

Long-Term Outcome of Clozapine in Treatment-Resistant Schizophrenia

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Abstract:

Purpose/Background: The favorable effect of clozapine on psychotic symptoms in patients with treatment-resistant (TR) schizophrenia (SCZ) in short-term studies is well established. However, prospective studies of the long-term outcome of clozapine treatment on psychopathology, cognition, quality of life, and functional outcome in TR-SCZ are limited.

Methods/Procedures: Here, we have examined the long-term (mean duration of follow-up 14 years) effects of clozapine on those outcomes in a prospective, open label study in 54 TR-SCZ patients. Assessments were performed at baseline, 6 weeks, 6 months, and at the last follow-up.

Findings/Results: Brief Psychiatric Rating Scale (BPRS) total, positive symptoms, and anxiety/depression at the last follow-up improved significantly from baseline, as well as from the 6-month evaluation ($P < 0.0001$), with a 70.5% responder rate ($\geq 20\%$ improvement at the last follow-up from baseline). Quality of Life Scale (QLS) total improved by 72% at the last follow-up, with 24% of patients rated as having “good” functioning compared with 0% at baseline. Suicidal thoughts/behavior was significantly reduced at the last follow-up from the baseline. No significant change in negative symptoms was found at the last follow-up in the total sample. Short-term memory function declined at the last follow-up from baseline, but there was no significant change in processing speed. The QLS total showed a significant negative correlation with BPRS positive symptoms but not with cognitive measures, or negative symptoms, at the last follow-up.

Implications/Conclusions: For patients with TR-SCZ, improving psychotic symptoms with clozapine seems to have a more significant impact than negative symptoms or cognition on improving psychosocial function.

Key Words: clozapine, long-term outcome, psychopathology, cognition, treatment-resistant schizophrenia

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Clozapine is the prototypical atypical antipsychotic drug (APD), particularly indicated for patients with treatment-resistant (TR) schizophrenia (SCZ)¹ and those at risk for suicide.^{2,3} It is the only APD that reduces mortality, in part, because of its unique antisuicidal advantages.^{2,3} It has also been reported to be effective for the treatment of tardive dyskinesia (TD).⁴ Despite these advantages, the risk of agranulocytosis and other adverse effect burden, including monitoring of white blood cell count, metabolic syndrome/weight gain, drowsiness, and cardiovascular adverse effects, limits its use for both TR and non-TR-SCZ,¹ although the all-cause mortality rate in pa-

tients treated with clozapine has been reported to be lower compared with that in patients treated with other APDs.^{5,6}

Numerous meta-analyses comparing clozapine versus first- and second-generation APDs with a duration of treatment, mostly 6 to 78 weeks, have reported that clozapine was superior to other APDs for the treatment of positive symptoms but not superior to other APDs for the treatment of negative symptoms.^{7,8} On the other hand, there are limited data on prospective studies on the long-term effects of clozapine treatment on psychopathology.

Clozapine is effective to treat psychosis in approximately 40% to 70% of TR-SCZ.^{9,10} However, improvement in psychosocial function, which affects daily living and quality of life,^{11,12} has not been as well studied. Although clozapine is superior in treating positive symptoms compared with other APDs in TR-SCZ, its effects on quality of life have been reported to be similar to that of other APDs in studies with shorter duration of treatment, up to 2 years.^{12,13} Cognitive function and negative symptoms were reported to be significant contributors to psychosocial functional outcomes.^{14–16}

Most patients with SCZ have a moderate-severe impaired cognitive function from the first psychotic episode.^{17,18} Their cognitive function has been reported to decline further 10 years after the first episode¹⁸ and 20 years after the first hospitalization.¹⁴ We reported that clozapine improves some, but not all, domains of cognition within the first 6 months of treatment, for example, verbal fluency, recall memory, and motor speed, but not executive function.^{19,20} Age-related cognitive decline has been reported to be greater in patients with SCZ, as well as an increased rate of dementia compared with the general population.^{14,18,21–23} In addition, Spangaro et al²⁴ reported, in a retrospective study, that cognitive decline during the mean duration of follow-up of 9 years was mainly found in TR-SCZ patients with less improvement in psychosis compared with patients whose psychotic symptoms responded to clozapine. On the other hand, Anderson et al²⁵ reported no significant difference in change in cognitive function in clozapine responders versus nonresponders in a cross-sectional study.

Although numerous short-term treatment studies reported clozapine's effectiveness for psychotic symptoms in TR-SCZ,^{7,8} prospective long-term outcome studies on psychopathology, quality of life, and cognition with clozapine treatment in patients with well-defined TR-SCZ are limited. Here, we prospectively examined those outcome measures in 54 patients with TR-SCZ, many of whom participated in the US Clozaril study.²⁶ We hypothesized further improvement in psychopathology and quality of life with continued treatment with clozapine. However, we predicted that cognitive function would decline with age, as has been reported for patients with SCZ and the general population.^{14,18,21–23} In addition, we examined the quality of life and cognitive function changes in relation to clozapine treatment responses at the last follow-up and the long-term effects of clozapine treatment on suicidality.

MATERIALS AND METHODS

Subjects

Fifty-four patients (33 male, mean age at last follow-up: 46.4 ± 9.8 years; Table 1) who met the *Diagnostic and Statistical*

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TABLE 1. Demographic and Clinical Data

	Clozapine (n = 54)
Age at baseline	32.3 ± 9.3 (SD) y
Age at last follow-up	46.4 ± 9.8 y
Duration of illness at baseline	12.7 ± 7.2 y (n = 52)
Education	11.8 ± 1.8 y (n = 49)
Hospitalization at baseline	7.06 ± 6.8 (n = 49)
Hospitalization at last follow-up	1.1 ± 1.4 (n = 42)
Duration of follow-up	14.1 ± 2.5 y (range, 9–19 y)
Sex (M/F)	33/21
TD (TD ⁺ /TD ⁻) at baseline	15/25 (n = 40)
TD at last follow-up	2/35 (n = 37)
Weight at baseline	167.3 ± 33.4 (n = 48) lb
Weight at last follow-up	201.3 ± 40.1 (n = 42) lb

Manual of Mental Disorders, Fourth Edition, criteria for SCZ or schizoaffective disorder were included in this long-term follow-up. The 54 patients are stable outpatients at the last follow-up evaluation and are a subsample of 180 patients admitted to a university inpatient unit beginning in 1987 through 1996 and treated with clozapine. An intensive effort was made from 2010 to 2015 to locate all 180 patients, many of whom remained in treatment at a community mental health center affiliated with the research program. We attempted to enroll every patient from the original sample for this study. We examined whether the subsample whom we were able to locate and enroll was representative of the 180-patient sample. There were no significant differences between the patients who re-enrolled or not enrolled in the demographic data (Supplemental Table 1, <http://links.lww.com/JCP/A844>), except for younger age in patients re-enrolled (32.3 ± 9.3 [SD] vs 36.0 ± 10.4). In addition, the Brief Psychiatric Rating Scale (BPRS)²⁷ total and subscales, the Quality of Life Scale (QLS)²⁸ total and subscales, and cognitive measures at baseline and at the time of the 6-month follow-up were not significantly different between groups (Supplemental Table 2, <http://links.lww.com/JCP/A844>). Thus, the subsample in this report can be considered to be representative of the whole sample. This follow-up study did not include a measure of retention on clozapine during the mean duration of 14-year follow-up period. We could not obtain information on those lost to follow-up as to whether they were still on clozapine. Those patients who continued to receive care in the community mental health center, which was affiliated with the principal investigator of this study, continued to opt for clozapine treatment.

The longitudinal assessment protocol and baseline assessment protocol were approved by both institutional review boards in the 2 clinics and the university hospital, which was the basis for this study. Written informed consent was obtained from all patients after a complete explanation of the protocol for both phases of the study.

Follow-up measures were assessed by interviewing patients, and additional information was collected by interviewing providers, family members, and/or by chart review after the mean duration of follow-up of 14.1 ± 2.5 years from baseline (range, 9–19 years) to obtain the outcome data. At baseline, all subjects were screened for TR-SCZ, medical, neurological, neuroendocrine illness, and substance abuse by history, physical examination, and comprehensive blood and urine tests. No patient had received a depot neuroleptic within 2 cycles of enrollment and was unmedicated for at least 1 week at baseline evaluation.

Patients were required to be free of substance abuse at least 3 months before baseline. During the unmedicated period, patients were closely monitored for any worsening of psychotic symptoms and provided immediate medical care if needed. We noted no significant changes in psychopathology during this brief wash-out before starting clozapine.

Psychopathology and Quality of Life Measurements and APD Treatment

Patients were evaluated at baseline, 6 weeks, 6 months, and at the last follow-up after initiation of clozapine treatment. Raters at all follow-ups were supervised and trained by the same investigators for rater consistency. The raters at the last follow-up were not the same raters at the baseline evaluation and were blinded to baseline assessments. The severity of psychopathology was evaluated with the BPRS²⁷ (0–6 scale) and BPRS total, and positive symptoms, negative symptoms (withdrawal-retardation), and anxiety/depression subscales were examined.

Quality of life was assessed with the QLS.²⁸ The QLS total and a subscale of the QLS instrumental role, which assesses work function, were examined. The QLS intrapsychic foundation scores were used along with QLS total to categorize functional levels at each time point according to the criteria of Ascher-Svanum et al²⁹: good: QLS total score ≥84.5; moderate: QLS total < 84.5 and intrapsychic foundation ≥15.5; poor: QLS total < 84.5 and intrapsychic foundation <15.5. In addition, employment information (full-time/part-time) was collected.

After baseline evaluation, clozapine was started as inpatients. Open-label clozapine monotherapy was initiated at 25 mg/d and slowly titrated to the target dose of 400 mg/d and upward according to clinical indication, and continued to the last follow-up and beyond.

Cognitive Function

Cognitive function was assessed at the same time points as psychopathology assessment. The cognitive test battery consists of (1) a measure of psychomotor speed and attention (Wechsler Adult Intelligence Scale–Revised Digit Symbol Substitution Test [DSST])³⁰; (2) verbal fluency (Controlled Word Association Test [CWAT])³¹ and Category Instance Generation Test [CIGT]³²; (3) immediate and delayed recall memory (Verbal List Learning immediate recall [VLL-IR] and delayed recall [VLL-DR])³³; and (5) executive function (Wisconsin Card Sorting Test [WCST])³⁴. To avoid practice effects, different versions of the same test were used for VLL-IR and VLL-DR at each time point.

Tardive Dyskinesia Assessments

Tardive dyskinesia was assessed by the Abnormal Involuntary Movement Scale,³⁵ and the modified Schooler-Kane criteria for TD³⁶ without duration requirement was applied.

Statistical Analysis

For BPRS, QLS, and cognition, treatment effects over time were analyzed using a mixed model analysis of covariance with repeated measures³⁷ after adjusting for age at the last follow-up and sex. All analyses were performed using SAS (SAS Institute, Inc, Cary, NC) statistical software. A multiple regression analysis was used to examine the relationships between QLS, BPRS measures, and cognitive function at the last follow-up. Age and/or sex were also included as independent variables. For this multiple regression analysis, composite scores of cognitive tests were used (see the supplemental materials for details, <http://links.lww.com/JCP/A844>). χ^2 analysis was applied for suicide, TD, and employment data analysis. Fifty-four

patients were in the study, but because of missing data, sample size varied for different measures.

RESULTS

Time Effects of Clozapine on Psychopathology

Results are presented in Table 2 and Figure 1. The BPRS total, positive symptoms, and anxiety/depression subscales showed significant time effects ($P \leq 0.0001$) from baseline to 6 months ($P < 0.02$; effect size [ES]: total 0.9; positive symptoms 0.8; anxiety/depression 0.5), from 6 months to the last follow-up ($P < 0.007$; ES: total 0.5; positive symptoms 0.6; anxiety/depression 0.4), and from baseline to the last follow-up ($P < 0.0001$; ES: total 1.3; positive symptoms 1.4; anxiety/depression 0.9). On the other hand, the BPRS negative symptoms subscale showed no significant time effect during follow-up periods (Table 2, Fig. 1). Responder rates (20% BPRS total score reduction) were from baseline to 6 months 20/50 (40%), from 6 months to the last follow-up 14/41 (34.1%), and baseline to the last follow-up 31/44 (70.5%). The responder rate at the last follow-up from the baseline was significantly greater

compared with the responder rate from baseline to 6 months ($\chi^2 = 8.75, P < 0.003$). In addition, the treatment responder rate was not significantly different between baseline to 6 months and from 6 months to the last follow-up ($\chi^2 = 0.33$, not significant). Using 30% BPRS- total score reduction as criteria for responders, 11 of 50 patients (22%) were responders from baseline to 6 months, and 17 of 44 patients (38.6%) were responders from baseline to the last follow-up, which showed a trend for the greater responder rate at the last follow-up ($\chi^2 = 3.10, P = 0.08$).

When examining differences between responders ($n = 31$) and nonresponders ($n = 13$) (Supplemental Table 4, <http://links.lww.com/JCP/A844>), at baseline, BPRS total scores were significantly higher in responders compared with nonresponders ($P = 0.03$). The similar trend was noted for BPRS positive symptoms at baseline ($P = 0.06$). However, at the last follow-up, in contrast to significantly lower BPRS total scores in the responders compared with nonresponders ($P = 0.02$), BPRS positive symptom was not significantly different between groups, because the responder group improved significantly (group \times time: $P = 0.03$) and numerical improvement in the nonresponders, resulting in no significant difference at the last follow-up. Interestingly, BPRS anxiety/depression

TABLE 2. Time Effects of Clozapine on BPRS and QLS in the Total Sample

	Time	LSM \pm SE	Time F (df), P	P (ES*), Base vs 6 mo	P (ES), 6 mo vs Last	P (ES), Base vs Last
BPRS (n = 54)						
Total	Base	29.8 \pm 1.4	22.63 (3144) <0.0001	<0.0001 (0.9)	<0.005 (0.5)	<0.0001 (1.3)
	6 wk	23.8 \pm 1.4				
	6 mo	21.5 \pm 1.4				
	Last	16.6 \pm 1.5				
Positive symptoms	Base	11.2 \pm 0.7	25.21 (3144) <0.0001	<0.0001 (0.8)	0.0002 (0.6)	<0.0001 (1.4)
	6 wk	8.6 \pm 0.7				
	6 mo	7.8 \pm 0.7				
	Last	5.0 \pm 0.7				
Negative symptoms	Base	4.1 \pm 0.4	1.20 (3144) ns	ns	ns	ns
	6 wk	4.2 \pm 0.4				
	6 mo	3.4 \pm 0.4				
	Last	4.1 \pm 0.5				
Anxiety/depression	Base	5.3 \pm 0.4	9.09 (3142) <0.0001	<0.02 (0.5)	<0.007 (0.4)	<0.0001 (0.9)
	6 wk	3.9 \pm 0.4				
	6 mo	4.1 \pm 0.5				
	Last	2.9 \pm 0.5				
QLS (n = 54)						
Total	Base	39.6 \pm 3.0	18.32 (3114) <0.0001	0.0008 (0.6)	0.0002 (0.7)	<0.0001 (1.3)
	6 wk	44.0 \pm 3.7				
	6 mo	51.6 \pm 3.1				
	Last	66.5 \pm 3.4				
Instrumental role	Base	3.5 \pm 0.9	12.31 (3113) <0.0001	ns	0.0002 (0.7)	<0.0001 (1.0)
	6 wk	2.9 \pm 1.1				
	6 mo	5.2 \pm 0.9				
	Last	9.9 \pm 1.0				
Intrapsychic foundation	Base	16.2 \pm 1.1	10.06 (3114) <0.0001	0.0005 (0.7)	ns	<0.0001 (1.0)
	6 wk	18.2 \pm 1.4				
	6 mo	21.1 \pm 1.1				
	Last	23.7 \pm 1.3				

LSM, least squares mean; ns, not significant.

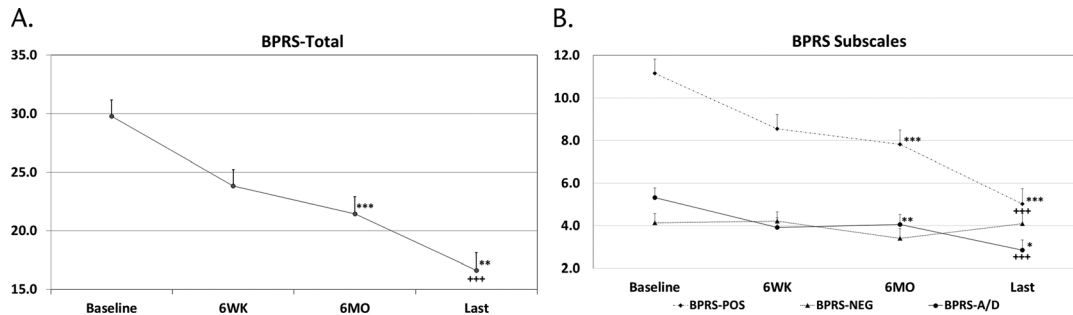


FIGURE 1. A and B, Effects of clozapine on BPRS total and subscales (BPRS positive symptoms, BPRS negative symptoms, BPRS anxiety/depression) from baseline to the last follow-up. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ for significance between baseline to 6 and 6 months to the last follow-up; + $P < 0.05$, ++ $P < 0.01$, +++ $P < 0.001$ for significance from baseline to the last follow-up.

improved significantly in both groups without group differences at any time points (time: $F(3,121) = 7.47, P = 0.0001$). On the other hand, BPRS negative symptoms significantly worsened in the nonresponders but significantly improved in responders (group \times time: $P = 0.0002, ES = 0.5$ for the responder group), resulting in significant differences in this measure at the last follow-up ($P = 0.004$).

Time Effects of Clozapine on QLS

The QLS total showed significant time effects ($P < 0.0001$), from baseline to 6 months ($P = 0.0008, ES = 0.6$), from 6 months to the last follow-up ($P = 0.0002, ES = 0.7$) and from baseline to the last follow-up ($P < 0.0001, ES = 1.3$; Table 2, Fig. 2). On the other hand, the QLS instrumental role showed no significant improvement from baseline to 6 months but was significantly improved from 6 months to the last follow-up ($P = 0.0002, ES = 0.7$) and from baseline to the last follow-up ($P < 0.0001, ES = 1.0$). The QLS intrapsychic foundation showed significant time effects from baseline to the last follow-up ($P < 0.0001, ES = 1.0$) and from baseline to 6 months ($P = 0.0005, ES = 0.7$), but not from 6 months to the last follow-up.

Significant improvement in QLS total and subscales was mainly due to treatment responders (group \times time: $P \leq 0.0008$; Supplemental Table 4, <http://links.lww.com/JCP/A844>). There was no significant difference in QLS total and subscale scores between treatment responders and nonresponders at any time point except for the last follow-up, which was significantly greater in responders (QLS total: $P = 0.007$; QLS instrumental role: $P = 0.002$; QLS intrapsychic foundation: $P = 0.01$) compared with nonresponders. This is due to significant improvement in the responder group from 6 months to the last follow-up ($P < 0.0001$). However, there was no significant worsening of QLS from baseline to the

last follow-up in nonresponders, who had at least numerical improvement in QLS total.

We applied QLS categorization according to the criteria of Ascher-Svanum et al²⁹ to examine functional changes at each time point; at baseline, 26 of 53 (49.1%) were functioning at the moderate level, 27 of 53 (50.9%) were functioning poorly, and none were in the good functioning category; at 6 months, only 1 of 47 (2.1%) were rated as good functioning, 37 of 47 (78.7%) were rated moderate functioning, and 9 of 47 (19.1%) were rated as poor; at the last follow-up, 9 of 38 (23.7%) were rated good, 22 of 38 (57.9%) moderate, and 7 of 38 (18.4%) were poor. This indicates steady improvement over a decade and a half.

We also look at part- and full-time employment at baseline, 6 months, and at the last follow-up. Because of small numbers of patients who had full time employment (at baseline 1 patient, 6 months 1 patient, and the last follow-up 2 patients), we combined part- and full-time employment. Employment at baseline was 8/46 patients (17.4%), at 6 months 15/31 patients (48.4%), and at the last follow-up 18/44 patients (40.9%). Compared with baseline, employment at 6 months ($\chi^2 = 8.494, P = 0.004$) and at the last follow-up ($\chi^2 = 6.055, P = 0.01$) were significantly greater, but there was no difference at 6 months and the last follow-up ($\chi^2 = 0.413$, not significant).

Time Effects of Clozapine on Cognitive Function

The CIGT ($P = 0.02$), VLL-IR ($P = 0.03$), VLL-DR ($P = 0.001$), and the more indicative composite score ($P = 0.03$) showed a significant improvement from baseline to 6 months (Fig. 3, Supplemental Table 3, <http://links.lww.com/JCP/A844>). However, all of those short-term gains at 6 months were lost and declined from 6 months to the last follow-up (CIGT, $P = 0.001$; VLL immediate

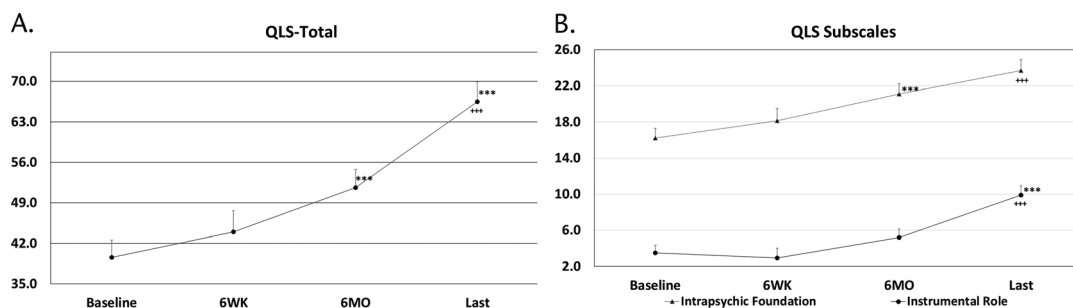


FIGURE 2. A and B, Effects of clozapine on QLS total and subscales (QLS instrumental role, QLS intrapsychic foundation) from baseline to the last follow-up. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ for significance between baseline to 6 and 6 months to the last follow-up; + $P < 0.05$, ++ $P < 0.01$, +++ $P < 0.001$ for significance from baseline to the last follow-up.

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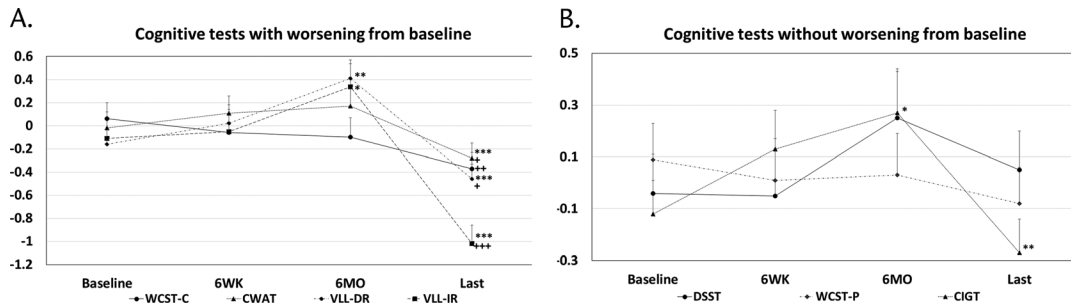


FIGURE 3. A, Cognitive tests worsened from baseline with clozapine treatment: WCST-C, Wisconsin Card Sorting Test Categories, CWAT, VLL-DR, and VLL-IR. B, Cognitive tests without worsening from baseline: DSST, WCST-P, Wisconsin Card Sorting Test perseveration, and CIGT. Y axis of cognitive test graphs is expressed in z scores. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ for significance between baseline to 6 and 6 months to the last follow-up; + $P < 0.05$, ++ $P < 0.01$, +++ $P < 0.001$ for significance from baseline to the last follow-up.

recall, $P < 0.0001$; VLL delayed recall, $P < 0.0001$; CWAT Categories, $P = 0.001$; composite scores, $P < 0.0001$; Fig. 3, Supplemental Table 3, <http://links.lww.com/JCP/A844>). At the last follow-up, CWAT ($P = 0.02$, ES 0.5), WCST categories ($P = 0.003$, ES 0.6), VLL immediate recall ($P < 0.0001$, ES = 1.1), VLL delayed recall ($P = 0.05$, ES = 0.4), and composite scores ($P = 0.002$, ES = 0.7) showed significant worsening from baseline (Fig. 3A, Supplemental Table 3, <http://links.lww.com/JCP/A844>). On the other hand, CIGT, WCST perseveration, and DSST showed no significant worsening from baseline to the last follow-up (Fig. 3B, Supplemental Table 3, <http://links.lww.com/JCP/A844>).

There was no significant group \times time interaction in subsets of cognitive tests and composite scores between clozapine responders and nonresponders (Supplemental Table 4, <http://links.lww.com/JCP/A844>), and no significant group differences at any time points, except for WCST perseveration at the last follow-up, which was significantly lower in the responders ($P = 0.02$). However, WCST perseveration showed no significant time effect.

Interactions Between Changes in QLS, Cognitive Measures, and BPRS

The regression analysis results are presented in Supplemental Table 5, <http://links.lww.com/JCP/A844>. The last follow-up QLS total ($\beta = -3.35$, $P = 0.02$), instrumental role ($\beta = -1.13$, $P = 0.004$), and intrapsychic foundation ($\beta = -0.99$, $P = 0.03$) subscales showed significant negative relationships with the last BPRS positive subscale, indicating more improvement in these QLS measures in patients with fewer positive symptoms. In the same way, the last QLS instrumental role also showed a significant negative relationship with the last BPRS total ($\beta = -0.38$, $P = 0.04$). The BPRS negative symptoms and the composite score of cognition at the last follow-up were not significant predictors for the last QLS total or subscale scores. In the regression models predicting changes from the baseline to the last follow-up (Δ : improvement) of QLS from Δ BPRS and Δ cognition, only Δ BPRS total showed a trend for a positive relationship with Δ QLS total ($\beta = 0.81$, $P = 0.07$). In addition, Δ QLS intrapsychic foundation showed significant positive relationships with Δ BPRS total ($\beta = 0.38$, $P = 0.04$) and Δ BPRS negative symptoms ($\beta = 1.13$, $P = 0.03$). Neither Δ BPRS nor Δ cognition showed a significant relationship with the Δ QLS instrumental role subscale.

The last follow-up composite score of cognition showed significant negative relationship with the last BPRS total ($\beta = -0.036$, $P = 0.007$), positive symptoms ($\beta = -0.07$, $P = 0.02$), and negative symptoms ($\beta = -0.10$, $P = 0.005$) scores. Thus, these analyses show that the fewer the psychotic symptoms at the last follow-up, the greater cognitive function at the last follow-up.

Effects of Clozapine on Suicidality

Suicide data are presented in Supplemental Table 6, <http://links.lww.com/JCP/A844>. In patients for whom there were either baseline ($n = 49$) and/or last follow-up ($n = 42$) suicide information, there was a significant reduction of suicide attempts (from 15 to 1) and an increase in no suicidality (from 18 to 28) at the last follow-up (Mentel-Haenzel $\chi^2 = 13.2$, $P = 0.0003$; Supplemental Table 6a, <http://links.lww.com/JCP/A844>). When examining patients with both baseline and the last follow-up information ($n = 39$), again, there was a significant reduction in suicide attempts (from 14 to 1) and an increase in no suicidality (from 12 to 25) at the last follow-up (Mentel-Haenzel $\chi^2 = 14.6$, $P = 0.0001$; Supplemental Table 6b, <http://links.lww.com/JCP/A844>); among 14 patients with a suicide attempt at baseline, 4 patients (28.6%) reported no suicidal thought, 9 reported suicidal thoughts/plans (64.3%), and 1 patient (7.1%) attempted suicide at the last follow-up; among 13 patients with suicidal thoughts/plans at baseline, 10 patients (76.9%) changed to no suicidal thought; among 12 patients with no suicidal thought at baseline, 1 patient (8.3%) had suicidal thoughts/plans at the last follow-up.

Clozapine Dosage, TD, and Weight

There was no significant change in clozapine dosage during the follow-up period (6 weeks: 415.6 ± 197.2 mg/d [range, 50–900 mg/d], $n = 44$; 6 months: 430.1 ± 180 mg/d [range, 62–850 mg/d], $n = 42$; at the last follow-up: 458.7 ± 226.3 mg/d [range: 75–900 mg/d], $n = 39$; time effect: $F(2,73) = 0.42$, $P =$ not significant).

In patients having a baseline and/or last TD evaluation, at baseline, 15 of 40 patients (37.5%) met criteria for TD, whereas at the last follow-up, only 2 of 35 patients (5.7%) met criteria for TD (Supplemental Table 7, <http://links.lww.com/JCP/A844>; Fisher exact test $P \leq 0.0008$). On the other hand, in patients with a 6-month TD evaluation, 8 of 29 patients (27.6%) had TD, which was not significantly different from that of baseline. Among patients who had both baseline and the last follow-up TD evaluations ($n = 30$), 11 of 30 (36.7%) had TD at baseline, 2 of 30 (6.7%) had TD at the last follow-up, and none had new onset of TD at the last follow-up.

During the follow-up, weight gain was continuous; they gained about 34.2 lb from baseline ($P < 0.0001$; Supplemental Table 8, <http://links.lww.com/JCP/A844>). Furthermore, weight gain from baseline to 6 months was not significantly different from weight gain from 6 months to the last follow-up (16.5 vs 18.1 lb not significant).

DISCUSSION

The major findings of this study are (1) patients with TR-SCZ treated with clozapine showed continued improvement in BPRS

positive symptoms and anxiety/depression, and the psychosocial function measured by QLS at the last follow-up with a mean duration of 14 years. On the other hand, BPRS negative symptoms did not improve significantly in the total sample over the 14-year follow-up, but the improvement was noted in the subset of patients who met the criteria for treatment response at the last follow-up; (2) cognitive function showed a significant decline at the last follow-up compared with baseline evaluation in all but 3 cognitive tests (CIGT, WCST perseveration, and DSST), with the greatest decline in immediate recall memory. In addition, cognitive decline was independent of psychotic symptom responsiveness, but cognitive composite scores at the last follow-up showed significant negative correlations with the last follow-up BPRS total, and positive symptoms and negative symptoms subscales; (3) QLS total, instrumental role, and intrapsychic foundation subscales at the last follow-up showed significant negative correlations with the last follow-up BPRS positive symptoms, but not with cognition or BPRS negative symptoms; (4) there was a significant reduction in suicide attempts and increase in no suicidality at the last follow-up; (5) the dosage of clozapine remained stable during the follow-up period, and (6) weight gain was continuous and weight gain from baseline to 6 months was similar to 6 months to the last follow-up.

This prospective follow-up study specifically evaluated extended long-term treatment effects of clozapine in a cohort of patients with TR-SCZ. Long-term treatment with clozapine improved psychopathology and psychosocial function measured by the QLS during the course of treatment. At the last follow-up, the responder rate was 70.5% (31/44) using a 20% BPRS total score reduction from the baseline as the definition of a responder. This rate is significantly greater than the 40% responder rate (20/50) from baseline to 6 months. Using a 30% BPRS total score reduction from the baseline, the responder rate at the last follow-up was 38.6% (17/44), a trend of greater responder rate compared with that of 6 months. Siskind et al⁹ have reported the responder rate with clozapine treatment as 40.1% in the meta-analysis with a duration of treatment from 3 months to 1.5 years, which is similar to data at 6 months presented here (40% responder rate). Results of the current study showed responder rates increased with prolonged treatment with clozapine, with continuous positive symptom reduction in patients who responded to clozapine, as well as in the group who did not meet the $\geq 20\%$ improvement criterion for responders, although nonsignificant improvement. The BPRS anxiety/depression symptoms also improved significantly in both responders and nonresponders without significant group differences at any time points, which may be one of the contributory factors for the low rate of suicide and suicide attempts reported here and in other studies with clozapine treatment.^{2,3} On the other hand, clozapine neither improved nor worsened BPRS negative symptoms in the total sample. This is due to significant improvement in the responder group but significant worsening in the no-responder group. Similar to prior reports,^{38,39} patients with more severe baseline psychopathology responded better to treatment. There was no significant clozapine dosage change during the follow-up, suggesting no tolerance development for treatment efficacy, as well as good adherence and compliance of the TR-SCZ patients in this study. It has been reported that in patients treated with clozapine, treatment compliance is high⁴⁰ and the rate of hospitalization is low,⁴¹ which could contribute to overall clinical stability with the prescribed clozapine treatment. The hereinabove results may partially explain the absence of significant clozapine dosage change during the follow-up period, as well as reflecting clinical stability during the long-term follow-up.

Nonresponders in this study can be considered to be ultra (clozapine)-TR-SCZ.⁴² However, they were continued on clozapine in this study, in part, because of lower baseline symptom se-

verity compared with responders, no significant difference in positive symptoms and anxiety/depression compared with responders at the last follow-up, and nonsignificant improvement in quality of life. In addition, the risk of late-onset agranulocytosis in this period is minimal, and there were no reasonable alternative treatments to offer. In addition, these patients were nonresponsive to clozapine mainly because of the worsening of negative symptoms, in contrast to most patients with ultra (clozapine)-TR-SCZ whose positive symptoms were nonresponsive to clozapine. However, the worsening of negative symptoms in patients with clozapine nonresponders in this study needs replication in a large sample with a comparison group, which did not receive clozapine. In addition, this finding can be useful to consider when assessing ultra (clozapine)-TR-SCZ, because criteria for clozapine-TR-SCZ are heterogeneous.⁴³ Considering the slow but marked improvement in some subjects between 6 months and the last evaluation and nonresponders in this study continued on clozapine, if and when someone should be switched to another APD from clozapine must consider that switching from clozapine may be associated with severe decompensation.⁴⁴

In this study, QLS ratings improved despite the worsening of subsets of cognitive tests and no significant improvement in negative symptoms in the total sample. However, most of the significant QLS improvement happened in the responder group, whose negative symptoms improved significantly. On the other hand, in the regression analysis, higher QLS total, instrumental role, and intrapsychic foundation subscales at the last follow-up were related to lower BPRS positive symptoms but not related to cognition or BPRS negative symptoms.

Patients in this study clearly met the criteria for TR-SCZ. For these patients, the level of psychotic symptoms was a predictor of better outcomes with regard to psychosocial function at the last follow-up. Thus, clozapine's significant improvement in positive symptoms seems to contribute to improved quality of life despite relatively less improvement in negative symptoms and worsening of cognitive function during long-term follow-up. As previously mentioned, this may be due to the expected decline in cognition over a decade and a half in the middle-aged patients in this study.^{14,18,21} The results of this study are consistent with reports of positive symptoms or total psychotic symptoms affecting the psychosocial functional outcome.^{12,16}

To further evaluate improvement in quality of life, we applied the classification by Ascher-Svanum et al²⁹ and examined category distribution at each time point. Ascher-Svanum et al²⁹ reported in mildly ill stable outpatients with SCZ that 63% of patients were in the moderate function category, while 19% of patients were classified as either good or poor. In this study, there was a gradual improvement in functional outcome by the last follow-up, which was 24% of patients were in the good category, 58% in the moderate, and 18% in the poor category, which is a similar pattern reported by Ascher-Svanum et al.²⁹ This supports the conclusion for improvement in psychosocial function with long-term treatment with clozapine in TR-SCZ. In addition, actual employment data maintained a similar rate of employment at the last follow-up to that in the 6 months, which reflected vocational functional stability despite the decline in cognitive function.

Long-term treatment with clozapine did not show increasing improvement in cognitive function in contrast to the improvement noted in the first 6 months in subsets of cognitive tests (Fig. 3, Supplemental Table 3, <http://links.lww.com/JCP/A844>). The current study showed short-term memory function declined the most, but processing speed did not change significantly during the follow-up. In addition, verbal fluency measured by CIGT and WCST perseveration did not change significantly from the baseline. Similar to the current study, prior long-term follow-up studies

have reported decline in memory function,^{14,17,18} but stability of processing speed, executive function,^{18,45} and verbal fluency.^{14,18} For example, the study by Zanelli et al¹⁸ reported a decline in memory function, but no decline in processing speed, executive function, and verbal fluency in a 10-year follow-up of the first episode SCZ, with the mean age at the last follow-up being younger than that of the current study. It seems that different subsets of cognitive function start to decline at different ages in both patients with SCZ and the general population.^{21,22} For example, Hughes et al²² reported in the 9-year follow-up study of the general population that measures of speed and reaction time start to decline in the 30s, immediate recall in the 40s, and category fluency in the 50s. In patients with SCZ, verbal memory function seems to start to decline from the initial phase of the first episode of SCZ,^{17,18} and processing speed, executive function (18, 45, current study), and verbal fluency (14, 18, current study) seem to be more stable in long-term follow-up. Both in SCZ and in the general population, age-related cognitive decline is steeper in older age.^{21,22} In addition, multiple studies have reported that aging-related accelerated cognitive decline in patients with SCZ is greater compared with the general population.^{14,18,21,23} Spangaro et al²⁴ reported that clozapine-responded patients with TR-SCZ showed improvement in global cognitive function, but clozapine nonresponders (ultra-TR-SCZ) showed cognitive decline in the retrospective 9-year follow-up study. In contrast to the finding by Spangaro et al,²⁴ this study did not find any difference in cognitive change during the follow-up between treatment responders and nonresponders to clozapine. However, the composite score of cognition showed significant negative correlations with both positive and negative symptoms at the last follow-up. This finding suggests that psychotic symptoms and cognitive function are more closely related than many previous studies have implied, particularly in TR-SCZ.^{17,24,46} Thus, timely use of clozapine in patients with TR-SCZ is important to prevent ultra-TR-SCZ⁴² and cognitive decline with time.²⁴

In this long-term follow-up study, suicidality was significantly reduced, particularly suicide attempts. This finding further supports clozapine's antisuicidal effect^{2,3} during long-term follow-up. In addition, clozapine treatment was associated with reduction of TD at the last follow-up, consistent with prior reports.⁴

There was continued weight gain during the follow-up (approximately 34.2-lb weigh gain). However, the magnitude of weight gain from 6 months to the last follow-up was the same as the weight gain during the initial 6 months of treatment with clozapine. Fast weight gain in initial 6 months could be related to younger age, as weight gain decreases with advancing age in general population.⁴⁷ Vázquez-Bourgon et al⁴⁸ reported the 10-year follow-up study of weight gain in patients with first episode psychosis (65.1% was SCZ) mostly on various atypical ADP's except clozapine. They reported 36.4-lb weight gain who were on medication for 10 years.⁴⁸ Vázquez-Bourgon et al⁴⁹ also reported that weight gain was greater in the first year after ADP initiation and was less pronounced during the 10-year follow-up period. Their mean age at the baseline was younger than that of current study subjects (29.3 ± 8.8 vs 32.3 ± 9.3). Thus, weight gain on clozapine during the 14-year follow-up seems to be similar to that with other APD's, although greater than that in healthy controls in 10-year period (6.4 lb).⁴⁸

The major limitations of this study are its small sample size and lack of concomitant comparison groups. However, this study was not designed to evaluate superiority or inferiority of clozapine; rather, this study was designed to fill the gap in literatures of prospective long-term effects of clozapine in patients who choose to continue to be on clozapine in the naturalistic setting. Although proportion of patients initially recruited to receive clozapine who could be followed at the last follow-up was relatively

small, the group who were followed up was found to be similar on key measures at the time of the 6-month follow-up compared with patients not available for the long-term follow-up (Supplemental Tables 1 and 2, <http://links.lww.com/JCP/A844>). Without a comparison group who did not receive clozapine, we cannot conclude that the time effects of clozapine on psychopathology and QLS were related to clozapine. However, patients in this study are TR-SCZ, whose symptoms generally do not improve without effective drug treatment or other forms of treatment.^{42,50} Cramer et al⁵⁰ reported a 50% increase in QLS as a “much better” improvement in a 12-month follow-up study with clozapine. In this study, the QLS total improved by 72% at the last follow-up from the baseline. Thus, the significant improvement in psychopathology and QLS at the last follow-up in this study suggests that it is the result of a beneficial effect of treatment with clozapine. However, because of lack of comparison group and small sample size, results of current study are applicable to patients who are compliant to treatment. Thus, whether results of the current study can be generalized to patients on long-term treatment of clozapine needs to be examined in the future study in a large sample and control group.

In addition, this study is unique, because it specifically examined prospectively well-defined TR-SCZ-treated with clozapine on changes in psychopathology, quality of life, and cognition simultaneously in the naturalistic long-term follow-up study. Prior reports on long-term follow-up studies on clozapine are mostly retrospective studies on symptom changes.^{42,51}

In summary, this prospective long-term follow-up of clozapine treatment suggests that multiyear treatment with clozapine can improve some, but not all, measures of psychopathology and quality of life further. Particularly, this study demonstrated that for TR-SCZ, improvement in positive symptoms was a significant contributor to further improvement in quality of life during long-term treatment. On the other hand, some of cognitive functions, particularly short-term memory, declined most during the follow-up. This could be related to anticholinergic effects of clozapine.⁵² However, considering that memory function improved in the initial 6-month treatment, and that *N*-desmethylozapine, a major metabolite of clozapine, is cholinergic M1 receptor agonist, which improves working memory/memory function,^{53,54} anticholinergic effects of clozapine may not be a major reason for short-term memory decline. Rather, the general decline of cognitive function with aging in patients with SCZ as well as in the general population^{14,18,21,22} may contribute to short-term memory function decline. Although overall quality of life improves with long-term treatment with clozapine, gainful employment was in 40.1% of patients. Thus, comprehensive intervention programs are needed to improve functional outcome in balance with work-related stress.^{55,56} In addition, intervention of weight gain to prevent metabolic syndrome seems to be important during the long-term follow-up.⁵⁷ Because of differences in biochemical effects among atypical APDs and individual differences in genetic background, the results reported here should also be examined for other atypical APDs in the future studies.

AUTHOR DISCLOSURE INFORMATION

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The data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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