Electrocardiographic Abnormalities in Patients Treated With Clozapine

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Background: Cardiovascular side effects of clozapine are not uncommon, but few systematic studies of these effects have been performed. In this study, we reviewed data on the electrocardiographic (ECG) abnormalities in patients treated with clozapine.

Method: Sixty-one patients treated with clozapine were selected from the Seoul National University Hospital Treatment-Resistant Schizophrenia Clinic. A retrospective chart review was conducted to identify ECG abnormalities and cardiovascular side effects.

Results: The prevalence of ECG abnormalities in patients who had been using antipsychotics other than clozapine was 13.6% at baseline, which increased significantly to 31.1% after commencement of clozapine treatment. Among the 53 patients without baseline ECG abnormalities, 13 showed new-onset ECG abnormalities after using clozapine. Normal ECG under previous antipsychotic medication reduced the risk of new-onset ECG abnormalities, whereas increased age was found to increase the risk. The occurrence of orthostatic hypotension or tachycardia was not related to the development of ECG abnormalities. Most of the newly developed abnormalities had little clinical significance, and they tended to occur during the initial phase of treatment. In 10 patients, ECGs normalized despite the continued use of clozapine. Clozapine increased corrected QT interval (QTc) in a dose-dependent fashion; however, the clinical significance of this observation is uncertain. Pathologic prolongation of QTc was found to be rare.

Conclusion: Although a substantial portion of patients treated with clozapine developed ECG abnormalities, most of the abnormalities were benign and did not hinder further treatment.

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Although clozapine is effective for the treatment of schizophrenia and other psychiatric conditions, various adverse effects limit its use as a first-line treatment. The most serious adverse effect of clozapine is agranulocytosis. However, the prevalence of this complication is as low as 0.38% to 0.91%,[1,2] and the standardized monitoring protocol for its early detection coupled with improved management strategies involving, for example, the use of cytokines has decreased mortality.[2] Cardiovascular side effects, including tachycardia and orthostatic hypotension, are more frequent. These side effects are relatively common and can adversely affect the patients' quality of life, but little attention is paid to them because they are believed to be benign. However, unexpected and sometimes fatal cardiovascular side effects such as hypertension,[3–5] pericarditis or ncocarditis,[6,7] cardiomyopathy,[8] ST elevation mimicking ischemic heart disease,[9] and arrhythmias[10] have also been reported in patients using clozapine. These reports demonstrate the need for systemic study of the cardiac and electrocardiographic effects of clozapine. In this study, we reviewed the data on the electrocardiographic abnormalities detected in patients treated with clozapine.

METHOD

Cases were selected from patients enrolled at the Seoul National University Hospital Treatment-Resistant Schizophrenia Clinic between January 1996 and June 1998. A total of 121 cases were reviewed. Electrocardiograms (ECGs) were taken before starting the clozapine treatment and repeated during the titration and maintenance periods. Although the timing of the ECGs was left to the clinicians, guidelines were given. Most of the patients underwent ECG within a few days before the first dose of clozapine, 1 week after starting clozapine, and again when the dose was raised to approximately 400 mg/day (and when clinically indicated). From this group of patients, those without a medical history of previous heart disease, with at least 2 ECGs (including the one taken during pretreatment), and with available vital sign recordings were selected, and their medical records were reviewed. A total of 61 patients (36 men and 25 women)

Table 1. Prevalence of ECG Abnormalities*

Combination	Baseline ECG	ECG After Clozapine	Antipsychotics at Baseline ECG		
			Yes	No	Total
1	Normal	Normal	32 (a)	8 (b)	40
2	Normal	Abnormal	6 (c)	7 (d)	13
3	Abnormal	Normal	2 (e)	0 (f)	2
4	Abnormal	Abnormal	4 (g)	2 (h)	6
Total			44 (i)	17 (j)	61

*Abbreviation: ECG = electrocardiogram.
Prevalence of ECG abnormalities in users of antipsychotics other than clozapine: k = (e + g)/i = 0.136.
Prevalence of ECG abnormalities in antipsychotic-free patients l = (f + h)/j = 0.118.
Prevalence of ECG abnormalities in any clozapine user: m = (c + d + g + h)/(i + j) = 0.311.
Prevalence of new-onset ECG abnormalities after clozapine use
In total patients (c + d)/(a + b + c + d) = 0.245.
In patients who had been antipsychotic-free at baseline: n = d/(b + d) = 0.467.
In patients who had been using other antipsychotics at baseline: o = c/(a + c) = 0.158.
No significant difference between k and l (p = .846, chi-square test).
No significant difference between l and m (p = .111, chi-square test).
Significant difference between k and m (p = .038, chi-square test).
Significant difference between n and o (p = .019, chi-square test).

were finally selected. The age distribution was from 18 to 54 years; mean age was 31.8 years for men and 31.3 years for women. Diagnoses included schizophrenia, schizoaffective disorder, and bipolar disorder, according to DSM-IV criteria. All of the patients were Korean. Forty-four patients were receiving antipsychotic medication when the baseline ECG was taken. Drugs used included chlorpromazine, haloperidol, loxapine, pimozide, risperidone, sulpiride, and thioridazine. Most of the patients used high-potency drugs, and their mean chlorpromazine-equivalent dose was 451 mg/day.

ECG readings were performed primarily using the automatic reading system and were inspected by experienced cardiologists in cases that suggested any abnormality. Cardiovascular variables (heart rate and blood pressure) were transcribed from regular vital sign records performed by nurses. Tachycardia was defined as a resting heart rate ≥ 100 beats per minute at any time during the observation period after clozapine use. Orthostatic hypotension was defined as ≥ 20 mm Hg change between the supine and standing systolic blood pressure at any time during the same period.

We first calculated the prevalence of ECG abnormalities under various conditions and then examined the abnormal ECG findings. Sinus tachycardia and axis deviations were not considered to be abnormal findings since the former was very common and the latter had questionable clinical significance. We then analyzed the relationship between ECG abnormalities and demographic variables and cardiovascular side effects. Next, we analyzed the relationship between change in the corrected QT interval (QTc), the dosage of clozapine, and the duration of clozapine use. Since QTc varies widely among individuals, QTc changes from the baseline (before clozapine use) were used as a measure. Because pimozide[11,12] and thioridazine[13–15] are well known for their ability to increase QTc or induce torsade de pointes, patients who were taking these drugs at the time of any ECG recording were excluded from QTc analysis. Recordings from patients using β-blockers, antidepressants, or diuretics were also excluded. None of the patients took sertindole, which is well known for its ability to increase the QT interval.[16]

RESULTS

Prevalence and Characteristics of ECG Abnormalities

ECG abnormalities present during the baseline recording. Among the 61 patients, 8 showed baseline ECG abnormalities before the initiation of clozapine treatment. Among these, 6 were receiving antipsychotic medication. The prevalence of ECG abnormalities in the antipsychotic users was 13.6% (6/44), while that in the antipsychotic-free patients was 11.8% (2/17), a difference that was not significant (p = .846, chi-square test; Table 1). The mean ± SD chlorpromazine-equivalent dose was not different between normal (376 ± 428.5 mg/day) and abnormal (550 ± 597.5 mg/day) baseline ECG groups (p = .668, Student t test).

The abnormalities included nonspecific ST-T changes, conduction abnormalities, left atrial enlargement, left ventricular hypertrophy, and a pattern suggesting myocardial infarction. Follow-up ECGs, recorded after the start of clozapine use, were normal in 2 patients. The other patients were found to have persistent abnormalities when the ECGs were rechecked after clozapine use for 30 days to > 2 years. Two showed new-onset conduction abnormalities during follow-up (Table 2).

Prevalence of ECG abnormalities in patients using clozapine. The prevalence of ECG abnormalities in patients using clozapine was 31.1% (19/61), including those with baseline ECG abnormalities but excluding those who reverted to normal ECG after clozapine use. This result was significantly different from the baseline prevalence of ECG abnormalities observed when the same group of patients were treated with the other antipsychotics (p = .038, chi-square test; see Table 1). None of the patients using clozapine were concomitantly using other antipsychotics when ECGs were taken (Tables 2 and 3).

New-onset ECG abnormalities after clozapine use. Among the 53 patients with normal baseline ECG findings, new-onset ECG abnormalities after clozapine use were detected in 13 (24.5%). In patients who had been using antipsychotics during baseline recording, the prevalence was 15.8% (6/38), whereas in drug-free patients, it was 46.7% (7/15). This difference was statistically significant (p = .019, chi-square test; see Table 1). Of the 6 patients who had been using antipsychotics and had abnormal ECG at baseline, 4 had persistent ECG abnormalities after clozapine use.

Table 2. Patients With Baseline ECG Abnormalities Before Clozapine Treatment[a]

Age (y)	Sex	Abnormality	Drugs Used at Baseline ECG	Follow-Up Interval	Dose of Clozapine at Follow-Up (mg/d)	Concomitant Drugs at Follow-Up	Follow-Up Result
27	M	Ventricular preexcitation (WPW pattern type A)	Pimozide	42 d	225	...	Normalized
27	F	Left atrial enlargement	Risperidone, clonazepam, lorazepam	45 d	362.5	Lorazepam	Normalized
43	M	NST	...	25 d	300	...	NST, prolonged QTc
				41 d	450	...	NST, incomplete RBBB
26	M	LVH	Risperidone, diazepam	> 1 y	350	Lorazepam	Occasional VPC
38	M	Nonspecific conduction abnormality	Sulpiride, pimozide, trihexyphenidyl, clonazepam	30 d	75	...	Persisted
46	F	NSST	...	> 1 y	450	...	Persisted
39	M	R/O inferior wall infarction	Haloperidol, benztropine	> 10 mo	500	...	Persisted
41	M	LVH, first-degree AV block	Haloperidol, carbamazepine	> 2 y	550	Lorazepam	Persisted

[a]Abbreviations: ECG = electrocardiogram, LVH = left ventricular hypertrophy, NSST = nonspecific ST segment change, NST = nonspecific T wave change, QTc = corrected QT interval, RBBB = right branch bundle block, R/O = rule out, VPC = ventricular premature contraction, WPW = Wolff-Parkinson-White.

Table 3. Patients With New-Onset ECG Abnormalities After Clozapine Treatment[a]

Age (y)	Sex	Abnormality	Days After Clozapine Use	Dose at ECG Recording (mg/d)	Concomitant Drugs	Treatment Phase	Dose at Follow-Up (mg/d)	Follow-Up Result
54	F	R/O inferior wall infarction	3	25	Clonazepam	Titration	100	Normalized
38	M	Acute pericarditis	4	75	...	Titration	400	Normalized
38	M	R/O inferior wall infarction	20	125	...	Titration	325	Normalized
47	M	Left atrial enlargement	21	68.75	...	Titration	100	Normalized
34	F	RVH, ST-T abnormality (R/O inferior ischemia)	21	200	...	Titration	337.5	Normalized
18	F	NST	30	175	Valproic acid	Titration	250	Normalized
28	F	NST	31	225	Lorazepam	Titration	400	Normalized
30	F	Prolonged QTc (533 ms)	39	137.5	...	Titration	200	Normalized
31	M	R/O inferior wall infarction	40	325	...	Titration	425	Normalized
31	M	NST	67	400	...	Titration	525	Persisted
36	M	LVH, ST elevation	141	550	...	Maintenance	262.5	Normalized
49	F	NST	219	112.5	...	Maintenance	112.5	Persisted
36	F	NST	408	250	...	Maintenance	250	Persisted

[a]Abbreviations: RVH = right ventricular hypertrophy; for the other abbreviations, see Table 2.

In 6 cases, the abnormalities were of little clinical significance. Five cases showed nonspecific T wave abnormality, and 1 showed left atrial enlargement. However, the others had potentially significant findings. Two cases showed ventricular hypertrophy with ischemic patterns, 3 showed findings suggesting inferior wall infarction, 1 showed an acute pericarditis pattern, and 1 showed significant QTc prolongation (QTc = 533 ms). Nevertheless, none of these patients experienced clinically significant subjective symptoms or objective signs of cardiovascular disease requiring specific intervention. Apparently, the ischemic, infarction, and pericarditis patterns were spurious findings. In the patient with prolonged QTc, the QTc reverted to the normal range (430 ms) 1 month later, despite the patient's having received a gradually increased dosage of clozapine (see Table 3).

Timing and Dosage

Most of the new-onset abnormalities (10/13) were detected during the upward titration period between 3 and 67 days after clozapine treatment commencement, in the dosage range between 12.5 and 400 mg/day. In these cases, incremental titration of clozapine dosage was successfully accomplished without problems even after the onset of ECG abnormalities. The maintenance doses for those with and without ECG abnormalities were not different (318.1 mg/day for normal vs. 298.1 mg/day for abnormal ECG groups, p = .618, Student t test; Table 4). However, in 3 patients, ECG abnormalities were first detected by incidental ECG during the stable maintenance period. Their previous recordings under the same or even higher doses were normal. Follow-up data after the onset of ECG abnormalities were available for all patients, and in 10 of these 13 patients, ECG findings reverted to normal despite the continued use of clozapine. In those who developed ECG abnormalities later during the maintenance period, only 1 patient had normalized ECG on follow-up (see Table 3).

Demographic Factors Related to the New-Onset ECG Abnormalities

For male patients, the prevalence of new-onset ECG abnormalities after clozapine use was 20% (6/30) (see

Table 4. Demographic Profiles and Dosage of Clozapine[a]

Variable	Women	Men	Total
Total N	25	36	61
Age, mean, y	31.3	31.8	31.6[b]
Maintenance dose, mg/d	310.0	336.8	325.8[c]
Abnormal baseline ECG, N	2	6	8
Age, mean, y	36.5	35.7	35.9[d]
Maintenance dose, mg/d	450.0	395.8	409.4[e]
Normal baseline ECG, N	23	30	53
Age, mean, y	30.9	31.0	30.9[d]
Maintenance dose, mg/d	297.8	325.0	313.2[e]
Normal baseline and follow-up ECG, N	16	24	40[f]
Age, mean, y	28.8	29.5	29.3[g]
Maintenance dose, mg/d	317.2	318.7	318.1[h]
New-onset ECG abnormality after clozapine, N	7	6	13[f]
Age, mean, y	35.6	36.8	36.2[g]
Maintenance dose, mg/d	253.6	350.0	298.1[h]

[a]Abbreviation: ECG = electrocardiogram.
[b]No significant difference between men and women (p = .838, Student t test).
[c]No significant difference between men and women (p = .373, Student t test).
[d]No significant difference between those with normal and abnormal baseline ECG (p = .189, Student t test).
[e]No significant difference between those with normal and abnormal baseline ECG (p = .089, Student t test).
[f]No significant difference in the prevalence of new-onset ECG abnormalities between male and female (p = .382, chi-square test).
[g]Significant difference between those with and without new-onset ECG abnormalities after clozapine use (p = .028, Student t test).
[h]No significant difference between those with and without new-onset ECG abnormalities after clozapine use (p = .688, Student t test).

Table 5. Relationship of New-Onset ECG Abnormalities to Cardiovascular Side Effects[a]

	Orthostatic Hypotension*		Tachycardia†	
Condition	Absent	Present	Absent	Present
No ECG abnormalities (N = 40)	32	8	18	22
ECG abnormalities (N = 13)	8	5	6	7

[a]Abbreviation: ECG = electrocardiogram.
*p = .178, chi-square test.
†p = .942, chi-square test.

Table 4). It was found to be 30.4% (7/23) in female patients. This difference between men and women was not statistically significant (p = .382, chi-square test). The mean age of those with new-onset ECG abnormalities after clozapine use was 36.2 years (men, 36.8 years; women, 35.6 years), and the mean age of those without ECG abnormalities was 29.3 years (men, 29.5 years; women, 28.8 years). Statistical analysis showed meaningful age differences for the total group (p = .028, Student t test). When the subjects were separated into groups of men and women, this significance disappeared for women (p = .029 for men, p = .210 for women), probably owing to insufficient sample numbers.

Relationship to Cardiovascular Side Effects

Orthostatic hypotension and tachycardia were analyzed for a possible relationship to the occurrence of ECG abnormalities (Table 5). Neither of them was found to be significantly related to new-onset ECG abnormalities after clozapine use.

QTc Change With Clozapine

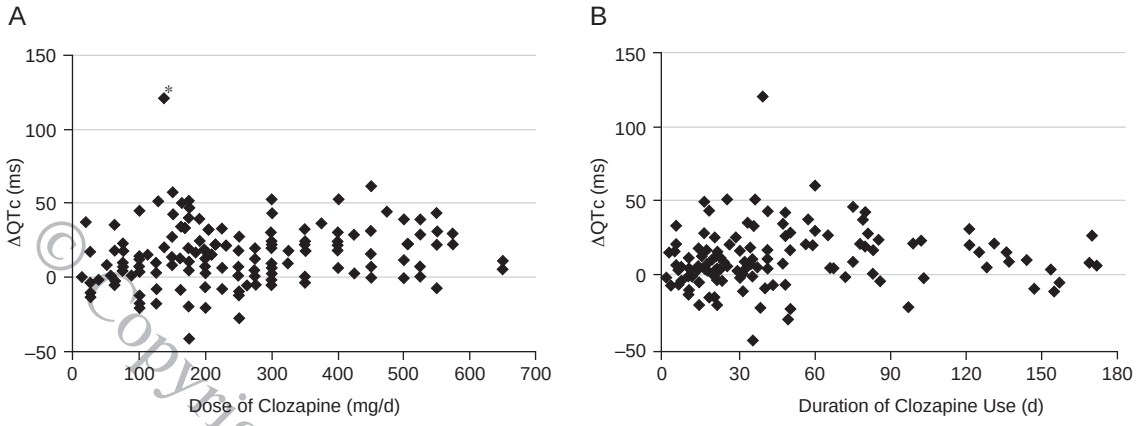
We analyzed the effect of clozapine on QTc using linear regression analysis of the QTc change from the baseline recording (ΔQTc) and the dosage of clozapine and duration of clozapine use. We excluded data from patients who had been taking β-blockers, antidepressants, diuretics, pimozide, or thioridazine at any recording. Excluding baseline recordings (where ΔQTc, duration, and dose were zero by definition), 165 recordings from 51 patients were analyzed. We found a significant positive linear relationship between the dosage of clozapine and ΔQTc (β = .029, t = 2.168, p = .032, Figure 1A). When the apparent "outlier" (see Figure 1A, asterisk) was excluded, the significance increased (β = .033, t = 2.558, p = .011). However, prolongation of QTc into the abnormal range was found in only 2 patients (patient 3 in Table 2 and patient 8 in Table 3). The duration of clozapine use had no significant relationship to ΔQTc (p = .565, Figure 1B). When recordings from patients with normal baseline ECGs were selected (total of 142 recordings from 45 patients), the relationship between the dosage and ΔQTc became more significant (β = .247, t = 2.894, p = .004).

DISCUSSION

To date, no systematic studies on ECG changes in patients treated with clozapine have been published. However, many case reports suggest that clozapine causes various cardiac effects. Since our study was naturalistic and retrospective, we could not assign control groups, and regular data on plasma concentrations of clozapine were unavailable. Although we had guidelines for ECG check-up during clozapine use, it was not a strict or mandatory protocol. These factors caused limitations in terms of the interpretation of our data. However, the patients' baseline ECG data served as a control, and our study may be regarded as natural crossover in design. The researchers were blind to ECG status during case selection, and no systematic bias during the selection of the subjects is likely. Therefore, we believe that this study gives a reasonable estimate of the general characteristics of clozapine-induced ECG abnormalities.

According to this study, a substantial portion (31.1%) of patients using clozapine had ECG abnormalities other than sinus tachycardia or axis deviations, especially at the initial stage of treatment. Other classical antipsychotics also cause a high incidence of ECG abnormalities. Chlorpromazine at as low a dosage as 125 mg/day may induce ECG abnormalities in 34.1% of patients,[17] a result which is similar to ours. However, a direct comparison could not be performed because different criteria were used to define ECG abnormality.

Figure 1. Relationship Between the Change in Corrected QT Interval (ΔQTc) and (A) the Daily Dosage of Clozapine and (B) the Duration of Clozapine Use[a,b]



[a]Multiple ECG recordings from 51 patients were pooled. Linear regression analysis showed a significant positive linear relationship between the dosage of clozapine and ΔQTc ($\beta = .029$, $t = 2.168$, $p = .032$).
[b]Linear regression analysis failed to show a linear relationship between the duration of clozapine use and ΔQTc ($p = .565$).
* = outlier.

Our baseline ECG data showed the prevalence of ECG abnormalities in the other antipsychotic users at a level of 13.6%, which was found to increase significantly after clozapine use. This suggested that clozapine could induce ECG abnormalities more frequently than other antipsychotics. However, since the prevalence of ECG abnormalities in the clozapine users decreased after prolonged use and we could not control the duration of antipsychotic use in the baseline recording, we cannot definitely state whether clozapine usage causes a higher rate of long-lasting ECG abnormalities.

Among those patients with normal baseline ECG findings, 24.5% of patients showed new-onset ECG abnormalities after clozapine use. Those without baseline antipsychotic medication had a particularly higher incidence of new-onset ECG abnormalities after clozapine use, which suggested that those showing no ECG abnormalities with previous antipsychotics may also have a lower probability of developing abnormal ECGs after clozapine treatment.

In our sample, nonspecific abnormality in the T wave was the most common finding. This suggests that clozapine affects cardiac repolarization. Abnormal patterns suggesting ischemic heart disease were also found, but the clinical status of the patients suggested that these findings were spurious. A similar case has been reported by Ketch et al.[9] These false-positive ischemic patterns occurred relatively frequently in our cohort. However, this finding may not be unique to clozapine, since similar findings have been described in patients with heterocyclic antidepressant overdoses.[18] Acute pericarditis after clozapine treatment has also been reported,[6] and 1 of our patients did produce ECG results suggestive of acute pericarditis. However, this too proved to be a false-positive finding, since the patient had no signs of cardiac problems. In fact, most of the new-onset ECG abnormalities were benign.

Most ECG abnormalities were detected during the titration phase when the dosage was being increased. Abnormalities were found as early as after a few days of commencement and at doses as low as 25 mg/day. However, there seemed to be an adaptation to the electrocardiographic effects of clozapine, and by cautiously increasing the dose, most patients could tolerate much higher maintenance dosages without showing persistent ECG abnormalities. In many cases, ischemia-like patterns reverted to normal during follow-up. A case with increased QTc showed no clinically significant arrhythmia, and QTc also reverted to the normal range during follow-up. Other changes such as nonspecific T wave changes and ventricular hypertrophy also tended to revert to normal on follow-up. However, some patients developed new-onset ECG abnormalities long after a stable maintenance dosage was reached.

Although women carry an increased risk of drug-induced cardiac arrhythmia,[19] this gender effect was not observed for clozapine-induced ECG changes. It is well known that the geriatric population is at an increased risk of medication-induced cardiac problems. Although none of our patients were in the geriatric age group, increased age may be a risk factor for the development of ECG abnormalities after clozapine use. Clinically detectable cardiovascular side effects such as orthostatic hypotension or sinus tachycardia were not related to ECG abnormalities.

Clozapine increased QTc in a dose-dependent manner. Increased QTc in patients treated with other antipsychotics has also been reported,[16,20–22] which suggests that antipsychotics may induce fatal arrhythmias, such as

torsade de pointes.[13–15] Although no reports exist of fatal arrhythmia in patients using clozapine, our results showed that use of clozapine might be a risk factor for the development of potentially fatal arrhythmia. However, in our sample of 61 patients, abnormally prolonged QTc was rare and was found only in 2 patients, one of whom had baseline ECG abnormality whereas the other showed prolonged QTc that normalized despite the continued use of clozapine. Although the duration of clozapine use was apparently related to the increase in QTc, this was not statistically significant and seemed to be related to the fact that the dosage of clozapine was increased over time.

We have recently observed a nonfatal ventricular tachycardia in a patient using clozapine, but in this patient QTc was within the normal range just a few hours before the onset of ventricular tachycardia (this patient had been referred to our clinic after the beginning of the data analysis and was thus excluded from the analysis). A case of fatal arrhythmia not preceded by increased QTc has also been reported in a haloperidol user.[23] Because the QTc constantly fluctuates, a single normal ECG may not rule out the possible prolongation.[22] Moreover, recent findings cast doubt on the usefulness of QTc measurement as a predictor of fatal arrhythmia.[21,22] Various methods of modifying the correction of QT[24,25] or QT dispersion[26] have been believed to be more valuable for the prediction of arrhythmia. These variables have not been analyzed in this article. Thus, more studies may be needed to elucidate the potential arrhythmogenecity of clozapine.

In conclusion, a substantial number of patients treated with clozapine developed ECG abnormalities. Most of these abnormalities occurred during the initial stage of treatment. Increased age was the main risk factor for new-onset ECG abnormalities after clozapine treatment, whereas normal ECG with previous antipsychotics may lower the risk. Most of the abnormalities were essentially benign and subsided despite the continued use or even increased dosages of clozapine. Therefore, we believe that ECG abnormalities generally do not hinder clozapine treatment if treatment is accompanied by judicious monitoring. Although clozapine increased QTc in a dose-dependent fashion, most of the QTc measurements were still within the normal range. Thus, the significance of QTc as a predictor of the future occurrence of ventricular arrhythmia in patients taking clozapine is uncertain.

Drug names: benztropine (Cogentin and others), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clonazepam (Klonopin and others), clozapine (Clozaril and others), diazepam (Valium and others), haloperidol (Haldol and others), lorazepam (Ativan and others), loxapine (Loxitane and others), pimozide (Orap), risperidone (Risperdal), thioridazine (Mellaril and others), trihexyphenidyl (Artane and others), valproic acid (Depakene).

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