Longer Time to Antipsychotic Treatment Discontinuation for Any Cause Is Associated With Better Functional Outcomes for Patients With Schizophrenia, Schizophreniform Disorder, or Schizoaffective Disorder

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Objective: Time to all-cause treatment discontinuation is considered a composite proxy measure of treatment efficacy, safety, and tolerability. Longer time to discontinuation of antipsychotic medication for any cause has been shown to be associated with greater symptom improvements in the treatment of schizophrenia. This study examines whether longer time to all-cause medication discontinuation is also linked to better functional outcomes.

Method: Using pooled data from 4 randomized, double-blind antipsychotic trials of 24- to 28-weeks' duration, this study examined the association between time to all-cause treatment discontinuation and functional outcomes, as assessed by a disease-specific, clinician-rated measure (Quality of Life Scale [QLS]) and a generic, patient-reported measure (Medical Outcomes Study Short Form 36 [SF-36]). Patients in these trials had a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder. This post hoc analysis used Pearson partial correlations to assess relationships between time to treatment discontinuation and changes in functional scores, adjusting for baseline scores. Repeated measures analyses were also conducted to compare post-baseline functional outcome change over time between completers and noncompleters.

Results: Longer time to all-cause treatment discontinuation was found to be significantly associated with greater improvements in all assessed functional domains ($p < .05$). Patients who completed their respective trials (46.8%, 761/1627) experienced significantly greater improvement in functional outcome measures (in 4 QLS domains and SF-36 mental health component summary score; all, $p < .001$) compared to patients who discontinued for any cause. In addition, greater symptom improvement was significantly associated with greater functional improvements in assessed domains.

Conclusions: Findings from this post hoc analysis illustrate the importance of longer treatment duration with antipsychotics for improving functional outcomes in the treatment of patients with schizophrenia.

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Time to all-cause treatment discontinuation is an integrated proxy measure of efficacy, safety, and tolerability that can be applied to both randomized clinical trials and clinical practice. The rationale is straightforward: efficacious and well-tolerated medications for chronic conditions are likely to be prescribed over longer periods than ineffective or poorly tolerated ones. Indeed, time to all-cause treatment discontinuation was chosen as the primary measure of long-term effectiveness, safety, and tolerability by the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study,[1] sponsored by the National Institute of Mental Health.

In the CATIE schizophrenia trial, longer time to all-cause treatment discontinuation was significantly associated with greater improvements in patients' clinical symptomatology.[1] Significant associations also have been reported between improvement in psychopathology, such as negative, positive, depressive, and anxious symptoms, and improvement in quality of life and functional outcomes.[2–4] Therefore, longer duration of therapy would be

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expected to be associated with greater improvement in functional outcomes. However, we are not aware of any report in the literature concerning this relationship.

In the analyses presented here, we sought to examine, in pooled data from 4 randomized schizophrenia clinical trials, the relationship between improvements in functional outcomes and longer time to all-cause treatment discontinuation. We also compared the magnitude of functional improvements over time between patients who completed their respective medication trials and patients who discontinued treatment early due to lack of efficacy, adverse events, or other reasons. Lastly, we examined the extent to which functional outcomes are associated with improvements in psychopathology during schizophrenia treatment.

METHOD

Data Source

A post hoc, pooled analysis of clinical trials within the Eli Lilly and Company database was conducted. Four studies met the following selection criteria: (1) randomized, double-blind, active-control; (2) duration of 24 to 28 weeks; and (3) patients diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder using DSM-IV criteria. These 4 studies included 1627 patients treated with 4 different atypical antipsychotics: olanzapine 10 to 20 mg/day (N = 822), risperidone 4 to 12 mg/day (N = 167), quetiapine 300 to 700 mg/day (N = 175), or ziprasidone 80 to 160 mg/day (N = 463). Study 1 was a 28-week trial comparing olanzapine (172 patients) and risperidone (167 patients) for treatment of schizophrenia, schizophreniform disorder, or schizoaffective disorder.[5] Study 2 was a 24-week trial comparing olanzapine (171 patients) and quetiapine (175 patients) for treatment of patients with prominent negative symptoms with diagnoses of schizophrenia or schizoaffective disorder.[6,7] Study 3 was a 28-week trial comparing olanzapine (277 patients) and ziprasidone (271 patients) for treatment of schizophrenia.[8] Study 4 was a 24-week trial comparing olanzapine (202 patients) and ziprasidone (192 patients) for treatment of schizophrenia or schizoaffective disorder with depressive symptoms.[9]

Outcome Measures

Time to all-cause treatment discontinuation was defined as the number of days from baseline to trial (and medication) discontinuation (up to week 24 or 28) for any cause. Patients were categorized based on whether they completed the study in which they were enrolled (completers) or not (noncompleters). Reasons for trial discontinuation among the noncompleters were obtained from trial case report forms and were further identified as follows: discontinuation for lack of efficacy (LE), which included symptom relapse or psychiatric adverse events (e.g., emergent psychosis or depression); discontinuation for medication intolerability (MI); and discontinuation for all other reasons (OR). "Other reasons" included patient conflict or decision, lost to follow-up, protocol violation, physician decision, noncompliance, protocol entry criteria not met, protocol variance, sponsor decision, moved away, protocol interim criteria not met, and satisfactory response.

Functional outcomes were measured using a patient-reported questionnaire (the Medical Outcomes Study Short Form 36 [SF-36])[10] and a clinician-rated scale (the Quality of Life Scale [QLS]).[11] The SF-36 is a generic measure of patient health often used in schizophrenia research.[12] It provides a mental component summary score (MCS) and a physical component summary score (PCS) in addition to 8 subscale scores: Physical Functioning, role limitations caused by physical problems (Role-Physical), Bodily Pain, General Health, Vitality, Social Functioning, role limitation due to emotional problems (Role-Emotional), and General Mental Health. The QLS is a schizophrenia-specific measure of 4 functional domains: interpersonal relationships ("Interpersonal Relations"), occupational achievements ("Instrumental Role"), level of engagement ("Intrapsychic Foundations"), and common activities ("Common Objects and Activities"). An aggregate measure of these 4 domains provides the QLS total score.

Statistical Analysis

This post hoc analysis used Pearson partial correlations to assess relationships between time to treatment discontinuation and changes in SF-36 and QLS scores, adjusting for baseline scores. Correlations between symptom improvements, assessed using the Positive and Negative Syndrome Scale (PANSS), and functional improvements (measured using the SF-36 and QLS scales) were also examined.

Two-sample t test was used to compare baseline functional outcome scores between completers and noncompleters. Repeated measures analyses were conducted to compare postbaseline functional outcome change over time between completers and noncompleters and among the 3 groups of noncompleters. Statistical analyses accommodated differences among the 4 studies used in this analysis in patient visit and assessment schedules. The QLS was collected at weeks 0, 8, 16, 24, and 28 or early discontinuation (DC) in study 1, at weeks 0, 8, 16, and 24 or early DC in studies 2 and 4, and at weeks 0, 6, 13, 20, and 28 or early DC in study 3. The SF-36 was collected at weeks 0, 8, 16, and 24 in study 4, at weeks 0, 6, 13, 20, and 28 for study 3, and was not collected in studies 1 and 2. To accommodate these schedule differences when performing repeated measures analyses, the last observations during each time period—week 1 through 8, week 8 through 16, and week 16 through 24—were carried

Table 1. Patient Characteristics in the Pooled Sample and by Clinical Trial

Characteristic	Clinical Trial				Total Pooled Sample (N = 1627)
	Study 1 (N = 339)	Study 2 (N = 346)	Study 3 (N = 548)	Study 4 (N = 394)	
Age, mean ± SD, y	36.2 ± 10.7	41.1 ± 9.6	39.2 ± 11.9	41.6 ± 9.7	39.5 ± 10.9
Male, N (%)	220 (64.9)	228 (65.9)	352 (64.2)	248 (62.9)	1048 (64.4)
White, N (%)	253 (74.6)	179 (51.7)	239 (43.6)	197 (50.0)	868 (53.3)
Diagnosis, N (%)					
Schizophrenia	277 (81.7)	230 (66.5)	548 (100)	223 (56.6)	1278 (78.5)[a]
Schizoaffective disorder	52 (15.3)	116 (33.5)	0 (0)	171 (43.4)	339 (20.8)[a]
Schizophreniform disorder	10 (3.0)	0 (0)	0 (0)	0 (0)	10 (0.6)[a]
Age at illness onset, mean ± SD, y	23.5 ± 7.5	23.4 ± 8.2	23.4 ± 8.3	23.7 ± 8.9	23.5 ± 8.3
PANSS total, mean ± SD	96.1 ± 16.6	84.8 ± 14.0	100.9 ± 20.2	79.4 ± 17.5	91.3 ± 19.7
QLS total, mean ± SD	48.6 ± 22.4	51.0 ± 19.8	44.5 ± 20.1	55.3 ± 20.9	49.8 ± 21.1
SF-36 MCS, mean ± SD	NA[b]	NA[b]	37.8 ± 12.7	32.8 ± 12.1	35.6 ± 12.7
SF-36 PCS, mean ± SD	NA[b]	NA[b]	48.1 ± 8.9	45.5 ± 10.8	47.0 ± 9.8
Completed treatment, N (%)	178 (52.5)	156 (45.1)	280 (51.1)	147 (37.3)	761 (46.8)
Discontinued due to, N (%)					
Lack of efficacy	67 (19.8)	78 (22.5)	99 (18.1)	71 (18.0)	315 (19.4)
Medication intolerability	19 (5.6)	16 (4.6)	31 (5.7)	40 (10.2)	106 (6.5)
Other reasons	75 (22.1)	96 (27.7)	138 (25.2)	136 (34.5)	445 (27.4)

[a]Percentages total less than 100 because of rounding.
[b]SF-36 not used in Studies 1 and 2; for pooled sample, N = 916.
Abbreviations: MCS = mental component summary, NA = not applicable, PANSS = Positive and Negative Syndrome Scale, PCS = physical component summary, QLS = Quality of Life Scale, SF-36 = Medical Outcomes Study Short Form 36.

forward to week 8, 16, and 24, respectively (interval last observation carried forward).

The mixed-model repeated measures (MMRM) model for comparison of completers and noncompleters included terms for baseline, week on study, protocol, status (completer vs. noncompleter), and baseline-by-week and status-by-week interactions. The MMRM model for comparison of noncompleter subgroups included terms for baseline, week on study, protocol, status (reason for discontinuation), and baseline-by-week on study and status-by-week interactions. All of these terms were considered fixed effects in the model. The heterogeneous Toeplitz covariance structure was selected to achieve model convergence, and Satterthwaite's method was used to estimate the denominator degree of freedom for the tests of fixed effects. p Values resulting from MMRM analysis of completers and noncompleters are reported both unadjusted and adjusted for multiple comparisons using the Hochberg method,[13] and adjustments were made for the multiple end points within each scale. p Values from baseline comparisons were not adjusted.

RESULTS

Baseline Patient Characteristics

Baseline clinical and demographic characteristics for participants in each of the 4 studies used in the analyses are provided in Table 1. Predominantly, patients were male, white, and diagnosed with schizophrenia. Mean baseline PANSS scores were consistent with moderate or greater disease severity. Within these studies, 37.3% to 52.5% of patients completed the 24- to 28-week treatment period, with an overall completion rate of 46.8%. Baseline characteristics of completers and noncompleters were comparable (Table 2). Among noncompleters, trial discontinuation was driven primarily by OR (27.4%) or LE (19.4%), with a small proportion discontinuing due to MI (6.5%). OR included the following: patient conflict or decision = 165 (10.1%); lost to follow-up = 103 (6.3%); protocol violation = 71 (4.4%); physician decision = 34 (2.1%); noncompliance = 17 (1.0%); protocol entry criteria not met = 16 (1.0%); protocol variance = 12 (0.7%); sponsor decision = 11 (0.7%); moved away = 8 (0.5%); protocol interim criteria not met = 6 (0.4%); and satisfactory response = 2 (0.1%).

Treatment Duration and Functional Outcomes

Across the pooled sample, longer time to all-cause treatment discontinuation was associated with significantly greater functional improvements, as measured by the QLS total score, its 4 domains, the SF-36 MCS, SF-36 PCS, and the 8 SF-36 subscales (Figure 1). Though small to moderate in magnitude, all correlations were statistically significant ($p < .001$).

Correlations greater than 0.25 were observed for SF-36 MCS (0.33) and the following SF-36 subscales: role limitation due to emotional reasons (0.29), social functioning (0.29), and general mental health (0.27) scores; and for the QLS total score (0.33), and the Interpersonal Relations (0.27), Intrapsychic Foundations (0.33), and Common Objects and Activities (0.27) subscale scores.

Completers vs. Noncompleters

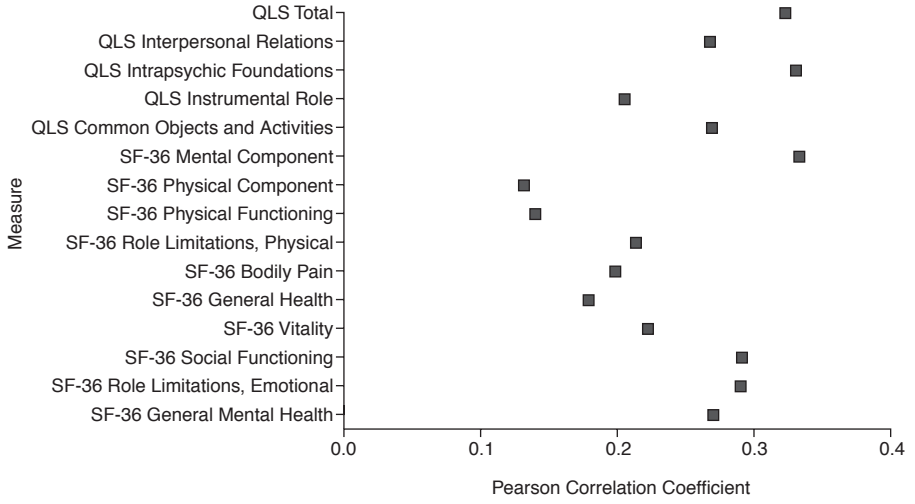
Baseline and postbaseline scores for completers and noncompleters on the SF-36 components and QLS total score and subscales are presented in Table 3. The 2 groups

Table 2. Baseline Patient Characteristics for Completers and Noncompleters, and Among Noncompleters by Reason for Discontinuation

Characteristic	Completers (N = 761)	Noncompleters (N = 866)	LE[a] (N = 315)	MI[b] (N = 106)	Other[c] (N = 445)
Age, mean ± SD, y	39.7 ± 11.0	39.4 ± 10.8	39.0 ± 10.8	40.2 ± 11.1	39.4 ± 10.6
Male, N (%)	489 (64.3)	559 (64.5)	211 (67.0)	55 (51.9)	293 (65.8)
White, N (%)	411 (54.0)	457 (52.8)	203 (64.4)	57 (53.8)	197 (44.3)
Diagnosis, N (%)					
Schizophrenia	632 (83.1)	646 (74.6)	249 (79.0)	77 (72.6)	320 (71.9)
Schizoaffective disorder	128 (16.8)	211 (24.4)	64 (20.3)	28 (26.4)	119 (26.7)
Schizophreniform disorder	1 (0.1)	9 (1.0)	2 (0.6)	1 (0.9)	6 (1.4)
Age at illness onset, mean ± SD, y	23.9 ± 8.2	23.1 ± 8.3	22.4 ± 7.2	23.4 ± 9.3	23.5 ± 8.7
PANSS total, mean ± SD	91.4 ± 19.2	91.1 ± 20.2	93.5 ± 20.4	89.1 ± 20.0	89.9 ± 20.1
QLS total, mean ± SD	49.8 ± 21.3	49.8 ± 20.8	47.3 ± 21.2	52.5 ± 23.0	50.8 ± 19.9
SF-36 MCS,[d] mean ± SD	36.6 ± 12.7	34.8 ± 12.6	34.7 ± 12.2	34.8 ± 13.8	34.9 ± 12.6
SF-36 PCS,[d] mean ± SD	47.9 ± 9.7	46.2 ± 9.8	46.2 ± 8.8	44.9 ± 9.4	46.6 ± 10.6

[a]Patients who discontinued due to lack of efficacy or symptom worsening (including psychiatric adverse events).
[b]Patients who discontinued due to medication intolerability (nonpsychiatric adverse events).
[c]Patients who discontinued for all other reasons.
[d]For SF-36, N = 418 for completers and 498 for noncompleters.
Abbreviations: LE = lack of efficacy, MCS = mental component summary, MI = medication intolerability, PANSS = Positive and Negative Syndrome Scale, PCS = physical component summary, QLS = Quality of Life Scale, SF-36 = Medical Outcomes Study Short Form 36.

Figure 1. Pearson Correlation Coefficients Between Time to Treatment Discontinuation for Any Cause and Functional Outcome Measures for Entire Patient Sample*



*All correlations are statistically significant ($p < .001$).
Abbreviations: QLS = Quality of Life Scale, SF-36 = Medical Outcomes Study Short Form 36.

had comparable QLS total and subscale scores at baseline. Completers had statistically significantly better baseline MCS and PCS scores, although the mean differences between the groups were small. Completers also had statistically significantly better baseline scores for Role-Physical problems, Bodily Pain, Vitality, Social Functioning, and General Mental Health. Significantly greater improvement was observed in the completer group for QLS total scores and all subscales, and MCS and PCS scores and all SF-36 subscales at all postbaseline measurements, except for PCS scores at week 8 and Physical Functioning at week 24 (Table 3 and Figures 2A, 3A, and 3C). If corrections for multiple comparisons[13] are applied to these analyses, completers and noncompleters still differ significantly on all postbaseline QLS domain scores and on QLS total score. Among SF-36–related comparisons, 4 additional assessments are not statistically significant after adjusting for multiple comparisons: PCS at week 24, Physical Functioning at week 8, Role-Physical at week 24, and Role-Emotional at week 24. Effect sizes ranged from 0.11, a very small effect, to 0.66, a moderate effect.

Comparisons between the OR, LE, and MI group scores on QLS, MCS, and PCS change scores are provided in Figures 2B, 3B, and 3D. The LE group generally showed less improvement in functional outcomes than the OR and MI groups.

Table 3. Mean Scores on Functional Outcome Measures Over Time, Comparing Patients Who Did and Did Not Complete 24 Weeks of Treatment[a]

	Baseline		Week 8			Week 16			Week 24		
Assessment	Completers	Noncompleters	Completers	Noncompleters	ES[b]	Completers	Noncompleters	ES[b]	Completers	Noncompleters	ES
Quality of Life Scale	N = 761[c]	N = 866[c]	N = 761[c]	N = 857[c]		N = 761[c]	N = 321[c]		N = 761[c]	N = 106[c]	
Total score	49.8 ± 21.3	49.8 ± 20.8	58.7 ± 22.4	53.4 ± 21.9***	0.39	62.3 ± 23.2	53.9 ± 22.6***	0.59	63.3 ± 23.9	54.1 ± 23.8***	0.62
Interpersonal relations	17.6 ± 9.1	17.9 ± 9.3	20.9 ± 9.5	19.4 ± 9.5***	0.29	22.5 ± 10.0	19.2 ± 9.7***	0.51	22.7 ± 10.1	19.4 ± 10.3***	0.54
Instrumental role	7.3 ± 6.1	6.7 ± 5.8	8.5 ± 6.4	7.5 ± 6.1***	0.19	9.2 ± 6.5	7.6 ± 6.5***	0.27	9.7 ± 6.8	7.4 ± 6.5**	0.31
Intrapsychic foundations	19.1 ± 7.6	19.0 ± 7.3	22.5 ± 7.6	20.0 ± 7.6***	0.46	23.6 ± 7.8	20.4 ± 7.4***	0.64	23.8 ± 8.0	20.4 ± 8.2***	0.66
Common objects/activities	5.9 ± 2.8	6.1 ± 2.7	6.7 ± 2.6	6.6 ± 2.7***	0.22	7.1 ± 2.6	6.6 ± 2.7***	0.42	7.2 ± 2.5	6.7 ± 2.6***	0.47
SF-36	N = 427[c]	N = 515[c]	N = 427[c]	N = 509[c]		N = 427[c]	N = 177[c]		N = 427[c]	N = 56[c]	
Mental component summary	36.6 ± 12.7	34.8 ± 12.6*	43.4 ± 10.9	37.7 ± 12.3***	0.51	44.3 ± 11.6	40.6 ± 13.3***	0.39	45.0 ± 11.1	39.8 ± 14.2***	0.53
Physical component summary	47.9 ± 9.7	46.2 ± 9.8**	48.4 ± 9.0	46.4 ± 9.5	0.11	48.9 ± 8.9	46.2 ± 9.6**	0.29	48.6 ± 9.4	46.3 ± 8.9[d]	0.34
Physical functioning	72.4 ± 26.2	69.5 ± 26.5	76.3 ± 25.4	71.2 ± 26.4[d]	0.14	77.7 ± 24.8	72.3 ± 25.1*	0.22	77.4 ± 25.7	73.2 ± 25.3	0.14
Role limitations, physical	55.1 ± 41.3	48.9 ± 40.8*	62.7 ± 38.9	49.8 ± 40.2***	0.27	64.7 ± 40.0	52.0 ± 41.6***	0.34	66.0 ± 39.1	53.4 ± 44.2*[d]	0.34
Bodily pain	73.5 ± 26.7	67.1 ± 28.6***	78.2 ± 24.0	70.8 ± 26.7**	0.20	79.2 ± 24.6	70.5 ± 27.0***	0.33	78.8 ± 25.1	72.6 ± 29.4**	0.41
General health	58.0 ± 21.2	55.2 ± 23.0	64.2 ± 20.6	57.5 ± 22.7***	0.29	65.4 ± 20.3	58.5 ± 23.4***	0.39	64.7 ± 21.0	52.1 ± 22.7***	0.61
Vitality	49.4 ± 22.2	45.7 ± 23.3*	57.8 ± 21.0	50.1 ± 23.4***	0.31	58.7 ± 21.6	53.6 ± 24.1*	0.22	59.5 ± 21.6	51.5 ± 22.7**	0.46
Social functioning	54.3 ± 28.9	49.7 ± 30.4*	66.2 ± 25.6	55.2 ± 28.5***	0.38	69.3 ± 25.7	63.1 ± 29.1**	0.27	70.5 ± 25.2	54.9 ± 32.3***	0.59
Role limitations, emotional	42.1 ± 41.6	38.0 ± 40.4	59.5 ± 40.3	43.7 ± 41.7***	0.37	61.0 ± 41.0	48.1 ± 44.7***	0.38	64.5 ± 40.5	54.4 ± 44.8*[d]	0.31
General mental health	53.3 ± 21.7	49.3 ± 22.8**	64.9 ± 19.6	55.0 ± 23.0***	0.46	66.2 ± 20.5	59.2 ± 23.1***	0.37	66.5 ± 20.4	58.1 ± 24.7**	0.44

[a]MMRM analysis; mean ± standard deviation; Completers = all patients who completed 24 to 28 weeks of antipsychotic treatment; Noncompleters = all patients who did not complete 24 to 28 weeks of antipsychotic treatment.
[b]In order to accommodate baseline differences between completers and noncompleters, effect sizes were calculated based on the difference in mean change between these 2 patient groups.
[c]Total patients who had a visit at this time point. Actual Ns for each assessment may vary as a small number of patients had missing data.
[d]Indicates adjusted p ≥ .05, no statistically significant difference between completers and noncompleters after adjusting for multiple comparisons. (All other comparisons in this table with statistically significant unadjusted p values also have statistically significant adjusted p values).
*For comparison of completers vs. noncompleters at this visit, unadjusted p < .050.
**For comparison of completers vs. noncompleters at this visit, unadjusted p < .010.
***For comparison of completers vs. noncompleters at this visit, unadjusted p < .001.
Abbreviations: ES = effect size, MMRM = mixed-model repeated measures, SF-36 = Medical Outcomes Study Short Form 36.

Functional Outcomes and Symptom Improvement

Pearson correlations between improvement in PANSS total score and improvements in QLS total and MCS scores in the pooled patient sample were 0.526 and 0.313, respectively. Correlations between improvement in PANSS positive symptoms and improvements in QLS total and MCS scores were 0.434 and 0.241, respectively. Correlations between improvement in PANSS negative symptoms and improvements in QLS total and MCS scores were 0.498 and 0.249, respectively. Correlations between improvement in PANSS general psychopathology score and improvements in QLS total and MCS were 0.501 and 0.341, respectively. All these correlations were statistically significant ($p < .001$).

DISCUSSION

Among patients with schizophrenia-spectrum disorders enrolled in four 6-month clinical trials, longer time to all-cause discontinuation was significantly correlated with improvements in functional outcomes as reported by patients or rated by clinicians. Correlations above 0.25 were associated with the patient-rated SF-36 mental component score, and the social functioning, general mental health, and role limitations caused by emotional problems subscales, as well as in the clinician-rated QLS total score, including the Interpersonal, Intrapsychic, and Common Objects and Activities measures. Though the effect sizes of these correlations are small, they are similar in size to effects, believed to be clinically meaningful, reported in a comparative meta-analytic study of antipsychotics for the treatment of schizophrenia.[14] Other correlations, such as those between longer time to all-cause discontinuation and improvement in PCS, Physical Functioning, General Health, and Bodily Pain, though statistically significant, may be too small to be clinically meaningful. Moreover, Physical Health status, as assessed by the PCS, showed minimal improvement during treatment. This outcome is consistent with previous findings[12] and may be partly due to baseline scores in the study sample that were comparable to those found in the general population.

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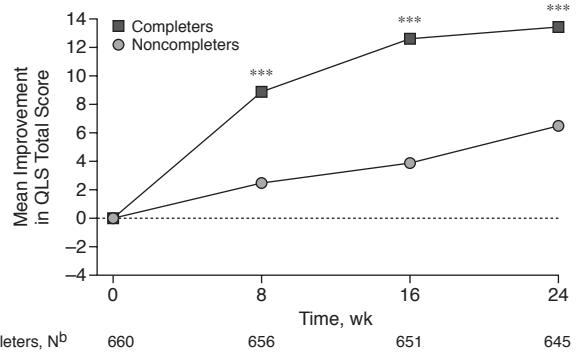
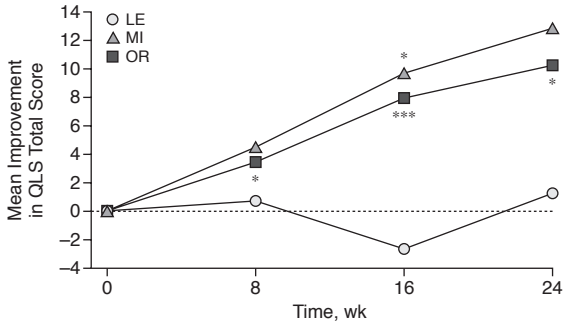
Figure 2. Mean Improvement in QLS Scores for Each Patient Group

A. Mean Improvement in Quality of Life Scale (QLS) Total Score Over Time, Completers and Noncompleters[a]



Completers, N[b]	660	656	651	645
Noncompleters, N	750	560	217	65

B. Mean Improvement in Quality of Life Scale (QLS) Total Score Over Time, Noncompleter Subgroups[c]

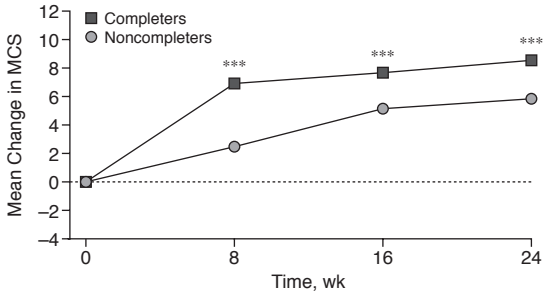


Noncompleters, N				
LE	265	214	88	30
MI	93	73	25	10
OR	392	273	104	25

[a]Improvement experienced by completers was statistically significantly greater than that experienced by the noncompleters group at all time points (***p < .001).
[b]Sample size for the completers group varied due to missing assessments.
[c]Asterisks indicate p value for comparison with LE group: ***p < .001; *p < .05.
Abbreviations: LE = lack of efficacy, MI = medication intolerability, OR = other reasons.

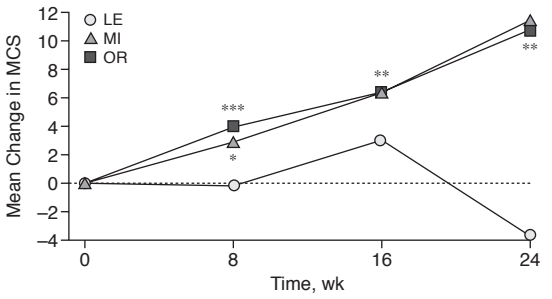
Figure 3. Mean Change in SF-36 Mental Component Summary Score (MCS) and Physical Component Summary Score (PCS) for Each Patient Group

A. Mean Change in Mental Component Score (MCS) Over Time, Completers and Noncompleters[a]



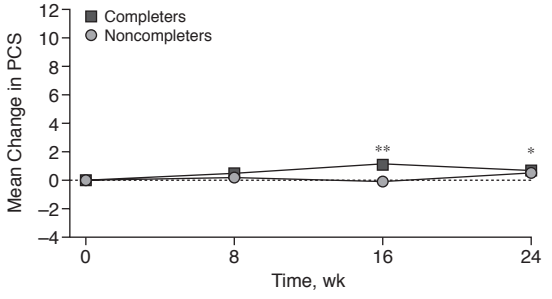
Completers, N	418	415	417	411
Noncompleters, N	498	372	136	37

B. Mean Change in Mental Component Score (MCS) Over Time, Noncompleter Subgroups[b]

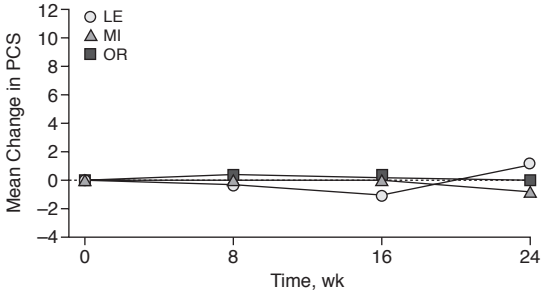


Noncompleters, N				
LE	164	130	45	13
MI	69	58	16	6
OR	265	184	75	18

C. Mean Change in Physical Component Score (PCS) Over Time, Completers and Noncompleters[c,d]



D. Mean Change in Physical Component Score (PCS) Over Time, Noncompleter Subgroups[e]



[a]Improvement in MCS experienced by completers was statistically significantly greater than that experienced by the noncompleters group at all time points (***p < .001). After adjustment for multiple comparisons, p values were still significant at all time points (for all, adjusted p < .005).
[b]Asterisks indicate p value for comparison with LE group: ***p < .001; **p < .01, *p < .05.
[c]Improvement in PCS experienced by completers was statistically significantly greater than that experienced by the noncompleters group at weeks 16 and 24 (**p < .01; *p < .05).
[d]After adjustment for multiple comparisons, PCS was only significantly different between completers and noncompleters at week 16 (adjusted p = .006).
[e]There were no significant differences among the 3 noncompleter subgroups for PCS at any time point.
Abbreviations: LE = lack of efficacy, MI = medication intolerability, OR = other reasons.

Additional evidence that longer duration of antipsychotic treatment leads to meaningful benefits in functional outcomes is provided by the findings from the repeated measures analysis; patients who completed these clinical trials had significantly greater improvements on functional outcome measures than those who discontinued the studies early. For almost all of the comparisons, the differences between the patients who discontinued early and the patients who completed the study were statistically significant. However, given the size of the samples involved here, measures of effect size may be a better way to evaluate whether a between-group difference is large enough to be clinically important. The smallest effect sizes found in this comparison (< 0.2) were for the SF-36 PCS at week 8, SF-36 Physical Functioning at weeks 8 and 24, and the QLS Instrumental Role at week 8. These data suggest that longer time on treatment is minimally related to these physical and occupational outcomes within the first 6 months. Assessment over a longer period of time will be needed to determine whether the effect on occupational-related outcomes remains minimal or merely lags behind other functional and clinical outcomes.

The largest effect sizes (> 0.5) were seen for SF-36 MCS at weeks 8 and 24, SF-36 General Health at week 24, SF-36 Social Functioning at week 24, QLS Intrapsychic Foundations at weeks 16 and 24, QLS Interpersonal Relations at weeks 16 and 24, and QLS total score at weeks 16 and 24. Thus, there are moderate relationships between longer time to treatment discontinuation and improvements in engagement, social functioning, general health, and quality of life.

For patients who discontinued early, outcome differences appeared to vary depending on reason for discontinuation, with patients discontinuing because of lack of efficacy displaying minimal or no functional improvement, unlike patients discontinuing for medication intolerability or other reasons. It is important to note that the substantial attrition in these groups over the duration of these studies makes the interpretation of these findings difficult. However, in a previous study using this pooled dataset, Liu-Seifert and colleagues noted adequate improvement in PANSS scores in patients in the MI group and suggested that "adverse events do not interfere with symptom response but do prevent an otherwise effective treatment."[15(p5)] In other words, the patients who discontinue trial participation due to adverse events (as well as those who discontinue due to "other reasons") appear to demonstrate some improvement in psychopathology. Interventions that ameliorate adverse events associated with antipsychotic treatment and thus delay treatment discontinuation may allow further clinical and functional benefits to occur with ongoing therapy, at least within the first 6 months after initiation of treatment. Patients discontinuing due to lack of efficacy, on the other hand, demonstrated the least improvement on functional outcomes and did not appear to benefit from greater time on therapy. This finding has clear implications for patient clinical management, as the potential benefit of sustained antipsychotic therapy on functional outcomes is unlikely to materialize in patients exhibiting poor treatment response in the early phase of treatment. Consistent with previous research on the importance of early symptom response,[16–18] our analyses indicate that early changes in clinical management may be warranted in patients with poor early-treatment response.

Another important finding is that improvement in at least some functional domains may relate to improvement in clinical symptoms.[15,18] Previous reports in the literature have suggested associations between functional outcomes and positive, negative, depressive, or anxiety symptoms or cognitive functioning.[3,4,19–22] In this dataset, the link between clinical and functional outcomes is suggested by the greatest degree of improvement in both clinical (reported previously by Liu-Seifert, et al.[15]) and functional outcomes occurring during the first 8 weeks of treatment, the associations (with correlations in the 0.3–0.5 range) between PANSS total scores and functional outcome scale scores, and the lack of improvement in these scores in patients who discontinued due to lack of efficacy. Measures of community functioning, such as activities of daily living and social competence, may display a different improvement time course than improvements in the QLS and SF-36. Future studies of the temporal relationship between functional and symptomatic improvements may benefit from longer treatment duration and more frequent and broader assessments earlier in the course of treatment to further address these questions.

Overall, the results of these analyses are both encouraging and sobering—they are encouraging because improvements in some functional outcomes occur early and may continue to accrue for at least 6 months after therapy initiation; they are sobering because the relationship between longer treatment duration and improvements in functional outcomes appears to be modest. Nonetheless, a large naturalistic observational study has found robust associations between greater adherence to antipsychotic treatment regimens and various functional outcomes over a 3-year period, indicating that extended treatment duration may offer meaningful functional benefits in usual care settings.[23]

To the best of our knowledge, this is the first report of the relationship between longer time to all-cause treatment discontinuation and functional outcomes in the treatment of schizophrenia. The CATIE trial, which used time to all-cause treatment discontinuation as its primary objective, also collected functional measures, including the QLS and the SF-12 (a modified version of the SF-36).[24] As we write this report, the CATIE functional outcome results have yet to be published. However, initial

CATIE results have shown an association between time to all-cause treatment discontinuation and improvements in symptoms of schizophrenia,[1] suggesting that an association between time to all-cause treatment discontinuation and change in functional outcomes should be expected in the CATIE trial as well. Those reports will be an important addition to understanding the relationship between duration of therapy and clinical and functional outcomes.

Limitations

Several limitations should be considered in interpreting these results. First, these are secondary analyses of a pooled dataset in which more than half of patients discontinued trial participation prior to the 6-month end point. Therefore, these results should be viewed as exploratory pending replication of findings in a separate sample. It should be noted, as well, that in analyses of large population samples, such as those presented here, some results that are statistically significant may still be too small to be clinically meaningful; thus, effect sizes should also be taken into account when interpreting these results. Second, data were pooled from 4 different double-blind, randomized clinical trials, which varied in design, patient population, and assessment schedule, and the SF-36 was used in only 2 of the 4 studies; these differences may have incorporated biases into the analyses reported here. Third, patients enrolling in clinical trials may have motivations and beliefs regarding treatment that differ from those of other patients, and their reasons for early discontinuation from treatment may not necessarily mirror those of the general schizophrenia patient population. Fourth, exclusion and inclusion criteria for the 4 trials may have resulted in a study population less subject to comorbid general medical conditions than typically seen in a clinical setting. However, the 1627 patients included in these analyses reflect a diverse patient population in terms of symptom type and severity as well as levels of functioning, including patients with prominent negative symptoms (study 2), with prominent depressive symptoms (study 4), and with overall symptom exacerbations (studies 1 and 3), suggesting that our findings may be applicable to the general schizophrenia patient population. Finally, no functional measurements were performed prior to the 8-week time point; thus, early effects in the course of treatment could not be assessed.

CONCLUSIONS

In this large pooled sample of patients with schizophrenia-spectrum disorders, longer time to all-cause treatment discontinuation was found to be associated with significantly greater improvements in various functional outcomes, as assessed from both patient and clinician perspectives. Functional outcomes improved early in the course of therapy, and in concert with improvement in clinical symptoms. Findings illustrate the importance of longer effective antipsychotic treatment duration as a means for achieving better functional outcomes in the treatment of patients with schizophrenia.

Drug names: olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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