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This article has Supplementary Material including a Supplementary Text, 11 Supplementary References and 18 Supplementary Tables.

Around 3% of 1,300 Levels Were Elevated during Infections in a Retrospective Review of 131 Beijing Hospital In-Patients with More than 24,000 Days of Clozapine Treatment

RUNNING TITLE: Infection clozapine

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Abstract:

Background: The clozapine literature describes 1) approximately 50 cases with level elevations during infections, including pneumonia, and 2) high lethality of pneumonia. There are no systematic studies of clozapine therapeutic drug monitoring (TDM) to establish: 1) the dose-correction factors to compensate for the effect of infections in individuals, and 2) the relative importance of these elevations in a large sample.

Methods: A previously published genotyping study with TDM in Beijing Anding Hopsital included 131 clozapine inpatients with trough steady-state TDMs. Their charts were retrospectively reviewed for clinical data including presence and duration of infections/inflammations and/or clozapine inhibitors.

Results: Eighteen episodes of infections/inflammations in 16 patients contaminated 2% (482/24,789) of clozapine days, and 3% (46/1,384) of trough steady-state TDMs. Sixteen episodes of inhibitor co-prescription in 13 patients contaminated 12% (2,888/24,789) of the days and 12% (171/1,384) of steady-state TDMs. At the individual level: 1) 11% of infection episodes had no clinically relevant effects on TDM (vs. 81% in inhibitors), 2) halving the clozapine dose would be advisable in 61% of the infection episodes (vs. 19% in inhibitors), and 3) reducing the clozapine dose to one-third would be advisable in 28% of infection episodes (vs. 0% in inhibitors). One of the two pneumonia cases required a 3-month medical admission.

Conclusions: This study reflects the clinical practice of one specific hospital located in one specific country but indicates that elevations in clozapine levels during infection/inflammations can be frequent. This may explain the risk of mortality of clozapine patients during severe infections, particularly pneumonia.

INTRODUCTION

CYP1A2 explains 70% of clozapine metabolism [1] and leads to its main metabolite, norclozapine. CYP1A2 activity is influenced by tobacco smoking (an inducer) and sex (estrogens are inhibitors). Asians have lower clozapine metabolism and need roughly half the clozapine dose of Caucasians [2]. A therapeutic drug monitoring (TDM) guideline recommends steady-state trough serum concentrations for clozapine of 350-600 ng/mL [3]. The concentration-to-dose (C/D) ratio is a measure of the ability to eliminate the drug and is influenced by genetic, personal and environmental factors [2].

In 2002, as infections can inhibit CYP1A2, the last author decreased the clozapine dose by half in a patient with a clozapine intoxication during an infection [4]. Then in 2004, he proposed that during severe inflammations/infections, the clozapine dose should be cut in half until TDM results are available [5]. In a systematic review extending until 2016, Clark et al. [6] described 40 cases of elevations of serum clozapine during infections. More recently, severe infections were also associated with roughly double the serum concentration levels in Chinese patients, [7, 8], while the effects of dermatitis depended more on severity of the systemic inflammation measured by the serum C-reactive protein (CRP) [8]. Pneumonia is one of the most frequent infections with potential for high lethality due to its associated increases in clozapine levels. Moreover, clozapine and pneumonia have strong bidirectional associations, since clozapine may increase the risk of pneumonia [9].

In summary, the literature describes cases of clozapine level elevations during infections and indicates high lethality of pneumonia in clozapine patients. There are no systematic studies of clozapine TDM establishing the influence of infections on clozapine TDM either at the patient level or in large samples of clozapine patients. Prospective studies with randomization are not possible in studying this peculiar clozapine drug interaction.

The goal of the retrospective review is to identify, in a sample of clozapine patients recruited for a pharmacogenetic study in a Beijing hospital, the effects of infection/inflammation on: 1) individual patients, through the calculation of the dose-correction factor needed to compensate for the increase in levels (Table

1); and 2) a large sample, through the calculation of the number of clozapine treatment days and levels contaminated by infection/inflammation (Supplementary Table S1). To compare clinical relevance, the same effects in the individual (Supplementary Table S2) and in the whole sample (Supplementary Table S1) were studied for inhibitors of clozapine metabolism.

METHODS

Sample

From September 2017 to February of 2018, 134 Han Chinese clozapine patients were recruited at the Beijing Anding Hospital after signing a consent form approved by the hospital's ethics committee for a pharmacogenetic study [2].

Retrospective review

The first author retrospectively reviewed medical records for clinical data including co-medications, smoking status, the presence of infections/inflammations and/or co-prescription of inhibitors of clozapine metabolism, and their duration.

Therapeutic drug monitoring (TDM)

Trough steady state clozapine and norclozapine levels were measured by high-performance liquid chromatography (HPLC) as described before [2]. Clozapine and total concentration C/D ratios were calculated. Three of the 134 patients had to be excluded due to lack of steady-state concentrations.

RESULTS

Clinical relevance of infections and inhibitors in the total clozapine sample

Supplementary Table S1 shows that the 131 inpatients had a total of 24,789 clozapine days (>67 clozapine years) and 1,384 steady state clozapine TDMs. There were 16 (12% of 131 patients) with a possible infection/inflammation during admission; they accounted for 2% of the clozapine days and 3% of the steady state TDMs contaminated by infections.

There were 13 patients (10% of 131 patients) taking an inhibitor some time during their admission; they represented 12% of the clozapine days and steady-state TDMs contaminated by inhibitors (Supplementary Table S2).

Types of infection/inflammation

Tables S3-S18 provide details of these cases. Of the maximum TDM peaks observed in the 16 patients with 18 episodes of infection, 11% (2/18) of the episodes did not require any relevant dosage changes; 61% (11/18) will need half the clozapine dose, according to peak data during the infection; and 28% (5/18) will need one-third of the usual dose (Table 1).

Patient 2 had four viral respiratory infections; TDM data was available for two of them. Patient 7 had two possible infection episodes. Therefore, there were 18 infection/inflammation episodes with TDM in 16 patients. The types of infections in order of frequency were: respiratory viral infections (61%, 11/18), pneumonia (11%, 2/18), undiagnosed (16%, 3/18), skin abscess (6%, 1/18) and a possible gastrointestinal infection/inflammation (6%, 1/18) treated symptomatically

Clinical Relevance of Infection at the Individual Level: Dose-correction Factor

The dose-correction factors in episodes of respiratory infection were: 1) 0.44 and 0.64 in 2 cases of pneumonia, 2) 0.27 to 0.72 in 6 episodes of viral infection and leukocytosis, and 3) 0.61 to 1 (no relevant changes) in 5 episodes of viral infection with no leukocytosis (Table 1). The rest of the infections were heterogeneous and required a dose correction factor of 0.60 for a skin abscess with leukocytosis, 0.39 and 0.66 in a patient with 2 undiagnosed episodes of possible viral infection, 0.62 for a gastrointestinal infection/inflammation and 0.27 for undiagnosed inflammation.

Description of Inhibitors

Some of the CYP1A2 inhibitors that may be prescribed in Western countries were not prescribed in our Beijing hospital. As the text reported, fluvoxamine was not prescribed. No patient was taking oral contraceptives or ciprofloxacin [S1]. Levofloxacin is not a CYP1A2 inhibitor [S2] so it was used to treat the two pneumonias. There is no access to caffeinated beverages in our hospital.

Supplementary Table S2 shows 13 patients (Patients 2, 10 and 16 to 26) who were prescribed imipramine, perphenazine, or sertraline, which are potentially clinically relevant clozapine inhibitors [S1, S3, S4].

Clinical Relevance of Inhibitors at the Individual Level: Dose-correction Factors

Of the maximum TDM peaks observed in the 13 patients with 16 episodes of treatment with inhibitors, 81% (13/16) did not need any relevant dosage changes and 19% (3/16) will need half the clozapine dose, according to peak data from the treatment period with inhibitors. The Supplementary Results and Discussion sections provide more details on inhibitors; the footnotes of Supplementary Table S2 note that in Patients 10, 24 and 25 the inhibitor dose appeared important. Fluvoxamine is a potent clozapine inhibitor [10] but after one death, it is no longer co-prescribed with clozapine in our hospital.

DISCUSSION

Clinical Relevance of Infections Compared with Inhibitors in Individual Patients

When focusing at the patient level, infections appeared much more clinically relevant in the contamination of clozapine TDM than did treatment with inhibitors. We considered 11% of the infection periods to have no apparent clinically relevant effect on TDM vs. 81% that corresponded with co-prescription of inhibitors. Approximately halving the clozapine dose would be advisable in 61% of the infection episodes vs. 19% of the inhibitor periods. Using approximately one-third the clozapine dose would be advisable in 28% of the infection episodes vs. none of the inhibitor periods.

Types of Infections/inflammations

The most important infections/inflammations were viral respiratory infections. The available TDM data suggested that when there was no leukocytosis some patients might not need clozapine dose changes while others need half the dose. When the viral infection was associated with leukocytosis and probably caused by the influenza virus, the clozapine dose corrections needed would reduce the dose to somewhere between 1/3 and 3/4.

Pneumonia was the second most frequent cause with two cases. The potential lethality of pneumonia in clozapine patients was demonstrated by one patient (Patient 10) who needed to be transferred to a medical hospital for 3 months.

Types of Inhibitors

Our retrospective review only found 3 potential inhibitors, imipramine, perphenazine, and sertraline, in 16 episodes of treatment with inhibitors in 13 patients. In most cases the available TDM data suggested that effects were not clinically relevant, but in some patients sertraline in high doses or the combination of sertraline and perphenazine was a clinically relevant inhibitor of clozapine metabolism, which is compatible with prior literature on high doses of these compounds [S3, S4].

Limitations

The most important limitation is that this data reflects the clinical practice of one specific hospital located in one specific country. Despite providing >24,000 clozapine treatment days (>67 clozapine years) and >1000 steady-state TDMs, our data may be weakened by missing infection peaks and the use of relatively weak inhibitors. Replication will require another hospital using repeated clozapine TDMs in a large sample of patients.

The second limitation is its retrospective nature. The patients were prospectively treated by clinicians who used TDM for clinical purposes, but we collected the data in a retrospective way. Based on prior cases [7, 8], clinicians learned to pay attention to clozapine TDM during infections and consider dose reductions. White blood cell counts (WBCs) were studied and sometimes during the infections c-reactive protein (CRP) levels were available [S5]. Infections were clinically diagnosed with no identification of the microbiological agent. In hindsight, we would have liked to have had CRPs and close fever monitoring in all patients and more TDM during infections/inflammations in order to have more chances to catch peak TDMs. We are planning to seek funding for a prospective study in which we will support treating psychiatrists with pharmacists to help remind psychiatrists to order CRP and TDM as soon as signs/symptoms of infection/inflammation appear. We cannot rule out that a prospective study including

more in situ education for treating psychiatrists may provide an even higher percentage than 2-3%. The infections/inflammations totaled 482 days with 46 trough steady-state TDMs (and a few not in steady state). We probably missed some of the TDM peaks during infections.

The third limitation is that the TDM data was collected for clinical purposes and not for research. The first author reviewed each level in order to verify steady-state concentrations (≥5 days or ≥5 clozapine half-lives after the last dose). All samples were trough collections (early morning before meds and >12 hours since the last dose). Three of the 134 patients had to be excluded due to lack of steady-state concentrations. In our prior case reports [7, 8], the peak of clozapine TDM during infection was not a steady-state concentration because for clinical reasons it was not possible to keep the doses stable. Eliminating them will undercalculate the effects of infection. Therefore, we calculated the mean dose of the last 5 days before the blood collection to approximate the clozapine concentration-to-dose (C/D) ratio. The peak clozapine C/D ratio was used to calculate the dose correction factor needed to compensate for the inhibition of clozapine metabolism. The clozapine C/D ratio without infection was divided by the clozapine C/D ratio during infection. If the value is close to 1, it was considered not relevant. Similar procedures were performed to calculate the effects of co-prescription of inhibitors in order to provide a comparison of the clinical relevance of infections.

The fourth limitation is that the medical records do not provide details about the presence or absence of signs of clozapine toxicity.

The fifth limitation is that this study reflect inpatient practice. Future studies will also need to be conducted with clozapine outpatients, but it will be more difficult to establish clozapine treatment adherence by patients, which may make it difficult to interpret clozapine levels. Lack of adherence is a major problem in the interpretation of clozapine TDM in outpatients [S6].

The sixth limitation is that smoking was not controlled and is frequent among male patients but rare among females. The hospital staff does not control smoking and there was no information on the number of daily cigarettes smoked by each patient who was a smoker. Our experience with a well-controlled double-

blind clozapine study in the United States (US), in which adherence was closely supervised and caffeine beverages were not available [S7, S8] is that the major reason for TDM variability is the variation in smoking in the patients who smoke [S9]. In that US hospital, each patient was given the same number of cigarettes every day by the staff, but the staff knew that patients traded cigarettes. In that study, we had the luxury of access to serum cotinine levels [S9] and we could observe that some smokers occasionally have greater diminutions in cotinine levels compatible with decrease in smoking that were associated with increases in the clozapine C/D ratio. In this study in Beijing Anding Hospital, 4 of the 16 patients (Patients 1, 3, 4 and 6) with infections were smokers. It is possible that during respiratory infections they may have decreased their smoking and this may be associated with some loss of CYP1A2 induction and increases in clozapine C/D ratios. It is believed that induction disappears 2-4 weeks after complete smoking cessation [S10]. Patient 1 had a skin abscess that lasted 15 days; we do not think it is likely that patient decreased smoking due to a skin abscess. However, even if he stopped smoking completely, the infection did not last long enough to see contamination of the increase in his clozapine C/D ratio due to smoking cessation. Supplementary Table S3 indicates that the peak clozapine C/D ratio was on day 1 of the infection, too early to see effects from the loss of induction due to smoking cessation. Patient 3 had a respiratory viral infection with fever that lasted 18 days, so some contamination in his clozapine C/D ratio due to smoking cessation cannot be completely ruled out in the last days of the infection. Supplementary Table S5 indicates that the peak clozapine C/D ratio occurred on day 10 of the infection, so it appears to be too early to see effects from the loss of induction due to smoking cessation. Patient 4 had a respiratory viral infection without leukocytosis that lasted 28 days, so some contamination in her clozapine C/D ratios through decreased smoking cannot be completely ruled out, but the increase in the C/D ratio (dose correction factor 0.70) was very mild, reflecting the mild infection. Supplementary Table S6 indicates that the peak clozapine C/D ratio was on day 12 of the infection (day 197; the infection started on day 185) so it appears to be too early to see the effects of loss of induction due to smoking cessation. Patient 6 had a respiratory viral infection without leukocytosis that lasted 33 days, so some contamination in her clozapine C/D ratio through

decreased smoking cannot be completely ruled out at the end of the infection. Supplementary Table S8 indicates that the peak clozapine C/D ratio was on day 4 of the infection (day 50; the infection started on day 46) so it is too early to see effects from the loss of induction due to smoking cessation. In summary, even if the four patients stopped smoking completely the effects of loss of induction were absent or minimal. Ideally, in future studies, we would want to have access to serum cotinine levels to explore the effects of smoking variations on clozapine C/D ratios. However, we do not think that we could convince the hospital administration to cover the cost of developing a chromatography assay to measure cotinine levels. We are not aware of any hospital in the world using routine serum cotinine levels in clinical practice. Smoking and caffeine intake variations have clinically relevant effects on clozapine metabolism. Ideally, having access to serum cotinine and caffeine (and paraxanthine) levels may be important for managing clozapine patients in in- and out-patient settings but, unfortunately, these determinations are not currently considered part of clinical practice and these assays are mainly limited to research laboratories.

Practical Recommendations for the Management of Infections in Clozapine Patients

Based on the literature [9] and this new study, in order to help clinicians managing clozapine patients, we have developed 3 sets of recommendations regarding infections: 1) prevention, 2) during the infection, and 3) after the infection.

For prevention, we recommend that psychiatrists using clozapine should educate their outpatients and families to be attentive to signs or symptoms of infection/inflammation or fever and to contact them immediately to prevent clozapine intoxications. To prevent pneumonia, psychiatrists should prescribe the lowest possible efficacious CLO Ds in each patient to decrease the risk for hypersalivation, sedation and swallowing disturbances. Hypersalivation should be managed with pharmacological and non-pharmacological interventions when required [S11].

Once an infection has developed, the psychiatrist should order a CRP level. When fever and/or CRP elevations develop, the psychiatrist should consider immediately halving the clozapine dose and monitor for signs of clozapine intoxication. If the clinician has access to clozapine TDM when the lab returns the

clozapine TDM, it will be possible to better adjust the dosage. If signs of clozapine intoxication are already present it may be safer to stop clozapine for 2-3 days or until the TDM report arrives. A severe infection, such as pneumonia combined with a clozapine intoxication, appears to be a highly lethal combination [9].

After the infection/inflammation has resolved and the CRP has normalized, we recommend going back to the prior clozapine dose, as long as it was a safe and efficacious dosage.

CONCLUSSION

We found that elevations in clozapine levels during infections/inflammations are frequent and this may be a major contributing factor in mortality risk for clozapine patients during severe infections, particularly pneumonia. As a matter of fact, we found that around 2% of clozapine days in a large sample of clozapine inpatients were contaminated by infection/inflammation. At the patient level, to avoid a clozapine intoxication during the peaks of the 18 episodes of infection/inflammation in 16 patients, 11% (2/18) of the episodes did not require any relevant changes; 61% (11/18) needed half the clozapine dose, and 28% (5/18) needed one-third of the usual dose. The risk of pneumonia was demonstrated in 2 patients by high TDM peaks in relation to the clozapine dose (Table 1) and the need to approximately halve the clozapine dose to protect from elevation in clozapine levels. One of the two patients with pneumonia required a 3-month medical admission to save his life.

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TABLE 1. Description of 16 patients with infections including the duration and type of infection and dose correction factors

Patient number: Age (yr) sex smoking	Infection	Time (days) Infection/total %[a]	Clozapine C/D ratio (ng/ml per mg/day) No infection mean	During infection mean	peak	D correction factor[b]	Peak total C on D (ng/ml on mg/day)
1:63 ♂ smoker	skin abscess	15/322	1.55	2.58		x 0.60	725 on 200
	leukocytosis	5%	N=29	N=1			
2: 55 ♀ non-smoker	1st viral respiratory[c]	13/896	2.53	4.17 sertraline		x 0.61	1284 on 225
	no leukocytosis	1%	N=13	N=1			
	4th viral respiratory	9/896		2.37 no sertraline		not relevant	786 on 225
	no leukocytosis	1%		N=1			
3: 56 ♂ smoker	viral respiratory	18/32	1.71	6.29		x 0.27	530 on 75
	leukocytosis, fever	56%	N=3	N=1			
4: 51 ♀ smoker	viral respiratory	28/75	2.33	3.02	3.35	x 0.70	1237 on 250
	no leukocytosis	37%	N=2	N=3	N=1		
5: 56 ♂ non-smoker	viral respiratory	56/654	1.74	1.69	2.01	not relevant	593 on 200
	no leukocytosis	9%	N=25	N=3	N=1		
6: 35 ♂ smoker	viral respiratory	33/338	1.37	2.84	3.86	x 0.35	1019 on 200
	leukocytosis	10%	N=12	N=4	N=1		
7: 41♀ non-smoker	1st undiagnosed episode	28/344	1.44	2.62	3.65	x 0.39	535 on 100
		8%[d]	N=15	N=3	N=1		
	2nd undiagnosed episode	44/344		1.89	2.17	x 0.66	316 on 100
		13%		N=4	N=1		
8: 32 ♂ non-smoker	pneumonia	9/41	1.25	3.29	3.86	x 0.64	656 on 125
	fever	22%	N=2	N=2	N=1		
9: 20 ♂ non-smoker	viral respiratory	13/37	1.74 no ss	1.85	3.78	x 0.46	1472 on 300
	leukocytosis	35%	N=1	N=4	N=1		
10: 39 ♂ non-smoker	pneumonia: 3-month	45/154	(1.62)[e] no ss	1.79	3.63[f] no ss	x 0.44	798 on 200
	medical admission	29%	N=2	N=3	N=1		
11: 31♂ non-smoker	viral respiratory	2/80	No[g]	2.65		x 0.64[h]	130 on 50
	no leukocytosis	3%		N=2			
12: 28 ♂ non-smoker	gastrointestinal	40/62	2.89	3.84	4.68	x 0.62	967 on 150
	leukocytosis	65%	N=1	N=5	N=1		
13: 19 ♂ non-smoker	viral respiratory	14/42	1.04	2.24		x 0.46	292 on 150
	leukocytosis	33%	N=3	N=1			
14: 23 ♂ non-smoker	viral respiratory	18/54	1.85	2.57		x 0.72	908 on 250
	leukocytosis	33%	N=2	N=1			
15: 25 ♂ non-smoker	viral respiratory	5/38	1.15	3.11		x 0.37	1224 on 300

	leukocytosis	13%	N=1	N=1			
27: 31 ♂ non-smoker	undiagnosed	76/76	(1.58)[i]	3.90	5.79	x 0.27	1170 on 150
	inflammation	100%	N=1	N=7			

C, concentration; C/D, concentration-to-dose; D, dose; ss, steady state, yr: years.

[a]Percentage of days with infection calculated by dividing duration of infection by duration of clozapine treatment.

[b]D correction factor is multiplied by the patient's clozapine dose to control for the effect of the infection on clozapine concentrations. It is calculated by dividing clozapine C/D ratio when there is no infection by clozapine C/D ratio when there is no infection. If the value is close to 1, it is described as not relevant. When there are two infections, two D correction factors are provided.

[c]Patient 4's episodes of respiratory viral infections lasted 13, 13, 3 and 9 days for a total of 38 days or 4% of 896 days.

[d]Two episodes together lasted 72 days or 20% of 344 days.

[e]There are 2 Cs that were not in ss because the prior dose was increased. We think that they provide a reasonable estimation because they were similar to other ss Cs in low Ds of sertraline unlikely to inhibit clozapine metabolism (see Supplementary Table S2).

[f]The patient had another peak C value that was not in ss; it was 4.27.

[g]Started on clozapine during respiratory viral infection that lasted only the first 2 days of clozapine treatment.

[h]To calculate an approximate D correction factor we used as a baseline the mean D correction value of the ♂ non-smokers of 1.71.

[i]This is the lowest clozapine C/D ratio after the dose was substantially decreased to 75 mg/day, leukocyte count had normalized, and the c-reactive protein was substantially decreased. We used this as the baseline C/D ratio for the purpose of calculations but are not sure that this is the baseline C/D ratio. We have no C that was free of the effects of contamination by inflammation.

SUPPLEMENTARY TABLE S1. Sample description: including total sample and patients with infections and/or co-prescription of inhibitors

	Patients						Duration (days)			Number of ss TDM samples		
	N	Age	% (♂ s	♀ s	♂ ns	♀ ns)	Total	Mean	mean %[a]	Total	Mean	%[b]
Total	131[c]	43.7±14.5	17%	4%	28%	51%	24789	189		1384	10.5	
			22/129	5/131	37/131	67/131		(9-896)[d]			(1-50)[d]	
2% (482[4]/24789) of clozapine-days and 3% (45[4]/1384) of ss TDM samples												
Infection	16	38.4±14.0	13%	6%	68%	13%	482[e]	30	30%	46[e]	2.8	39%
			2/16	1/16	11/16	2/16		(2-76)[d]	(3-100%)[d]		(0-7)[d]	(0-100%)[d]
12% (2888[4]/24789) of clozapine-days and 12% (171[4]/1384) of ss TDM samples												
Inhibitor	13	44.8±13.4	23%		23%	54%	2888[e]	222	67%	172[e]	13	73%
			3/13		3/13	7/13		(12-735)[d]	(22-100)[d]		(1-37)[d]	(15-100)[d]

ss, steady state; TDM, therapeutic drug monitoring.

[a]The percentages of days each patient's TDM samples were contaminated by inflammation or inhibitor were calculated. The table provides the mean and ranges.

[b]The percentages of numbers of ss TDM samples contaminated by inflammation or inhibitor were calculated for each patient. The table provides the mean and ranges.

[c]The 131 inpatients included 104 who never had an infection or inhibitor, 14 who had at least one infection during their admission, 2 who had an infection and were also treated with an inhibitor sometime during the admission and 11 who were treated with an inhibitor sometime during the admission but never were diagnosed with an infection.

[d]Ranges.

[e]Two patients (patients 2 and 10) had both infection and inhibitor co-prescription. Of the total of 24,380 days, there were 13 days in which infection and inhibition co-prescription overlapped. From 1358 ss TDM samples, 1 sample was influenced by the overlap of infection and inhibition co-prescription.

SUPPLMENTARY TABLE S2. Description of 13 patients with inhibitors including the duration and type of inhibitor and dose correction factors

			Clozapine C/D ratio (ng/ml per mg/day)		
Patient number	**Inhibitor**	**Time**	**No inhibitor**	**During**	**Dose correction**
Age (yr) sex smoking	**mg/day**	**Inhibitor/total;%**	**mean; N**	**mean; N**	**factor[a]**
2: 55 ♀ non-smoker	sertraline 150	735/896;82%	2.53;N=13	2.34;N=26	not relevant
10: 39 ♂ non-smoker	any inhibitor	81/154;53%	(1.62 no ss; N=2)[b]		
	sertraline 150			1.70;N=5	not relevant
	+perphenazine 8			1.53;N=1	not relevant
	+perphenazine 12[c]			2.36;N=1[c]	0.69 may be relevant
16:62 ♀ non-smoker	any sertraline dose	36/36;100%			
	sertraline <150	22/36; 61%		2.29;N=3	not relevant
	≥ 150	14 /36; 39%	2.11♀ non-smokers[d]	2.52;N=2	not relevant (vs group mean)
17:51 ♀ non-smoker	sertraline 50	512/512 100%	2.11 ♀ non-smokers[d]	1.97;N=32	not relevant (vs group mean
18:49 ♂non-smoker	sertraline 150	339/339;100%	1.71 ♂ non-smokers[d]	2.01; N=23	not relevant (vs group mean)
19:41♂ smoker	imipramine 25-50	213/521;40%	1.14;N=17	0.81; N=3	not relevant
20:62 ♂ smoker	sertraline 50	99/359;28%	2.10; N=27	2.53;N=11	not relevant
21:33 ♀ non-smoker	sertraline 50	357/357;100%	2.11 ♀ non-smokers[d]	1.81;N=27	not relevant (vs group mean)
22:31 ♀ non-smoker	sertraline 25-50	381/381;100%	2.11	2.59; N=18	not relevant (vs group mean)
23:29 ♂ non-smoker	perphenazine 4-40	39/80;49%	1.46; N=2	1.41; N=5	not relevant
24:21 ♂ smoker	sertraline 50-150	20/54;37%	0.79; N=1	1.68; N=3	0.54 relevant
25:51 ♀ non-smoker	perphenazine 12-32	12/54;22%	2.66; N=2	5.56; N=1[e]	0.48 relevant
26:58 ♀ non-smoker	sertraline 50-100	46/73;63%	(2.55; N=2)[b]	2.43; N=4	not relevant

C/D, concentration-to-dose; ss, steady state.

[a]Dose correction factor is multiplied by the patient's clozapine dose to control for the effect of the inhibitor on clozapine concentrations. It is calculated by dividing clozapine C/D ratio when there is no inhibitor by clozapine C/D ratio when there is no inhibitor. If the value is close to 1, it is described as not relevant.

[b]These patients had no ss clozapine C/D ratio in the absence of the inhibitors. They had 2 values with no inhibitor that were not in ss. We approximated the calculation of the clozapine C/D ratio by using the mean dose of the last 5 days.

[c]Supplementary Table S12 describes the first value of clozapine C/D ratio on sertraline 150 mg/day and perphenazine 12 mg/day as 1.64, but it might not have been in steady state due to perphenazine inhibition. Supplementary Table S2 (shown above) describes the peak value 13 days after perphenazine was increased to 12 mg/day, which is likely to provide ss after the inhibition by perphenazine.

[d]These patients had no clozapine C/D ratio in the absence of inhibitors, so we compared their clozapine C/D ratios with the mean from the group with the same sex and smoking status.

[e]On day 12 of the clozapine treatment, a concentration contaminated by treatment with perphenazine was collected. The perphenazine dose was 16 mg/day on that day but its inhibitory effects were not in ss and the patient took higher doses of 22 mg/day on day 5, 26 mg/day on day 4, and 32 mg/day on day 1. We calculated the mean perphenazine dose over the prior 7 days, which was 26 mg/day.

SUPPLEMENTARY TABLE S3. Patient 1: Changes in clozapine steady-state TDM, clozapine dosages and WBC before, during and after skin abscess with leukocytosis

Day	Infection	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	CRP mg/dL 0.0-0.8	WBC count (x 10^9 cell/L) 4.0-10.0
1	Before	200							
17	Before	200	210.0	122.0	332.0	1.05	1.66		
35	Before	200	287.5	162.3	449.8	1.44	2.25		
52[a]	Infection	200	**516.6**	**208.4**	**725.0**	**2.58**	**3.63**	**1.76**	**12.6**
65[b]	1 day after	200	327.9	218.4	546.3	1.64	2.73		
70	After	200	280.3	147.7	428.0	1.40	2.14		
77	After	200	281.4	169.3	450.7	1.41	2.25		
80	After	200	300.0	185.5	485.8	1.50	2.43		
94	After	200	302.8	215.2	518.0	1.51	2.59		
148	After	200	334.7	157.8	492.5	1.67	2.46		
157	After	200	299.8	175.9	475.7	1.50	2.38		
163	After	200	300.8	157.1	457.9	1.50	2.29		
174	After	200	343.5	157.8	501.3	1.72	2.51		
182	After	200	336.2	172.7	508.9	1.68	2.54		
189	After	200	363.6	180.4	544.0	1.82	2.72		
197	After	200	290.0	143.3	433.3	1.45	2.17		
204	After	200	342.1	172.9	515.0	1.71	2.58		
211	After	200	371.5	178.8	550.3	1.86	2.75		
217	After	200	400.3	170.0	570.3	2.00	2.85		
225	After	200	227.8	141.4	369.2	1.14	1.85		
232	After	200	274.0	131.0	405.0	1.37	2.03		
239	After	200	304.3	145.9	450.2	1.52	2.25		
253	After	200	343.7	175.2	518.9	1.72	2.59		
260	After	200	387.9	171.8	559.7	1.94	2.80		
271	After	200	280.9	143.8	424.7	1.40	2.12		
280	After	200	201.8	138.2	340.0	1.01	1.70		
281	After	250							
288	After	250	387.3	247.9	635.2	1.55	2.54		
295	After	250	399.1	239.1	638.2	1.60	2.55		
302	After	250	307.4	207.4	514.8	1.23	2.06		
309	After	250	326.7	199.8	526.5	1.31	2.11		

316	After	250	429.2	280.6	709.8	1.72	2.84
322	After	250	342.5	226.9	569.4	1.37	2.28

C/D, concentration-to-dose; CRP, c-reactive protein; TDM, therapeutic drug monitoring; WBC, white blood cell count. **The TDM that provided the peak results is in orange font. WBC and CRP abnormal values are in blue font.**

[a]The topical treatment was benzalkonium with chloride and fusidic acid cream.

[b]This value was not used in calculating the mean of C/D ratios when there was no infection. The patient was recovering from the skin abscess.

SUPPLEMENTARY TABLE S4. Patient 2: Changes in clozapine steady-state TDM, clozapine dosages, sertraline dosage and WBC before, during and after four viral respiratory infections

Day	Influenza	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	Sertraline (mg/day)	WBC count (x 10^9 cell/L) 4.0-10.0
1[a]	Before	225						150	
13[a]	Before	225						150	8.3
32[a]	Before	225	685.0	283.3	968.3	3.04	4.30	150	7.4
53[a]	Before	225						150	7.0
54[a,b]	1st infection	225						150	7.0
57[a,b]	1st infection	225	**939.1**	**345.1**	**1284.2**	**4.17**	**5.71**	150	5.6
68[a,b]	1st infection	225						150	
69[a]	After	150						100	
78[a]	After	150						100	
79[a]	After	175						150	
83[a]	After	225						150	
105[a]	After	225	624.6	295.5	920.1	2.78	4.09	150	
119[a]	After	225	550.7	234.5	785.2	2.45	3.49	150	
175[a]	After	225	630.1	213.2	843.3	2.80	3.75	150	
216[a]	After	225	670.8	245.1	915.9	2.98	4.07	150	
244[a]	After	225	549.5	188.5	738.0	2.44	3.28	150	
322[a]	After	225	631.6	250.7	882.3	2.81	3.92	150	
343[a]	After	225	431.6	199.6	631.2	1.92	2.81	150	
378[c]	After	225						150	
379[c]	After	225	570.0	242.4	812.4	2.53	3.61	150	8.2
394[c,d]	2nd infection	225						150	**12.2**
395[c,d]	2nd infection	225						150	7.7
406[c,d]	2nd infection	225						150	7.7
407[c]	After	225						150	
411[c]	After	225						150	8.9
481[c]	After	225						150	9.4
495[c]	After	225						150	9.0
496[c,b]	3rd infection	225						150	
498[c,b]	3rd infection	225						150	
499[c]	After	225						150	
510[c]	After	225	551.1	231.7	782.8	2.45	3.48	150	9.2
524[c]	After	225	420.2	186.7	606.9	1.87	2.70	150	

538[c]	After	225	494.2	204.3	698.5	2.20	3.10	150		
552[c]	After	225	507.12	195.9	703.1	2.25	3.12	150		
567[c]	After	225	380.2	152.8	533.0	1.69	2.37	150		
579[c]	After	225	518.9	192.9	711.9	2.31	3.16	150		
594[c]	After	225	489.6	192.8	682.4	2.18	3.03	150		
608[c]	After	225	574.1	169.9	744.0	2.55	3.31	150		
623[c]	After	225	478.9	173.4	652.3	2.13	2.90	150		
637[c]	After	225	569.5	183.8	753.3	2.53	3.35	150		
651[c]	After	225	512.5	162.1	674.6	2.28	3.00	150		
665[c]	After	225	484.6	181.1	665.7	2.15	2.96	150		
678[c]	After	225	383.9	156.1	540.0	1.71	2.40	150		
693[c]	After	225	531.2	192.0	732.2	2.36	3.21	150		
708[c]	After	225	484.5	144.3	628.8	2.15	3.79	150		
721[c]	After	225	461.2	192.9	654.1	2.05	2.91	150		
735[c]	After	225	518.6	136.9	655.5	2.30	2.91	150	8.5	
736[c]	After	225						0		
748[c]	After	225	529.3	172.3	701.6	2.35	3.12	0		
749[c]	After	225						0	8.2	
755[c]	After	250								
762[c,e]	4th infection	250								
763[c,e]	4th infection	250	**592.7**	**193.3**	**786.0**	**2.37**	**3.14**	0	9.0	
770[c,e]	4th infection	250								
771[c]	After	250								
774[c]	After	250	531.2	233.6	764.8	2.12	3.06	0	8.0	
791[c]	After	250	657.6	214.8	872.4	2.63	3.49	0	6.7	
804[c]	After	250	551.3	201.8	753.1	2.21	3.01	0		
819[c]	After	250	636.5	251.2	887.7	2.55	3.55	0		
825[c]	After	250	487.5	205.7	693.2	1.95	2.77	0		
847[c]	After	250	604.2	249.2	853.4	2.42	3.41	0		
861[c]	After	250	672.6	258.7	931.3	2.69	3.73	0		
874[c]	After	250	812.5	301.3	1113.8	3.25	4.46	0		
888[c]	After	250	731.4	262.3	993.5	2.93	3.97	0		
903[c]	After	250	755.9	312.0	1067.9	3.02	4.27	0		
917[c]	After	250	697.4	247.53	944.9	2.79	3.78	0		
930[c]	After	250	489.9	194.3	684.2	1.96	2.74	0		

C/D, concentration-to-dose; TDM, therapeutic drug monitoring; WBC, white blood cell count. **The TDM that provided the peak results is in orange font.** **WBC abnormal values are in blue font.**

[a]The first admission lasted 343 days.

[b]The patient was treated with Chinese treatments for influenza called Jing Hua Qing Gan Ke Li and Qing Re Jie Du Ke Li. The first episode of infection lasted 13 days. The third episode of infection lasted 3 days.

[c]The second admission lasted 553 days.

[d]The patient was treated with a Chinese treatment for influenza called Jing Hua Qing Gan Ke Li. The second episode of infection lasted 13 days.

[e]The patient was treated with a Chinese treatment for influenza called Fu Fang Xuan Zhu Li. The fourth episode of infection lasted 9 days.

SUPPLEMENTARY TABLE S5. Patient 3: Changes in clozapine steady-state TDM, clozapine dosages and WBC during and after viral respiratory infection with leukocytosis and fever (possibly influenza)

Day	Respiratory viral infection	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	Temperature ^{0}C	WBC count (x 10^9 cell/L) 4.0-10.0
1[a]	Infection	75						37.5	**18.0**
8[a]	Infection	75						**38.5**	8.6
9[a]	Infection	75						**38.0**	
10[a]	Infection	75	**471.8**	**58.5**	**510.3**	**6.29**	**7.07**		
16[a]	Recovering	75	125.7	50.9	176.6[b]	1.68	2.35		
18[a]	Recovering	75							
19[a]	After	75							
23	After	100	103.2	45.4	148.6[c]	1.38	1.98		
30	After	100	189.4	45.7	235.1[c]	1.89	2.35		
33	After	100	185.2	62.6	247.8[c]	1.85	2.48		

C/D, concentration-to-dose; TDM, therapeutic drug monitoring; WBC, white blood cell count. **The TDM that provided the peak results is in orange font. Fever and WBC abnormal values are in blue font.**

[a]Treatment with Chinese medication for influenza called Jin Lian Hua capsules.

[b]This value was not used in calculating the mean of C/D ratios after influenza.. The patient was recovering from influenza.

[c]These 3 values were used in calculating a mean of 2.27 for the total C/D ratios after influenza.

SUPPLEMENTARY TABLE S6. Patient 4: Changes in clozapine steady-state TDM, clozapine dosages and WBC before and during a respiratory viral infection with no leukocytosis

Day	Respiratory viral infection	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	WBC count (x 10^9 cell/L) 4.0-10.0
1[a]	Before	200						
23[a]	Before	200	468.3	147.2	615.5	2.34	3.08[d]	
31[a]	Before	200	463.9	132.6	596.5	2.32	2.98[d]	
169[b]	Before	100						
185[b,c]	Infection	250						6.4
187[b,c]	Infection	250						
190[b,c]	Infection	250	800.0	348.0	1,148.0	3.20	4.59[e]	9.7
197[b,c]	Infection	250	**837.9**	**399.1**	**1,237.0**	**3.35**	**4.95[e]**	
206[b,c]	Infection	250	633.3	342.2	975.0	2.53	3.90[e]	6.7
212[b,c]	Infection	250						

C/D, concentration-to-dose; TDM, therapeutic drug monitoring; WBC, white blood cell count. **The TDM that provided the peak results is in orange font.**

[a]First admission.

[b]Second admission.

[c]The patient was intermittently treated with a Chinese treatment for influenza called Jin Lian Hua capsules.

[d]These 2 values were used to calculate a mean of 3.03 for the total C/D ratios before the influenza.

[e]These 3 values were used to calculate a mean of 4.48 for the total C/D ratios during the influenza. The total C/D ratio of 4.95 was considered the peak value.

SUPPLEMENTARY TABLE S7. Patient 5: Changes in clozapine steady-state TDM, clozapine dosages and WBC before, during and after respiratory viral infection with no leukocytosis

Day	Respiratory viral infection	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	WBC count (x 10^9 cell/L) 4.0-10.0
1[a]	Before	200						
34[a]	Before	200	403.3	201.9	605.2	2.02	3.03	
59[a]	Before	200	358.1	186.9	544.0	1.79	2.73	
91[a]	Before	200	359.1	156.5	515.6	1.80	2.58	
129[a]	Before	200	340.5	140.8	481.3	1.70	2.41	
167[a]	Before	200	381.0	130.2	511.2	1.91	2.56	
195[a]	Before	200	334.2	132.8	467.0	1.67	2.34	
209[a]	Before	200	359.1	144.3	503.4	1.80	2.52	
226[a]	Before	200	338.1	152.0	490.1	1.69	2.45	
244[a]	Before	200	376.4	169.7	546.1	1.88	2.73	
264[a]	Before	200	261.4	113.5	374.9	1.31	1.87	
276[a]	Before	200	315.0	160.4	475.4	1.58	2.38	
286[a]	Before	200	297.0	143.1	440.1	1.49	2.20	
299[a]	Before	200	306.7	147.5	454.2	1.53	2.27	
315[a]	Before	200	355.2	174.9	530.1	1.78	2.65	
341[b]	Before	200						
349[b]	Before	200	292.9	134.0	426.9	1.46	2.13	5.6
362[b]	Before	200	316.5	150.1	466.6	1.58	2.33	
363[b]	Infection	200						
377[b]	Infection	200	**402.4**	**190.4**	**592.8**	**2.01**	**2.96**	
381[b]	Infection	200	258.9	135.5	394.4	1.29	1.97	
412[b]	Infection	200	350.2	145.1	495.3	1.75	2.48	5.5
418[b]	Last day	200						
431[b]	After	200	370.8	156.8	527.6	1.85	2.64	
458[b]	After	200	408.5	175.3	583.8	2.04	2.92	5.4
492[b]	After	200	306.5	136.8	443.3	1.53	2.22	
499[b]	After	200	260.8	125.8	386.6	1.30	1.93	
513[b]	After	200	397.8	160.4	558.2	1.99	2.79	
519[b]	After	200	347.5	173.7	521.2	1.74	2.61	
519[b]	After	200	347.5	173.7	521.2	1.74	2.61	
527[b]	After	200	307.6	143.7	451.3	1.54	2.26	
534[b]	After	200	351.0	165.3	516.3	1.76	2.58	

542[b]	After	200	407.5	163.6	571.1	2.04	2.86
552[b]	After	200	397.5	152.6	550.1	1.99	2.75
559[b]	After	200	297.5	136.2	433.7	1.49	2.17
566[b]	After	200	354.9	152.1	507.0	1.77	2.54
573[b]	After	200	372.5	131.8	504.3	1.86	2.52
580[b]	After	200	411.4	173.4	584.8	2.06	2.92
587[b]	After	200	262.2	118.0	380.2	1.31	1.90
594[b]	After	200	326.4	129.6	456.0	1.63	2.28
600[b]	After	200	392.5	142.1	534.6	1.96	2.67
608[b]	After	200	419.6	168.4	588.0	2.10	2.94
624[b]	After	200	329.6	142.4	472.0	1.65	2.36
630[b]	After	200	401.9	145.4	547.3	2.01	2.74
646[b]	After	200	388.5	152.1	540.6	1.94	2.70
671[b]	After	200	241.8	126.4	368.2	1.21	1.84
679[b]	After	200	345.6	145.3	490.9	1.73	2.45

C/D, concentration-to-dose; TDM, therapeutic drug monitoring; WBC, white blood cell count. **The TDM that provided the peak results is in orange font.**

[a]First admission.

[b]Second admission.

SUPPLEMENTARY TABLE S8. Patient 6: Changes in clozapine steady-state TDM, clozapine dosages and WBC before, during and after respiratory viral infection with leukocytosis

Day	Respiratory viral infection	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	WBC count (x 10^9 cell/L) 4.0-10.0
1[a]	Before	400						
2[a]	Before	375						
6[a]	Before	350						
7[a]	Before	325						
8[a]	Before	300						
20[a]	Before	275						
35[b]	Before	275						
43[b]	Before	275						7.2
44[b]	Before	275(200)[d]	233.3	120.9	354.2	0.85	1.29	
46[b,c]	Infection	200						
50[b,c]	Infection	200	**772.0**	**247.0**	**1019.0**	**3.86**	**5.10**	
55[b,c]	Infection	200						
59[b]	Infection	200	348.8	130.7	479.5	1.74	2.40	
63[b]	Infection	200	589.8	195.6	785.4	2.95	3.93	
70[b]	Infection	200						8.1
71[b]	Infection	200	562.3	209.2	771.5	2.81	3.86	
75[b]	Infection	175						
78[b]	Last day	150						**15.0**
84[b]	After	150	265.9	126.7	392.6	1.77	2.62	
94[b]	After	150	211.8	96.5	308.3	1.41	2.06	**11.5**
280[b]	After	150	144.5	60.4	204.9	0.96	1.37	
282[b]	After	200						
287[b]	After	200	231.6	81.8	313.4	1.16	1.57	
288[b]	After	250						
294[b]	After	250	285.5	113.2	398.7	1.14	1.59	
308[b]	After	250	466.9	181.9	648.8	1.87	2.60	
310[b]	After	275						
315[b]	After	275	324.8	147.2	472.0	1.18	1.72	
316[b]	After	250						
322[b]	After	250	367.3	147.6	514.9	1.47	2.06	
329[b]	After	250	291.4	134.0	425.4	1.17	1.70	
336[b]	After	250	275.7	121.7	397.4	1.10	1.59	

343[b]	After	200					
346[b]	After	200	283.0	142.3	425.3	1.42	2.13
351[b]	After	200	468.2	149.5	617.7	2.34	3.09

C/D, concentration-to-dose; TDM, therapeutic drug monitoring; WBC, white blood cell count. **The TDM that provided the peak results is in orange font. In blue, WBC abnormal values are in blue font.**

[a]First admission.

[b]Second admission.

[c]The patient was treated with Chinese treatments for influenza called Jing Hua Qing Gan Ke Li and Qing Re Jie Du Ke Li.

[d]The clozapine dose was changed after collecting blood. The clozapine dose of 200 mg/day was used to calculate the C/D ratios.

SUPPLEMENTARY TABLE S9. Patient 7: Changes in clozapine steady-state TDM, clozapine dosages and WBC during and after 2 possible undiagnosed infections with leukocytosis

Day	Possible infection	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	WBC count (x 10^9 cell/L) 4.0-10.0
1	Before	100						
16	Before	100	168.0	71.9	239.9	1.68	2.40	
28	Before	100	179.1	85.2	264.3	1.79	2.64	
46	Before	100	125.8	50.9	176.7	1.26	1.77	
60	Before	100	119.0	67.5	186.5	1.19	1.87	
78	Before	100	144.0	82.2	226.2	1.44	2.26	
92	Before	100	160.5	85.6	246.1	1.61	2.46	
107	Before	100	164.2	63.7	227.9	1.64	2.28	
119	Before	100	121.9	58.5	180.4	1.22	1.80	
133	Before	100	110.8	53.1	163.9	1.11	1.64	
147	Before	100	129.9	58.1	188.0	1.30	1.88	
161	Before	100	130.3	58.7	189.0	1.30	1.89	
175	Before	100	133.2	58.7	191.9	1.33	1.92	
189	Before	100	109.2	50.8	160.0	1.09	1.60	
204	Infection[a]	100	**365.4**	**169.1**	**534.5**	**3.65**	**5.35**	
207	Infection[a]	100						9.2
217	Infection[a]	100	202.7	86.6	289.3	2.03	2.89	
231	Infection[a]	100	221.8	86.3	308.1	2.22	3.08	**12.2**
244	After	100	172.3	73.8	246.1	1.72	2.46	8.8
273	After	100						7.5
287	Infection[b]	100	196.7	87.3	284.0	1.97	2.84	**11.1**
289	Infection[b]	100						
301	Infection[b]	100	167.3	74.1	241.4	1.67	2.41	9.2
315	Infection[b]	100	175.9	98.1	274.0	1.76	2.74	6.3
330	Infection[b]	100	216.8	99.3	316.1	2.17	3.16	**14.6**
344	After	100	185.9	85.5	271.4	1.86	2.71	7.4

C/D, concentration-to-dose; TDM, therapeutic drug monitoring; WBC, white blood cell count. **The TDM that provided the peak results is in orange font. In blue, WBC abnormal values are in blue font.**

[a]The patient complained of headache and sore body. The treating physician thought there were no symptoms to treat. This possible episode of infection may have lasted up to 28 days.

[b]The patient complained of cold-like symptoms. The treating physician thought there were no symptoms to treat. This possible episode of infection may have lasted up to 44 days.

SUPPLEMENTARY TABLE S10. Patient 8: Changes in clozapine steady-state TDM, clozapine dosages, temperature and WBC before, during and after pneumonia

Day	Pneumonia	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	Temperature ^{0}C	WBC count (x 10^9 cell/L) 4.0-10.0
1	Before	125							10.0
6	Infection	125	**483.1**	**172.6**	**655.7**	**3.86**	**5.25**		**12.8**
7[a]	Infection								
8[b]	Infection							**39.2**	9.0
9[c]	Infection								7.9
12[c]	Infection								9.8
14[c]	Last day	125	339.7	148.4	488.1	2.72	3.90		
15[d]	After								
21	After	125	355.4	86.7	442.1	2.84	3.54		8.9
25	After	150							
27	After								**11.9**
32	After	125							
34	After								9.0
41	After	125	262.1	91.2	353.3	2.10	2.83		**10.8**

C/D, concentration-to-dose; TDM, therapeutic drug monitoring; WBC, white blood cell count. **The TDM that provided the peak results is in orange font. Fever and WBC abnormal values are in blue font.**

[a]Initially the patient was treated with oral Chinese medications for influenza: Jing Hua Qing Gan capsule and Qiang Re Jie Du liquid.

[b]After the diagnosis of pneumonia, Jing Hua Qing Gan capsule and Qiang Re Jie Du liquid was continued and intravenous levofloxacin was added. Levofloxacin is not a CYP1A2 inhibitor [S2] and it was prescribed for only 1 day.

[c]Jing Hua Qing Gan capsule, Qiang Re Jie Du liquid, intravenous cefotiam and intravenous azithromycin.

[d]The medication for influenza and the antibiotics were discontinued.

SUPPLEMENTARY TABLE S11. Patient 9: Changes in clozapine steady-state TDM, clozapine dosages and WBC before, during and after viral infection with leukocytosis (possible influenza)

Day	Respiratory viral infection	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	WBC count (x 10^9 cell/L) 4.0-10.0
1		unknown						
3	Before	150						
6	Before	200						
8	Before	200 170	295.1[a]	70.8[a]	365.9[a]	1.74	2.15	
15	Infection[b]	200 (250)	330.7	84.7	415.4	1.65	2.08	**14.1**
17	Infection[b]	250						**14.5**
21	Infection[b]	275						
24	Infection[b]	300						
29	Infection[b]	300	370.3	93.2	463.5	1.23	1.55	**10.4**
30	Infection[b]	300						
33	Infection[b]	300	216.2	72.9	289.1	0.72	0.96	8.8
36	Infection[b]	300	**1132.5**	**339.8**	**1472.3**	**3.78**	**4.91**	
37	Discharged[b]	300						
38	Outpatient[c]	300 (400)[d]	741.6	199.1	940.7	1.85	2.35	
43	Outpatient[c]	400	655.8	169.5	825.3	1.64	2.06	
50	Outpatient[c]	400	906.5	248.7	1155.2	2.27	2.87	
52	Outpatient[c]	375						
64	Outpatient[c]	375	639.7	173.7	813.4	1.71	2.17	

C/D, concentration-to-dose; TDM, therapeutic drug monitoring; WBC, white blood cell count. Red font is used to explain that the concentrations were not in steady state. **The TDM that provided the peak results is in orange font. WBC abnormal values are in blue font.**

[a]This concentration is not steady state. It reflects 3 days on 150 mg/day and 2 days on 200 mg/day. The average dose during these 5 days is 170 mg/day. We had no baseline steady-state concentration before influenza, so we estimated the C/D ratios using this concentration that is not in steady state.

[b]The medical record with data on co-medication could not be found. We do not know whether or not the patient was treated with Chinese medication for influenza.

[c]After discharge the outpatient doctor sent the clozapine TDM to our lab, but we had no access to the outpatient record. We do not know whether or not the patient had recovered from the influenza. Only inpatient data was used to establish the elevation of the total clozapine C/D ratio.

SUPPLEMENTARY TABLE S12. Patient 10: Changes in clozapine steady-state TDM, clozapine dosages, temperature and WBC before, during and after pneumonia

Day	Pneumonia	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	Temperature ^{0}C	WBC count (x 10^9 cell/L) 4.0-10.0	Sertraline /perphenazine (mg/day)
1[a]	Before	50								0/0
4[a]	Before	125								0/0
5[a]	Before	200								0/0
7[a]	Infection	200 (155)	561.9	235.9	797.8	**3.63**	**5.15**			0/0
8[a]	Infection	225								0/0
11[a]	Infection	225							8.1	0/0
12[a,b]	Infection	225						**39.2**	**10.1**	0/0
13[a,b]	Infection	225						**39.2**		0/0
15[a,b]	Infection	225	523.0	254.3	777.3	2.32	3.45			0/0
16[a,b]	Infection	200								0/0
21[a,b]	Infection	200								0/0
22[a]	Improved	200	319.5	165.4	484.9	1.60	2.42		5.8	0/0
24[a,c]	Infection	200						**38.6**	**15.9**	0/0
25[a,d]	Infection	200						**38.5**		0/0
26[a,d]	Infection	200							**13.9**	0/0
28[a,e,f]	Infection	200								0/0
29[a,g]	Infection	200								0/0
30[a,g]	Infection	200								0/0
31[a,f,g]	Infection	200								0/0
35[a,f,g]	Infection	200								0/0
41[a,g]	Infection	200	289.3	170.1	459.4	1.45	2.30		**10.3**	0/0
43[a,h]	Infection	250								0/0
44[a,i]	Infection	250								0/0
46[a,i]	Infection	275								0/0
47[a,i]	Infection	275							**13.6**	0/0
48[a,f,i]	Infection	275								0/0
49[a,f,i]	Infection	200								0/0
50[a,f,i]	Infection	200 (260)	811.1	298.5	1,109.6	3.12	4.27			0/0
51[a,i,j]	Infection	200								0/0
153[k]	After	150								0/0
160[k]	After	175								0/0
162[k]	After	200								0/0

164[k]	After	200 (185)	323.3	137.4	460.7	1.75	2.49			0/0
165[k]	After	225								0/0
170[k]	After	250								0/0
171[k]	After	250 (230)	339.4	168.4	507.8	1.48	2.21			0/0
172[k]	After	275								0/0
175[k]	After	250								50/0
176[k]	After	300								50/0
178[k]	After	300							9.6	50/0
183[k]	After	350								50/0
184[k]	After	300								50/0
185[k]	After	350								100/0
189[k]	After	350								150/0
191[k]	After	350	691.6	318.7	1,010.3	1.98	2.89			150/0
205[k]	After	350	616.7	309.9	926.6	1.76	2.65			150/0
209[k]	After	350	524.8	309.4	834.2	1.50	2.38			150/0
223[k]	After	350	529.4	214.9	744.3	1.51	2.13			150/4
225[k]	After	350								150/8
230[k]	After	350	534.7	238.2	772.9	1.53	2.21			150/8
235[k]	After	350								150/12
241[k]	After	350	573.8	313.9	887.7	1.64	2.54			150/12
248[k]	After	350	824.5	431.4	1,255.9	2.36	3.59			150/12
255[k]	After	350	614.9	355.9	970.8	1.76	2.77			150/0

C/D, concentration-to-dose; TDM, therapeutic drug monitoring; WBC, white blood cell count. Red font is used to explain that the concentrations were not in steady state. **The TDM that provided the peak results is in orange font.** **Fever and WBC abnormal values are in blue font.**

[a]The first admission lasted 51 days.

[b]Intravenous ceftriaxone sodium and Chinese medicine called Jing Hua Qing Gan Capsule.

[c]Intravenous levofloxacin. Levofloxacin is not a CYP1A2 inhibitor [S2]

[d]Intravenous levofloxacin and intravenous cefoperazone.

[e]Intravenous levofloxacin, intravenous cefoperazone and intravenous azithromycin.

[f]The patient was sent to a medical hospital for several hours.

[g]Intravenous cefoperazone and intravenous azithromycin.

[h]Moving from intravenous cefoperazone and intravenous azithromycin oral formulation of both antibiotics.

[i]Oral cefuroxime axetil and oral azithromycin.

[j]The patient was sent to a medical hospital for more than 3 months.

[k]The second admission lasted 103 days after the patient recovered from pneumonia and returned from the medical hospital.

SUPPLEMENTARY TABLE S13. Patient 11: Not described because he had no steady-state therapeutic drug monitoring during the viral infection.

SUPPLEMENTARY TABLE S14. Patient 12: Changes in clozapine steady-state TDM, clozapine dosages and WBC before and during gastrointestinal infection/inflammation with leukocytosis

Day	Gastro-intestinal infection	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	WBC count (x 10^9 cell/L) 4.0-10.0
1	Before	250						
3	Before	200						
6	Before	150						
7	Before	150						
9	Before	150						
16	Before	150	433.4	187.8	621.2	2.89	4.14	9.2
23	Infection	150	428.6	205.9	634.5	2.86	4.23	**13.6**
30	Infection	150	492.2	173.6	665.8	3.28	4.44	**11.9**
31[a]	Infection	150						
34[a]	Infection	150						
35	Infection	150						
37	Infection	150	657.7	190.8	848.5	4.38	5.66	**14.1**
44	Infection	150	**702.6**	**264.0**	**966.6**	**4.68**	**6.44**	**11.6**
50	Infection	200						
54	Infection	200						**11.3**
62	Infection	200	760.4	245.9	1006.3	3.80	5.03	9.7

C/D, concentration-to-dose; TDM, therapeutic drug monitoring; WBC, white blood cell count. **The TDM that provided the peak results is in orange font. WBC abnormal values are in blue font.**

[a]Diarrhea was treated with a medicinal clay (Smectite Dispersible Tablets).

SUPPLEMENTARY TABLE S15. Patient 13: Changes in clozapine steady-state TDM, clozapine dosages and WBC during and after viral respiratory infection with fever and leukocytosis (possible influenza)

Day	Respiratory viral infection	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	Temperature ^{0}C	WBC count (x 10^9 cell/L) 4.0-10.0
1	Infection	50							
2[a]	Infection	100						**38.0**	**14.4**
6[a]	Infection	100							
7	Infection	150	**224.3**	**68.0**	**292.3**	**2.24**	**2.92**		**16.8**
8	Infection	200							
13	Infection	250							
14	Infection	300(210)[b]	321.9	105.7	427.6	1.53	2.04		**15.4**
16	After	350							
17	After	400							
20	After	450							
21	After	450							7.3
29	After	450	462.3	185.2	647.5	1.03	1.44		
36	After	450	495.0	185.3	580.4	1.10	1.51		
42	After	450	449.0	188.0	637.0	1.00	1.42		

C/D, concentration-to-dose; TDM, therapeutic drug monitoring; WBC, white blood cell count. Red font is used to explain that the concentrations were not in steady state. **The TDM that provided the peak results is in orange font. Fever and WBC abnormal values are in blue font.**

[a]Treatment with Chinese medications for influenza called Jing Hua Qing Gan capsule and Qing Re Jie Du Liquid were used.

[b]This concentration was not steady state, so we approximated the C/D ratios by dividing by the mean clozapine dose during the last 5 days, which was 210 mg/day. It was not used in the calculation of Table 1.

SUPPLEMENTARY TABLE S16. Patient 14: Changes in clozapine steady-state TDM, clozapine dosages and WBC before, during and after respiratory viral infection with leukocytosis (possibly influenza)

Day	Influenza	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	WBC count (x 10^9 cell/L) 4.0-10.0
-3	Before							
1	Before	50						
4	Before	100						
6	Before	150						
7	Before	150						4.7
9	Before	175						
15	Before	175	319.9	181.4	501.3	1.83	2.86	**12.5**
19[a]	Infection	225						7.9
22[a]	Infection	225[b] (215)	404.9	210.4	615.3	1.88	2.86	**12.0**
26[a]	Infection	250						
27[a]	Infection	250						**12.9**
29[a]	Infection	250	**642.7**	**264.9**	**907.6**	**2.57**	**3.63**	**12.2**
32[a]	Infection	275						
33	Infection	275						
35	Infection	250						
36	Infection	250[c] (265)	720.1	271.5	991.6	2.72	3.74	**15.6**
43	Recovering[d]	250	548.7	220.7	769.4	2.19	3.08	**10.2**
54	After	250	444.	185.8	629.9	1.78	2.52	10.0

C/D, concentration-to-dose; TDM, therapeutic drug monitoring; WBC, white blood cell count. Red font is used to explain that the concentrations were not in steady state. **The TDM that provided the peak results is in orange font.** **WBC abnormal values are in blue font.**

[a]Jing Hua Qing Gan capsule, a Chinese medicine for influenza.

[b]The average dose during the last 5 days was 215 mg/day, which was used for calculating C/D ratios. They were not used for calculations in Table 1.

[c]The average dose during the last 5 days was 265 mg/day, which was used for calculating C/D ratios. They were not used for calculations in Table 1.

[d]This value was not entered in Table 1 as it was possibly contaminated because the patient was recovering from a long episode of respiratory viral infection and the leukocytes were slightly elevated.

SUPPLEMENTARY TABLE S17. Patient 15: Changes in clozapine steady-state TDM, clozapine dosages and WBC before and during respiratory viral infection

Day	Influenza	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	WBC count (x 10^9 cell/L) 4.0-10.0
-4	Before							
1	Before	175						
4	Before	200						
6	Before	200						9.6
10	Before	225						
13	Before	225						7.0
15	Before	275						
18	Before	300						
27	Before	300	346.1	168.9	515.0	1.15	1.72	
34[a]	Infection	300	**931.9**	**292.4**	**1224.3**	**3.11**	**4.08**	
38[a]	Infection	300						**10.6**

C/D, concentration-to-dose; TDM, therapeutic drug monitoring; WBC, white blood cell count. **The TDM that provided the peak results is in orange font. The WBC abnormal value is in blue font.**

[a]Jing Hua Qing Gan capsule, a Chinese medicine for influenza.

SUPPLEMENTARY TABLE S18. Patient 27:[a] Changes in clozapine steady-state TDM, clozapine dosages and WBC during undiagnosed inflammation

Day	Inflammation	Clozapine dose (mg/day)	Clozapine concentration (ng/ml)	Norclozapine concentration (ng/ml)	Total concentration (ng/ml)	Clozapine C/D ratio (ng/ml per mg/day)	Total C/D ratio (ng/ml per mg/day)	CRP mg/dL 0.0-0.8	WBC count (x 10^9 cell/L) 4.0-10.0
-37	Inflammation	0							**11.1**
-36	Inflammation	0						**3.68**	9.3
-29	Inflammation	0							9.4
-22	Inflammation	0							7.6
1	Inflammation	50							
2	Inflammation	100[b]							
6	Inflammation	125 (90)	356.2	116.2	472.4	3.18	5.25		
8	Inflammation	175							
13	Inflammation	175	777.3	260.4	1037.7	4.44	5.93	**3.14**	9.6
17	Inflammation	150							
20	Inflammation	150	679.4	249.8	929.2	4.53	6.19		**10.7**
21	Inflammation	150						**5.55**	
27	Inflammation	150	433.9	197.2	631.1	2.89	4.21		**11.1**
28	Inflammation	75[c]							
34	Improvement[d]	75	118.3	31.9	150.2	1.58	2.00	**1.37**	7.1
40	Improvement	100							
41	Improvement	100 (80)[e]	340.8	101.5	442.3	4.26	5.53	0.45	6.9
48	Inflammation	125 (100)[f]	314.4	113.6	428.0	3.14	4.28		9.8
50	Inflammation	150							
55	Inflammation	150	410.4	159.9	570.3	2.74	3.80		7.8
56	Inflammation	150						0.65	
62	Inflammation	150	**867.9**	**302.4**	**1170.3**	**5.79**	**7.80**		**11.0**
69	Inflammation	150	566.9	233.1	800.0	3.78	5.33	**1.7**	**10.1**
74	Inflammation	125							
76	Inflammation	125 (140)[g]	690.3	234.9	925.2	4.93	6.61		**12.7**

C/D, concentration-to-dose; CRP, c-reactive protein; TDM, therapeutic drug monitoring; WBC, white blood cell count. Green font is used to describe the TDM that was used as a baseline. It was partly contaminated by infection, but it appeared to us the most reasonable option that we had. Red font is used to explain that the concentrations were not in steady state. **The TDM that provided the peak results is in orange font. WBC and CRP abnormal values are in blue font.**

[a]When we reviewed the 5 patients previously classified as possible genetic clozapine poor metabolizers [3], we discovered that the treating physician had missed an inflammation in one of the patients that was present before clozapine treatment and throughout the admission. Patient

27 appeared to have an undiagnosed inflammation/infection that lasted >100 days during hospital admission (37 before clozapine and 77 while on clozapine). The CRP was elevated almost all the time and leukocytosis was intermittently elevated.

[b]The patient was diagnosed with sinus tachycardia.

[c]The clozapine dose was probably reduced because of high serum concentration.

[d]After the clozapine dose was reduced to 75 mg/day, leukocytes became normal and the CRP level was substantially decreased although it did not become normal.

[d]The average clozapine dose during the last 5 days was 80 mg/day, which was used for calculating C/D ratios. They were not used for calculations in Table 1.

[e]The clozapine dose during the prior 5 days was 100 mg/day and was steady-state.

[f]The average clozapine dose during the last 5 days was 140 mg/day, which was used for calculating C/D ratios. They were not used for calculations in Table 1.