A descriptive study of 10-year clozapine use from the nationwide database in Japan

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ABSTRACT

This survey was conducted to identify the actual usage of clozapine and changes required to increase the number of patients with schizophrenia who would benefit from clozapine. We obtained Clozaril® Patient Monitoring Service (CPMS) data for 8,263 patients that received clozapine between July 2009 and January 2020. Patients were divided into the early (n=3,696 cases, which have been analyzed previously) and late groups (n=4,567 cases) according to the date of the treatment initiation. In total, 417 facilities offered the drug, with a surge in cases in the late group (40.0 hospitals/year, 568.6 cases/year vs. 39.3 hospitals/year, 1,141.8 cases/year). We found a significant between-group difference in the mean dosage during treatment (early group: 309.1 mg/day; late group: 247.9 mg/day). The treatment continuation rates at 1 and 4 years in all study participants were 77.2% and 65.1%, respectively. The incidences of granulocytopenia and agranulocytosis were 5.5% and 1.0%, respectively. The discontinuation rate because of granulocytopenia was significantly lower in the late group. There were no differences in the discontinuation rate because of glucose intolerance between the groups. An assessment of the current CPMS regulations may be required to further examine the clozapine use effectiveness.

1. Introduction

The effectiveness of clozapine is superior to that of other drugs in the treatment of schizophrenia (Chakos et al., 2001). Clozapine significantly reduces suicides (Taipale et al., 2020; Tiitinen et al., 2009), psychiatric symptoms (Nucifora et al., 2017), readmissions and recurrences (Tiitinen et al., 2006), and medical expenses (Essock et al., 2000). However, concerns about severe adverse drug reactions (e.g., agranulocytosis and myocarditis) and strict monitoring protocols have limited clozapine utilization (Knoph et al., 2018).

In Japan, clozapine was first commercially released in 2009. All patients with schizophrenia who are prescribed clozapine must be registered with the Clozaril® Patient Monitoring Service (CPMS), which requires relatively strict patient management procedures. For example, patients must be admitted to hospital to receive the drug, and undergo blood testing to monitor the white blood cell and neutrophil counts at least once every two weeks, even after continued long-term (1 year) use. These monitoring requirements have, in part, contributed to a low clozapine utilization rate in Japan. Indeed, Japan has the lowest rate of clozapine use in Asia (Xu et al., 2020), with only 0.2% of patients with schizophrenia receiving clozapine (Hata et al., 2020).

In a study by Inada et al., 3,780 patients treated with clozapine were analyzed for the first time in Japan using data collected from the CPMS spanning over a 6.5-year period (July 2009–January 2016) (Inada et al., 2018; Matsui et al., 2020). Since January 2016, the number of patients treated with clozapine increased significantly in Japan, and as of November 2019, more than 9,000 patients have been registered. In order to better understand this recent increase in clozapine utilization, we sought to compare clinical backgrounds, dosage, and therapeutic outcomes of patients that received clozapine before and after January 2016.
2. Methods

2.1. Data source

Data were obtained from the CPMS Center in Novartis Pharma K.K (Tokyo, Japan). CPMS data comprised anonymized data from all patients treated with clozapine in Japan from July 31, 2009 to January 26, 2020. A unique identification code was assigned to each datum, and extra care was taken to protect personal information; thus, the requirement of consent was waived. CPMS data included the date of patient registration, registered medical institution, sex, date of birth, date of examination, white blood cell count, neutrophil count, blood glucose level, hemoglobin A1c (HbA1c) level, date of prescription, and clozapine dosage. The blood level of clozapine was not monitored.

When a patient who discontinued clozapine treatment for some reason in the past resumed clozapine treatment, he/she was registered anew and treated as a separate patient. Additionally, since augmentation therapy with other antipsychotics is not approved in Japan, treatment was stopped for all non-responders to clozapine. In total, 9,635 patients were registered in the CPMS database. Among these patients, 1,196 were enrolled in duplicate after being transferred to another hospital, and were, therefore, excluded after consolidating data from the previous and later hospitals. From the remaining pool of 8,439 patients, we removed those who had privately imported clozapine prior to its introduction in Japan (n=22), participated in clinical trials (n=48), ended up not receiving clozapine after CPMS registration (n=69), or received an initial dosage other than 12.5 mg, which fell outside the current protocol (n=37). As a result, a total of 8,263 patients were included in our analyses.

Prior to analysis, we divided patients into those introduced to clozapine during the 6.5 years from July 31, 2009 to January 20, 2016 (early group: 3,696 patients) and those introduced during the last 4 years from January 21, 2016 to January 26, 2020 (late group: 4,567 patients). This division of data was performed to separate patients that were included in a previous analysis of the CPMS data by Inada and colleagues (early group) (Inada et al., 2018) from those that had yet to be analyzed (late group). In addition, the early group consisted of patients who were introduced to clozapine treatment during a period when clozapine use had not increased much since its launch in Japan. Whereas, patients in the late group received clozapine during a period when the number of patients using clozapine had increased significantly.

2.2. Definition of terms

The age was defined as the age at which clozapine was first prescribed. The clozapine treatment period was defined as the period from the first to the last prescription date plus the number of prescription days. Patients who did not have registered records of clozapine discontinuation in the CPMS by January 26, 2020, our observation days. Patients who did not have registered records of clozapine (early group: 3,696 patients) and those introduced during the last 4 years from January 21, 2016 to January 26, 2020 (late group: 4,567 patients). This division of data was performed to separate patients that were included in a previous analysis of the CPMS data by Inada and colleagues (early group) (Inada et al., 2018) from those that had yet to be analyzed (late group). In addition, the early group consisted of patients who were introduced to clozapine treatment during a period when clozapine use had not increased much since its launch in Japan. Whereas, patients in the late group received clozapine during a period when the number of patients using clozapine had increased significantly.

2.3. Statistical analysis

Fisher’s exact test was used to analyze the categorical data. The Wilcoxon rank-sum test was used to analyze the numerical data. The Kaplan–Meier event-free curve was employed to calculate the event-free probability of the discontinuation of clozapine. The log-rank test was applied to verify the between-group differences. All reported P-values were two-tailed and the significance level was set at P<0.05. Statistical analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Cumulative number of patients and facilities

Figure 1 shows the number of facilities offering clozapine treatment and the number of patients registered in the CPMS. The number of facilities and patients steadily increased; this was particularly true for the period starting in January 2016, when the late observation period began. The most recent assessment showed that there were 417 facilities offering clozapine treatment. A clear increase in the number of patients was noted during the late period (early period: 40.0 hospitals/year, 568.6 patients/year; late period: 39.3 hospitals/year, 1,141.8 patients/year).

3.2. Patient demographics and clinical characteristics

Table 1 shows the statistical parameters of the clinical data of patients registered in the CPMS. In both groups, there were more male patients. The median age was 40 and 41 years in the early and late groups, respectively; hence, the latter was slightly older (P<0.001). The number of cases patients with a poor response to previously used antipsychotics were significantly higher (P<0.001) in the early group (94.5%) compared to the late group (91.2%) but the two groups did not differ in regards to previous intolerance to antipsychotics (6.7% vs. 6.3%, P=0.560). The late group had a significantly higher (P<0.001) proportion of patients with a history of clozapine treatment (6.7%) compared to the early group (3.5%). Median HbA1c levels were significantly higher in the late group relative to the early group (P<0.001).

The most common reason for the introduction of clozapine was a poor response to previously used antipsychotics. The breakdown of previously used antipsychotics was different between the early and late groups, with higher proportions of aripiprazole, blonanserin, and paliperidone use and lower proportions of olanzapine, quetiapine, risperidone, and first-generation antipsychotic use in the late group relative to the early group (Table 2).

3.3. Dosage of clozapine during treatment

Table 3 shows the dosage of clozapine in each group. The mean
glucose intolerance (Figure 3).

Differences regarding the discontinuation rate because of glucose intolerance (Figure 3).

Continuation rate of clozapine

The discontinuation rate because of granulocytopenia was significantly lower in the late group (P<0.040). There were no between-group differences regarding the discontinuation rate because of glucose intolerance (Figure 3).

Reason for clozapine introduction, n (%)^d

Poor response to previously used antipsychotics

Intolerance to previously used antipsychotics

Previously treated with clozapine, n (%)^d

a Age is expressed as the age at introduction of clozapine
b As some patients met neither or both requirements, the sum is not 100%
c Fisher’s exact test
d Wilcoxon rank-sum test

dose (mg/day) during treatment in each patient was calculated. In the early group, the mean dosage was 309.1 mg/day, while in the late group it was significantly lower, at 247.9 mg/day (P<0.001). Given that the observation period differed between the groups, the latest dosage (mg/day) was also compared between the two groups. The mean dosage during treatment was subjected to bias because of the effects of the upward titration period. We found that the latest dosage was significantly lower in the late group (P=0.040). Further between-group comparisons revealed that the maximal dosage during treatment was significantly lower in the late (350 mg/day) than in the early group (450 mg/day; P<0.001).

3.4. Continuation rate of clozapine

Figure 2 shows the Kaplan–Meier curve representing the rates of clozapine continuation in all the study participants. The overall 1-year and 4-year continuation rates were 77.2% and 65.1%, respectively. In the early group, the 1-year and 4-year continuation rates were 77.4% and 65.4%, respectively. In the late group, the 1-year and 4-year continuation rates were 77.1% and 65.4%, respectively, and no between-group differences were found.

3.5. Time to clozapine discontinuation due to neutropenia/leucopenia or glucose intolerance

The discontinuation rate because of granulocytopenia was significantly lower in the late group (P<0.040). There were no between-group differences regarding the discontinuation rate because of glucose intolerance (Figure 3).

3.6. Onset of hematopathy

Over more than 10 years of observation, 458 out of 8,263 cases developed agranulocytosis (5.5%), and 84 out of 8,263 cases developed agranulocytosis (1.0%). The proportion of male patients (P=0.017), median age (P<0.001), and median dosage (P<0.001) were higher in granulocytopenia cases compared to granulocyteopenia cases. The onset period of agranulocytosis was not significantly later than that of granulocytopenia (P=0.328), as some patients developed agranulocytosis in the initial phase of treatment. For both adverse events, the clozapine dosage was higher for cases that developed hematopathy after 52 weeks or more of clozapine treatment (Table 4).

4. Discussion

To our knowledge, this is the initial study to report all cases treated with clozapine in Japan since its release in 2009. We showed that the initial utilization of clozapine use was slow in Japan but in more recent years, has increase at a rate of around 1,000 cases/year. As of January 2020, approximately 9,000 patients had been prescribed clozapine. However, these patients account for only 16%-40% of those with refractory schizophrenia, which are estimated to be 20,000-50,000 in number (Takeuchi et al., 2016). According to the Japanese government’s statistical data, there was minimal change in the number of schizophrenia patients and psychiatric hospitals between 2002 and 2017. The overall number of patients with schizophrenia were 734,000 and 793,000 in 2002 and 2017, respectively (Regional Mental Health Resources Analyzing Database, 2020) and the number of psychiatric hospitals were 1,069 and 1,059, respectively (Ministry Health, Labor, Health, and Welfare, 2020). Therefore, the observed increase in the number of patients using clozapine in Japan is unlikely a result of increases in schizophrenia diagnosis rates or treatment capacity.

We did detect several differences in clinical characteristics of the patients in the early and late groups. The number of patients previously treated with clozapine in the late group was approximately twice that of the early group, suggesting the late group may have a greater proportion of patients with a history of discontinuation because of poor tolerability or an insufficient effect, including non-adherence. One could speculate
will be needed to validate this notion. There was no between-group difference in the tendency for more males to be treated with clozapine. In both groups, there was a tendency for patients to be in their 30s and 40s. We also found that the therapeutic effects of clozapine may differ depending on which antipsychotics were used prior to clozapine. The late group were more likely to have been exposed to relatively new antipsychotics in Japan such as aripiprazole, blonanserin, and paliperidone, but were less likely to have used older antipsychotics, such as olanzapine, quetiapine, risperidone, and first-generation antipsychotics. Thus, it could be hypothesized that patients for whom administration of antipsychotics with similar pharmacological properties to clozapine, such as olanzapine, have failed (McEvoy et al., 2006; Pillinger et al., 2020), are less likely to benefit from clozapine. Future studies to test this hypothesis are warranted.

Side effects such as granulocytopenia and glucose intolerance are strongly associated with clozapine discontinuation rates. In the current study, we found that discontinuation rates because of granulocytopenia were significantly lower in the late group relative to the early group, suggesting clinical strategies to mitigate these side effects have changed from the early to late observation period. Clinical strategies, including the administration of lithium carbonate (Hogan, 2017) and reduction in clozapine dosage, are thought to contribute to the level of continuation of clozapine treatment. According to a systematic review using data from a randomized controlled trial of 25,000 individuals, olanzapine and clozapine have a higher incidence of metabolic side effects (Pillinger et al., 2020), and both are considered to be associated with a higher risk of elevated blood glucose levels. We found that discontinuation due to glucose intolerance was lower than that due to granulocytopenia, suggesting glucose intolerance is a less severe problem compared to granulocytopenia in Japan. According to reports from outside Japan, the 24-month and the 400-day clozapine continuation rates were 55% (Legge et al., 2016) and 80% (Ascher-Svanum et al., 2006), respectively. In the present study, the 1-year continuation rate since treatment initiation was approximately 80%, which is comparable to these reports.

The rate of developing agranulocytosis was higher in male patients, older adults, and those with higher treatment dosages (Table 4). Hence, it is particularly important to thoroughly monitor these high-risk patients. The present data also showed that patients who developed agranulocytosis at 52 weeks or more after treatment initiation received higher doses, which indicated that patients on long-term treatment should be cautiously monitored for the incidence of these adverse events, especially in the case of dose escalation. The incidences of granulocytopenia and agranulocytosis during the 10-year observation period were 5.5% and 1.0%, respectively. A meta-analysis revealed that the incidence rate of neutropenia in patients outside of Japan receiving clozapine was 5.32% (Asenjo Lobos et al., 2010), which was supported by the present study despite evidence suggesting Asians are 2.4 times more likely to develop granulocytopenia than Caucasians (Munro et al., 1999). In the United Kingdom (UK), the recommended maximum dose...
Table 4
Demographics and clinical characteristics of patients with an onset of hematopathy

| Characteristics                        | The onset of neutropenia/leukopenia | The onset of agranulocytosis | P-value
|----------------------------------------|-------------------------------------|-----------------------------|-------
|                                        | Before 52 weeks                     | After 52 weeks              | Before 52 weeks | After 52 weeks |
| Number of patients                     | 352                                 | 106                         | 79             | 5             |
| Sex, n (%)                             |                                     |                              |                |
| Male                                   | 175 (49.7)                          | 53 (50)                     | 50 (63.3)      | 4 (80)        |
| Female                                 | 177 (50.3)                          | 53 (50)                     | 29 (36.7)      | 1 (20)        |
| Age, Median (Range), year              | 43 (14–77)                          | 41.5 (18–71)                | 49 (21–77)     | 54 (23–58)    |
| Baseline lymphocyte, Median (Range), /mm$^3$ | 5,300 (4,000–12,400)                | 5,400 (4,070–12,710)        | 5,600 (4,000–13,800) | 6,200 (5,100–12,710) |
| Baseline neutrophil, Median (Range), /mm$^3$ | 2,945.5 (2,000–9,808)               | 2,955.5 (2,096–11,439)      | 3,270 (2,128–10,378) | 3,683 (3,091–11,439)  |
| Dosage at the onset, Median (Range), mg/day | 200 (5–600)                          | 250 (12.5–600)              | 300 (12.5–600)  | 450 (300–600) |
| Time to onset, Median (Range), week    | 10 (0.9–51.3)                       | 115.4 (52.1–423.9)          | 12 (4.6–44.9)   | 77.6 (66.1–235.9) |

a Statistical analysis was performed for two-group comparisons between neutropenia/leukopenia and agranulocytosis
b Fisher’s exact test
c Wilcoxon rank-sum test.

d of clozapine is 900 mg/day (Munro et al., 1999), but in Japan it is 600 mg/day. In fact, the maximum average dose was 462 mg/day in the UK (Munro et al., 1999) compared with 400 mg/day in this study. Thus, an appropriate clinical strategy for the prevention of the onset of granulocytopenia in Japan could be the use of lower clozapine doses than those used in other countries. Conversely, it has been reported that clozapine-induced granulocytopenia does not develop in a dose-dependent manner (Munro et al., 1999), but is instead largely affected by genetic factors, such as human leukocyte antigen (HLA) (Bachmann et al., 2017). In a subsequent study using a Japanese population, the HLA-B*57:01 serotype was identified as a genetic risk factor for clozapine-induced agranulocytosis and granulocytopenia (Saito et al., 2016). As shown in Table 4, some patients developed granulocytopenia or agranulocytosis even at a low clozapine dose, and the large individual differences in the dose at the time of onset could suggest that there is an association with genetic factors. Unfortunately, these genetic data were not included in the CPMS database. Tables 3 and 4 also show that the dose at onset was significantly higher for agranulocytosis than for granulocytopenia (P<0.001), suggesting that a higher dose increases hemopathy severity.

As shown in Figure 3A and Table 3, the lower discontinuation rate due to granulocytopenia in the late vs. the early group may be related to the lower dose. There were also differences in age, previous treatment with clozapine, and HbA1c measurements between the early and late groups (Table 1). However, it is unclear how these differences affected the discontinuation rate. This rate was the highest at week 18 (Figure 3A), which was in line with the regulations of the current Japanese CPMS indicating that in-hospital treatment management should begin at treatment initiation and last until week 18 of treatment. In Japan, the use of clozapine requires registration with the CPMS for monitoring management, and the prescription criteria are strictly followed to secure the patients’ safety. Consequently, serious side effects, such as agranulocytosis and myocarditis, can be promptly detected without oversight. In contrast, the stringent CPMS monitoring management could limit the introduction of clozapine for patients with treatment-resistant schizophrenia. In the United States and the UK, at 52 weeks after clozapine initiation, patients are required to have blood tests once every 4 weeks. Conversely, in Japan, patients have to get their blood tested once every 2 weeks at 26 weeks after clozapine initiation, and blood testing is required at the same interval after 52 weeks. Furthermore, the clozapine indication criteria require patients to have a history of treatment with at least two antipsychotic agents. These relatively strict criteria for administrating the clozapine are still limiting the number of this treatment.

There were several limitations to the present study. First, adherence to clozapine could not be verified because clozapine blood levels were not available. Second, the CPMS data do not include efficacy of clozapine assessed by the Positive and Negative Syndrome Scale scores, comorbidities other than diabetes mellitus, the age of onset for schizophrenia, the subtype of schizophrenia, history and severity of schizophrenia, family history, concomitant medications, or metabolism-related data, such as genetic data; thus, we could not include these variables in our analysis. One strength of the present study is that the CPMS database covers all patients receiving clozapine in Japan. In
addition, as there is little doubt that the patients treated with clozapine are those with treatment-resistant schizophrenia, our cohort did not include cases in whom off-label clozapine was used.

In conclusion, clozapine was administered in Japan to a total of 8,263 patients from July 31, 2009, to January 26, 2020. Despite the differences in clinical backgrounds, such as a higher number of patients previously treated with clozapine in the late group, the drug continuation rate was maintained by adjusting the dose and other factors such as improved monitoring strategy. Especially, one conceivable factor for the rise in the number of prescriptions was that the scope of clozapine indication had broadened from its initial release to include patients who were considered to be at high risk for treatment discontinuation. To further examine the effectiveness of clozapine use, an assessment of the current CPMS regulations may be required. To achieve this goal, further studies on the efficacy of clozapine, factors affecting its safety, and information regarding the onset of adverse events, would be necessary.

CRediT author statement

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Declarations of Competing Interest

Dr. Toyoda has received speaker’s honoraria from Eisai. Dr. Yamauchi has received speaker’s honoraria from Meiji Seika Pharma, Otsuka. Dr. Kinoshita has received speaker’s honoraria from Meiji Seika Pharma, Otsuka, Sumitomo Dainippon Pharma, EA Pharma and Eisai. Dr. Inada has received speaker’s honoraria from Eisai, Eli Lilly, Jansen, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, Mochnida, MSD, Novartis, Otsuka, Shionogi, Sumitomo Dainippon Pharma, and Yoshitomiyukan, and research grants from Ministry of Health, Labor and Welfare, Mitsubishi Tanabe Pharma, MSD, and National Center of Neurology and Psychiatry. Dr. Kanazawa has received speaker’s honoraria from Janssen, Meiji Seika Pharma, Otsuka, Shionogi, Sumitomo Dainippon Pharma, and Takeda Pharmaceutical Company and research grants from Ministry of Health, Labor and Welfare. The other authors declare no conflicts of interest.

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References

Ascher-Svanum, H., Zhu, B., Faries, D., Landblom, R., Swartz, M., Swanson, J., 2006. Time to discontinuation of atypical versus typical antipsychotics in the naturalistic treatment of schizophrenia. BMC Psychiatry 6, 8. https://doi.org/10.1186/1471-244X-6-8.
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 Db. Syst. Rev. 11, CD006623 https://doi.org/10.1002/14651858.CD006623.pub2.
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. American Journal of Psychiatry 158 (4), 518-526.
Eskow, S.M., Frisman, I.K., Covell, N.H., Hargreaves, W.A., 2000. Cost-effectiveness of clozapine compared with conventional antipsychotic medication for patients in state hospitals. Arch. Gen. Psychiat. 57, 987-994. https://doi.org/10.1001/archpsyc.57.10.987.
Hata, T., Kanazawa, T., Hamada, T., Nishihara, M., Yoneda, H., Nakajima, M., Katsutama, T., 2020. The 12-year trend report of antipsychotic usage in a nationwide claims database derived from four million people in Japan. J. Psychiatr. Res. 127, 28-34. https://doi.org/10.1016/j.jpsychires.2020.05.012.
Hogan, M.F., 2017. Increasing the use of lithium and clozapine in US suicide prevention- reply. JAMA Psychiatry 74, 423-424. https://doi.org/10.1001/jamapsychiatry.2016.4067.
Inada, K., Oshibuchi, H., Ishigooka, J., Nishihara, K., 2020. Effectiveness of atypical antipsychotics and clozapine in schizophrenia (FIN20). World Psychiatry 19, 61. https://doi.org/10.1002/wps.28. https://www.mhlw.go.jp/index.html.
Matsui, K., Iwashibashi, M., Kawanoo, M., Oshibuchi, H., Ishigooka, J., Nishihara, K., Inada, K., 2020. Clozapine-induced agranulocytosis in Japan: Changes in leucocyte/neutrophil counts before and after discontinuation of clozapine. Hum. Psychopharmac. Clin. https://doi.org/10.1002/hup.2739.
McEvoy, J.P., Lieberman, J.A., Stroup, T.S., Davis, C.E., Meltzer, H.Y., Rosenheck, R.A., Swartz, M.S., Perkins, D.O., Keefe, R.S.E., Davis, C.E., Severe, J., Hsiang, J.K., Investigators, CATIE, 2006. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am. J. Psychiat. 163, 600-610. https://doi.org/10.1176/appi.ajp.163.4.600. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5530121/.
Munuro, 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. Brit. J. Psychiat. 175, 576-580. https://doi.org/10.1192/bjp.175.6.576.
Nucifora, F.C., Mihajlevic, M., Lee, B.J., Mizuno, Y., Arumahuida, A., Hindley, G., Beck, K., Natesan, S., Elfunihou, O., Cipriani, A., Howes, O.D., 2020. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiat 7, 64-77. https://doi.org/10.1016/S2215-0366(19)30416-X.
Pilling, T., McCutcheon, R.A., Vano, L., Mizuno, Y., Arumahuida, A., Hindley, G., Beck, K., Natesan, S., Elfunihou, O., Cipriani, A., Howes, O.D., 2020. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiat 7, 64-77. https://doi.org/10.1016/S2215-0366(19)30416-X.
Risberg, J., 2015. The risk of clozapine-induced agranulocytosis. JAMA Psychiat 72, 732-734. https://doi.org/10.1001/jamapsychiatry.2014.2367.
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References

Ascher-Svanum, H., Zhu, B., Faries, D., Landblom, R., Swartz, M., Swanson, J., 2006. Time to discontinuation of atypical versus typical antipsychotics in the naturalistic treatment of schizophrenia. BMC Psychiatry 6, 8. https://doi.org/10.1186/1471-244X-6-8.
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 Db. Syst. Rev. 11, CD006623 https://doi.org/10.1002/14651858.CD006623.pub2.
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. American Journal of Psychiatry 158 (4), 518-526.
Eskow, S.M., Frisman, I.K., Covell, N.H., Hargreaves, W.A., 2000. Cost-effectiveness of clozapine compared with conventional antipsychotic medication for patients in state hospitals. Arch. Gen. Psychiat. 57, 987-994. https://doi.org/10.1001/archpsyc.57.10.987.