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Effects of titration speed, gender, obesity and concomitant medications on the risk and onset time of clozapine-associated fever among Japanese patients with schizophrenia: retrospective review of charts from 21 hospitals

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Background

Clozapine-induced inflammation, such as myocarditis and pneumonia, can occur during initial titration and can be fatal. Fever is often the first sign of severe inflammation, and early detection and prevention are essential. Few studies have investigated the effects of clozapine titration speed and concomitant medication use on the risk of clozapine-induced inflammation.

Aims

We evaluated the risk factors for clozapine-associated fever, including titration speed, concomitant medication use, gender and obesity, and their impact on the risk of fever and the fever onset date.

Method

We conducted a case-control study. The medical records of 539 Japanese participants with treatment-resistant schizophrenia at 21 hospitals in Japan who received clozapine for the first time between 2010 and 2022 were retrospectively investigated. Of these, 512 individuals were included in the analysis. Individuals were divided into three groups according to the titration rate recommended by international guidelines for East Asians: the faster titration group, the slower titration group and the ultra-slower titration group. The use of concomitant medications (such as antipsychotics, mood stabilisers, hypnotics and anxiolytics) at clozapine initiation was comprehensively investigated. Logistic regression analysis was performed to identify the explanatory variables for the risk of a fever of 37.5°C or higher lasting at least 2 days.

Results

Fever risk significantly increased with faster titration, male gender and concomitant use of valproic acid or quetiapine. No increased fever risk was detected with the use of other concomitant drugs, such as olanzapine, lithium or orexin receptor antagonists. Fever onset occurred significantly earlier with faster titration. Multivariate analysis identified obesity as being a factor that accelerated fever onset.

Conclusion

A faster titration speed and concomitant treatment with valproic acid and quetiapine at clozapine initiation increased the risk of clozapine-associated fever. Clinicians should titrate clozapine with caution and consider both the titration speed and concomitant medications.

Keywords

Adverse effects; DRESS; fever; myocarditis; pneumonia.

Clozapine is underused despite its exceptional efficacy in treatment-resistant schizophrenia because it can cause serious side-effects, such as agranulocytosis and myocarditis.[1,2] Among the diverse side-effects of clozapine, inflammatory side-effects such as myocarditis and pneumonia, which mainly occur within 4 weeks after initiation, have recently received increasing attention because of their high relative lethality.[3] Clozapine-related drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome has also been reported to occur both during initial titration and during maintenance.[4] Fever is the first sign of severe inflammation, and early detection and prevention are essential. Jose de Leon et al published international guidelines to prevent early inflammatory side-effects.[5,6] The guidelines propose a titration protocol based on the ability of different ethnic groups to metabolise clozapine relative to previously measured blood concentrations. The frequency of inflammatory side-effects of clozapine is greater in Japanese people.[7] A more gradual titration is recommended for East Asians, as their blood levels of clozapine are more likely to increase than those of Caucasians at the same dose.[5,6,8] Our previous study provided evidence for this guideline by retrospectively showing that there were fewer inflammatory side-effects in Japanese people who received a slower titration speed than that recommended by the guidelines.[9] Limitations of the previous study included the small sample size of 241 people from seven hospitals in three prefectures in Japan, as well as the investigation of only valproic acid as a concomitant medication at clozapine initiation. Only a few studies have reported the risk of inflammatory side-effects of clozapine based on titration speed.[9–11] Valproic acid has been most consistently reported to increase the risk of clozapine-induced inflammation;[3,10–13] however, the evidence is limited for other drugs (number of antipsychotics at initiation,[14,15] olanzapine,[14,16–18] quetiapine,[17–20] benzodiazepines[15] and orexin receptor antagonists).[21,22] Furthermore, a previous study suggested an association between the clozapine titration rate (CTR) and fever onset date (FOD), and that overweight or valproic acid combination affected hastening FOD.[23] However, because of the small number of individuals included in that study and the lack of multivariate analysis, we were not able to verify whether overweight or concomitant valproate had a true effect, or whether other factors may have also had an effect. The identification of predictors of FOD is important because clinicians should be more vigilant about inflammatory side-effects on the day of clozapine titration.

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In the present study, we aimed to conduct an integrated analysis of the effects of titration speed, obesity and concomitant medication use on the risk and onset date of clozapine-associated fever by collecting data from hospitals throughout Japan (241 people from the seven hospitals in our previous study[9] were not included in the current study) and by comprehensively investigating concomitant medication use (antipsychotics, mood stabilisers, benzodiazepines, hypnotics and anticholinergics) at the time of clozapine initiation.

Method

Study design and study population

We conducted a case-control study. Cases were individuals who had an episode of fever of 37.5°C or higher lasting at least 2 days within 6 weeks of starting clozapine; controls were individuals who did not develop a fever. We minimised bias by dividing people based on the presence or absence of fever within the same cohort. From a previous study,[9] we estimated the frequency of fever to be 20% and the required number of cases to be 500, using 10 explanatory variables for the logistic regression analysis. A total of 539 Japanese patients with treatment-resistant schizophrenia at 21 hospitals across Japan who received clozapine for the first time from March 2010 to November 2022 were included in the study. In Japan, clozapine can only be initiated during hospitalisation. The individuals were diagnosed with schizophrenia using the International Classification of Diseases, 10th revision (ICD-10). Treatment resistance was diagnosed by the use of two or more antipsychotics (chlorpromazine equivalent ≥600 mg) for at least 4 weeks without achieving a Global Assessment of Functioning score ≥41. Since the study was a retrospective study using anonymous data, an opt-out form was displayed on each hospital's bulletin board or website before collecting the data, and individuals who did not express the intent for exclusion were included in the study. The authors assert that all of the procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The Dokkyo University Hospital Ethics Review Board approved this study (Approval ID: R-66-4J).

The following data were collected from medical records: age, gender, height, weight, concomitant psychotropics at the initiation of clozapine, fever status, fever onset date, fever duration and daily clozapine dose for the first 6 weeks after clozapine initiation. Fever was defined as an armpit temperature of 37.5°C or higher. Fever duration was determined by the maximum number of consecutive fever days. However, days with intermittent fever occurring within 5 days were considered to be one episode, and the fever days were combined (12 individuals). Chlorpromazine and diazepam equivalents were calculated by methods described in a previous paper.[24]

We were unable to determine whether individual participants smoked, but we did identify whether participants received clozapine treatment in either a smoking-allowed or non-smoking hospital.

The calculation of the CTR was detailed in a previous paper.[9] According to the Japanese package insert, the clozapine titration protocol was as follows: 12.5 mg on day 1, 25 mg on days 2–4, 50 mg on days 5–7, 75 mg on days 8–9, 100 mg on days 10–11, 125 mg on days 12–14, 150 mg on days 15–17, 175 mg on days 18–20 and 200 mg on day 21. This titration rate was defined as the reference protocol rate for the following analyses (CTR = 1). We calculated individual CTRs as follows: CTR = the cumulative clozapine dose within the first X days/the cumulative clozapine dose within the first X days according to the reference protocol. X was the date of fever onset and was set as 21 if no fever occurred within 21 days of starting clozapine.

The recommended protocol for normal-metabolising Asians in the international guidelines issued by Jose de Leon's group[5] is 12.5 mg on day 1, 25 mg on days 2–3, 37.5 mg on days 4–5, 50 mg on days 6–7, 62.5 mg on days 8–9, 75 mg on days 10–11, 87.5 mg on days 12–13, 100 mg on days 14–17, 125 mg on days 18–20 and 150 mg on day 21. This protocol yields a CTR of approximately 0.75. The CTR based on the titration rate recommended by international guidelines for Asians with low metabolism is 0.40.[5] Using CTR levels of 0.75 and 0.40, participants were divided into three groups: the faster titration group (CTR ≥ 0.75), slower titration group (0.75 > CTR ≥ 0.40) and ultra-slower titration group (CTR < 0.40).

Statistical analysis

All of the statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Differences in demographic data between cases and controls were analysed using Fisher's exact test for categorical variables, and t tests or Mann–Whitney U tests for continuous variables. Titration group (faster titration group, slower titration group and ultra-slower titration group), gender, obesity status (BMI > 30) and concomitant drug use were selected as variables influencing fever risk due to clozapine and were evaluated via logistic regression analysis. In addition, a sensitivity analysis was performed by adding whether the hospital allowed smoking as an explanatory factor.

Pearson's product-moment correlation coefficient was calculated for the correlation between CTR and FOD. FOD among the three groups (faster titration group, slower titration group and ultra-slower titration group) was analysed using the Kruskal–Wallis test. Multiple comparison tests between the two groups were adjusted using the Bonferroni method. Multiple regression analysis was performed to analyse variables affecting FOD. These variables were selected based on previous studies.[5,9,12,14–16,22] Differences were considered to be statistically significant at $P < 0.05$.

Results

Of 539 participants at 21 hospitals in Japan, 23 were excluded because of insufficient information, and 4 were excluded because of electroconvulsive therapy (ECT) that was performed during clozapine titration. Thus, 512 people were included in the subsequent analysis. Supplementary Table 1 available at https://doi.org/10.1192/bjp.2024.113 shows the demographic data and frequency of fever for each titration category in all 512 participants.

There were 96 cases (individuals with fever lasting at least 2 days) and 371 controls (individuals without fever).

Comparison of demographic data between cases and controls

Table 1 shows the differences in demographic characteristics between cases and controls. There was a significantly greater proportion of males among the cases than among the controls (68% versus 55%, respectively), but there were no differences in age or the number of obese people. The mean CTR was also significantly greater in the cases (0.70 versus 0.56); compared with the titration category, the number of faster titration group individuals was significantly greater in the cases (45.8% versus 20.8%). The mean chlorpromazine equivalent of concomitant antipsychotics at the start of clozapine administration was significantly greater in controls (425 mg versus 568 mg). There was no significant difference in the mean diazepam equivalent of concomitant benzodiazepines.

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Table 1 Comparison of demographic data between cases and controls

	Controls	Cases	Statistical test	*P*
Number of patients, *n*	371	96		
Age, years, mean (s.d.)	44.0 (12.8)	43.7 (12.6)	t = 0.24, d.f. = 465	0.81
Male, *n* (%)	204 (55)	65 (68)	Fisher's exact test	0.028
Obesity, *n* (%)	45 (12)	12 (13)	Fisher's exact test	0.86
CP equivalent of concomitant antipsychotics at start of clozapine, mg, mean (s.d.)	568 (568)	425 (473)	Mann–Whitney U test	0.036
Diazepam equivalent of concomitant benzodiazepines at start of clozapine, mg, mean (s.d.)	11.4 (13.7)	11.4 (17.0)	Mann–Whitney U test	0.40
CTR, mean (s.d.)	0.56 (0.23)	0.70 (0.27)	Mann–Whitney U test	<0.001
Titration				
Ultra-slower, *n* (%)	84 (22.6)	15 (15.6)	Fisher's exact test	<0.001[a]
Slower, *n* (%)	210 (56.8)	37 (38.5)		
Faster, *n* (%)	77 (20.8)	44 (45.8)		
Antipsychotics				
Olanzapine	86 (23)	23 (24)	Fisher's exact test	0.89
Risperidone	56 (15)	10 (10)		0.32
Zotepine	45 (12)	7 (7.3)		0.21
Paliperidone	31 (8.4)	6 (6.2)		0.67
Levomepromazine	30 (8.1)	6 (6.2)		0.67
Aripiprazole	23 (6.2)	11 (12)		0.08
Blonanserin	30 (8.1)	5 (5.2)		0.39
Quetiapine	19 (5.1)	10 (10)		0.09
Haloperidol	26 (7.0)	4 (4.2)		0.48
Mood stabilisers				
Valproic acid	73 (20)	27 (28)		0.09
Lithium	74 (20)	20 (21)		0.89
Benzodiazepines				
Nitrazepam	100 (27)	23 (24)		0.60
Flunitrazepam	53 (14)	12 (13)		0.74
Brotizolam	41 (11)	11 (11)		0.86
Clonazepam	21 (5.7)	9 (9.4)		0.24
Lorazepam	25 (6.7)	6 (6.2)		1
Hypnotics				
Suvorexant	47 (13)	9 (9.4)		0.48
Lemborexant	32 (8.6)	8 (8.3)		1
Anticholinergics				
Biperiden	49 (13)	11 (12)		0.73

Medications used by more than 5% (23/467) of patients were presented.
CP, chlorpromazine; CTR, clozapine titration rate.
a. Ultra-slower—Slower, $P = 1$; Ultra-slower—Faster, $P = 0.0013$; Slower—Faster, $P < 0.001$ (Bonferroni).

Concomitant medications at clozapine initiation (Table 1)

The most frequently used concomitant antipsychotics were olanzapine, risperidone and zotepine. The most frequently used benzodiazepines were nitrazepam, flunitrazepam and brotizolam. Valproic acid and lithium were each used in combination with clozapine in more than 20% of the people. There was no significant difference in the frequency of concomitant drug use between cases and controls; however, there was a trend towards more frequent use of valproic acid, quetiapine and aripiprazole in cases.

Logistic regression analysis for the risk of clozapine-associated fever

Logistic regression analysis was performed on the risk of clozapine-associated fever (Table 2). First, regarding titration speed, a significantly greater risk of fever was observed in the faster titration group than in the ultra-slower titration group (adjusted odds ratio: 4.05; 95% CI: 1.99–8.24; $P < 0.001$). In contrast, no significant increase in the risk of fever was observed in the slower titration group compared with the ultra-slower titration group (adjusted odds ratio: 1.10; 95% CI: 0.56–2.17; $P = 0.79$). Second, a significant increase in the risk of fever was observed in males (adjusted odds ratio: 1.69; 95% confidence interval: 1.03–2.79; $P = 0.039$). Obese participants did not have a significantly increased risk of fever (adjusted odds ratio: 1.11; 95% confidence interval: 0.54–2.29; $P = 0.78$). Third, regarding concomitant medications at clozapine initiation, significant increases in fever risk were observed with valproic acid (adjusted odds ratio: 1.90; 95% confidence interval: 1.09–3.29; $P = 0.023$) and quetiapine (adjusted odds ratio: 2.50; 95% confidence interval: 1.05–5.96; $P = 0.038$). The mean dose (s.d.) of valproic acid for cases was 730 (254) mg, and the mean dose (s.d.) of quetiapine for cases was 248 (197) mg. In contrast, olanzapine, lithium, suvorexant and lemborexant did not increase fever risk.

Table 2 Logistic regression analysis for the risk of clozapine-associated fever

	OR	95% CI	*P*
Titration group (Slower)[a]	1.10	0.56–2.17	0.79
Titration group (Faster)[a]	4.05	1.99–8.24	<0.001
Gender (Male)	1.69	1.03–2.79	0.039
Obesity (BMI > 30)	1.11	0.54–2.29	0.78
Concomitant drugs at start of clozapine			
Valproic acid	1.90	1.09–3.29	0.023
Lithium	1.25	0.69–2.26	0.45
Olanzapine	0.85	0.48–1.51	0.59
Quetiapine	2.50	1.05–5.96	0.038
Suvorexant	0.72	0.32–1.61	0.43
Lemborexant	1.07	0.46–2.49	0.88

BMI, body mass index; OR, odds ratio.
a. Ultra-slower is the reference.

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Effect of smoking availability on the risk of clozapine-associated fever

We compared the frequency of fever in 238 people from 8 hospitals where smoking was allowed and in 274 people from 13 non-smoking hospitals. In the hospitals where smoking was allowed, 14.7% (35/238) were cases; in the non-smoking hospitals, 22.3% (61/274) were cases. Fisher's exact test demonstrated a significant difference (odds ratio: 0.60; 95% confidence interval: 0.37–0.97; $P = 0.031$). Afterwards, as a sensitivity analysis, we included hospitals where smoking was allowed as an explanatory factor in the logistic regression analysis. The results were still significant after adjusting for other factors (Supplementary Table 2).

Correlation between CTR and FOD

Pearson's product-moment correlation indicated a significant correlation between CTR and FOD (correlation coefficient = −0.535, 95% confidence interval: −0.644 to −0.374, $P < 0.0001$), as shown in Fig. 1(a). Afterwards, we analysed whether there was a difference in FOD among the faster titration group, slower titration group and ultra-slower titration group (Fig. 1(b)). The means (s.d.) of FOD were 9.8 (5.7), 15.3 (6.0) and 19.1 (7.2) days for the faster titration group, slower titration group and ultra-slower titration group, respectively. The median FODs were 12, 15 and 19 days for the faster titration group, slower titration group and ultra-slower titration group, respectively. The Kruskal–Wallis test and subsequent Mann–Whitney U test (Bonferroni adjustment) demonstrated significant differences in FOD between the faster titration group and slower titration group ($P = 0.00037$) and between the faster titration group and ultra-slower titration group ($P = 0.00013$), respectively. There were no significant differences between the slower titration group and ultra-slower titration group ($P = 0.187$).

Multiple regression analysis for FOD

Although the impact of CTR on FOD was evident, a multiple regression analysis was performed to explore whether other factors may have influenced FOD (Table 3). The CTR had a strong effect on FOD, even after adjusting for other factors (estimate: −13.37; 95% confidence interval: −17.92 to −8.81; $P < 0.0001$). A BMI >30 kg/m^2 (obese) was found to be associated with a more rapid FOD (estimate: −4.26; 95% confidence interval: −7.94 to −0.58; $P = 0.024$). Gender and concomitant use of valproic acid and quetiapine at the start of clozapine administration had no significant effect on FOD.

Table 3 Multiple regression analysis for fever onset date

	Estimate	SE	95% CI LL	95% CI UL	T	*P*
Clozapine titration rate	−13.37	2.29	−17.92	−8.81	−5.83	<0.0001
Gender (Male)	−0.17	1.32	−2.78	2.45	−0.12	0.90
Obesity (BMI > 30)	−4.26	1.85	−7.94	−0.58	−2.3	0.024
Concomitant drugs at start of clozapine						
Valproic acid	0.89	1.35	−1.79	3.57	0.66	0.51
Quetiapine	1.02	1.99	−2.93	4.70	0.51	0.61

BMI, body mass index; LL, lower limit; SE, standard error; UL, upper limit.

Discussion

This was the most extensive study to comprehensively examine the effects of clozapine titration speed, gender, obesity and concomitant medication use on the risk and timing of clozapine-associated fever.

Relationship between clozapine titration speed and the risk of clozapine-associated fever

According to both univariate and multivariate analyses, the fever risk was significantly greater in the faster titration group than in the slower titration group and ultra-slower titration group. These results are consistent with those of our previous study.[9] There were no differences in the frequency of fever between the slower titration group and ultra-slower titration group. This suggests that

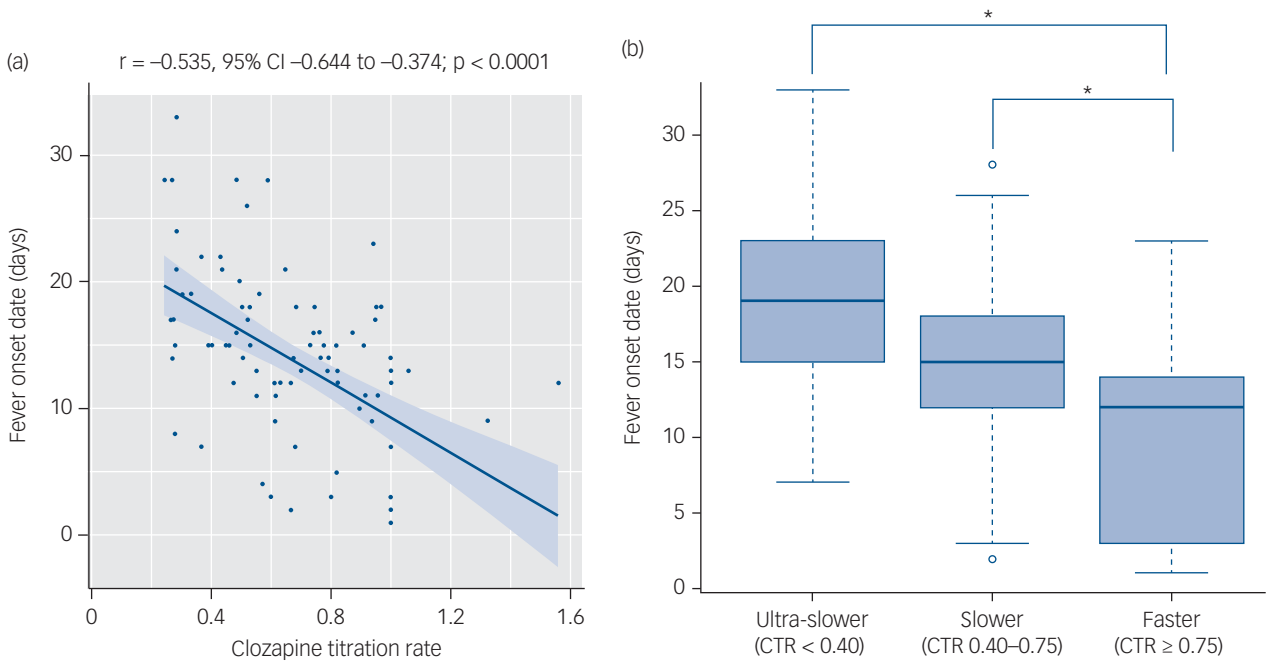

Fig. 1 (a) Scatterplot and Pearson's correlation coefficients for fever onset date and clozapine titration rate (CTR). The blue shaded area indicates the confidence interval at the 95% confidence level. (b) Box-and-whisker plot comparing fever onset date among the three groups. Significant differences are indicated by asterisks in multiple comparisons according to the Mann–Whitney U test (Bonferroni adjustment).

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the fever risk does not decrease with slower CTRs. A total of 8% (9/113) of people in the ultra-slower titration group had a fever lasting for at least 4 days (Supplementary Table 1). This suggests that approximately 10% of participants may have some immunological or metabolic disposition. In this subset of participants, an even slower titration than a CTR of 0.3 may be necessary.

Relationship between concomitant drug use and the risk of clozapine-associated fever

Multivariate analysis demonstrated a significantly increased risk of fever with concomitant valproic acid and quetiapine use.

A meta-analysis reported that concomitant use of valproic acid is a risk factor for clozapine-induced myocarditis (k = 6, n = 903, pooled odds ratio: 3.58, 95% confidence interval: 1.81–7.06).[12] Pui-yin Chung et al also reported that valproic acid is a risk factor for clozapine-induced fever in Asian people.[11] The results of this study are consistent with these findings. The situation in Japan regarding the use of valproic acid at clozapine initiation, which is not common in Europe, was detailed in a previous article.[13] The mechanism by which concomitant valproic acid increases the risk of clozapine-associated fever is unknown. The effect of valproic acid on clozapine metabolism appears to be rather complex, as it acts both as an inhibitor and an inducer.[25] However, during clozapine titration, the inhibitory effect of valproic acid may predominate, as induction may take a few weeks to occur.[25] Two case series of clozapine-induced myocarditis reported high plasma/serum clozapine concentrations in people taking valproate, which is compatible with inhibition.[26,27] A recent study reported that concomitant valproic acid increased the formation of cysteinyl derivatives of the toxic nitrenium ions of clozapine.[28]

A previous study reported that concomitant prescription of quetiapine increased the risk of clozapine-associated myocarditis.[20] In addition, there have been reports of increased severity of clozapine-induced myocarditis.[16,17,19] Therefore, international guidelines recommend a gradual increase in dosage when quetiapine is used concomitantly.[6] Similar recommendations have been made for olanzapine;[6] however, in this study, olanzapine did not increase the risk of fever. The mechanism by which the concomitant use of quetiapine increases the risk of fever is unknown, but sedation and aspiration with quetiapine may have an effect. Quetiapine may occasionally cause myocarditis by itself and may have pharmacodynamic effects at the immunological level that contribute to the risk of myocarditis.[17]

No increased risk of fever was detected with the concomitant use of lithium, suvorexant or lemborexant. This is consistent with the fact that the concomitant use of lithium with clozapine has been widely reported in Japan[29] (presumably to increase white blood cell counts) and that orexin receptor antagonists are increasingly being prescribed instead of benzodiazepines.[30,31]

Other factors associated with the risk of clozapine-associated fever

An increased fever risk was observed in males. This result is difficult to explain, given that men have a better metabolism than women. It is possible that immunological mechanisms or other confounding factors may be involved. The results also suggest that hospitals where smoking is allowed reduce the incidence of clozapine-associated fever. This result is reasonable, given that smoking decreases the blood concentration of clozapine.

Correlations between FOD and CTR

There is a correlation between FOD and CTR; moreover, although there is variation among individuals, the time of susceptibility to fever can be identified (to some extent) by titration speed. First, for faster titration group, the median FOD is on day 12, and the mean is at approximately day 10. In contrast, for ultra-slower titration group, the median and mean FOD are on day 19. As Fig. 1(b) shows, the median FOD is between days 10 and 20 in the three groups, thus indicating that as the titration speed slows, the FOD is delayed from approximately day 10 to day 20. Therefore, clinicians can (to some extent) predict when to be cautious about the onset of fever according to titration speed.

Factors affecting FOD other than CTR

A BMI >30 kg/m^2 (obesity) was identified as a factor that accelerated FOD. Other factors, such as gender and concomitant use of valproic acid and quetiapine, had no significant effect on FOD. The international guidelines recommend slow clozapine titration in obese individuals because they metabolise clozapine poorly.[5] The striking relationship between CTR and FOD suggests that elevated blood levels of clozapine are associated with the early onset of fever. Therefore, the fact that obesity hastens FOD may suggest that obesity increases the blood concentration of clozapine.

Clinical recommendations

These results suggest that a slower titration rate in Japanese people than that recommended by the international guidelines reduces the development of clozapine-associated fever. This result may also apply to East Asians. Clinicians should be aware of the individual's ethnicity when titrating clozapine. It is also essential to be aware of inflammation during clozapine titration, given that approximately 30% of participants developed fever during the faster titration, and approximately 10% developed fever during the slower titration in this study. In our previous study analysing 241 Japanese people, all of the severe inflammation caused by clozapine, including myocarditis and pneumonia, was triggered by fever, and the disease became more severe over several days.[9] Because of the fact that inflammation increases blood levels of clozapine, international guidelines recommend baseline and weekly C-reactive protein (CRP) monitoring during clozapine titration, and discontinuation of clozapine titration during fever and elevated CRP.[5] Our case series showed that CRP often rises simultaneously with fever.[32] Although it is difficult to measure CRP daily, the detection of fever is clinically easy, even on a daily basis. Thus, fever is useful for detecting and preventing clozapine-induced inflammation. Nevertheless, clinicians should also be aware of asymptomatic inflammation. In an Australian report, 20% of people with clozapine-induced myocarditis had no fever.[33] CRP monitoring is useful for detecting asymptomatic inflammation, preventing fever and preventing inflammation from worsening.

Our recommendations for clozapine titration in Japanese people have been summarised in a previous paper.[9] The risk of inflammatory side-effects with clozapine is likely to vary among individuals and is influenced by multiple factors, including ethnicity, titration speed and concomitant medication use. Since clozapine metabolism varies widely among individuals, a fixed protocol, such as increasing the dose to 300 mg/day in 2 weeks, is illogical and should be adjusted based on clozapine blood levels. After assessing the risk of inflammatory side-effects, the clinician must decide what titration speed to adopt, considering the severity of psychiatric symptoms. CRP monitoring may be helpful in this clinical decision.

Future study

Further similar studies in other ethnic groups are warranted. Genetic studies are warranted to determine whether immunological or metabolic mechanisms predispose the Japanese population to inflammatory side-effects. The development of models to predict

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therapeutic doses of clozapine for each individual based on multiple factors, including ethnicity[8] and genetic variants,[34] is also desirable.

Limitations

This study had several limitations. First, this study was retrospective, and the titration speed at which clinicians titrated clozapine could have differed depending on each individual's background. The severity of psychiatric symptoms, physical status and comorbidities were not investigated. Second, because we included all fevers, we were unable to distinguish between direct inflammation caused by clozapine and inflammation caused by other mechanisms, such as aspiration. It is also possible that some fevers were included that were not strictly caused by clozapine. However, there were no cases in which the cause of fever, such as COVID-19, was clearly identified. Third, only fever duration was investigated; clinical diagnoses (such as myocarditis and pneumonia) and whether they were fatal were unknown. Fourth, we investigated concomitant medications at the time of clozapine initiation; however, it was unclear whether they were strictly concomitant at fever onset. However, as shown in Fig. 1(a), most cases of fever occurred early after the start of clozapine administration, thus suggesting that the effect of concomitant medications at the start of clozapine administration was substantial. Fifth, it was difficult to address the relationship between postfebrile dose adjustment and clinical outcomes in this study because the clinical symptoms, severity and outcomes associated with fever, as well as clinicians' attitudes towards fever, were unknown. A total of 94% (133/141) of people did not receive a dose increase of clozapine within 2 days immediately after fever. The number of cases of discontinuation due to fever is shown in Supplementary Table 1; however, it is difficult to interpret this finding because it is unclear whether the discontinuation was due to severe disease or preventive measures before severe disease developed. Sixth, fever was the only indicator of inflammation that was used in this study, and we were unable to measure other important indicators, such as CRP and clozapine blood levels. Seventh, we were unable to investigate other non-psychotropic medications that may be associated with inflammation.

Conclusion

This study demonstrated an association between clozapine titration speed and increased fever risk among Japanese participants. The results also suggested that concomitant use of valproic acid and quetiapine at the start of clozapine administration was associated with an increased risk of fever. Clinicians should adjust the clozapine dose to prevent clozapine-induced inflammation, thus focusing attention on the clozapine titration speed and concomitant medication use.

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Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjp.2024.113

Data availability

The data are not publicly available because they contain information that could compromise the research participants' privacy/consent.

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Author contributions

Y.K. analysed the data and wrote the first draft. N.Y.-F. and M.K. conceived, administered and supervised the study. All authors reviewed and approved the final manuscript.

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Declaration of interest

None.

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