. In the comparison group, mean follow up was 720 days  
257 from the date of clozapine initiation and 365 days from discharge. In the subgroup of patients who  
258 were prescribed and administered IM clozapine median follow up was 509 (IQR 302 – 720) days  
259 from prescription and 236 (IQR 0 – 365) days from discharge, while in the subgroup of patients who



260 were prescribed but not administered IM clozapine mean follow up was 683 (IQR 534 – 720) days  
261 from prescription and 287 (IQR 0 – 365) days from discharge.

262

263 Fig. 1A displays a Kaplan-Meier survival curve for the clozapine discontinuation rates after clozapine  
264 prescription in the cohort of patients who were prescribed IM clozapine and in the comparison group.  
265 Discontinuation rates at two-year follow up were lower in the cohort of patients who were initially  
266 prescribed IM clozapine than in the comparison group (24% and 50% respectively), with a reduced  
267 hazard of clozapine discontinuation (HR 0.39, 95% CI 0.19 – 0.80) although this became non-  
268 significant after the model was adjusted for propensity scores (HR 0.39, 95% CI 0.14 – 1.06). In a  
269 post-hoc analysis, higher discontinuation rates were found in those who received the injection  
270 compared to those who chose to receive oral clozapine after being offered the enforced choice  
271 between the two formulations (52% and 6% respectively; HR 10.34, 95% CI 1.26 - 84.70). The  
272 Kaplan-Meier survival curve is shown in Fig. 1B. Table 3 summarizes the results of the Cox  
273 regression analyses.

274

275 Data were available after discharge for 29 of the IM patients (74%; 5 of which had received at least  
276 1 injection) as the remaining 10 (26%) were still in hospital at the end of the study. Twenty-two (76%  
277 of those discharged) patients were maintained on oral clozapine until the end of follow-up; in the  
278 comparison group 81/162 patients remained on clozapine one year after discharge. Among the  
279 seven patients who were clozapine-naïve at IM prescription, three (43%) were still on oral clozapine  
280 at the end of follow-up.

281

282 Patients included in the post-discharge survival analysis are shown in Fig. 2. Discontinuation rates  
283 at one year after discharge for the IM cohort and the comparison group were 21% and 44%  
284 respectively (Fig. 1C). Fig. 1D graphs the post-hoc survival analysis for the subgroup of patients who  
285 were administered and those who were not administered IM clozapine. Compared to oral, IM  
286 clozapine prescription was associated with a non-significantly reduced risk of clozapine  
287 discontinuation after discharge after adjusting for propensity scores (HR 0.37, 95% CI 0.11 - 1.24).  
288 Post-hoc Cox regression analysis showed an increased risk of clozapine discontinuation after  
289 discharge in the subgroup of patients who were administered IM clozapine compared to those  
290 prescribed but not administered IM clozapine, although this was not statistically significant (adjusted  
291 HR 5.35, 95% CI 0.62 - 45.87).

292

293 In the entire cohort of 39 patients, eight (20%) discontinued clozapine treatment during the follow-  
294 up period. Four (10%) were due to non-adherence or unknown reasons and four due to adverse  
295 effects (10%) unrelated to the IM formulation but rather to clozapine's established adverse effect  
296 profile (neutropenia, recurrent pneumonia).

297

298 On a practical level, the majority of patients who received IM clozapine were administered less than  
299 10 injections (n=13; 68%), with a discontinuation rate of 39% after 2 years of treatment. However,  
300 amongst the 6 patients who received more than 10 injections, two (33%) switched to oral clozapine  
301 and remained on it at the end of follow-up, whilst four discontinued it. The maximum number of  
302 injections administered before successful transition to oral treatment was 47.

303

304 Among the nine patients who required manual restraints during IM clozapine administration, seven  
305 remained on clozapine at follow-up, whilst two discontinued, one of which never agreed to transition  
306 from IM to oral clozapine.

307

308

## 309 **DISCUSSION**

310

311 In this retrospective clinical effectiveness study of patients prescribed IM clozapine, 92% of patients  
312 were successfully initiated on oral clozapine after IM prescription after a median of two IM  
313 administrations. Of patients with sufficient follow-up data, 76% remained on clozapine at two years  
314 from initiation. Clozapine discontinuation rates at two-year follow up were similar to a comparison  
315 group of patients who were prescribed only oral clozapine under the MHA in routine clinical practice.  
316 Correspondingly, clozapine discontinuation rates of 21% were observed at one-year follow-up post-  
317 discharge. This is at the lower end of that shown in previous studies, which demonstrate clozapine  
318 discontinuation rates between 16 and 66% across various countries (17).

319

320 Clozapine has consistently been shown to provide superior therapeutic benefits in treatment-  
321 resistant psychotic disorders (1) and should therefore be offered to all patients that meet these  
322 criteria. NICE guidelines highlight the importance of involving patients in decisions about the choice  
323 of medication (18). Nonetheless, some people diagnosed with a psychotic disorder lack insight and  
324 capacity to make an informed decision about optimal treatment options, particularly during acute  
325 illness, and may therefore make a non-capacitous decision to decline medication. Moreover, patients  
326 may be non-adherent as a direct response to delusional beliefs. There is compelling evidence to  
327 suggest that patients' refusal of clozapine in treatment-resistant psychotic disorders may have a  
328 significant negative impact on their long-term outcomes, and in the best interest of selected cases,  
329 enforced treatment may be the most appropriate option.

330

331 Presently, few naturalistic studies have demonstrated the potential of IM clozapine in initiating  
332 treatment, with a total enrolment of approximately 100 patients (9,10,11,12,13). To our knowledge,  
333 this is the largest study in the UK to report the use of short-acting IM clozapine for treatment initiation

334 and maintenance in patients with a treatment-resistant psychotic disorder. Our study further adds to  
335 the evidence for IM clozapine as a viable tool to allow patients whose illness is compromising their  
336 capacity to consent to appropriate treatment for their resistant psychotic disorder to access and  
337 benefit from clozapine.

338

339 Post-discharge discontinuation rates were as good as, or better than, a comparison group prescribed  
340 only oral clozapine. This suggests that the prescription of IM clozapine may achieve long-term clinical  
341 improvement and adherence to oral medication, even in those patients who are initially reluctant to  
342 engage with clozapine treatment, and that this is maintained even in a less restrictive setting.  
343 Consistent with previous studies (9,11,13), our data found no evidence that IM clozapine differs  
344 markedly from oral clozapine tolerability and adverse effects, with the one reported adverse event  
345 related to its formulation being swelling at the injection site. However, the lack of additional side  
346 effects reported may be attributed to its short-term use, often during titration and therefore at low  
347 doses, and this study was not powered nor designed to assess safety.

348

349 In the observational cohort, over half of those who had been prescribed IM clozapine chose to accept  
350 oral clozapine after being offered the choice between the two formulations. This finding is in line with  
351 an observational study by Hoge *et al.*, (20), according to which drug refusal developed into voluntary  
352 acceptance of treatment by most patients. Although preliminary, our data on discontinuation rates  
353 among those who did not require IM administrations is in line with previous findings (9,11) that the  
354 mere prescription of IM clozapine can increase adherence to clozapine without the need of IM  
355 administration. Post hoc analysis also showed that those patients who accepted oral clozapine when  
356 offered the IM had lower discontinuation rates compared to patients who declined oral and were  
357 administered IM clozapine. Although this result should be interpreted with caution due to small  
358 numbers, this may be attributed to a more entrenched attitude towards medication in the latter  
359 subgroup. Nevertheless, future qualitative work is required to understand the decision-making  
360 process underpinning a patient's decision to accept oral treatment when there is a choice between  
361 IM and oral dispensation.

362

363 Enforcement of treatment in psychiatry remains an ethically and clinically contentious practice.  
364 Previous literature has raised questions about the risks and benefits of enforcing clozapine treatment  
365 (22). This debate is ongoing, and it is beyond the scope of this article. However, in an investigation  
366 on patients' perception towards their involuntary admission, O'Donoghue *et al.*, (23) found that prior  
367 to discharge 72% of patients reported admission to have been necessary and almost 80% felt that  
368 the received treatment had been beneficial. Furthermore, previous studies have demonstrated  
369 improvement in inpatients with schizophrenia, irrespective of whether they received treatment  
370 voluntarily or involuntarily (24). Of interest, patients treated involuntarily tended to show even greater

371 symptom improvement than voluntary patients (24). Consistent with our findings, a recent small-  
372 scale study in the UK demonstrated positive outcomes with compulsory clozapine treatment by  
373 nasogastric administration. Nevertheless, the IM route remains well-established in clinical practice  
374 and avoids the considerably more invasive and distressing nature of nasogastric administration and  
375 its greater resource requirements (8).

376  
377 While our sample is too small to draw any firm conclusions, our findings may justify safely persisting  
378 with IM clozapine to achieve transition to oral, despite a prolonged refusal of oral treatment.  
379 Nevertheless, individual-based decisions are paramount to ensure the best interest of every patient.  
380 In our study, the use of manual restraints by nursing staff did not appear to influence clozapine  
381 discontinuation rates. Clozapine treatment has been shown to demonstrate a reduction in incidents  
382 of aggression and subsequent restraints, but whether this is comparable with IM administration  
383 remains unanswered. Furthermore, due to the lack of a formal evaluation, the psychological impact  
384 of restraint on both patients and nursing could not be investigated in our study.

385  
386 Our experience also suggests IM clozapine can be used to achieve oral clozapine initiation and avoid  
387 treatment interruption when used both consecutively and intermittently with oral clozapine. Previous  
388 authors have shown clozapine to be a cost-effective therapy in TRS (21), it is likely that an economic  
389 evaluation will demonstrate that IM clozapine prescription is highly cost-effective, especially in light  
390 of the absence of alternative treatments for this population.

391  
392 Despite the encouraging evidence generated from our study, it must be emphasized that those who  
393 declined treatment do not form a homogenous group and might have done so for a variety of reasons  
394 that warrant further examination before any actions are taken. Similarly, different factors could have  
395 played a role in favouring a transition from IM to oral clozapine, such as clinician-patient relationship  
396 or familiarity with nursing staff providing medication. In addition, relevant differences were observed  
397 between the two study groups. The patients offered IM clozapine had greater severity (CGI: mean  
398 6.18, SD 0.45) and longer duration of illness (mean years 21.32, SD 11.18) than the comparison  
399 population (CGI:  $5.35 \pm 0.64$ ; DOI:  $9.42 \pm 8.01$ ). However, previous studies on patients with a  
400 schizophrenia-spectrum disorder have suggested that those who refuse treatment tend to be more  
401 symptomatic and with worse functioning than those who agree to treatment (25). Furthermore, only  
402 18% of our patients were clozapine naïve at IM clozapine prescription, which might reflect the fact  
403 that IM clozapine is more likely to be recommended in patients with a previous good response to  
404 clozapine. Nevertheless, previous work has demonstrated clinical effectiveness in clozapine-naïve  
405 patients (11).

406  
407

408 *Limitations and future research*

409

410 The most important limitation of our study is the small sample size; however, this is consistent  
411 with previous studies evaluating IM clozapine use (9,11,13). This limits the interpretability of our  
412 results, as evidenced by the fairly large confidence intervals around the results. The limited number  
413 of patients included in the study has also prevented us from conducting further post-hoc analysis  
414 which could be useful in order to identify specific sub-groups of patients who could benefit from IM  
415 clozapine administration. Secondly, as follow-up data collection ended in July 2019, 26% (n=10) of  
416 patients could not be followed up after discharge since they were still in hospital. In addition, not  
417 all patients who were discharged had sufficient follow-up, as they were in the community for less  
418 than one year at data collection. Furthermore, the naturalistic nature of our study meant that  
419 clozapine continuation post-discharge was confirmed by prescription refills of oral clozapine and  
420 adherence to haematological monitoring requirements opposed to the more objective method of  
421 measuring serum clozapine levels. Equally, the quality of data available for reasons for clozapine  
422 discontinuation were limited to the information provided in electronic clinical record systems by the  
423 patient's clinical team. Our study needs to be replicated prospectively in a larger sample  
424 size possibly with a longer follow-up period.

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426 Another limitation lies in the comparator group. Patients who are prescribed IM clozapine are  
427 intrinsically different from those who accept oral clozapine, being less compliant and willing to accept  
428 any kind of treatment. Our comparator group differed from the cohort in age, and they had longer  
429 length of illness and higher CGI at clozapine initiation. We addressed this confounding-by-indication  
430 by calculating and adjusting for propensity scores in the Cox regression analyses, although some  
431 potential confounders may not have been measured and hence not included in the adjustment.  
432 Nonetheless, as the IM clozapine cohort included more severely unwell patients than the historical  
433 comparator, this would have, if anything, biased the results in favour of the latter. Another difference  
434 to highlight in the comparator group is the involvement of patients who were clozapine-naïve, whilst  
435 our IM clozapine cohort only had 18% of patients who had never taken clozapine before. It could be  
436 argued that the historical cohort covers a different timeframe compared to the IM clozapine cohort.  
437 Although this should be highlighted as a limitation, there hasn't been any major recent  
438 implementation of clozapine-focused services in SLAM,

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440 Due to the retrospective nature of the study, we did not have standardised scales on side effects,  
441 nor could we collect data on patients' subjective experience of IM clozapine treatment, which would  
442 have enhanced the study findings. Further research is needed to explore patients' perspectives on  
443 IM treatment both at the time of administration and longer term. In particular, qualitative analysis  
444 would add to our understanding and reveal avenues for more focused quantitative work. Finally,

445 future work should focus on which sub-groups of patients are more likely to benefit from IM clozapine  
446 prescription to support more targeted approaches to interventions.

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## 449 **CONCLUSIONS**

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451 The main finding of our study is that most of patients prescribed IM clozapine were able to  
452 successfully initiate oral clozapine after IM prescription, with half of patients not requiring  
453 administration of the injection. Discontinuation rates after initial IM clozapine prescription were  
454 consistent with current literature and similar to the comparison group. Discontinuation rates post  
455 discharge did not differ from those who were only prescribed oral treatment with clozapine from  
456 initiation. Our data, though preliminary, suggest that prescribing IM clozapine is a viable short-term  
457 tool to allow patients to access oral clozapine, the most effective available treatment for treatment-  
458 resistant psychotic disorders. Pain and swelling at injection site were the only reported side effects  
459 specific to the IM formulation and occurred only in a minority of patients. Additional evidence,  
460 possibly derived from robust prospective studies, is needed to provide new and more definite insights  
461 about the transition from IM to oral formulations of clozapine.

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465

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470 *of the NHS, the NIHR or the Department of Health.*

471

472 **Conflict of interest:**

473 *The authors declare that they have no conflict of interest.*

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475 **Authors contributions:**

476 *CC, EW, DT, AS and JM contributed to the conception and design of the study; CC, EO, SL and OD*  
477 *collected and analysed the data; FG, SS and JO took part in to the interpretation of the data; all*  
478 *authors contributed to the drafting and revision of the manuscript.*

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480 **Data Availability Statement**

481 *Authors had free access to the study data. All data will be available upon request to the authors.*

Table 1. Demographic and clinical characteristics

Characteristic	IM clozapine cohort			Comparison group
	Total sample (n=39) n (%)	IM clozapine prescribed and administered (n=19) n (%)	IM clozapine prescribed, not administered (n=20) n (%)	Oral clozapine prescribed (n=162) n (%)
Male gender	26 (56)	10 (53)	12 (60)	102 (63)
Ethnicity				
Caucasian	22 (56)	11 (58)	11 (55)	55 (34)
African or Caribbean	14 (36)	8 (42)	6 (30)	73 (45)
Others	3 (8)	0	3 (15)	33 (21)
Age at IM clozapine prescription (years $\pm$ SD)	46 $\pm$ 10.86	48 $\pm$ 9.25	44 $\pm$ 12.03	31 $\pm$ 11.54
Length of illness (years $\pm$ SD)	21.32 $\pm$ 11.18	23 $\pm$ 12.08	19.63 $\pm$ 10.31	9.42 $\pm$ 8.01
Diagnosis				
F20 Paranoid Schizophrenia	18 (46)	9 (47)	9 (45)	154 (95)
F32 Bipolar disorder / F25 Schizoaffective disorder*	21 (54)	10 (52)	11 (55)	8 (5)
CGI score at clozapine prescription (mean $\pm$ SD)	6.18 $\pm$ 0.45	6.26 $\pm$ 0.45	6.10 $\pm$ 0.45	5.32 $\pm$ 0.66
Hospital setting				
Acute ward	16 (41)	7 (37)	9 (45)	<i>na</i>
Psychiatric Intensive Care Unit	8 (20)	5 (26)	3 (15)	<i>na</i>
National psychosis Unit	14 (36)	7 (37)	7 (35)	<i>na</i>
Forensic ward	1 (3)	0 (0)	1 (5)	<i>na</i>
Concomitant medication				
Antipsychotic polypharmacy	9 (23)	5 (26)	4 (20)	<i>na</i>
Antidepressants	4 (10)	2 (11)	2 (10)	<i>na</i>
Mood stabiliser	9 (23)	4 (22)	5 (25)	<i>na</i>
Antihypertensive	13 (31)	6 (32)	7 (35)	<i>na</i>
Anticholinergic	7 (18)	2 (11)	5 (25)	<i>na</i>
Other	23 (60)	12 (63)	11 (55)	<i>na</i>

Length of admission (days ± SD)**	387.07±296.42	415.27 ± 281.16	369.83 ± 312.07	444.95 ± 712.21
Length of admission after clozapine prescription (days ± SD)**	280.07±225.41	232.18 ± 185.75	309.33 ± 246.98	239.16 ± 297.39
No previous trial with clozapine	7 (18)	5 (26)	2 (10)	162 (100)

\* *Schizoaffective disorder and Bipolar disorder combined to avoid presenting identifiable data*

\*\* *Only included patients who were discharged during the study period*

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515 Table 2. Characteristics of IM clozapine administrations

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<b>Characteristic</b>	<b>Median (min-max)</b>
Number of days of injection	2 (1 - 56)
Number of injections	- 1 injection: 6 patients - 2 injections: 4 patients - 3 – 10 injections: 3 patients - >10 injections: 6 patients
Maximum IM daily dose (mg)	75 (6.25 - 200)
Physical restraints required (n, %)	9 (47)
Number of restraints	- 0 restraints: 10 patients - 1 restraint: 5 patients - >1 restraint: 4 patients
Titration (n, %)	16 (84)
IM administered consecutively (n,%)	7 (50)
Patients who did not transition to oral clozapine (n,%)	3 (16)
Patients still in hospital at data collection (n,%)	8 (42)

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536 Table 3. Results from the Cox regression analyses

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<b>Cox regression analysis</b>	<b>Hazard ratio (95%CI)</b>	<b>Hazard Ratio adjusted for propensity scores (95%CI)</b>
<b><i>IM clozapine cohort vs oral clozapine comparison group</i></b>		
Clozapine discontinuation at 2-year follow-up	0.39 (0.19 – 0.80)	0.39 (0.14 – 1.06)
Clozapine discontinuation at 1-year post-discharge follow-up	0.54 (0.23 - 1.28)	0.37 (0.11 - 1.24)
<b><i>Post-hoc analysis: IM clozapine administered vs non-administered</i></b>		
Post-hoc analysis: Clozapine discontinuation at 2-year follow-up	10.34 (CI 1.26 - 84.70)	<i>Not applicable</i>
Post-hoc analysis: Clozapine discontinuation at 1-year post- discharge follow-up	5.35 (0.62 - 45.86)	<i>Not applicable</i>

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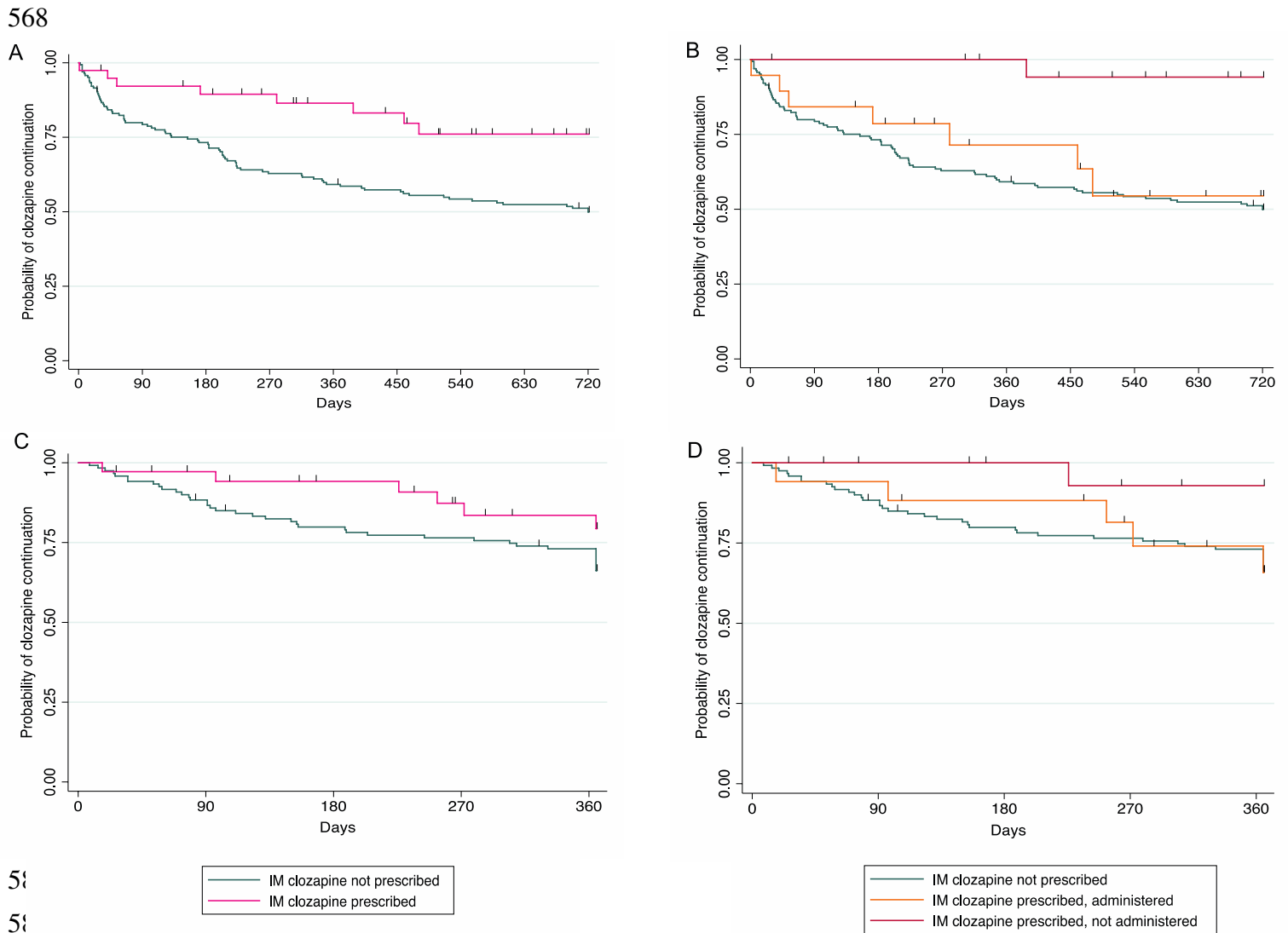
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561 Fig. 1. Kaplan-Meier survival curves - A. Clozapine discontinuation rates after IM (IM cohort) or oral  
 562 (comparison group) clozapine prescription. B. Post-hoc analysis of clozapine discontinuation rates  
 563 after IM or oral (comparison group) clozapine prescription after subdividing patients according to  
 564 whether they were administered and not administered IM clozapine. C. Clozapine discontinuation  
 565 rates after discharge in the cohort and the comparison group. D. Clozapine discontinuation rates  
 566 after discharge subdivided by whether IM clozapine was administered, versus the comparison group  
 567 of patients prescribed oral clozapine.



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598 Fig. 2. Study Profile for post-discharge survival analysis

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