Irish Journal of Psychological Medicine (2024), 1–7
doi:10.1017/ipm.2024.35

CAMBRIDGE UNIVERSITY PRESS

Original Research

Psychiatrists' views on clozapine prescribing in Ireland

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Abstract

Introduction: Despite proven effectiveness in refractory schizophrenia, clozapine remains underutilised, and it is important to understand potential reasons for this. This study's aim was to examine in a National sample of Consultant Psychiatrists their knowledge of, attitudes and perceived barriers to clozapine use.

Methods: A novel questionnaire was designed and distributed by email to 275 Consultant Psychiatrists in Republic of Ireland.

Results: Twenty-eight percent ($n = 77$) completed the survey, with 55% of respondents practicing for 15 or more years. Clinicians expressed confidence in managing clozapine treatment and side effects and were well aware of clozapine's clinical effectiveness and guideline-based use. A majority indicated insufficient experience managing rechallenge and half expressed insufficient experience managing adverse events. Perceived patient factors were highlighted as barriers with 69% of respondents reporting patients' concern about effectiveness and 50% regarding tolerability. Sixty-four percent ($n = 40$) indicated that a specialised/tertiary clozapine service would facilitate initiation, with 57% ($n = 36$) reporting less frequent blood monitoring would aid clozapine prescribing. A majority identified that access to dedicated staff (81%, $n = 51$) and dedicated day hospital services (84%, $n = 53$) would facilitate community initiation.

Conclusion: Consultants are familiar with clozapine use and related guidelines. Dedicated staff and facilities for clozapine use is one identified structural change to enhance clozapine prescribing in Ireland. Tertiary service or clinical advice service would assist in clozapine rechallenge cases or in managing significant adverse events. More structured patient education regarding clozapine effectiveness and professional development programmes focused on managing side effects and rechallenge may promote clozapine use.

Keywords: Treatment-resistant schizophrenia; psychosis; antipsychotics; clozapine; attitude

(Received 30 January 2024; revised 13 June 2024; accepted 9 August 2024)

Introduction

Clozapine is the only evidence-based treatment for treatment-resistant schizophrenia (TRS) (Lally & Gaughran 2019; Wagner *et al.* 2021; Siskind *et al.* 2021). It is well established that clozapine is under prescribed in many different countries (Bachmann *et al.* 2017; Bogers *et al.* 2016; Farooq *et al.* 2019; Warnez and Alessi-Severini 2014), with delays in initiation of clozapine treatment ranging from four to ten years depending on the setting (Barnes *et al.* 2022; Howes *et al.* 2012; Wheeler 2008). This may lead to reduced response rates and poorer outcomes (Griffith *et al,* 2021).

There is a paucity of studies assessing clozapine use in Ireland, with the limited research in this area suggestive of a pattern of underutilisation consistent with international findings (Bachmann *et al*, 2017; Bogers *et al.* 2016; Farooq *et al.* 2019; Warnez & Alessi-Severini 2014). In their twenty-year cohort study, Doyle *et al.* (2017) found that only 16% of eligible cases in their sample were prescribed clozapine. This is significantly lower than expected, given that 1 in 3 schizophrenia cases are anticipated to have TRS (Siskind *et al.* 2021; Lally & Gaughran 2019).

Understanding why the only antipsychotic medication known to be effective in treatment-resistant schizophrenia is underutilised is critical to ensuring appropriate and evidence-based treatment is available to patients with TRS.

Farooq *et al.* (2019), in their systematic review, identified three categories of factors that can delay clozapine initiation. These factors can be classified as barriers related to patients and the drug, clinician-related barriers, and health and system related factors. Primary clinician-related barriers were a lack of prescribing experience and concerns with monitoring requirements and pharmacological characteristics of clozapine (blood monitoring and adverse effects). Institutional characteristics that may favour increased clozapine prescribing include a local 'culture' of clozapine prescribing, prescriber's adherence to evidence-based medicine principles, higher rates of linkage to primary care, and higher funding allocated to research and education among others. This study identified key interventions which may favour clozapine prescribing such as education for prescribers and psychiatric trainees, audit of antipsychotic prescribing, integrated clozapine community clinics, clozapine community initiation teams, and simplification of blood monitoring (Farooq *et al.* 2019).

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Cite this article: Grant A, McManus R, Belay H, Mahon M, Murad F, O' Donoghue B, and Lally J. Psychiatrists' views on clozapine prescribing in Ireland. *Irish Journal of Psychological Medicine* https://doi.org/10.1017/ipm.2024.35

Patients declining to undergo blood tests, psychiatrists personal experience of prescribing, and concerns related to clozapine side effects are key factors, which may delay prescribing as highlighted in different studies (Nielsen *et al.* 2010; Gee *et al.* 2014; Daod *et al.* 2019; Okhuijsen-Pfeifer *et al.* 2019; Verdoux *et al.* 2018; Apiquian *et al.* 2004; de Hert *et al.* 2016; Flanagan *et al.* 2020; Ignatovic Ristic *et al.* 2022).

There are limited data with respect to psychiatrists' attitudes towards and experience with prescribing clozapine (Daod *et al.* 2019; Gee *et al.* 2014; Rezaie *et al.* 2022; Ignjatovic Ristic *et al.* 2022; Grover *et al.* 2015), and this has not previously been examined in Ireland. Understanding psychiatrists' attitudes and experiences relating to clozapine prescribing, along with institutional and service level barriers to prescribing are critical to improving clozapine services and access to recommended treatment for patients. Available evidence indicates that delays in initiating clozapine, where indicated, is associated with poorer clinical outcomes, and jeopardises the likelihood of response (Griffith *et al.* 2021; Nielsen *et al.* 2012; Üçok *et al.* 2015; Yoshimura *et al.* 2017).

As this knowledge is lacking in Ireland, this study aimed to assess a representative range of psychiatrists attitudes to clozapine use, knowledge about clozapine, and perceived barriers to clozapine use in practice.

Methods

Study design

We conducted a cross-sectional study examining consultant psychiatrists' attitudes and experience with clozapine prescribing and use. Consultant psychiatrists in Ireland were invited by email to participate in an online questionnaire hosted on Survey Monkey from November 2021 to January 2022. Participation was voluntary and all responses were anonymised.

Participants

Questionnaires were distributed by email to 275 consultant psychiatrists practicing in Ireland inviting them to participate in the online questionnaire. A total of 77 (28%) consultant psychiatrists participated in the survey.

Data collection

A novel questionnaire assessing clinicians' attitudes, experience with, and perceived barriers to clozapine was designed by two of the study authors (AG & JL). The questionnaire items were selected from a review of the literature relevant to clozapine use and prescribing by consultant psychiatrists (Gee *et al*, 2014; Nielsen *et al.* 2010; Ignjatovic Ristic, 2021; Daod *et al.* 2019). It consisted of 65 questions in total and was made up of four sections (see appendix 1). The structured questionnaire included the following sections: demographic details; perceived patient factors which may delay clozapine initiation; clinician factors which may delay initiation; factors that may facilitate clozapine initiation – these questions were scored by participants using a Likert scale (Likert responses varied from strongly agree to strongly disagree, and very frequent to not frequent at all where appropriate to the phrasing of the questions). There was a final section of questions which addressed participant knowledge, experience, and views on clozapine.

Statistical analysis

Descriptive analyses (frequencies, percentages, means, and standard deviation) on demographic data and the individual survey item scores were performed as appropriate. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 26.0 for Windows (SPSS Inc., IBM, New York, USA).

Results

Demographics (See Appendix for Table 1)

Twenty-eight percent ($n = 78$) of consultant psychiatrists completed the survey. Fifty eight percent of participants were male ($n = 45$), Fifty-five percent ($n = 42$) had 16 or more years clinical experience as psychiatrists and a majority (71.4%) of participants worked in both inpatient and outpatient settings.

Knowledge/experience

Ninety-five percent ($n = 56$) reported being familiar with the treatment guidelines and algorithms in schizophrenia. Ninety-two percent ($n = 54$) reported that medication was the most important treatment for schizophrenia.

Ninety-two percent ($n = 54$) of consultants had 10 or more patients currently on clozapine, while 3% ($n = 2$) had never prescribed clozapine. Ninety-two percent ($n = 44$) reported their patients were satisfied or very satisfied with clozapine, whilst 85% ($n = 50$) reported that patients were more satisfied with clozapine than other second-generation antipsychotics.

Eighty-one percent ($n = 48$) would use clozapine after two failed antipsychotic treatment trials, while 52% ($n = 31$) would combine antipsychotics before using clozapine and 59% ($n = 35$) would prescribe a long-acting injectable antipsychotic before using clozapine.

A majority of respondents reported that access to information about clozapine's safety or ease of access to advice on clozapine use would delay initiation. Most respondents stated that insufficient training or a lack of confidence were not factors that would delay initiation (see Table 2).

Over seventy percent of clinicians disagreed that either risk of agranulocytosis ($n = 52$) or cardiometabolic side effects would delay initiation ($n = 47$).

Ninety-three percent ($n = 62$) of respondents reported that clozapine was safe to initiate in the community. Seventy-one percent ($n = 51$) reported clozapine to be suitable in the first year of illness.

Over seventy-eight percent ($n = 52$) agreed that clozapine was associated with reduced mortality compared to other antipsychotics and that clozapine was associated with reduced suicide risk.

Respondents reported the number of their patients currently on clozapine ranged from zero to seventy-five, with a median of fifteen. Respondents reported prescribing clozapine from three times in their career to over five hundred times, with some unable to quantify due to high frequency. Eight percent ($n = 5$) have prescribed clozapine less than ten times in their career.

Patient factors that may delay clozapine initiation (see Table 3)

Sixty percent ($n = 45$) of consultants reported that patients' reticence or declining to provide baseline blood tests would delay initiation, whilst eighty four percent ($n = 63$) reported declining / reticence about regular blood monitoring would delay initiation.

https://doi.org/10.1017/ipm.2024.35 Published online by Cambridge University Press

In relation to patient reticence/declining regarding the need for hospital admission for titration of medication, forty six percent ($n = 35$) reported this would not frequently delay initiation, whilst 33% ($n = 25$) reported it would somewhat frequently delay initiation, with 13% ($n = 10$) and 5% ($n = 4$) reporting fairly frequently and very frequently delaying initiation, respectively.

Patients being unconvinced about clozapine's effectiveness was reported by sixty-nine percent ($n = 52$) of consultants as frequently delaying initiation, with 70% ($n = 53$) reporting that patients not perceiving advantages with clozapine would delay initiation.

Clinician factors

Eighty-one percent ($n = 58$) reported that administrative issues, such as time taken to register with clozapine monitoring service, would not frequently be an issue. Seventy-eight percent ($n = 56$) reported that lack of specialised service for initiation would not frequently delay initiation; seventy-two percent ($n = 52$) reported that staff resources (i.e. lack of staff to monitor) did not delay initiation, with 50% ($n = 36$) reporting that need for admission or delay in obtaining admission would serve to delay.

Sixty-seven percent ($n = 48$) reported difficulty getting patients' carers to agree to use clozapine would frequently delay initiation.

A majority of consultants, 79% ($n = 57$) and 88% ($n = 63$) respectively, did not feel that difficulty in identifying suitable patients or diagnostic uncertainty were frequently factors that delayed prescribing of clozapine.

Factors that facilitate initiation of clozapine (see Table 4)

Eighty-one percent ($n = 51$) and 84% ($n = 53$) of respondents reported that dedicated staff to arrange initiation of clozapine as an outpatient, and dedicated day hospital placements, respectively, would facilitate initiation of clozapine. Fifty-one percent ($n = 32$) reported that additional administrative support was likely to facilitate initiation. Ninety three percent ($n = 62$) of participants disagreed that clozapine is unsafe to initiate in the community. Over seventy-percent ($n = 45$) of clinicians reported that access to clozapine advice would facilitate initiation, and over sixty percent ($n = 40$) indicated that a specialised/tertiary clozapine service would.

Discussion

This study found that the majority of consultant psychiatrists report adequate experience, training, and familiarity in using clozapine. It identified that respondents considered patient reticence regarding blood monitoring as a barrier to initiating clozapine. Service level interventions such as dedicated community-based facilities (day hospitals/clinics) and additional clinical staff to support initiation would improve clozapine use in Ireland. Similarly access to specialist advice service and possible educational programmes aimed at increasing understanding of clozapine, risks and benefits was identified as a means of improving clozapine use.

Most psychiatrists identified community initiation as a feasible approach and highlighted additional community-based support as facilitating clozapine use. This contrasts with UK survey data in which one third of clinicians did not know that clozapine could be initiated in a community setting (Tunagaraza *et al.* 2015). These results were the highest rated agreements in our findings and consistent with findings from Gee et al. (2014). Hospital initiation of clozapine has been the historically accepted practice and was previously required by the Clozaril Prescribing Monitoring Service as part of the product licensing requirement, due to the risk of hypotension, excess sedation, seizures, and other adverse events. This practice places a high resource burden on teams (O'Brien 2004). A recent mirror image cohort study found commencing clozapine in the community to be safe and cost effective (Butler et al., 2022).

Nearly half (46%) of psychiatrists agreed that insufficient experience managing clozapine rechallenge would delay initiation, highlighting the need for more understanding of prescribers' confidence specifically in complex case management. Despite 95% of consultants reporting familiarity with treatment guidelines and the majority disagreeing that insufficient training in using clozapine/managing adverse events, or a lack of confidence in managing clozapine treatment would delay initiation, nearly half (46%) of psychiatrists agreed that insufficient experience managing clozapine rechallenge would delay initiation. This could highlight a specific knowledge gap and could indicate a role for specific training or education for prescribers in the management of these complex cases, particularly in the absence of access to tertiary or specialised clozapine services. In this context, with 72% of psychiatrists reported that access to clozapine advice would likely or very likely facilitate initiation, and with 64% reporting that access to a specialised or tertiary clozapine service would also likely facilitate initiation it is imperative to further evaluate the role of or potential benefit of a specialist advice resource in reducing delay in clozapine initiation.

High levels of perceived patient reticence to adhere to phlebotomy as a factor that may delay initiation is common in international literature (Nielsen *et al.* 2010; Daod *et al.* 2019) however the possibility of overestimation by psychiatrists as a delaying factor is possible (Angermeyer *et al.* 2001; Taylor *et al.* 2000). This serves to highlight the importance in future work of evaluating patient views on the use of clozapine. Further, it may be mitigated by the wider use of point of care leukocyte testing (POCT) for monitoring. There is increasing evidence to support the use of POCT haematological monitoring allowing the measure of an FBC using capillary blood from a fingerprick sample with comparable results to that from a venous sample (Atkins, 2023; Bogers *et al.* 2016). The use of POCT is favourable to patients (Bogers *et al.* 2016), and its use may contribute to removal of venous blood sampling as a perceived barrier to clozapine use. Additionally, our study suggested that the level of acceptability and quality of life improvements for patients treated with clozapine are high, and this along with improved education regarding effectiveness and tolerability should be provided to all clozapine eligible patients to improve clozapine uptake. Given that 69% of respondents perceived that patients being unconvinced of clozapine effectiveness was a barrier to initiation, this may reflect the way in which clozapine treatment is introduced to patients, with a tendency to emphasise the negative aspects of clozapine use such as monitoring and side effects, with a secondary focus on the benefits, such as improved clinical response, and the negative consequences of not proceeding with a clozapine trial. Interventions to improve patient education ensuring understanding of potential benefits and risks of not commencing clozapine may be beneficial.

A high degree of self-reported familiarity with treatment guidelines was reported (95%, $n = 56$) in contrast with the staff in the South London Maudsley NHS Foundation Trust where 52% ($n = 75$) reported being familiar with initiation of clozapine (Gee et al 2014). Over ninety percent of respondents had ten or

https://doi.org/10.1017/ipm.2024.35 Published online by Cambridge University Press

more patients on clozapine. This contrasts with Nielsen et al (2009) who found that forty-eight percent of their psychiatrists surveyed had treatment responsibility for fewer than five patients on clozapine. The high degree of familiarity and confidence is consistent with an Iranian study carried out by Rezaie *et al.* (2023) and Zheng et al.'s work in Singapore and Hong Kong (2022).

Despite the expressed familiarity with clozapine use and prescribing, it remains the case that clozapine is underutilised in Ireland. A longitudinal FEP cohort study identified 16% ($n = 28$) were prescribed clozapine at twenty years follow up, with a 6.7 year delay in clozapine initiation (Doyle *et al.* 2017). This is characteristic of significant delay especially considering that early onset treatment resistance is characteristic for the majority of TRS patients (Lally & Gaughran 2016). Further, while 71% respondents reported clozapine use to be suitable in the first year of illness, there remains a proportion of clozapine prescribers who may not yet be aware that the majority of treatment resistant cases are of early onset in the illness course. Outside of this FEP service data (Doyle *et al.* 2017), National clozapine prescribing information is not readily available. In our study, lack of experience or unfamiliarity with clozapine is not a prescriber related barrier to clozapine use, though how this translates to actual clozapine use in practice is yet to be determined in an Irish setting.

Strengths and limitations

Our study was a cross-sectional study conducted among a convenience sample of Irish psychiatrists; we did not have access to contact details for the total population of practicing Consultant Psychiatrists in Ireland (estimated to be 700), There was a 28% response rate, and we could not assess the knowledge and attitudes of the non-responders, potentially limiting the generalisability of our findings to all Irish psychiatrists. There may be a selection bias introduced, in that, those responding are clinicians more familiar with clozapine and who recognise the strong evidence base for its use in TRS. Further, non responders may be those who do not use clozapine in practice or would not be as familiar with clozapine use. A response rate of 28% is reasonably consistent with other surveys of psychiatrists' attitudes to clozapine (Farooq *et al.* 2019; Oloyede *et al.* 2023) and while a selection bias may have been introduced, all respondents were clinicians with responsibility for prescribing clozapine, and it remains a reasonable level of response with some key emerging themes identifiable. We did not collect data on differences in attitudes of prescribers based on location or place of work, with a large scale UK study identifying geographical differences in clozapine prescription rates. (Whiskey *et al.* 2021).

The survey was self-reported, thus introducing potential for individual responder bias, though as all responses were anonymised, potentially reducing the risk of this. In a survey of attitudes towards clozapine, assessing patient and carer perspectives would be valuable, to allow for a better understanding how prescriber related factors are interacting with patient and carer barriers to clozapine use. In our study, patient and carer perceptions of clozapine were estimated by psychiatrists, limiting this interpretation from our study.

Conclusion

Irish psychiatrists have good knowledge about the clinical indications and effectiveness of clozapine. Key service level improvements including improved infrastructure to allow for community initiation and development of tertiary referral service to offer recommendations in relation to complex clozapine resistance and rechallenge cases would be interventions to support wider clozapine prescribing. Future study is required to ascertain rates of clozapine use and underutilisation nationally and to evaluate patient and carer views and experience with clozapine use to better understand other barriers and facilitators for clozapine prescribing.

Financial support. The study is undertaken as part of the Health Research Board (HRB) funded PROGRESS study (HRB Grant ID: APRO-20023-005). The funding source(s) had no role in the design of this study and did not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Competing Interests. The authors declare none.

Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that ethical approval for publication of this paper has been provided by St Vincent's University Hospital Audit Committee.

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https://doi.org/10.1017/ipm.2024.35 Published online by Cambridge University Press

Appendix A

Table 1. Demographic data of participants (n = 77)

	n	(%)
Gender		
Female	31	(40.3%)
Male	45	(58.4%)
Prefer Not To Say	1	(1.3%)
Length of time practicing as psychiatrist		
0–5	8	(10.4%)
6–10	13	(16.9%)
11–15	14	(18.2%)
16–20	17	(22.1%)
>20	25	(32.5%)
Place of Work		
Inpatient	5	(6.5%)
Outpatient	12	(15.6%)
Inpatient/Outpatient	55	(71.4%)
General Hospital	5	(6.5%)

Table 2. Factors relating\ to prescriber knowledge and experience

Prescriber Knowledge/\experience	Strongly Disagree % (n)	Disagree	Agree	Strongly Agree
There is conflicting information about its safety	50.7% (34)	35.8% (24)	11.9% (8)	1.5%(1)
Ease of access to advice on clozapine use	59.7% (40)	31.3% (21)	5.9% (4)	2.9% (2)
Insufficient training in clozapine use	46.1% (35)	32.9% (25)	13.2% (10)	5.3% (4)
Lack of confidence/experience in managing clozapine treatment	64.2% (43)	23.8% (16)	11.9% (8)	0% (0)
Insufficient experience in managing clozapine adverse events	50.7% (34)	25.3% (17)	38.8% (26)	0% (0)
Insufficient experience in clozapine rechallenge for patients with a clozapine discontinuation due to side-effects	26.8% (18)	26.8% (18)	38.8% (26)	7.4% (5)
Risk of agranulocytosis delays initiation	40.3% (27)	37.3% (25)	19.4% (13)	2.9% (2)
Risk of cardiometabolic side effects delays initiation	35.8% (24)	34.3% (23)	23.8% (16)	5.9% (4)
Risk of Agranulocytosis remains the same throughout the treatment course	30.3% (20)	46.9% (31)	22.7% (15)	0% (0)
It is associated with increased mortality compared with to other antipsychotics	28.8% (19)	50% (33)	21.2% (14)	0% (0)
It is associated with reduced suicide risk	13.4% (9)	9.9% (6)	65.7% (44)	11.9% (8)
It is not safe to initiate in community	32.8% (22)	59.7% (40)	5.9% (4)	1.5% (1)

https://doi.org/10.1017/ipm.2024.35 Published online by Cambridge University Press

Table 3. Rate of psychiatrists' report of patient factors that may delay clozapine initiation

Patient Factors	Not Frequently % (n)	Somewhat Frequently	Fairly Frequently	Very Frequently
Refusal/reticence about obtaining baseline blood tests	40% (30)	34.7% (26)	14.7% (11)	10.7% (8)
Refusal/reticence about regular blood monitoring	16% (12)	45.3% (34)	25.3% (19)	13.3% (10)
Refusal/reticence due to need for hospital admission for titration	46.1% (35)	32.9% (25)	13.2% (10)	5.3% (4)
Patient unconvinced about clozapine effectiveness	30.3% (23)	35.5% (27)	5.3% (4)	1.3% (1)
Patient concerned about tolerability	14.5% (11)	36.8% (28)	30.3% (23)	18.4% (14)
Significant medical factors/complications	31.6% (24)	31.6% (24)	27.6% (21)	9.2% (7)
Patients do not perceive advantages with clozapine	26.3% (20)	38.2% (29)	22.4% (17)	9.2% (7)

Table 4. Rate of psychiatrists' report of factors that may facilitate initiation of clozapine were they available

	Very Unlikely % (n)	Unlikely	Likely	Very Likely
Additional administrative support (e.g. patient registration)	11.1% (7)	38.1% (24)	34.9% (22)	15.9% (10)
Additional staff dedicated to obtaining baseline blood tests	12.7% (8)	23.8% (15)	41.2% (26)	22.2% (14)
Dedicated hospital beds to enable initiation of clozapine as an inpatient	12.7% (8)	28.9% (18)	39.7% (25)	19.05% (12)
Dedicated staff to arrange and monitor initiation of clozapine as an outpatient	6.4% (4)	12.7% (8)	50.7% (32)	30.2% (19)
Dedicated day-hospital placements to initiate clozapine as an outpatient	4.8% (3)	11.1% (7)	49.2% (31)	34.9% (22)
Access to clozapine advice	12.7% (8)	15.9% (10)	59.7% (37)	12.7% (8)
Specialised/tertiary clozapine service	9.5% (6)	27.0% (17)	41.3% (26)	22.2% (14)
Less frequent blood monitoring	9.5% (6)	33.3% (21)	38.1% (24)	19.1% (12)

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