



Psychiatrists' attitude towards the use of clozapine in the treatment of refractory schizophrenia: A nationwide survey

Essam Daod^{a,1}, Amir Krivoy^{b,c,d,1,*}, Gal Shoval^{b,c}, Salman Zubedat^e, John Lally^{d,f,g,h},
Limor Vadas^a, Abraham Weizman^c, Alon Reshef^a, Boaz Bloch^a

^a Psychiatry department, Emek Medical Center, Afula, Israel

^b Geha Mental Health Center, Petach-Tikva, Israel

^c Sackler Faculty of Medicine, Tel-Aviv University, Ramat-Aviv, Israel

^d Psychosis Studies Department, Institute of Psychiatry, Psychology and Neuroscience, King's College, London, UK

^e Physiology department, Faculty of medicine, Technion, Haifa, Israel

^f Department of Psychiatry, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland

^g Department of Psychiatry, School of Medicine and Medical Sciences, University College Dublin, St Vincent's University Hospital, Dublin, Ireland

^h St Vincent's Hospital Fairview, Dublin, Ireland



ARTICLE INFO

Keywords:

Treatment-resistant schizophrenia

Clozapine

Antipsychotics

Attitudes

Knowledge

ABSTRACT

Objectives: Clozapine is the most effective treatment for refractory schizophrenia, yet it remains underused in clinical practice. The current study examined the awareness, familiarity and attitude of a nationwide sample of Israeli psychiatrists regarding the use of clozapine.

Methods: Data were collected using questionnaires, completed by 295 psychiatrists. Participants were asked to score questions regarding clozapine procedures; familiarity with guidelines, drug properties, prescription and attitude towards specialized clozapine resources.

Results: About half (53.3%) of the psychiatrists reported initiating treatment with clozapine according to the guidelines, whereas 33% reported that they administered clozapine only after three or more unsuccessful antipsychotic treatments. Surprisingly, availability of specialized resources for clozapine treatment (such as clozapine clinics) was associated with delayed initiation of clozapine treatment, and a lower rate of clozapine administration. Barriers to clozapine use included concerns about patient adherence, side effects and partial compliance with the required blood monitoring.

Conclusions: Delaying or avoiding clozapine treatment to potentially eligible patients, despite familiarity with the drug efficacy and treatment guidelines, is a major mental health concern. However, executive allocation of resources to support the use of clozapine may be ineffective in promoting clozapine use.

1. Introduction

Clozapine was first shown to be an effective antipsychotic in the 1960s (Crilly, 2007). It was approved across Europe for the treatment of schizophrenia with the evident advantage of its low rate of extrapyramidal side effects, compared to the available first-generation antipsychotic drugs. Yet, potentially life-threatening side effects, such as agranulocytosis and paralytic ileus (Cohen, 2017), led to infrequent use of the drug. In 1988 the "US Clozaril Study" marked a turning point in clozapine treatment. This study showed for the first time the superiority of clozapine over chlorpromazine in alleviating psychotic symptoms in treatment refractory schizophrenia (TRS) (Kane et al., 1988). This

finding led to the reintroduction of clozapine for the treatment of refractory schizophrenia in Europe and USA. Consequently, the Food and Drug Agency approved the use of clozapine for resistant-schizophrenia under restricted clinical follow up and side effects monitoring.

TRS, defined as a treatment failure of two adequate trials of antipsychotic drugs, affects up to third of patients with schizophrenia (Lally et al., 2016). Clozapine was shown to be more effective than any other antipsychotic compound (Asenjo Lobos et al., 2010) for this patient population. Moreover, studies have shown that patients under clozapine treatment have the lowest rate of re-hospitalization and antipsychotic discontinuation compared to other antipsychotics (Ciudad et al., 2008; Taipale et al., 2018; Werneck et al., 2011). Yet, clozapine

* Corresponding author at: Geha Mental Health Center, Helsinki 1 St., Petach-Tikva, 49100, Israel.

E-mail address: Akrivoy@clalit.org.il (A. Krivoy).

¹ Both authors contributed equally to this manuscript.

continues to be underused in many countries (Bachmann et al., 2017; Bogers et al., 2016; Farooq et al., 2019; Warnez and Alessi-Severini, 2014) and there is a substantial delay of about four to ten years on average before clozapine initiation (Howes et al., 2012; Wheeler, 2008). Polypharmacy (two or more antipsychotics concurrently) in high doses are commonly used prior to clozapine, despite clear guidelines, indicating otherwise (Howes et al., 2012). Part of the reluctance to use clozapine is related to prescribers' negative attitude towards clozapine prescription.

A previous study exploring psychiatrists' attitudes towards clozapine treatment in Denmark showed that 64% of psychiatrists would rather combine two antipsychotics, than use clozapine, in contrast to the guidelines for the treatment of TRS (Nielsen et al., 2010). Another recent study showed that only 17% of outpatients with TRS were prescribed clozapine, while 68% of them continued to receive antipsychotics despite failure of more than three different antipsychotic agent (Alessi-Severini et al., 2013). In addition, this study showed that the median length of therapy prior to clozapine initiation was 8.9 years in males and 7.7 years in females (Alessi-Severini et al., 2013), exposing the patients to a lengthy period of active psychosis due to suboptimal response to antipsychotics prior to clozapine prescription. Another study from England, examined para-medical practitioners' (pharmacists, nurses, psychologists and occupational therapists) attitudes to clozapine initiation. It showed that though 81% of them were aware of the guidelines for schizophrenia, only 48% were aware of the particular guidelines for clozapine initiation (Gee et al., 2014). Most respondents reported that the requirement for weekly blood test monitoring is a major contributor to patient's refusal to clozapine initiation.

The Israeli guidelines state that the indication for commencing clozapine is following an unsuccessful trail of two antipsychotic compounds from different classes, for a sufficient duration and dose. In addition the guidelines detail the procedure for clozapine initiation and the measures needed for maintenance and safety regulation during clozapine treatment. In Israel, up to November 2013, the initiation of clozapine treatment was allowed only at psychiatric inpatient wards or hospital-affiliated psychiatry outpatient clinics. Currently, the initiation of clozapine is allowed at any psychiatric clinic or ward under mandatory weekly blood count monitoring for the first 18 weeks of treatment, and the prescription is issued weekly only after blood cell count test within normal range. Following these initial 18 weeks, the prescription is issued based on a monthly blood cell count monitoring.

The current study examined psychiatrists' awareness and familiarity with procedures associated with clozapine administration and their attitudes towards the use of clozapine. Based on the current literature, we hypothesized there will be low rate of familiarity and adherence with the guidelines for clozapine initiation and prescription. We also evaluated effects of various treatment settings (e.g. hospitals, clinics etc.) and the availability of special resources allocated to clozapine treatment (i.e. clozapine clinics) on psychiatrists' attitude towards clozapine use. We hypothesized that special resources would be associated with higher reported prescription rate of clozapine and familiarity with guidelines.

2. Materials and methods

2.1. Sample

We conducted a survey of psychiatrists across Israel to examine awareness, attitudes and experience regarding the use of clozapine in clinical practice. Questionnaires were distributed via e-mail (23.4%), air mail (8.1%) or delivered by hand (68.5%) in clinical settings or during professional conferences over two years from March 2015 to March 2017. During the study period (24 months), 620 out of 800 (78%), the total number of registered psychiatrists in the country, were randomly approached and of them 295 responded (response rate 47.5%).

2.2. Questionnaire

Data were collected regarding demographic information: gender, age, professional status, and place of work (see Appendix 1 for the complete questionnaire). Medical residents in Israel are allowed to prescribe medications, including clozapine under supervision of a senior physician. Residents participate actively in pharmacotherapeutic decision making. Moreover, after passing the board certification they are even more involved in clozapine initiation and prescribing, therefore their attitudes toward this medication are highly relevant. In order to assess awareness to clozapine treatment guidelines, participants were asked about their awareness of the Israeli Ministry of Health guidelines for the treatment of schizophrenia, and familiarity with the guidelines for initiating clozapine treatment and the use of therapeutic blood monitoring of clozapine levels.

The structured questionnaire also included items regarding the degree of clinical experience with clozapine: (A) the current number of clozapine treated patients under one's care and (B) under what clinical circumstances they initiate clozapine treatment. In addition, the participants were asked "How many unsuccessful antipsychotic treatment attempts are needed for you to consider commencing clozapine treatment?". In addition they were asked to rate the effectiveness of clozapine in the treatment of refractory schizophrenia on a Likert-like scale from 1 ("much less effective than other antipsychotics") to 5 ("greater effectiveness than other antipsychotics"). Similarly, participants were asked to rate their impression of patients' satisfaction with clozapine compared to other antipsychotics. Finally, participants were asked to rate items which they considered to be barriers to clozapine use or delays in clozapine initiation (e.g. side effects, logistics, cost, use).

2.3. Statistical analysis

Descriptive statistics were used for the demographic data and the scores of the various items. Student's *t*-test and analysis of variance (ANOVA) for parametric data were used as appropriate. Association and correlations between different variables were evaluated using Pearson's Chi-square or Pearson's correlation tests. All statistical tests were two-sided and the level for statistical significance was set to less than 0.05. The statistical analysis was performed using the Statistical Package for Social Sciences 21.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Demographics

Demographic characteristics are shown in Table 1. Fifty four percent of responders were males. Fifty three percent worked in inpatient wards and the remaining 47% in an outpatient setting. Of the sample, 40% were residents (trainees in senior level) and 60% specialists. Thirty two percent of the psychiatrists were in managerial positions.

3.2. Familiarity with clozapine prescription guidelines

Sixty six percent of psychiatrists reported familiarity with the general treatment guidelines for schizophrenia, 64.4% indicated that they knew the guidelines for prescribing clozapine in schizophrenia and 69.5% were familiar with the procedures for clozapine initiation in treatment resistant schizophrenia. Only 15% were aware of the recommended therapeutic plasma clozapine level.

3.3. Attitude toward clozapine usage

There was a discrepancy between the reported mean rate of patients who met the criteria for the treatment of clozapine (34% of patients under the participants' personal care) and the mean 14.6% patients who

Table 1
Demographic data of the participants ($N = 259$).

	n	%
Gender		
Males	160	54.2
Females	130	44.1
Missing value	5	1.7
Age (years)		
Up to 35	82	27.8
36–45	106	35.9
46–55	62	21
More than 56	40	13.6
Missing value	5	1.7
Main workplace		
Community clinic	41	13.9
Outpatient Clinic (General Hospital)	51	17.3
Outpatient Clinic (Psychiatric Hospital)	35	11.9
Private clinic	6	2
Total	(133)	(45.1)
Psychiatric open ward (General Hospital)	30	10.2
Psychiatric open ward (Psychiatric Hospital)	29	9.8
Psychiatric locked ward (Psychiatric Hospital)	52	17.6
Psychiatric locked ward (Chronic)	4	1.4
Psychiatric Combined wards (General Hospital)	18	6.1
Psychiatric Combined wards (Psychiatric Hospital)	23	7.8
Total	(156)	(52.9)
Missing value	8	2.7
Professional status		
Specialist psychiatrist with more than 5 years experience	127	43.1
Specialist psychiatrist with less than 5 years experience	47	15.9
Total	(174)	(59)
Resident psychiatrist – Junior	71	24.1
Resident psychiatrist – Senior	45	15.3
Total	(126)	(39.4)
General doctor	1	0.3
Missing value	4	1.4
Management position		
Yes	95	32.2
No	196	66.4
Missing value	4	1.4

were reported to be actually treated with clozapine (42% of potential patient candidates) by the participants. In addition, about half (53.3%) of all respondents reported initiating treatment with clozapine according to the accepted guidelines (initiating clozapine following two unsuccessful antipsychotic trials), while 33% of the respondents noted that they initiated clozapine only after three or more failures of treatment with other antipsychotics.

3.4. Knowledge on effectiveness

While most psychiatrists (90.6%) acknowledged that clozapine is more effective or much more effective than atypical antipsychotics in the treatment of TRS, two thirds (66.7%) thought that it is also more effective for treatment-responsive schizophrenia.

3.5. Satisfaction

Most of the psychiatrists (65.4%) reported that schizophrenia patients are satisfied with clozapine treatment more or the same as with atypical antipsychotics. However, 25.8% reported that patients are more satisfied with non-clozapine compounds. Only 8.5% of the psychiatrists thought that patients are not satisfied with clozapine treatment.

3.6. Factors encouraging vs. delaying clozapine treatment

Factors that encourage clinicians in initiating clozapine treatment and their effect on their decision making are shown in Fig. 1. Most of the clinicians (62%) thought that availability of monitoring plasma

clozapine level would support their decision to initiate clozapine. In addition, 60.4% of clinicians noted that availability of institutional / regional specialized clozapine clinic may be helpful, and more than half (53%) reported that the availability of institutional care coordinators, who would monitor the treatment process, may also encourage their decision to initiate clozapine treatment. There was no difference between participants with or without additional resources with regards their preference for future additional resources to support them.

Factors that may delay clinicians' decision to commence clozapine are shown in Fig. 2. Eighty two percent and 64.1% of the participants reported that the risk of non-adherence and their own concerns regarding clozapine's adverse effect burden, respectively, were the leading factors for delaying their decision to initiate clozapine. With regards to side effects, the risk of agranulocytosis (71.3%) was the most concerning factor contributing to a delay in clozapine initiation, followed by myocarditis (34.2%), electrocardiogram changes (18.0%), diabetes (9.5%), constipation (4.7%) and hypersalivation (3.4%).

Ninety four percent of the sampled psychiatrists reported that the burden of blood testing was the main reason for patients' decision to avoid clozapine initiation, whereas 83.4% thought that patients' concerns regarding clozapine side effects are a leading barrier for delaying clozapine initiation.

3.7. Effect of special resources allocated to clozapine treatment (Clozapine clinics)

Forty-six psychiatrists (15.9%) reported having additional resources for the treatment of clozapine in their local mental health services. Interestingly, only 36.9% of the psychiatrists who have additional resources consider initiation of clozapine treatment according to the guidelines compared to 58.9% of those who do not have additional resources ($\chi^2_{(7)} = 23.9, P < 0.001$)

Psychiatrists with additional resources in their workplace report they tend to prescribe more oral atypical antipsychotics as an alternative to clozapine treatment (53.2%), with fewer using typical and atypical antipsychotics combinations (8.5%) than psychiatrists who do not have available additional resources (28.6% and 24.1%, respectively, $\chi^2_{(5)} = 16.5, P < 0.005$).

3.8. Residents versus specialists

Certified specialists ($n = 174$) compared to residents ($n = 126$) were more familiar with the guidelines for initiating clozapine treatment (mean score 4.08 ± 0.95 vs. 3.24 ± 1.13 , $t_{(217)} = 6.54, P < 0.0001$, respectively). Similarly, specialists were more familiar with the guidelines for clozapine treatment in resistant schizophrenia compared to residents (score 4.17 ± 0.82 vs. 3.22 ± 1.29 , $t_{(176)} = 6.98, P < 0.0001$, respectively). In addition, specialists were more familiar with the guidelines for clozapine treatment monitoring compared to residents (score 4.23 ± 0.80 vs. 3.34 ± 1.23 , $t_{(180)} = 6.87, P < 0.0001$, respectively).

Surprisingly, despite the residents' apparent lower familiarity with the guidelines, the majority of them (63%) noted that they support initiating treatment according to the guidelines and only 25% advocate clozapine initiation after failure of three or more antipsychotic treatment trials. In contrast, only 47.6% of specialists reported to initiate treatment with clozapine according to the guidelines, whereas 39.5% of the specialists indicated that they begin treatment with clozapine following failure of three or more treatment trials ($\chi^2_{(7)} = 17.364, P < 0.015$).

There was no difference between specialists with more than five years of experience compared to specialists with less experience in regards to familiarity with the guidelines.

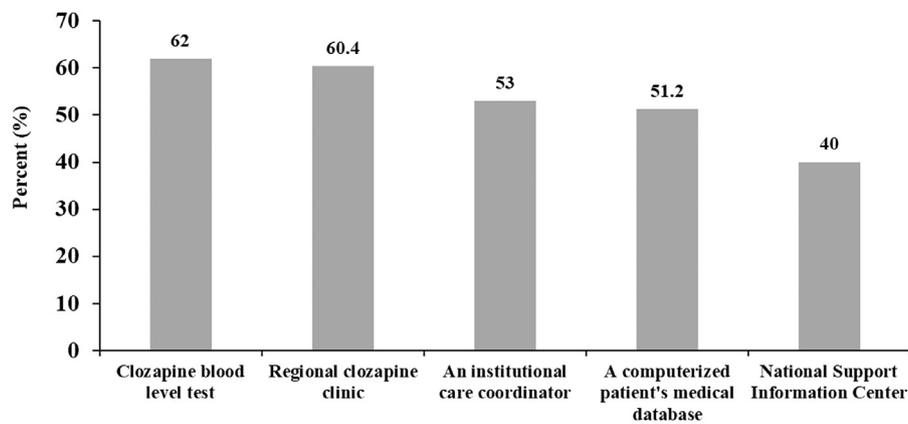


Fig. 1. Rate of psychiatrists' reports of factors encouraging clinicians to initiate clozapine treatment.

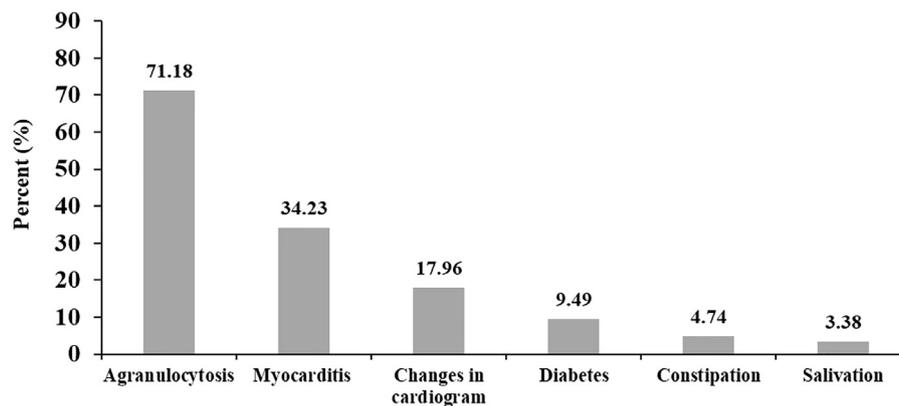


Fig. 2. Rate of psychiatrists' reports of side effects as a cause of delaying/avoiding initiation of clozapine treatment.

4. Discussion

In this study, we examined the attitude to clozapine administration and the awareness of its treatment guidelines in a sample of 259 psychiatrists. The main findings of this study were that only about two thirds of the sample prescribers are familiar with clozapine initiation guidelines and indications and that only about half reported adherence with guidelines in their practice.

Participants noted that they are familiar with treatment refractory schizophrenia treatment guidelines, and the general guidelines for clozapine initiation. However, only about half (53.3%) of the psychiatrists reported adherence with the guidelines. Likewise, most psychiatrists (90.6%) thought that clozapine is a more effective antipsychotic, or a much more effective than other antipsychotics for the treatment of refractory schizophrenia. Yet, the actual rate of clozapine treated patients in Israel is low (6.5% of schizophrenia patients) (Unpublished data).

The leading clozapine-associated adverse effects that could discourage psychiatrists from prescribing clozapine in Israel are similar to those reported in other countries (Alessi-Severini et al., 2013; Gee et al., 2014; Sernyak and Rosenheck, 2008) in previous studies. Specifically, the risk for agranulocytosis (71.18%) was the leading factor, followed by myocarditis, changes in electrocardiogram, emerging diabetes, constipation and hyper-salivation. This is despite the fact that agranulocytosis is a relatively rare side effect with incidence rate of around 3% (Cohen et al., 2012; Lally et al., 2017; Malik et al., 2018; Munro et al., 1999) and constipation is the leading fatal side effect with incidence rate of around 10% and case-fatality rate of 15%–27.5%. (Cohen, 2017; Cohen et al., 2012; Shirazi et al., 2016; West et al., 2017).

Interestingly, the availability of specific resources for clozapine treatment did not affect the reported rate of use of the compound. This

counterintuitive finding suggests that allocating special resources for clozapine treatment (such as dedicated clozapine clinics or institutional care coordinators) does not increase the consideration of psychiatrists to initiate clozapine according to the guidelines. It is possible, however, that such additional resources may reduce the exposure of psychiatrists to this option or they may rely on the knowledge of the specialized team, therefore their own knowledge and familiarity with guidelines might be lower. This assumption is supported by the fact that those who had access to specialized resources reported to consider clozapine initiation later. Surprisingly, 43.3% of the psychiatrists who reported to have additional resources available in their workplace reported that they initiate clozapine after the failure of three or more treatment trials (more than the guidelines require) compared to 31% of psychiatrists without additional resources in their workplace. Yet, 60.4% of the total sample noted that an institutional / regional specialized clinic may be helpful and about a half (53%) noted that an institutional care coordinator who monitors the treatment process may assist in the decision to start clozapine treatment.

Almost all of the sampled psychiatrists (94%) thought that the burden of blood testing was the main reason for patients' decision to avoid clozapine initiation. This finding was indeed found in several other studies as barrier for initiating clozapine on behalf of patients (Bogers et al., 2016; Farooq et al., 2019). One potential modality to overcome this barrier might be using a point of care leukocyte count for monitoring. It was shown that patients tolerated capillary blood testing with a point-of-care device better than traditional venous sampling at a laboratory (Bogers et al., 2015).

Limitations of this study should be considered. It is a survey among a cross-sectional sample of psychiatrists in Israel; therefore, the generalizability of the findings is unclear. However, although we collected data from about 20% of Israeli psychiatrists, the distribution of age,

gender and levels of expertise is representative of the entire psychiatrists' population.

5. Conclusions

In this study, we found that most psychiatrists are aware of the efficacy of clozapine, though only half of those were familiar with the recommendations for the initiation of clozapine in refractory

schizophrenia. However, despite psychiatrists' awareness of clozapine's efficacy, the psychiatrists reported underuse of clozapine for treatment-resistant schizophrenia. Barriers for initiation of clozapine include concerns about compliance, tolerance, comorbid physical health disorders and difficulty in adhering with blood monitoring. It appears that the exclusive allocation of resources to encourage, facilitate and support clozapine use does not increase the appropriate guideline-recommended use of clozapine

Appendix. Clozapine attitudes questionnaire (Daod et al.)

1 Professional status:

- A Specialist psychiatrist, over 5 years
- A Specialist psychiatrist, less than 5 years
- A Resident Psychiatrist before Stage 1
- A Resident Psychiatrist after stage 1
- A Physician without any specialty *

*A physician who works in the field of psychiatry but does not have the status of intern or specialist

1 Are you in a managerial position?

- A Yes
- A No

1 Your main place of work:

- A Community clinic
- A Outpatient clinic in general hospital
- A An outpatient in a psychiatric hospital
- A An open department is active in a general hospital
- A The Open Department is active in a psychiatric hospital
- A An active closed ward in a psychiatric hospital
- A A chronic closed ward
- A An integrated department (open and closed) in a general hospital
- A Combined department (open and closed) in a psychiatric hospital
- A private clinic

1 sex:

- A male
- A female

1 age:

- A Up to 35
- A 36–45
- A 46–55
- A Over 56

1 What proportion of patients who are directly under your care meets CLOZAPINE treatment criteria?

- A 0–20%
- A 21% – 40%
- A 41% – 60%
- A 61% – 80%
- A 81% – 100%
- A Do not know

1 When will you recommend starting CLOZAPINE in schizophrenia patients?

- A As a first line of treatment
- A As a second treatment line
- A After a failed treatment attempt with two antipsychotics (typical and atypical)
- A After a failed treatment attempt with two antipsychotics
- A After a failed treatment attempt with three antipsychotics
- A After a failed treatment attempt with four antipsychotics
- A other, specify: _____
- A Do not know

1 Do other clinical / administrative resources are being allocated in your workplace to support starting CLOZAPINE (such as a treatment center doctor, a special clinic, etc.)?

- A No
- A Yes, please specify: _____
- A Do not know

1 Of the total number of patients under your direct care, how many of them are being treated with CLOZAPINE?

- A 0–20%
- A 21% – 40%
- A 41% – 60%
- A 61% – 80%
- A 81% – 100%
- A Do not know

1 How well do you know the treatment guidelines and algorithms in schizophrenia?

not familiar at all 1 2 3 4 5 very familiar

1 How well do you know the current Ministry of Health criteria for treating CLOZAPINE for patients with schizophrenia?

not familiar at all 1 2 3 4 5 very familiar

1 How well do you know the procedure for initiating CLOZAPINE in resistant schizophrenia patients?

not familiar at all 1 2 3 4 5 very familiar

1 To the best of your knowledge, what is the therapeutic level of CLOZAPINE in the blood?

- A 50–149ng/mL
- A 150–249ng/mL
- A 250–350ng/mL

A 351–450ng/mL

A Do not know

1 How would you rate the efficacy of CLOZAPINE in resistant schizophrenia patients compared to other SGA?

No efficacy at all 1 2 3 4 5 very effective

1 How would you rate the efficacy of CLOZAPINE in non-resistant schizophrenia compared with the other SGA?

No efficacy at all 1 2 3 4 5 very effective

1 In your opinion, what is the degree of satisfaction of patients with CLOZAPINE compared to patients with other SGA?

Not satisfied at all 1 2 3 4 5 very satisfied

1 If you decide that the patient, despite meeting the criteria, cannot get CLOZAPINE. What alternative treatment would you recommend?

A SGA

A FGA

A SGA long - term INJECTION

A FGA long - term INJECTION

A A combination of SGA & FRA

A Do not know

* We would appreciate if you state your answer: _____

1 What do you think is the most dangerous side effect of CLOZAPINE?

A Agranulocytosis

A Myocarditis

A Constipation

A Changes in ECG heart chart

A Diabetes

A Do not know

A Other _____

1 Choose three of the following side effects that will prevent you from starting CLOZAPINE treatment and rate them according to the degree of disturbance (from 1 less to 3 the most)

A Myocarditis ____

A Constipation ____

A Changes in the heart chart ____

A Diabetes ____

A Drooling__

A Urinary incontinence ____

A OCD ____

A No side effect

A Do not know

1 In your opinion, to what extent do the following factors (A-F) delay the patient's decision to start CLOZAPINE treatment?

A The patient's need for full physical and laboratory assessment before starting treatment?

No delay at all 1 2 3 4 5 very delay

A The patient's need for weekly blood tests?

No delay at all 1 2 3 4 5 very delay

A The patient's doubt about the efficacy of CLOZAPINE treatment

No delay at all 1 2 3 4 5 very delay

A The patient's fear of the side effects of CLOZAPINE

No delay at all 1 2 3 4 5 very delay

A The cost of the drug

No delay at all 1 2 3 4 5 very delay

A Other, please specify if: _____

No delay at all 1 2 3 4 5 very delay

1 In your opinion, to what extent do the following factors (A-I) delay your decision as a clinician to start CLOZAPINE treatment?

A Your unfamiliarity with CLOZAPINE

No delay at all 1 2 3 4 5 very delay

A Your concern about the administrative factors related to the initiation of treatment (Receiving treatment approval, weekly prescription)

No delay at all 1 2 3 4 5 very delay

A Your concern about patient's intolerance to the drug

No delay at all 1 2 3 4 5 very delay

A Your doubt about the efficacy of CLOZAPINE

No delay at all 1 2 3 4 5 very delay

A Your concern of the life threatening side effects of CLOZAPINE

No delay at all 1 2 3 4 5 very delay

A Your concern that the patient will not continue the treatment

No delay at all 1 2 3 4 5 very delay

A Your concern that the patient would not attend the weekly blood tests

No delay at all 1 2 3 4 5 very delay

A Your concern that the CLOZAPINE will worsen existing psychopathology, such as OCD

No delay at all 1 2 3 4 5 very delay

A Other (please specify if there is one) _____

No delay at all 1 2 3 4 5 very delay

1 In your opinion, to what extent would the following factors (A and F) support your decision to start CLOZAPINE treatment?

A A computerized database that coordinates the medical data of CLOZAPINE patients

don't support at all 1 2 3 4 5 very supportive

A An institutional care coordinator, who coordinates and monitors the CLOZAPINE treatment process

don't support at all 1 2 3 4 5 very supportive

A CLOZAPINE National Information Center (safety, etc.)

don't support at all 1 2 3 4 5 very supportive

A CLOZAPINE Institutional / Regional Clinic which coordinates and monitors the treatment process.

don't support at all 1 2 3 4 5 very supportive

A Available blood test (Therapeutic Blood Monitoring – TDM)

don't support at all 1 2 3 4 5 very supportive

A Other (please specify if there is one) _____

don't support at all 1 2 3 4 5 very supportive

SUPPLEMENTARY INFORMATION

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2019.03.029](https://doi.org/10.1016/j.psychres.2019.03.029).

References

- Alessi-Severini, S., Le Dorze, J.-A., Nguyen, D., Honcharik, P., Eleff, M., 2013. Clozapine prescribing in a Canadian outpatient population. *APLoS One* 8, e83539. <https://doi.org/10.1371/journal.pone.0083539>.
- Asenjo Lobos, C., Komossa, K., Rummel-Kluge, C., Hunger, H., Schmid, F., Schwarz, S., Leucht, S., 2010. Clozapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst. Rev.*, CD006633. <https://doi.org/10.1002/14651858.CD006633.pub2>.
- Bachmann, C.J., Aagaard, L., Bernardo, M., Brandt, L., Cartabia, M., Clavenna, A., Coma Fusté, A., Furu, K., Garuolienė, K., Hoffmann, F., Hollingworth, S., Huybrechts, K.F., Kalverdijk, L.J., Kawakami, K., Kieler, H., Kinoshita, T., López, S.C., Machado-Alba, J.E., Machado-Duque, M.E., Mahesri, M., Nishtala, P.S., Piovani, D., Reutfors, J., Saastamoinen, L.K., Sato, I., Schuiling-Veninga, C.C.M., Shyu, Y.-C., Siskind, D., Skurtveit, S., Verdoux, H., Wang, L.-J., Zara Yahní, C., Zoëga, H., Taylor, D., 2017. International trends in clozapine use: a study in 17 countries. *Acta Psychiatr. Scand.* 136, 37–51. <https://doi.org/10.1111/acps.12742>.
- Bogers, J.P.A.M., Bui, H., Herruer, M., Cohen, D., 2015. Capillary compared to venous blood sampling in clozapine treatment: patients' and healthcare practitioners' experiences with a point-of-care device. *Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol.* 25, 319–324. <https://doi.org/10.1016/j.euroneuro.2014.11.022>.
- Bogers, J.P.A.M., Schulte, P.F.J., Van Dijk, D., Bakker, B., Cohen, D., 2016. Clozapine underutilization in the treatment of schizophrenia: how can clozapine prescription rates be improved? *J. Clin. Psychopharmacol.* 36, 109–111. <https://doi.org/10.1097/JCP.0000000000000478>.
- Ciudad, A., Haro, J.M., Alonso, J., Bousoño, M., Suárez, D., Novick, D., Gilaberte, I., 2008. The Schizophrenia Outpatient Health Outcomes (SOHO) study: 3-year results of antipsychotic treatment discontinuation and related clinical factors in Spain. *Eur. Psychiatry J. Assoc. Eur. Psychiatr.* 23, 1–7. <https://doi.org/10.1016/j.eurpsy.2007.09.008>.
- Cohen, D., 2017. Clozapine and gastrointestinal hypomotility. *CNS Drugs* 31, 1083–1091. <https://doi.org/10.1007/s40263-017-0481-5>.
- Cohen, D., Bogers, J.P.A.M., van Dijk, D., Bakker, B., Schulte, P.F.J., 2012. Beyond white blood cell monitoring: screening in the initial phase of clozapine therapy. *J. Clin. Psychiatry* 73, 1307–1312. <https://doi.org/10.4088/JCP.11r06977>.
- Crilly, J., 2007. The history of clozapine and its emergence in the US market: a review and analysis. *Hist. Psychiatry* 18, 39–60. <https://doi.org/10.1177/0957154X07070335>.
- Farooq, S., Choudry, A., Cohen, D., Naeem, F., Ayub, M., 2019. Barriers to using clozapine in treatment-resistant schizophrenia: systematic review. *BJPsych Bull* 43, 8–16. <https://doi.org/10.1192/bjb.2018.67>.
- Gee, S., Vergunst, F., Howes, O., Taylor, D., 2014. Practitioner attitudes to clozapine initiation. *Acta Psychiatr. Scand.* 130, 16–24. <https://doi.org/10.1111/acps.12193>.
- Howes, O.D., Vergunst, F., Gee, S., McGuire, P., Kapur, S., Taylor, D., 2012. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *Br. J. Psychiatry J. Ment. Sci.* 201, 481–485. <https://doi.org/10.1192/bjp.bp.111.105833>.
- Kane, J., Honigfeld, G., Singer, J., Meltzer, H., 1988. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch. Gen. Psychiatry* 45, 789–796.
- Lally, J., Ajnakina, O., Di Forti, M., Trotta, A., Demjaha, A., Kolliakou, A., Mondelli, V., Reis Marques, T., Pariante, C., Dazzan, P., Shergil, S.S., Howes, O.D., David, A.S., MacCabe, J.H., Gaughran, F., Murray, R.M., 2016. Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. *Psychol. Med.* 46, 3231–3240. <https://doi.org/10.1017/S0033291716002014>.
- Lally, J., Malik, S., Krivoy, A., Whiskey, E., Taylor, D.M., Gaughran, F.P., Flanagan, R.J., Mijovic, A., MacCabe, J.H., 2017. The use of granulocyte colony-stimulating factor in clozapine rechallenge: a systematic review. *J. Clin. Psychopharmacol.* 37, 600–604. <https://doi.org/10.1097/JCP.0000000000000767>.
- Malik, S., Lally, J., Ajnakina, O., Pritchard, M., Krivoy, A., Gaughran, F., Shetty, H., Flanagan, R.J., MacCabe, J.H., 2018. Sodium valproate and clozapine induced neurotropenia: a case control study using register data. *Schizophr. Res.* 195, 267–273. <https://doi.org/10.1016/j.schres.2017.08.041>.
- Munro, J., O'Sullivan, D., Andrews, C., Arana, A., Mortimer, A., Kerwin, R., 1999. Active monitoring of 12,760 clozapine recipients in the UK and Ireland. *Beyond pharmacovigilance. Br. J. Psychiatry J. Ment. Sci.* 175, 576–580.
- Nielsen, J., Dahm, M., Lublin, H., Taylor, D., 2010. Psychiatrists' attitude towards and knowledge of clozapine treatment. *J. Psychopharmacol. Oxf. Engl.* 24, 965–971. <https://doi.org/10.1177/0269881108100320>.
- Sernyak, M.J., Rosenheck, R.A., 2008. Antipsychotic use in the treatment of outpatients with schizophrenia in the VA from fiscal years 1999 to 2006. *Psychiatr. Serv. Wash. DC* 59, 567–569. <https://doi.org/10.1176/ps.2008.59.5.567>.
- Shirazi, A., Stubbs, B., Gomez, L., Moore, S., Gaughran, F., Flanagan, R.J., MacCabe, J.H., Lally, J., 2016. Prevalence and predictors of clozapine-associated constipation: a systematic review and meta-analysis. *Int. J. Mol. Sci.* 17. <https://doi.org/10.3390/ijms17060863>.
- Taipale, H., Mehtälä, J., Tanskanen, A., Tiihonen, J., 2018. Comparative effectiveness of antipsychotic drugs for rehospitalization in schizophrenia—a nationwide study with 20-year follow-up. *Schizophr. Bull.* 44, 1381–1387. <https://doi.org/10.1093/schbul/sbx176>.
- Warnez, S., Alessi-Severini, S., 2014. Clozapine: a review of clinical practice guidelines and prescribing trends. *BMC Psychiatry* 14, 102. <https://doi.org/10.1186/1471-244X-14-102>.
- Werneck, A.P., Hallak, J.C., Nakano, E., Elkis, H., 2011. Time to rehospitalization in patients with schizophrenia discharged on first generation antipsychotics, non-clozapine second generation antipsychotics, or clozapine. *Psychiatry Res.* 188, 315–319. <https://doi.org/10.1016/j.psychres.2011.04.004>.
- West, S., Rowbotham, D., Xiong, G., Kenedi, C., 2017. Clozapine induced gastrointestinal hypomotility: a potentially life threatening adverse event. A review of the literature. *Gen. Hosp. Psychiatry* 46, 32–37. <https://doi.org/10.1016/j.genhosppsych.2017.02.004>.
- Wheeler, A.J., 2008. Treatment pathway and patterns of clozapine prescribing for schizophrenia in New Zealand. *Ann. Pharmacother.* 42, 852–860. <https://doi.org/10.1345/aph.1K662>.