Delays and barriers to the commencement of clozapine in eligible people with a psychotic disorder: A Literature Review

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/eip.12683](https://doi.org/10.1111/eip.12683)

Abstract

Background:

While the majority of individuals with a first episode of psychosis (FEP) achieve symptomatic remission with the appropriate treatment, there is a small but significant proportion who do not achieve remission of symptoms despite adequate treatment with at least two antipsychotic medications (termed treatment resistance). Clozapine is indicated in individuals who fulfil criteria for treatment resistant schizophrenia, however, despite it being the most effective antipsychotic medication, there can be delays in commencement of clozapine in eligible patients.

Methods:

A systematic search was performed to identify articles reporting either the time taken to commence clozapine (or delays) in eligible individuals or articles reporting barriers to the commencement of clozapine. The initial search generated 5588 articles and of these, eighteen were eligible.

Results:

Thirteen studies described delays in commencing clozapine and five studies reported on the barriers to the commencement of clozapine. The duration of delay from when individual was

deemed eligible for clozapine treatment to the time of clozapine commencement ranged from 19.3 weeks to 5.5 years. In addition, the duration of illness prior to clozapine initiation ranged from 1.1 to 9.7 years. It was found that some clinicians were more inclined to prescribe polypharmacy or doses higher than recommended than to prescribe clozapine.

Conclusion:

Delays in commencing clozapine have been consistently demonstrated. Early intervention for psychosis services are ideal settings to identify individuals with persistent positive psychotic symptoms and commence clozapine if indicated.

Introduction

While the majority of individuals with a first episode of psychosis (FEP) achieve symptomatic remission with the appropriate treatment, there is a small but significant proportion who do not achieve full remission of symptoms with initial treatment (Edwards, Maude, McGorry, Harrigan, & Cocks, 1998). A consensus definition of treatment-resistant schizophrenia has been developed and it is defined as a lack of satisfactory clinical response in psychotic symptoms to trials of two different antipsychotic medications with adequate duration, dose and adherence (Howes et al., 2017). It is estimated that one-third of individuals diagnosed with schizophrenia experience prolonged and persistent positive psychotic symptoms and therefore can be classified as treatment-resistant (Lehman et al., 2004).

Clozapine is the most effective antipsychotic medication for the treatment of positive psychotic symptoms (Leucht et al., 2013; Leucht et al., 2009). However, its use is limited as a

third line medication in individuals with treatment resistant schizophrenia due its potentially fatal cardiac and haematological side effects. In addition to the superior effectiveness of clozapine in treating positive psychotic symptoms, longitudinal studies demonstrate better outcomes in terms of morbidity and mortality (Tiihonen et al., 2009). Despite this evidence, it has been reported that clozapine is under-prescribed and underutilised (Goren et al., 2013). It is estimated that the prevalence of treatment resistance is 16-20% in those with a diagnosis of schizophrenia (Chakos, Lieberman, Hoffman, Bradford, & Sheitman, 2001; Mortimer, Singh, Shepherd, & Puthiryackal, 2010; Remington et al., 2013), yet the rate of clozapine prescription is as low as 2-3% in the United States (Sernyak & Rosenheck, 2008), 7% in Canada (Latimer et al., 2013), 19% in Australia (Malalagama, Bastiampillai, & Dhillon, 2011) and 20% in New Zealand (Dey, Menkes, Obertova, Chaudhuri, & Mellsop, 2016). In the United Kingdom, it was reported that only 14-50% of eligible patients were treated with clozapine (Stroup et al., 2009). Despite its superior effectiveness and longer-term outcomes, it would appear that not all individuals with treatment resistant schizophrenia receive a trial of clozapine.

This literature review aims to determine the delays in the initiation of clozapine in individuals with treatment resistant schizophrenia and to examine barriers to the commencing of clozapine in eligible individuals.

Methods

Inclusion and exclusion criteria

The Inclusion criteria for this literature review were articles published in English, that reported the time taken to commence clozapine in individuals deemed eligible according to any guidelines or defined criteria of treatment resistant schizophrenia. Additionally, articles examining delays or barriers to the commencement of clozapine were included.

Search strategy

The following search terms were entered into MedLine database: “first episode psychosis”, “psychosis”. “psychotic”, “schizophreni*”, “early intervention”, “factors”, “delay”, “commence”, “start”, “initiate”, and “clozapine”. The initial search generated 5588 articles and after a review of titles, 126 abstracts were identified and reviewed. Of these, 43 articles were reviewed in full and of these, 18 fulfilled the inclusion criteria, thirteen of which were on delay in commencing clozapine and five on the barriers to such delays. Additionally, reference lists of articles were reviewed for other eligible articles. The last search was conducted on 07.07.17.

Definitions

The mean theoretical delay in the commencement of clozapine was defined as the duration from the end of week six of second antipsychotic trial to the initiation of clozapine.

Results

Time to commencement of clozapine and number of preceding trials of different antipsychotic medication

A total of thirteen studies examined the delays to the commencement of clozapine and these are summarised in Table 1. In 2003, Taylor et al. reported on the prescribing patterns of antipsychotics for 112 individuals with a diagnosis of schizophrenia or schizoaffective disorder in the United Kingdom between 1990 and 2001 (D. M. Taylor, Young, & Paton, 2003). There was a mean of 5.7 adequate trials of other antipsychotic medications prior to the commencement of clozapine and 65% of individuals had been subjected to polypharmacy. The mean theoretical delay to the commencement of clozapine was five years. Older age (greater 30) and a diagnosis of treatment resistant schizophrenia made prior to introduction of clozapine in the United Kingdom were found to be associated with a greater delay in clozapine initiation.

In 2008, Wheeler conducted a retrospective chart review of 2796 individuals with a diagnosis of schizophrenia or schizoaffective disorder from four community mental health centre in Auckland, New Zealand (Wheeler, 2008). A total of 917 (32.8%) were prescribed clozapine after a mean duration of illness of 9.7 years. The number of trials of antipsychotic medications prior to clozapine initiation was 3.5 and it was found that those who were younger, male and had a longer duration of illness more likely to be prescribed clozapine.

In 2012, Howes et al. conducted a study involving 149 individuals prescribed clozapine and found that the mean time of delay to clozapine initiation was 47.7 months (Howes et al., 2012). Furthermore, they found that the average number of adequate trials of antipsychotics prior to clozapine treatment was 2.8 and that polypharmacy was also a common practice. In the same year, Nielson et al. conducted a retrospective study including 633 individuals and the mean duration between diagnosis of a psychotic disorder to clozapine initiation was one

to two years (Nielsen, Nielsen, & Correll, 2012). The mean number of antipsychotic trials prior to clozapine initiation was 2.9, with 20.1% having had five or more antipsychotic trials and 13.7% with four trials. It was observed that females received more trials of antipsychotic medications prior to the commencement of clozapine.

In 2013, Alessi-Severini et al. conducted a retrospective chart review of 74 individuals treated with clozapine in a Canadian outpatient setting and found that the median duration of treatment prior to clozapine treatment was 8.9 years for males and 7.7 years for females (Alessi-Severini, Le Dorze, Nguyen, Honcharik, & Eleff, 2013). The mean number of different antipsychotic trials prior to clozapine initiation was 3.3 and 68% of individuals had three trials. Also in 2013, Najim et al. reported on a retrospective file review of 42 outpatients treated with clozapine in the United Kingdom and found that the mean theoretical delay in the commencement of clozapine was five years (Najim, Heath, & Singh, 2013). Individuals aged less than 30 years had a delay in commencement of 2.3 years compared to 6 years in those aged over 30 years. Additionally, those who were diagnosed with treatment resistant schizophrenia prior to the reintroduction of clozapine in 1992 had longer delays in clozapine initiation. The mean number of adequate trials of antipsychotic medication was four and only 16.6% had been initiated on clozapine treatment after just two antipsychotic trials and it was found that over 35% had five or more different antipsychotic medications.

In 2014, Grover et al. conducted a retrospective study in India of 200 individuals with diagnosis of schizophrenia, schizophreniform disorder and psychosis not otherwise specified (NOS) (Grover, Hazari, Chakrabarti, & Avasthi, 2015). They found that the mean delay to the commencement of clozapine was 1.93 years and the mean number of adequate trials of

antipsychotic medications was three. In addition, 27.5% of individuals received polypharmacy.

In 2014, Wheeler et al. reported a retrospective cross-sectional study on the prescribing trend of clozapine in Auckland, New Zealand and Birmingham, United Kingdom (Wheeler, Feetam, & Harrison, 2014). This study involved 664 individuals (402 in Auckland and 262 in Birmingham) in the public secondary care mental health services and found there was the mean time to clozapine initiation was 5.3 years in Auckland and 6.5 years in Birmingham. There was a mean of 3.1 antipsychotic trials in Auckland and 4.3 in Birmingham, but with a shift towards two antipsychotic trials prior clozapine treatment in both cohorts in the recent years.

In 2015, Ucok et al. reported a retrospective chart review study which included 162 individuals from outpatient units in Istanbul who were treated with clozapine (Ucok et al., 2015). The mean theoretical delay was found to be 29 months. In the same year, Yada et al. conducted a retrospective observational chart review of 90 patients diagnosed with treatment resistant schizophrenia in Japan and found the delay in commencement of clozapine to be mean of 5.5 years (Yada, Yoshimura, & Kishi, 2015). Also in 2015, Schneider et al. reported on a nationwide population-based study in Denmark on clozapine use in 108 young people with a diagnosis of childhood schizophrenia (Schneider et al., 2015). They found that the mean duration between their initial treatment to commencement of clozapine was 3.2 years, with approximately three trials of different antipsychotic prior. Older age at diagnosis, previous suicide attempt and positive family history of schizophrenia were significant positive predictors to initiation of clozapine.

In 2016, Tang et al. reported a retrospective study conducted between 2001-2012 to investigate clozapine prescribing pattern in Singapore (C. Tang et al., 2016). They analysed data of 1603 individuals cared under the Singapore early Psychosis Intervention Programme (EPIP). They found that only 4.3% individuals from the study cohort were prescribed clozapine. The time to clozapine initiation from first presentation was 57.4 weeks, with mean theoretical delay of 19.3 weeks. However, the authors acknowledged that this may be underestimated as individuals in the program was only followed up for two years, hence any delays of more than two years would have been undetected in this study. The mean number of different antipsychotic trial prior to clozapine initiation was 3.4, with 75% of patients subjected to polypharmacy with three or more antipsychotics prescribed at the same time. They also identified several predictors associated with more timely access to clozapine treatment in this cohort, including younger age at onset, individuals who were unemployed as well as those who were more symptomatic at baseline and had lower baseline functioning.

Doyle et al (2017) found that 16.3% of a cohort of 171 individuals who had a FEP between 1995 and 1999 within a defined catchment area in Dublin were commenced on clozapine at follow-up by 2013 (Doyle et al., 2017). The mean time to first trial of clozapine was 6.7 years and the mean number of antipsychotic medications trialled before clozapine was 4.9.

Barriers to the commencement of clozapine

A total of five studies were identified as being eligible on reporting barriers to the commencement of clozapine, one of these pertained to patients and four to clinicians.

Patient Perspectives and Barriers

Taylor et al. conducted a structured questionnaire survey of patients attending clozapine clinics in the U.K. in 1999 and included 570 respondents (D. Taylor, Shapland, Laverick, Bond, & Munro, 2000). The study found that most patients reported positive experience with clozapine treatment and 86.1% rated clozapine as being better than previous antipsychotics they have received. While 24.2% reported that they did not like clozapine due to regular blood monitoring, 87.0% acknowledged that the advantages of clozapine outweighed the disadvantages. Overall, 88.6% expressed a preference to remain on clozapine.

Clinician Perspectives and Barriers

Nielson et al. (2010) conducted a phone interview of 100 psychiatrists in Denmark regarding their attitude to and experience with clozapine (Nielsen, Dahm, Lublin, & Taylor, 2010). The study found that while the majority (87.8%) of consultant psychiatrists were aware of the recommendation from clinical guidelines to commence clozapine after two adequate unsuccessful trials of antipsychotic trials, 64.7% reported that they would rather use polypharmacy than prescribe clozapine. Psychiatrists identified the requirement for initial weekly and then routine blood monitoring as a problematic issue and perceived it as a burdens for patients.

Gee et al. (2013) conducted a survey amongst clinical staff, consisting of consultant psychiatrists, trainee psychiatrists, nurses and pharmacy staff, at the South London and Maudsley NHS Trust in the UK (Gee, Vergunst, Howes, & Taylor, 2014). Of the 144 respondents, 81% reported being familiar with current treatment guidelines for clozapine and 35% identified that between 0-20% of their patients would be eligible to commence clozapine

according to the guidelines. In addition, 14% and 4% reported they would only consider clozapine treatment for their patients after three or four unsuccessful trials of antipsychotics respectively.

Paranthaman et al. (2016) conducted a survey on clinicians' attitude towards clozapine use in the treatment of schizophrenia specifically in those aged older than 65 in the U.K. (R & RC, 2006). A total of 45% of consultant psychiatrists reported having patients under their care who were treated with clozapine and 67% regarded clozapine as a useful treatment in elderly patients. Consultant psychiatrists reported practical difficulties in regular haematological monitoring, with a third of responders commenting that they would consider using clozapine more if community blood monitoring services were available. Concerns relating to the use of clozapine (specifically in those aged 65 or over) mainly related to safety, specifically agranulocytosis, cardiovascular side effects, anticholinergic side effects as well as patients' medical comorbidities. Other clinicians' factors identified include limited published data supporting the use in this cohort as well as limited personal experience in management of clozapine treatment.

Tungaraza et al. (2016) conducted a survey of consultant psychiatrists and of the 243 responses, over half (56.2%) experienced difficulties in getting patients and carers to agree to trial of clozapine and 40.5% reported a preference of prescribing several trials of other antipsychotics prior to consideration of clozapine (Tungaraza & Farooq, 2015).. It was also noted that 36.2% reported difficulty in identifying patients eligible for clozapine treatment. 80.7% acknowledged that there was a delay in commencement of clozapine treatment. 42.9% felt that initiation of clozapine therapy was complex and 25.1% felt that it was not safe to be

carried out in the community. In regards to perceived factors in the delay in commencement of clozapine, the most frequently reported reason was side effects including metabolic problems. Other factors included patients' reluctance to have regular blood tests, patients or carers' reluctance and concerns regarding compliance. Clinicians' factors included lack of experience or knowledge, complexity of initiation and management of clozapine therapy, lack of community support, bed shortage of admission to initiate therapy, a preference to prescribe other antipsychotics first and delayed diagnosis.

Discussion

Summary of findings

All studies identified a theoretical delay in the commencement of clozapine in eligible individuals with a diagnosis of treatment resistant schizophrenia and these delays tended to be counted in years, as all but one service had a theoretical delay of over one year.

Additionally, individuals tended to undergo more than two trials of antipsychotic medications prior to commencing clozapine. Psychiatrists view the requirements for blood testing as a barrier to the commencement of clozapine, while the limited studies conducted in patient populations indicate that they do not perceive the blood tests as a barrier. Psychiatrists also expressed a preference for more trials of different antipsychotic medication and even polypharmacy over prescribing clozapine.

Interpretation of studies

There are two situations in which an individual may be considered treatment resistant. The first clinical scenario is when an individual never achieves symptomatic remission despite

adequate trials of at least two different antipsychotic medication. Additionally, individuals with a diagnosis of schizophrenia may also be considered treatment resistant if after a period of symptomatic remission, they experience a relapse, which subsequently does not respond to a further two trials of antipsychotic medication. Studies included in this review may not have made this distinction and hence for the later scenario the mean theoretical delay in the commencement of clozapine may be over-estimated. However, studies included individuals who were commenced on clozapine and retrospectively determined the delay, however this method excludes individuals who were eligible for clozapine but were never had a trial. Hence, in addition to considering theoretical delays, it is important to consider those individuals who experienced a continual persistent 'delay' as a result of never having a trial of clozapine.

Clinical Implications

This review has highlighted a number of important clinical issues and it is likely that the significant delays identified in the commencement of clozapine will not be addressed unless there is reform in both clinical services and attitudes of clinicians towards clozapine.

Early intervention for psychosis services have now been adopted world-wide, with over 200 services internationally (Jackson, 2009). These services have the aim of reducing both help-seeking delays in individuals with psychotic disorders and also service delays in the commencement of the appropriate treatment. Considering that the tenure of care for early intervention services typically ranges from two to five years, this is the ideal setting to screen individuals for persistent positive psychotic symptoms who may be eligible for a trial of

clozapine. The finding that the shortest delay to the commencement of clozapine was in an early intervention for psychosis service is supportive of this recommendation.

Another key finding from this review is that individuals tend to have a between three and five trials of different antipsychotic medications prior to commencing clozapine and this is in keeping with the expressed preference of consultant psychiatrists to have more trials prior to considering clozapine. However, what is striking that even when up to five trials are considered, there are still delays of up to five years to commencing clozapine which indicates trials of ineffective antipsychotic medications are unnecessarily long. Therefore, a more effective way to reduce the delays in commencing clozapine would be for trials of antipsychotic medications to be kept to six to eight weeks, as per clinical guidelines. In this scenario, an individual could have three to four trials of antipsychotic medications and if they continued to experience persistent positive psychotic symptoms, they could be eligible for clozapine within six months.

Strengths and Limitations

This literature review has a number of limitations. First, we only included studies published in English and as a result, potentially missing studies from non-English speaking countries. This has particular relevance, as clozapine is one of the most commonly used antipsychotic medications in China and can be prescribed as a first line treatment (Y. L. Tang et al., 2008). Additionally, we only searched one database however we used a broad search strategy and checked references in order to identify other eligible articles.

Conclusion

The superiority of the effectiveness of clozapine is well established, yet significant delays exist internationally in its commencement in those who would be eligible for a trial. Despite the limited studies, the indications are that clinicians' knowledge of and attitude to clozapine remain a more significant barrier to the commencement of clozapine in eligible patients.

Education resources for clinicians as well as services specifically dedicated to early identification of eligible patients and management of their care thereafter would be beneficial in reducing the delays.

References

- Alessi-Severini, S., Le Dorze, J. A., Nguyen, D., Honcharik, P., & Eleff, M. (2013). Clozapine Prescribing in a Canadian Outpatient Population. *PLoS One*, 8(12). doi:10.1371/journal.pone.0083539
- Chakos, M., Lieberman, J., Hoffman, E., Bradford, D., & Sheitman, B. (2001). Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *Am J Psychiatry*, 158(4), 518-526. doi:10.1176/appi.ajp.158.4.518
- Dey, S., Menkes, D. B., Obertova, Z., Chaudhuri, S., & Mellsop, G. (2016). Antipsychotic prescribing and its correlates in New Zealand. *Australas Psychiatry*, 24(4), 360-364. doi:10.1177/1039856215626644
- Doyle, R., Behan, C., O'Keeffe, D., Masterson, S., Kinsella, A., Kelly, A., . . . Clarke, M. (2017). Clozapine Use in a Cohort of First-Episode Psychosis. *J Clin Psychopharmacol*. doi:10.1097/JCP.0000000000000734
- Edwards, J., Maude, D., McGorry, P. D., Harrigan, S. M., & Cocks, J. T. (1998). Prolonged recovery in first-episode psychosis. *Br J Psychiatry Suppl*, 172(33), 107-116.
- Gee, S., Vergunst, F., Howes, O., & Taylor, D. (2014). Practitioner attitudes to clozapine initiation. *Acta Psychiatr Scand*, 130(1), 16-24. doi:10.1111/acps.12193
- Goren, J. L., Meterko, M., Williams, S., Young, G. J., Baker, E., Chou, C. H., . . . Bauer, M. S. (2013). Antipsychotic prescribing pathways, polypharmacy, and clozapine use in treatment of schizophrenia. *Psychiatr Serv*, 64(6), 527-533. doi:10.1176/appi.ps.002022012
- Grover, S., Hazari, N., Chakrabarti, S., & Avasthi, A. (2015). Delay in initiation of clozapine: a retrospective study from a tertiary care hospital in North India. *Psychiatry Res*, 226(1), 181-185. doi:10.1016/j.psychres.2014.12.046
- Howes, O. D., McCutcheon, R., Agid, O., de Bartolomeis, A., van Beveren, N. J., Birnbaum, M. L., . . . Correll, C. U. (2017). Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. *Am J Psychiatry*, 174(3), 216-229. doi:10.1176/appi.ajp.2016.16050503
- 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*, 201(6), 481-485. doi:10.1192/bjp.bp.111.105833
- Jackson, H. M., P. (2009). *The Recognition and Management of Early Psychosis. A Preventive Approach* (2nd Edition ed.): Cambridge University Press.
- Latimer, E., Wynant, W., Clark, R., Malla, A., Moodie, E., Tamblyn, R., & Naidu, A. (2013). Underprescribing of clozapine and unexplained variation in use across hospitals and regions in the Canadian province of Quebec. *Clin Schizophr Relat Psychoses*, 7(1), 33-41. doi:10.3371/csrp.lawy.012513

- Lehman, A. F., Lieberman, J. A., Dixon, L. B., McGlashan, T. H., Miller, A. L., Perkins, D. O., & Kreyenbuhl, J. (2004). Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry*, 161(2 Suppl), 1-56.
- Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., . . . Davis, J. M. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*, 382(9896), 951-962. doi:10.1016/s0140-6736(13)60733-3
- Leucht, S., Komossa, K., Rummel-Kluge, C., Corves, C., Hunger, H., Schmid, F., . . . Davis, J. M. (2009). A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry*, 166(2), 152-163. doi:10.1176/appi.ajp.2008.08030368
- Malalagama, G., Bastiampillai, T., & Dhillon, R. (2011). Clozapine use in Australia. *Australas Psychiatry*, 19(2), 175. doi:10.3109/10398562.2010.525646
- Mortimer, A. M., Singh, P., Shepherd, C. J., & Puthiyackal, J. (2010). Clozapine for treatment-resistant schizophrenia: National Institute of Clinical Excellence (NICE) guidance in the real world. *Clin Schizophr Relat Psychoses*, 4(1), 49-55. doi:10.3371/csrp.4.1.4
- Najim, H., Heath, D., & Singh, P. (2013). Antipsychotic prescribing before clozapine in a community psychiatric hospital: a case note review. *Psychiatr Danub*, 25 Suppl 2, S165-170.
- Nielsen, J., Dahm, M., Lublin, H., & Taylor, D. (2010). Psychiatrists' attitude towards and knowledge of clozapine treatment. *J Psychopharmacol*, 24(7), 965-971. doi:10.1177/0269881108100320
- Nielsen, J., Nielsen, R. E., & Correll, C. U. (2012). Predictors of clozapine response in patients with treatment-refractory schizophrenia: results from a Danish Register Study. *J Clin Psychopharmacol*, 32(5), 678-683. doi:10.1097/JCP.0b013e318267b3cd
- R, P., & RC, B. (2006). Survey of clozapine use by consultant old age psychiatrists. *Psychiatric Bulletin*, 30, 410-412.
- Remington, G., Agid, O., Foussias, G., Hahn, M., Rao, N., & Sinyor, M. (2013). Clozapine's role in the treatment of first-episode schizophrenia. *Am J Psychiatry*, 170(2), 146-151. doi:10.1176/appi.ajp.2012.12060778
- Schneider, C., Papachristou, E., Wimberley, T., Gasse, C., Dima, D., MacCabe, J. H., . . . Frangou, S. (2015). Clozapine use in childhood and adolescent schizophrenia: A nationwide population-based study. *Eur Neuropsychopharmacol*, 25(6), 857-863. doi:10.1016/j.euroneuro.2015.02.003
- 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*, 59(5), 567-569. doi:10.1176/ps.2008.59.5.567
- Stroup, T. S., Lieberman, J. A., McEvoy, J. P., Davis, S. M., Swartz, M. S., Keefe, R. S., . . . Hsiao, J. K. (2009). Results of phase 3 of the CATIE schizophrenia trial. *Schizophr Res*, 107(1), 1-12. doi:10.1016/j.schres.2008.10.011

- Tang, C., Subramaniam, M., Ng, B. T., Abidin, E., Poon, L. Y., & Verma, S. K. (2016). Clozapine Use in First-Episode Psychosis: The Singapore Early Psychosis Intervention Programme (EPIP) Perspective. *J Clin Psychiatry*, 77(11), e1447-e1453. doi:10.4088/JCP.15m10063
- Tang, Y. L., Mao, P. X., Jiang, F., Chen, Q., Wang, C. Y., Cai, Z. J., & Mitchell, P. B. (2008). Clozapine in China. *Pharmacopsychiatry*, 41(1), 1-9. doi:10.1055/s-2007-993224
- Taylor, D., Shapland, L., Laverick, G., Bond, J., & Munro, J. (2000). Clozapine - a survey of patient perceptions. *The Psychiatrist*, 24(12), 450-452. doi:10.1192/pb.24.12.450
- Taylor, D. M., Young, C., & Paton, C. (2003). Prior antipsychotic prescribing in patients currently receiving clozapine: a case note review. *J Clin Psychiatry*, 64(1), 30-34.
- Tiihonen, J., Lonnqvist, J., Wahlbeck, K., Klaukka, T., Niskanen, L., Tanskanen, A., & Haukka, J. (2009). 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet*, 374(9690), 620-627. doi:10.1016/S0140-6736(09)60742-X
- Tungaraza, T. E., & Farooq, S. (2015). Clozapine prescribing in the UK: views and experience of consultant psychiatrists. *Ther Adv Psychopharmacol*, 5(2), 88-96. doi:10.1177/2045125314566808
- Ucok, A., Cikrikcili, U., Karabulut, S., Salaj, A., Ozturk, M., Tabak, O., & Durak, R. (2015). Delayed initiation of clozapine may be related to poor response in treatment-resistant schizophrenia. *Int Clin Psychopharmacol*, 30(5), 290-295. doi:10.1097/yic.0000000000000086
- Wheeler, A. J. (2008). Treatment pathway and patterns of clozapine prescribing for schizophrenia in New Zealand. *Ann Pharmacother*, 42(6), 852-860. doi:10.1345/aph.1K662
- Wheeler, A. J., Feetam, C. L., & Harrison, J. (2014). Pathway to clozapine use: a comparison between a patient cohort from New Zealand and a cohort from the United Kingdom. *Clin Drug Investig*, 34(3), 203-211. doi:10.1007/s40261-013-0166-x
- Yada, Y., Yoshimura, B., & Kishi, Y. (2015). Correlation between delay in initiating clozapine and symptomatic improvement. *Schizophr Res*, 168(1-2), 585-586. doi:10.1016/j.schres.2015.07.045

First author, country, (year)	Type of study	Size	Mean age $\pm$ SD	Gender	Starting point for time to initiation	Time to initiation (years)	Mean theoretical delay in initiation (years)	No of APM prior to initiation (SD)	Factors attributing to delay
Doyle, Ireland,	Retrospective file review	171	29	M: 57.9% F: 42.1%	End of 2 failed APM trials	6.7 (3.5)	NS	4.9 (3.5)	NS
Tang, Singapore, 2016	Retrospective study	1603	26.1 $\pm$ 6.2	M: 56.5% F: 43.5%	End of 2 failed APM trials	1.1 (57.4 weeks)	0.37 (19.3 weeks)	3.4 (1.2)	Older age, employed less symptomatic at baseline Better baseline functioning
Schneider, Denmark, 2015	Retrospective observational review	108	16.6 $\pm$ 1.0	M: 44.4% F: 55.6%	Start of first APM tx	3.2 ($\pm$ 2.9)	NS*	3	Younger age No family history of schizophrenia No previous suicide attempts
Ucok, Turkey, 2015	Retrospective chart-review study	162	35.8 $\pm$ 10.8	M: 64.8% F: 35.2%	End of 2 failed APM trials	NS	2.4 (29 months)	NS	Female Patients not in FEP program

Yada, Japan, 2015	Retrospective observational review	90	35.2 ± 11.1	M: 61% F: 39%	Onset of a treatment- resistant psychotic episode	14.0 (±9.2)	5.5 ± 5.9	NS	NS
Grover, North India, 2014	Retrospective study	200	32.6 ± 11.1	M: 64% F: 36%	End of 2 failed APM trials	NS	1.93	3	Older age, Longer DUI, Polypharmacy, Urban locality Illness onset prior to introduction of clozapine
Wheeler, U.K. & NZ, 2014	Retrospective cross- sectional study	<u>U.K.</u> 262 <u>NZ</u> 402	<u>U.K.</u> 38.7 ± 10.2 <u>NZ</u> 39.7 ± 11.5	<u>U.K.</u> M: 74.0 F: 26.0 <u>NZ</u> M: 72.6 F: 27.4	First presentation to services	<u>U.K.</u> 6.5 (± 3.8) NZ 5.3 (± 3.6)	NS	<u>U.K.</u> 4.3 (± 1.6) NZ 3.1 (± 1.2)	NS
Najim, U.K, 2013	Retrospective case note review	42	40.1	NS	End of 2 failed APM trials	5.5	5	Mean = 4.0	Age over 30, Diagnosis of TRS prior to 1991, Completion of second adequate antipsychotic trial prior to introduction of risperidone
Alessi- Severini, Canada, 2013	Retrospective chart review study	74	39.4 ± 11.8	M: 68% F: 32%	Start of first APM	M: 8.9 F: 7.7	NS	1 (11%) 2 (21%) 3 (68%)	NS

Nielson, Denmark, 2012	Retrospective database study	633	25.9	M: 58.5% F: 41.5%	Diagnosis	1-2	NS	Mean = 2.9	NS
Howes, U.K, 2012	Retrospective study	149	34.0 ± 10.2	M: 68.5% F: 31.5%	End of 2 failed APM trials	NS	3.98 (47.7 months)	3.7 (± 2.4)	Older age, Longer illness duration
Wheeler, NZ, 2008	Retrospective cross-sectional study	2796	<u>CLZ</u> 37.1 ± 10.1	<u>CLZ</u> M: 71.1% F: 28.9%	First presentation to services	9.7 (± 7.8)	NS	3.5 (± 3.0)	Female, Patient age >50, European ethnicity, Started clozapine prior to 1999
Taylor, U.K, 2003,	Retrospective analysis of file reviews	112	35.7	M: 77% F: 23%	End of 2 failed APM trials	5.0	NS	5.7	Patient aged >30, Diagnosis prior to introduction of clozapine Completion of 2 adequate trials of antipsychotic prior to introduction of clozapine
APM – Antipsychotic medication, DUI – Duration of illness, F- Female, M- Male, NS – Not stated, NZ – New Zealand, tx – Treatment, UK – United Kingdom,

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Title:

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Date:

2019-02-01

Citation:

Thien, K. & O'Donoghue, B. (2019). Delays and barriers to the commencement of clozapine in eligible people with a psychotic disorder: A literature review. *EARLY INTERVENTION IN PSYCHIATRY*, 13 (1), pp.18-23. <https://doi.org/10.1111/eip.12683>.

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