

Clozapine prescribing in the UK: views and experience of consultant psychiatrists

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Abstract

Objectives: It has been repeatedly shown that clozapine is underutilized and there is delayed use of it in clinical practice.

Method: An online survey was sent to 2771 consultant psychiatrists registered with the Royal College of Psychiatrists in the UK. A total of 243 responded to this survey. The survey elicited their views and experiences in using clozapine as well as to identify what may be the underlying causes for its underutilization.

Results: Over 75% acknowledged that they had good training in using clozapine and about 56% had clozapine-dedicated service. However, 40.5% preferred to use several other antipsychotics prior to considering clozapine. A third felt it was not safe to start clozapine in the community and 42% had less than five patients on clozapine. Eleven possible reasons for clozapine underutilization were identified including concerns about side effects, patients not wanting to have blood tests and lack of experience or knowledge. Knowledge deficiency in certain aspects of clozapine use were identified, e.g. a third of respondents did not know that the risk of agranulocytosis changes with time, 42.7% did not think that clozapine can reduce substance use, while 20% were not aware of its benefit in reducing suicidal risk.

Conclusions: Important areas of concern such as managing side effects and deficiency in evidence-based use of clozapine were identified. These can be targeted in training and professional development programme.

Keywords: antipsychotics, clozapine, treatment-resistant schizophrenia

Background

Clozapine was reintroduced in clinical practice worldwide following a seminal study by Kane and colleagues [Kane *et al.* 1988]. Since then, several other studies [Rosenheck *et al.* 1997; Lewis *et al.* 2006; McEvoy *et al.* 2006], meta-analysis [Davis *et al.* 2003; Wahlbeck *et al.* 1999; Essali *et al.* 2009] and reviews [Agid *et al.* 2010] have repeatedly shown that clozapine is more efficacious than other antipsychotics in treatment-resistant schizophrenia (TRS). Despite good evidence of efficacy, clozapine is associated with a number of side effects. A review by Safferman and colleagues [Safferman *et al.* 1991] lists drowsiness or sedation (39%), salivation (31%), tachycardia (25%), dizziness (19%), constipation (14%), nausea and vomiting (11%) as among the commonly reported side effects of clozapine. Other side effects include weight gain, hypotension, sweating, seizures, and dry mouth [Safferman *et al.* 1991; Kumlien and

Lundberg, 2010]. In addition, clozapine has other rare but serious side effects such as agranulocytosis, cardiomyopathies and myocarditis [Killian *et al.* 1999; Raja, 2011]. There are some suggestions that clozapine's side-effects profile and the need to undergo regular blood tests are some of the underlying reasons why patients and clinicians are less likely to opt for its use [Nielsen *et al.* 2010; Raja, 2011; Patel, 2012]. Despite all of the above-mentioned challenges, however, under the current stringent monitoring system which includes regular blood tests, clozapine continues to be administered safely and is well tolerated by many [Agid *et al.* 2010].

Evidence from a number of studies suggests that clozapine remains underutilized in many parts of the world [Weissman, 2002; Joobar and Boksa, 2010]. The reasons for the inadequate use remain speculative and may include the perception of the

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drug as dangerous medicine [Farooq and Taylor, 2011] or difficulties associated with initiating and maintaining the treatment. A study by Taylor and colleagues [Taylor *et al.* 2003] showed that on average it took 5 years before patients are started on clozapine in the UK. It was 9.7 years for patients in New Zealand [Wheeler, 2008]. The reasons for delayed use of clozapine remain obscure, and may include several factors related to patients, carers and clinicians. A recent survey by Nielsen and colleagues [Nielsen *et al.* 2010] on the attitude and knowledge of 137 psychiatrists in Denmark of which only 100 were consultants revealed that some have never prescribed clozapine despite having worked for over 5 years. A total of 64% preferred to use combinations first and 66% felt patients on clozapine were less satisfied. There is no UK based study in peer-reviewed journals that has looked into the attitudes and the practice of consultant psychiatrists regarding the use of clozapine. We aimed to explore their views and their experience on the use of clozapine.

Methodology

We conducted an online survey of consultant psychiatrists (herein addressed as psychiatrists) registered with the faculty of the general adult and community psychiatry of the Royal College of Psychiatrists. Following the approval by the faculty, the College sent the link to the survey through email shot to its members in September 2013, requesting to complete the survey. No follow-up or reminder email was sent. Two weeks after the email, all responses were collected and analysed.

A questionnaire was designed to elicit the views and the experiences of practising psychiatrists about the use and barriers in using clozapine. The questionnaire was based on the evidence gathered from literature and experience in clinical practice. The questionnaire was piloted first for clarity, relevance and ease of administration, in a group of 10 local psychiatrists. The questionnaire consisted of three main parts: part one dealt with general demographic information and in which sector they worked, e.g. community mental health team, inpatients or assertive outreach. The second part had open-ended questions asking about the experience and views in using clozapine. Part three had 16 statements that dealt with their experience, knowledge and attitude toward using clozapine in clinical practice. Responders had five options to choose from based on a five-point

Likert scale: strongly agree, agree, do not know, disagree and strongly disagree. The questionnaire is available from the authors on request. Data analysis was carried out using SPSS 21 for window. Descriptive statistics were used to describe demographic information and views of the participants. Chi-square test was used to examine association between categorical responses.

Results

The survey was sent to 2771 members, 245 (8.8%) responded within 2 weeks of the survey. Two were excluded for the following reasons; one was a nurse prescriber and the other has worked as a consultant for just a month. The final analysis is based on 243 responses (total responses may not add to 243 in some areas due to differing proportions responding to each question). Table 1 gives a summary of the demographic details of participants and clozapine service characteristics. The majority of respondents were male ($n = 141$, 58.8%), in the age group 41–50 years ($n = 104$, 43.5%) and almost half ($n = 122$, 50.2%) worked as community mental health team (CMHT) psychiatrists. Only a small proportion ($n = 28$, 11.7%) were in academic posts. On average consultants have been in their current posts for 7.2 years, and have worked as consultant for 11.2 years. Due to functionalization of the teams, the majority ($n = 182$, 74.9%) had worked in just one sector while 61 (25.1%) worked across several sectors.

Service characteristics and delay in starting clozapine

A total of 230 responded to the question about having clozapine-dedicated service in their trusts. The majority ($n = 130$, 56.5%) agreed that they have a dedicated service for patients on clozapine. Most consultants agreed that they have started someone on clozapine either in the last 6 months ($n = 144$, 65.2%) or during the last 1 year ($n = 113$, 67.7%). There was no significant association between having a dedicated service for clozapine and consultant starting patients on clozapine in the previous 6 ($\chi^2 = 0.154$, d.f. = 1, $p = 0.70$) or 12 months ($\chi^2 = 0.019$, d.f. = 1, $p = 0.89$).

Figure 1 outlines the average number of patients on clozapine for each consultant. Of the 192 who provided the estimates, 32 (16.7%) had no patients despite having been in their current posts for 7 years, 48 (25%) had between 1–4 patients, an indication that nearly 42% had less

Table 1. Demographics and clozapine service characteristic.

Description	n (%)
Gender	
Female	99 (41.3)
Male	141 (58.8)
Academic post	
YES	28 (11.7)
NO	212 (88.3)
Age distribution	
31–40	59 (24.7)
41–50	104 (43.5)
51–60	62 (25.9)
Over 61	14 (5.9)
Sector currently working in	
Community mental health team	122 (50.2)
Inpatient	66 (27.2)
Crisis/home treatment team	27 (11.1)
Rehabilitation	25 (10.3)
Assertive outreach	19 (7.8)
Early intervention team	18 (7.4)
Forensic	8 (3.3)
Others	44 (18.1)
Working in one sector of mental health	
YES	182 (74.9)
NO	61 (25.1)
Have clozapine dedicated service	
YES	130 (56.5)
NO	100 (43.5)
Agreed there was a delay in starting clozapine	
YES	184 (80.7)
NO	44 (19.3)
Have started clozapine in past 6 months	
YES	144 (65.2)
NO	77 (34.8)
Have started clozapine in past 12 months	
YES	113 (67.7)
NO	54 (32.3)
Have used clozapine for other conditions	
YES	104 (45.4)
NO	125 (54.6)

than 5 patients on their caseload at the time of the survey. There was association of having less than five patients and working as inpatient ($\chi^2 = 15.33$, d.f. = 1, $p < 0.001$) or crisis and home treatment team (HTT) psychiatrist ($\chi^2 = 4.02$, d.f. = 1, $p < 0.05$). There was no

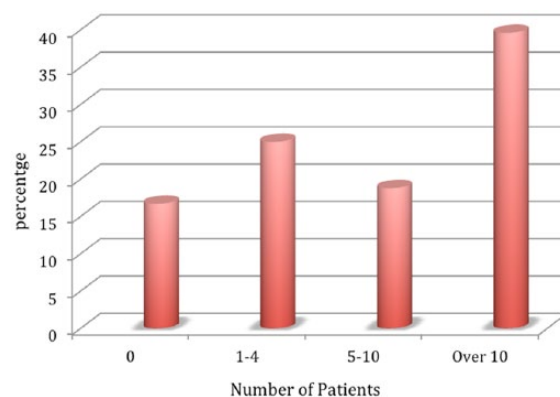


Figure 1. Number of patients on clozapine per consultant.

Table 2. Reasons for delayed use of clozapine.

	Frequency
Side effects/metabolic problems	80
Reluctance to have blood test	74
Lack of experience/knowledge	71
Patient/family reluctance to use clozapine	60
Clinicians concerns about poor compliance	54
Complex to initiate and manage	42
Service fragmentation/no community support	39
Need to admit/bed shortage	32
Tendency to try other antipsychotics first	28
Delayed diagnosis/not sure about diagnosis	12
Negative views of others	8

association with working as CMHT, assertive outreach team, early intervention service or rehabilitation consultants.

Out of 228 participants who responded to the question about the possible delay in starting clozapine, 184 (80.7%) agreed that there was a delay in initiating clozapine treatment. Table 2 summarizes what clinicians believed to be the underlying reasons. The frequently mentioned reasons were concerns about side effects including metabolic problems, reluctance to have blood test, knowledge deficiency or lack of experience, the general reluctance among patients to take clozapine, concerns about poor compliance and service fragmentation and poor community support.

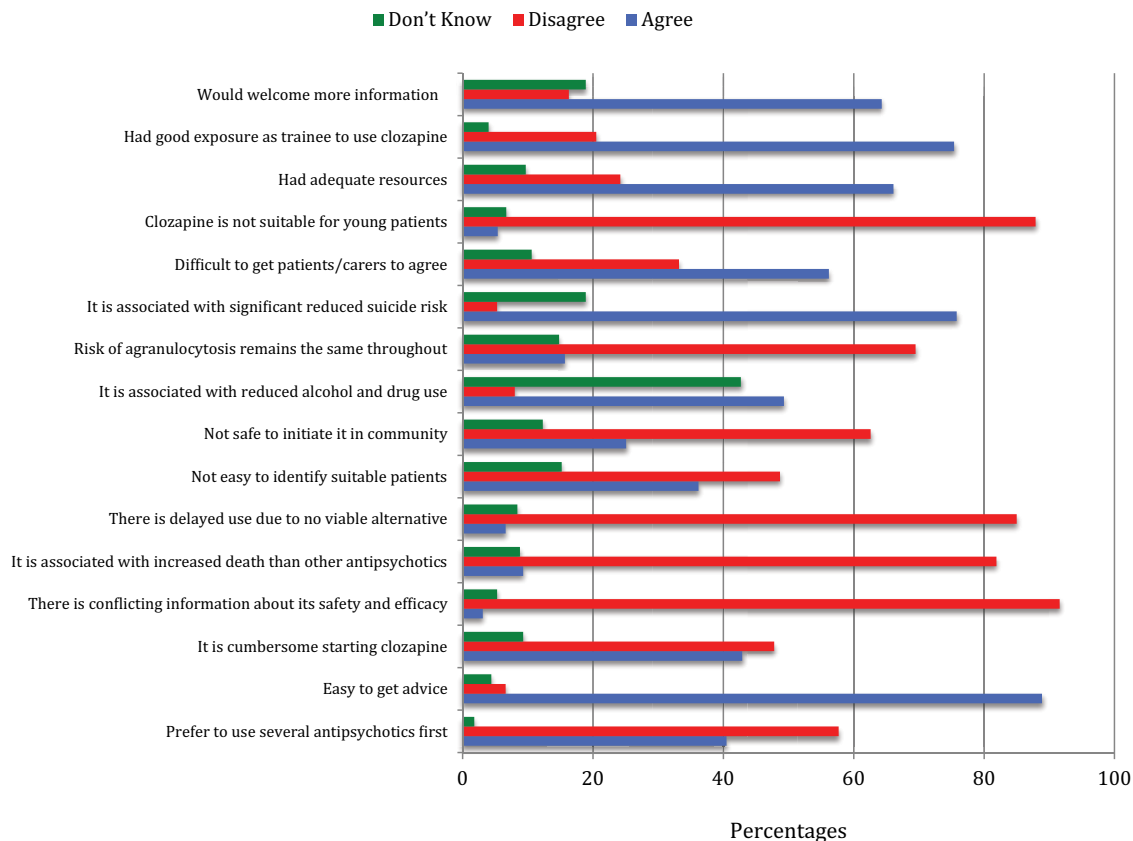


Figure 2. Knowledge, attitude and experience of using clozapine.

Some specific issues highlighted as regards to delayed use of clozapine included the need for inpatient admission before starting clozapine; with some trusts insisting that patients must be admitted first. However, for those earmarked for clozapine, most were not acutely ill and hence were not given priority for inpatient beds or even under HTTs. Psychiatrists trying several antipsychotics felt that clozapine was the last resort or were concerned about serious side effects and the drug was perceived to be associated with high risks. Lack of experience/knowledge was attributed to several factors such as frequent job changes, lack of exposure as trainee and inadequate pharmacological knowledge, resulting in overestimation of side effect and not appreciating higher efficacy of clozapine in TRS.

Knowledge and attitude in the use of clozapine

Figure 2 summarizes the findings on the general knowledge and attitude towards clozapine utilization. About three quarters of respondents ($n = 169$, 75.4%) agreed that they had good

exposure in using clozapine as trainees. Nearly 90% agreed that clozapine is suitable for young patients. About a quarter ($n = 55$, 24.2%) felt that they lacked adequate resources and 127 (56.2%) agreed that it is difficult to get patients and carers to accept to go on clozapine. Nearly a third either felt that the risk of agranulocytosis remains the same throughout treatment with clozapine or did not know that the risk changes. A significant number, 42.7% did not know that there is some evidence that the use of clozapine may be associated with reduced alcohol and drug use in patients with schizophrenia. Although over 75% were aware that clozapine reduces suicide risk, nearly a fifth (18.9%) did not know. About 40.5% preferred to use several other antipsychotics before considering clozapine. A quarter of consultants (57, 25.1%) felt it was not safe to start clozapine in the community and a further (28, 12.3%) did not know whether it was safe to do so. Over a third of clinicians (36.2%) felt it was not easy to identify suitable patients for clozapine. The initiation of clozapine was acknowledged as being cumbersome by 42.9%.

Table 3. Reported clozapine-related adverse events.

	Frequency
Myocarditis	21
Cardiomyopathy	10
Severe tachycardia	7
Arrhythmias	4
Hypotension	8
Sudden death	16
Constipation	17
Liver problems	5
Deep vein thrombosis/pulmonary embolism	3
Overdose	4
Toxicity	4
Seizure	16

Clozapine's other indications and untoward effects

A total of 104 (45.4%) out of 229 acknowledged that they have used clozapine to treat other conditions. The frequently mentioned diagnoses were resistant schizoaffective disorders (52 times), difficult to treat bipolar affective disorder (38 times), borderline personality disorder (25 times) and schizophrenia where patients were unable to tolerate other antipsychotics (13 times). Mentioned less than 10 times in decreasing order were psychosis related to parkinsonism, persistent delusional disorder, psychotic depression and severe head injury.

A total of 105 (45.5%) out of 231 respondents acknowledged that their patients had experienced untoward effects while on clozapine. The frequently mentioned undesirable events were myocarditis, constipation, seizure, sudden death, and cardiomyopathy (see Table 3). We observed that there was a significant association of psychiatrists recalling to have started someone on clozapine in the past 6 months and reporting of patients experiencing serious side effects ($\chi^2 = 6.11$, d.f. = 1, $p < 0.05$).

Discussion

Consultant psychiatrists play a leading role in starting clozapine. Previous studies have explored the use of clozapine in older adult psychiatrists [Paranthaman and Baldwin, 2006] and a mixed group of clinicians (doctors, nursing staffs and pharmacists) working in one mental health trust [Gee *et al.* 2013]. To the best of the authors'

knowledge this is the first study to focus on the views of consultant psychiatrists nationwide working with adult patients aged 18–65 on the use of clozapine in practice.

Major limitations of our study include the low response rate, which was understandable as we could only send one email shot, and that data was collected within 2 weeks of the email request. The online surveys have their limitations and a number of reminders are usually required with some incentive to participate. Survey response rates among physicians are generally low and rate as low as 3% are reported [Thomas *et al.* 2002]. Although overall response rate was low, we were still able to elicit views of 243 consultant psychiatrists, the largest number of respondents in such a study. In addition, we were not in a position to verify what clinicians felt were the reasons for clozapine underutilization. Although our respondents represented all of the major sectors of general adult psychiatry, there may be some limitations in the generalization of our findings given a low response rate. However, more likely than not, our findings reflect the perception and the practise of psychiatrists given the known variability in clozapine prescribing and utilization. Our findings also mirror and extend what has been observed previously [Nielsen *et al.* 2010; Gee *et al.* 2013].

Our main findings are as follows: the reasons for clozapine underutilization are multiple, however, a significant number were related to clinicians' factors. Over half of the consultants worked in a trust that had a dedicated clozapine service, a significant number (42%) had less than five patients on clozapine despite being in the current post for about 7 years. About 80% agreed that there was a delay in starting clozapine. Three quarters of respondents agreed that they had good exposure in using clozapine as a trainee, but there appeared to be significant gaps in knowledge, e.g. about one fifth of respondents did not know that clozapine use is associated with reduced suicidality. Just over a third felt that it was not safe to start patients on clozapine in the community and the same proportion felt that they were unable to identify suitable patients for clozapine treatment and just over 40% preferred to use several other antipsychotics before considering clozapine.

Why there is a delay in using clozapine

This survey observed that clinicians are aware of the delayed use of clozapine and like previous

studies, they are aware of its underutilization [Nielsen *et al.* 2010; Howes *et al.* 2012]. The cost does not seem to be a barrier now as clozapine has become generic with a significant cost reduction. However, the underutilization appears to have remained [Joober and Boksa, 2010; Farooq and Taylor, 2011].

Eleven factors were identified as important causes of delayed use of clozapine in this survey. The major concerns in the mind of psychiatrists were side effects including metabolic problems. This is understandable, as it appears that a significant number of respondents in this survey had observed serious side effects in their patients. Concerns about side effects of clozapine by clinicians have been highlighted previously as a significant reason for clozapine underutilization [Nielsen *et al.* 2010]. It is recognized that side effects are a common cause of all antipsychotics discontinuation [Davis *et al.* 2013]. Clozapine is known to have low extrapyramidal side effects including tardive dyskinesia and low tendency to elevate prolactin. However, it has a number of uncommon but life-threatening side effects such as agranulocytosis, myocarditis and cardiomyopathy. Overestimation of side effects, clinicians' perception of them and lack of knowledge on how to manage them has been hypothesized as underlying reasons for clinicians' hesitation in using clozapine [Patel, 2012; Nielsen *et al.* 2010]. However, with adequate resources and monitoring, a significant number of them can be identified early on and appropriate measures taken to minimize their impact [Young *et al.* 1998; Miller, 2000; Raja, 2011]. This is demonstrated by a significant change in the incidence of agranulocytosis from 1–2% in mid-1970s prior to blood monitoring to 0.38% after the introduction of monitoring [Honigfeld *et al.* 1998].

Reluctance to have blood test was the second commonest reason mentioned. The views of patients who refuse to accept clozapine treatment have not been captured systematically and may be different from those who subsequently go on to take clozapine. Interestingly, however, when asked about clozapine and the associated blood test requirement, patients on clozapine appears to have views that are contrary to psychiatrists' concerns. A survey of patients on clozapine by Taylor and colleagues [Taylor *et al.* 2000] revealed that majority of patients (64%) on clozapine had a positive view of blood test and viewed it as part of their treatment. A small study that followed

patients on clozapine for just over 8 years found that blood test accounted for only 21.4% of discontinuation despite high overall discontinuation rates [Krivoy *et al.* 2011]. It is also interesting to note that those taking clozapine have been repeatedly shown to have the longest period of medication adherence prior to discontinue their medication [Taylor *et al.* 2008; McEvoy *et al.* 2006; Rosenheck *et al.* 1997; Valenstein *et al.* 2004]. It may be more helpful in the future to involve patients already on clozapine as expert patients in educating service users who are candidates to start clozapine. Having evidence-based perspective should also help to alleviate the concerns of many clinicians.

Knowledge, attitudes and practice

Lack of knowledge or experience in using clozapine by psychiatrists was the third frequently mentioned reason. Lack of knowledge or experience has been highlighted earlier [Nielsen *et al.* 2010; Patel, 2012; Farooq and Taylor, 2011]. Despite the fact that a high proportion (75.4%) of our responders indicated that they had a good exposure in the use of clozapine during their training, a significant number of clinicians in our study had less than five patients on clozapine on their caseload. Psychiatrists' perception was that functionalization has resulted in more service fragmentation. They felt as well that there was lack of community support. Taken together, all of these factors can result in increased ambivalence among clinicians, magnifying clozapine underutilization given the intense monitoring required and the extra work it generates [O'Brien, 2004; De Berardis *et al.* 2012; Marder and Van Putten, 1988]. Interestingly, we observed that psychiatrists, who worked in the acute wards or crisis and home treatment, the two important areas for clozapine initiation and support in the early phase, were more likely to have less than five patients on clozapine on their caseload.

Deficiency in knowledge in certain aspect of clozapine use was apparent is response to specific questions about clozapine. It is well known, for example, that the risk of agranulocytosis is highest in the first 6 months following clozapine initiation [Munro *et al.* 1999; Alphs and Anand, 1999; Nielsen *et al.* 2013], decreasing to levels similar to other antipsychotics after 1 year of treatment. Likewise clozapine is well established in reducing suicidality and substance abuse in patients suffering from schizophrenia. However, a significant

proportion of psychiatrists had deficient knowledge in these aspects. Lack of clarity may have a significant implication when information is conveyed to patients and carers and in the choice of the next antipsychotic once two or more have failed.

The general reluctance of patients and families to start clozapine was another frequently mentioned reason. Psychiatrists pointed out about the importance of patient choice and the need for self-determination. However, this has been challenged given the effect of TRS on the patient outcomes and service utilization [Patel, 2012; Hermes and Rosenheck, 2012]. Conservative estimates indicate that TRS adds more than US\$34 billion in annual direct medical costs in the USA [Kennedy *et al.* 2013]. It was observed in the phase II CATIE study that if left to patients and their clinicians only 31.2% of eligible patients were allocated to the clozapine treatment arm and most were men with severe symptoms and having increased service utilization [Hermes and Rosenheck, 2012]. A recent Report of the National Audit of Schizophrenia (NAS) in the UK [Royal College of Psychiatry, 2012] also noted that 43% of patient with TRS were not on clozapine and no reason was documented. Decision-making process in medicine is complex and several factors are involved on both parties including knowledge of the drug of interest, side effects and efficacy, experience, preference and values and the level of communication between clinician and the patient [Mistler and Drake, 2008]. The observation by Whiskey and colleagues [Whiskey *et al.* 2003] that clinicians with a long history of using clozapine had a large number of patients on clozapine and also had the lowest discontinuation rates is interesting and demands that clozapine service provision be re-examined again in the light of current mounting evidences. Our survey noted that negative views of other healthcare professionals might have undesirable influence on both the treating doctor and the patient.

Over a third of respondents felt that it was not easy to identify suitable patients to start clozapine despite the clear National Institute for Health and Care Excellence (NICE) guidelines on the subject. Previous studies have shown that clinicians are aware of the NICE guidance and the definition of treatment resistance [Nielsen *et al.* 2010]. However, despite this, consultants still seem to want to try several antipsychotics before

considering clozapine. Over 40% of respondents in our survey said they would do this before considering clozapine. A higher proportion (two thirds) was reported by Nielsen and colleagues [Nielsen *et al.* 2010].

Implications of the study

Out of the 11 identified possible reasons for delayed clozapine use, at least 7 if not more can be directly or indirectly attributed to psychiatrists' knowledge, attitudes or local practices for starting clozapine. Following the introduction of clozapine, it was part of license agreement and mandatory for inpatient admission before clozapine was initiated. This is no longer a requirement; for example NICE (2014) guidelines do not recommend admission as a prerequisite for starting clozapine. Over the years through research observations and experiences, clozapine can be started safely in the community with the support of the community teams such as the HTT [O'Brien, 2004]. Frequent visits and the frequent monitoring of blood pressure, temperature and pulse at least twice daily in the community is seen as added burden given the limited resources and makes clozapine a less preferred drug [O'Brien, 2004]. It is appreciated that there will always be a need to start clozapine as inpatient in some patients especially where the risk of relapse is high when clozapine is being titrated, and where there is concern about physical health problems [De Berardis *et al.* 2012; Nielsen *et al.* 2013]. Over a third of clinicians either felt it was not safe to start clozapine in the community or did not know that they could do so. Evidence-based local protocols should be able to address this issue.

Having clozapine-dedicated services need to be seriously considered given the plight of patients with schizophrenia 'a forgotten illness' [The Schizophrenia Commission, 2012]. Lessons can be learnt from our medical colleagues who have specialists with specific experience or interest in dealing with specific conditions, e.g. diabetes (diabetologist) and rheumatic disease (rheumatologists). Services based on a similar model need to be considered to improve the uptake and early use of clozapine and possibly the outcome of TRS given the complexity of clozapine initiation and monitoring, the concerns about life-threatening side effects, the high attrition rate and the lack of best alternative when patients with TRS fail to use clozapine.

A major implication of the study is that the education needs of the practicing psychiatrists are identified and addressed. It is also interesting to know that over 63% of psychiatrist would welcome receiving more information on clozapine. Considering that increasingly psychiatric services in the UK are focused on the complex cases and work in subspecialty-type setting it is important that the educational needs for management of TRS becomes a priority both in training and continued professional development. Our study identifies some important areas, such as managing side effects, current evidence regarding use of clozapine and identification of treatment resistance at an early stage, which should be targeted in training and professional development programme by organizations such as the BAP (British Association of Psychopharmacology) and The Royal College of Psychiatrists.

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Conflict of interest statement

TET has attended meeting sponsored by Lilly and Otsuka. SF has received funding to attend meetings and honoraria from Novartis. No pharmaceutical companies had any role in designing or conducting this survey.

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