

Published in final edited form as:

*Int J Geriatr Psychiatry*. 2010 February ; 25(2): 183–190. doi:10.1002/gps.2318.

## Treatment of subsyndromal depressive symptoms in middle-aged and older adults with schizophrenia: effect on functioning

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### Abstract

**Background**—Subsyndromal symptoms of depression (SSD) in patients with schizophrenia are common and clinically important. SSRI's appear to be helpful in alleviating depressive symptoms in patients with schizophrenia who have SSD in patients age 40 and greater. It is not known whether SSRI's help improve functioning in this population. We hypothesized that treating this population with the SSRI citalopram would lead to improvements in social, mental and physical functioning as well as improvements in medication management and quality of life.

**Methods**—Participants were 198 adults  $\geq$  40 years old with schizophrenia or schizoaffective disorder who met study criteria for subsyndromal depression based on having two or more of the nine DSM-IV symptoms of a major depressive episode, for at least 2 weeks, and a Hamilton depression rating scale (HAM-D 17) score  $\geq$  8. Patients were randomly assigned to flexible-dose treatment with citalopram or placebo augmentation of their current antipsychotic medication(s) which was stable for 1 month. Subjects were assessed with the following functional scales at baseline and at the end of the 12-week trial: (1) social skills performance assessment (SSPA), (2) medication management ability assessment (MMAA), (3) mental and physical components of the medical outcomes study SF-12 Scale, and (4) the Heinrichs quality of life scale (QOLS). Analysis of covariance (ANCOVA) was used to compare differences between endpoint scores of the citalopram and placebo treated groups, controlling for site and baseline scores. ANCOVAs were also used to compare differences in the above endpoint scores in responders *versus* non-responders (responders = those with  $>$  50% reduction in depressive symptoms).

**Results**—Overall, the citalopram group had significantly higher SSPA, mental functioning SF-12, and quality of life scale (QOLS) scores compared to the placebo group. There was no effect on MMAA or physical functioning SF-12 scores. Responders had significantly better endpoint mental SF-12 and QOLS scores compared to non-responders. Response to citalopram in

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Parts of this paper were presented in a symposium at the 2008 American Psychiatric Association Annual Meeting.

#### Conflict of interest

Sidney Zisook, MD has received research support from Aspect Medical and PamLab and speaker's honoraria from Forest Pharmaceuticals, Inc and GlaxoSmithKline. John Kasckow, MD, PhD has received grant support as well as honoraria for speaking and consultation from Forest, Astra Zeneca, Bristol Meyers Squibb, Pfizer, Johnson, and Johnson, Solvay and Eli Lilly.

terms of depressive symptoms mediated the effect of citalopram on mental functioning, but not on the quality of life.

**Conclusions**—Citalopram augmentation of antipsychotic treatment in middle aged and older patients with schizophrenia and subsyndromal depression appears to improve social and mental health functioning as well as quality of life. Thus it is important for clinicians to monitor these aspects of functioning when treating this population of patients with schizophrenia with SSRI agents.

### Keywords

schizophrenia; citalopram; depression; functioning; social skills

## Introduction

Depressive symptoms and syndromes occur commonly and worsen the already considerable disease burden among people with chronic schizophrenia. Clinically significant depressive symptoms which meet criteria for major depressive episodes are common in patients with schizophrenia; clinically meaningful subsyndromal depressive symptoms have been reported to be more prevalent than full depressive episodes in this patient population (Kasckow and Zisook, 2008). Over 60% of middle aged and older adults with schizophrenia experience depressive symptoms, and rates of depressive symptoms in this population have been noted to be significantly higher compared to age and gender matched controls (Jin *et al.*, 2001; Diwan *et al.*, 2007). Indeed, they are so prevalent that some investigators have argued that depression is a core component of schizophrenia, similar to positive, negative, and disorganized symptom clusters (Bartels and Drake, 1988; Leiff, 1990).

A prospective study assessing depression during the longitudinal course of schizophrenia found that only 24% of subjects remained free of depressive symptoms. While slightly over one-third (36%) met criteria for major depressive episodes, even more (40%) experienced only two to four symptoms of depression (Kay and Sevy, 1990). Zisook *et al.* (1999) have previously reported more than two-thirds of middle aged and older patients with schizophrenia who do not have major depressive episodes have at least mild depressive symptoms, and over 30% of patients experienced depressed mood, feelings of guilt, and/or feelings of hopelessness.

Among middle aged and older people with schizophrenia, depressive symptoms have been associated with disability, diminished quality of life, increased health service utilization, greater positive symptom severity, demoralization, worsened physical health, poor motivation, and suicidal ideation (Cohen, 1995; Jin *et al.*, 2001; Siris, 2001; Zisook *et al.*, 1999; Diwan *et al.*, 2007; Mittal *et al.*, 2006). Kasckow *et al.* (2008) also demonstrated that worse negative symptoms in these middle aged and older subjects with schizophrenia and subsyndromal depressive symptoms are associated with worse social functioning and worse medication management (Kasckow *et al.*, 2008).

Zisook *et al.* (2009) recently reported that the SSRI citalopram improved depressive and negative symptoms as well as quality of life in middle aged and older patients with schizophrenia and subsyndromal depressive symptoms (SSD). It is not known whether functioning in areas such as social skills and medication management also improves with SSRI treatment. However, given the findings that worse negative symptoms are associated with worse medication management and worse social functioning (Kasckow *et al.*, 2008) in patients with schizophrenia and SSD and that citalopram improved negative symptoms (Zisook *et al.*, 2009), we hypothesized that citalopram may also help improve social functioning and medication management.

It also appears that SSRI treatment helps improve physical functioning in patients with depression. For instance, Taylor *et al.* (2001) reported that patients in primary care settings treated with SSRIs had a significant improvement in physical functioning as measured by the physical component of the SF-36 in addition to improvements in depressive symptoms. Given these recent research findings, we investigated whether SSRI treatment also helps improve overall functioning and quality of life. We thus hypothesized that citalopram treatment in middle aged and older patients with schizophrenia and SSD would lead to improvements in social functioning, medication management, mental health functioning, physical functioning, and quality of life. We also hypothesized that treatment response would be associated with better functional outcomes and quality of life.

## Methods

As described previously (Zisook *et al.*, 2009) participants were outpatients  $\geq 40$  years of age with schizophrenia or schizoaffective disorder from the San Diego VA/University of California, San Diego and Cincinnati VA/University of Cincinnati. They were participating in an NIMH trial examining SSRI augmentation of antipsychotic treatment in patients with schizophrenia and subsyndromal depression. Subjects had at least 2/9 items required for major depression and a baseline 17 item Hamilton depression score (HAMD; Hamilton, 1960)  $> 8$ . Exclusions were major depression or mania within 2 months, active substance abuse/dependence in the past month and dementia.

Participants were recruited from sites at the University of California, San Diego and the University of Cincinnati, at board-and-care facilities, the affiliated VA Health Care Centers and general outpatient settings. The study was performed in accordance with the principles of Helsinki and good clinical practice. Study approval was obtained from each site's institutional review board, and a written informed consent was obtained from participants or their legally authorized representatives prior to the initiation of study procedures.

### Study treatments

Patients were randomly assigned to treatment with citalopram (20mg/day) or placebo augmentation of their current antipsychotic medication as described by Zisook *et al.* (2009). After the first week, study dose could be reduced to 10 mg/day or increased, based on clinical response and/or side effects (minimum dose 10 mg/day, maximum dose 40 mg/day) at the blinded study physician's discretion.

### Assessments

Scales assessing depression included the 17-item Hamilton depression rating scale (Hamilton, 1960) and the Calgary Depression Rating Scale (CDRS; Addington *et al.*, 1992). From the original study reported by Zisook *et al.* (2009), the 17 item Hamilton depression rating scale and CDRS were the primary efficacy measures. Social functioning and medication management were assessed using the social skills performance assessment (SSPA; Patterson *et al.*, 2001) and the medication management ability assessment (MMAA; Patterson *et al.*, 2002) scales, respectively. In addition, we measured mental and physical functioning using the self-report mental and physical subscales of the medical outcome studies—short form -12 (SF-12; Ware *et al.*, 1996), and quality of life using the quality of life scale (QOLS; Heinrichs *et al.*, 1984). Study visits assessing these outcomes were performed at baseline and at week 12 (end of double-blind treatment.)

The SSPA tests interpersonal relatedness and was designed for older patients with schizophrenia. The MMAA tests abilities needed to organize a medication regimen similar to what an older outpatient with schizophrenia would be expected to manage. The physical

component of the SF-12 is a self-rated scale which asks the subject to rate their overall health, comment as to whether their physical health limits their activities or work, and comment as to whether they experience any pain which interfered with their normal work. The SF-12 mental component measures whether subjects had trouble with work or social activities as a result of emotional problems; also it assesses whether the subject felt calm, “downhearted/blue” or energetic. Both the physical and mental component scores of the SF-12 range from 0 to 100 and are adjusted so that the mean US population score is normalized to a score of 50 with a standard deviation of 10. The QOLS assesses quality of life by focusing on the schizophrenia deficit syndrome (Heinrichs *et al.*, 1984). Inter-rater reliability between the two sites was reported previously (Kasckow *et al.*, 2001).

### Statistical analysis

For summary statistics, means and standard deviations were computed for continuous variables, and counts and percentages for discrete variables. Two-way ANOVAs were used to compare continuous baseline clinical and demographic characteristics and Cochran-Mantel-Haenszel tests were used to compare discrete characteristics across treatments, adjusting for site. The data was analyzed on a modified intent-to-treat basis. All analyses included participants who underwent randomized assignment, took at least one dose of the study medication, and completed at least one post-baseline visit. All statistical tests were two-tailed and the level of statistical significance was set at  $p < 0.05$ . The statistical package for social sciences (SPSS), version 15, was used.

Analysis of covariance (ANCOVA) was used to compare functional assessments between the two treatment groups, as well as between the responder and non-responder groups. The model was formulated with outcome at the study end point as the dependent variable. Treatment group, site, baseline severity, and treatment group by site interaction were included as independent variables. A treatment-by-site interaction term was added to the primary and key secondary analysis models to explore the possibility of treatment-by-site interactions. Since both mental SF-12 and quality of life were significantly improved in both the citalopram and responder groups (see below), we conducted a mediator analysis (Baron and Kenny, 1986) to assess whether response of depressive symptoms to citalopram mediated the relationship between citalopram treatment and both the mental component of the SF-12 scale and also the QOLS scores.

## Results

### Overall and group baseline characteristics

Table 1 depicts the demographic and clinical characteristics of 198 participants. There were no significant differences observed between the two groups with regards to age, age of onset of 1st psychotic episode, education level, race, gender, diagnoses (schizophrenia vs. schizoaffective disorder), classes of medications, (typical antipsychotics, atypical antipsychotics or both typical and atypical antipsychotics) or in the number of individuals taking anticholinergic medications. None of the site-by-group interactions was significant. There were differences in marital status such that the citalopram group had a greater proportion of participants who were widowed ( $\chi^2 = 15.17$ ;  $df = 3$ ,  $p = 0.002$ ).

### Functional outcomes for citalopram and placebo augmentation

Table 2 summarizes differences between the two groups on the SSPA, MMAA, Physical/Mental component SF-12 scores, and QOLS. For each outcome variable assessed, there was a different number of subjects in each subgroup due to missing data. For each of these subgroups, we compared demographic variables (age, age of onset, education level, race, marital status [single, married/cohabitating, separated/divorced, widowed]) and diagnostic

status (schizophrenia vs. schizoaffective disorder]). For each subgroup, there were no differences noted between any of the demographic or diagnostic variables. There were significant improvements in endpoint SSPA scores following citalopram treatment. Based on ANCOVA which adjusted for both site and baseline SSPA score, there was a significant drug effect ( $F = 5.6$ ;  $df = 1,134$ ;  $p = 0.019$ ). For MMAA scores, there were no significant differences with treatment ( $F = 0.115$ ;  $df = 1,131$ ;  $p = 0.735$ ) nor were there any improvements in physical SF-12 scores with treatment ( $F = 0.411$ ;  $df = 1,149$ ;  $P = 0.552$ ). However, there were significant differences in SF-12 mental component scores ( $F = 13.2$ ;  $df = 1,149$ ;  $p = .001$ ) and in QOLS scores ( $F = 4$ ;  $df = 1,135$ ,  $p = 0.046$ ) with citalopram treatment.

### Treatment response and functional outcomes and mediator analysis

Treatment response was defined as at least a 50% improvement in endpoint CDRS scores relative to baseline. Table 3 shows the relationship between treatment response and functional outcomes. Responders to citalopram or placebo had significantly higher endpoint mental SF-12 ( $F = 33.22$ ;  $df = 1,149$ ;  $p < 0.001$ ) and quality of life ( $F = 5.18$ ;  $df = 1,134$ ;  $p = 0.024$ ) scores compared to non-responders. There were no significant differences between adjusted endpoint means on physical SF-12 ( $F = 6.21$ ;  $df = 1,150$ ;  $p = 0.791$ ), SSPA ( $F = 0.23$ ;  $df = 1,134$ ;  $p = 0.632$ ), and MMAA scores ( $F = 0.153$ ;  $df = 1,131$ ;  $p = 0.697$ ).

In order for response to treatment to be considered a mediator of citalopram's relationship with functional improvement, three conditions must hold (Baron and Kenny, 1986):

- Citalopram must affect depression as measured by a 50% improvement in CDRS.
- Citalopram must affect the functional measure.
- In a regression with both Citalopram, and 50% improvement in CDRS predicting functional outcome, improvement must affect the functional measure, and the magnitude of the relationship found in condition 1 must be reduced.

In investigating condition 1, it was found that citalopram had a response rate of 50%, while placebo had a response rate of 30.9%. A Mantel–haenszel test was conducted controlling for site, which revealed a significant treatment effect ( $\chi^2 = 6.57$ ;  $df = 1$ ;  $p = .011$ ). Table 2 establishes citalopram's effect on functioning (condition 2) for the SF-12 mental component, and quality of life.

To determine whether condition 3 held for SF-12 mental, and quality of life, an additional term was added to the models used in condition 2 representing CDRS response. Treatment response was found to affect the SF-12 mental component ( $F = 27.3$ ,  $df = 1,147$ ;  $p < .001$ ), and the effect of citalopram (i.e., its beta coefficient) was reduced from 5.28 to 4.11, a 22% reduction indicating that at least some of its effect can be explained by reduction in depression. Because conditions 1–3 hold, the effect of citalopram on SF-12 mental functioning scores, can, at least in part, be explained by depression response. Quality of life as measured on the QOLS did not meet the three criteria for being a mediator because “treatment response based on > 50% decrease in HAMD scores” was no longer significantly associated with QOLS in the presence of treatment group ( $p = 0.069$ ).

## Discussion

In this study of 198 middle aged and older adults with schizophrenia or schizoaffective disorder, we confirmed our hypotheses that citalopram treatment would lead to improvements in social functioning, mental health related functioning, and quality of life. However, neither physical functioning nor medication management ability improved. We also hypothesized that treatment response would be associated with better functional



outcomes. Participants who experienced response to either citalopram or placebo (>50% reduction in symptoms) had significantly better mental health functioning and quality of life than non-responders, while physical functioning was not different between the groups. Furthermore, social functioning and medication management were not significantly different at endpoint between responders and non-responders. In addition, response to citalopram was found to mediate the relationship between citalopram and mental health functioning, but it did not mediate the effect of citalopram on quality of life.

Double blind placebo controlled trials examining SSRI augmentation of antipsychotics have been published (Kasckow and Zisook, 2008). Most of these trials were limited by small sample sizes. The results on depressive symptoms, when provided, were mixed. None of the double blind trials looked specifically at age differences and there were very few subjects over the age of 65. In addition, none of these trials examined functional outcome measures to the best of our knowledge.

Our finding that mental health functioning improved with citalopram treatment and that response mediated this improvement was consistent with previous findings by Jin *et al.* (2001) who demonstrated that patients with schizophrenia and worse depression had lower scores on the medical outcomes scale SF-36. It is not known why we did not find an improvement in physical functioning with SSRI treatment given that Zisook *et al.* (2006) reported that patients with schizophrenia and subsyndromal depression exhibit numerous somatic symptoms such as hypochondriasis. Perhaps, in patients with schizophrenia and SSD, it is the lower frequency of depressive symptoms in this patient population (i.e., subsyndromal symptoms) which explain why a signal could not be detected with SSRI treatment.

The SSPA and MMAA are performance-based scales developed specifically for an older population of patients with schizophrenia (Patterson *et al.*, 2001, 2002). The use of these measures circumvent the need for informants and avoid potential response bias. Furthermore, they are proximal in nature, measure capacity and at the time of testing do not require that the skills are actually deployed in the real-world environment. Obtaining improvements in these areas of functioning in this population of patients is important. For instance, previous studies indicated that achieving a remission in patients with schizophrenia is associated with improvements in social functioning (Helldin *et al.*, 2007).

The findings that worse negative symptoms are associated with worse medication management and social functioning (Kasckow *et al.*, 2008) in patients with schizophrenia and SSD and that citalopram treatment improved negative symptoms (Zisook *et al.*, 2009), led us to hypothesize that citalopram would help improve medication management and social functioning. While we confirmed our hypothesis that social functioning improved significantly with citalopram, medication management ability did not.

A patient's ability to manage their medication is an important component of optimizing treatment response in patients with schizophrenia (Bies *et al.*, 2002). Lack of adherence to medication regimens in patients with schizophrenia is common and represents one of the most significant risk factors for relapse (Lenroot *et al.*, 2003). The inability of citalopram to improve medication management in this trial confirms that new treatment approaches are needed to improve this outcome.

There was a variety of both typical and atypical antipsychotic medications which participants took. There were no differences between the two treatment groups in terms of numbers of typical or atypical antipsychotics and even combinations of these antipsychotics. A recent review by Furtado and Srihari (2008) explored whether atypical antipsychotics are different from typical antipsychotics in terms of their effects on depressive symptoms in

patients with schizophrenia. The authors stated that there are too few data at this time to make any definitive conclusions. Clearly more research is needed to address this issue.

The results of this report must be interpreted within the context of several of the study's limitations. First, the SSD group was heterogeneous, comprising individuals with and without past histories of major depression, schizoaffective disorder, and schizophrenia. In addition our sample possibly included subjects with residual or prodromal symptoms of depression, and even some with prominent negative symptoms or movement abnormalities. In addition, there was variability in the adequacy and type of treatment of the underlying disorder. It is also important to note that while the difference between treatment groups on the SSPA was statistically significant, it is not clear how clinically significant this is given it was relatively small. Thus, from a practical standpoint, the use of SSRI's in this population may not be as important for improving social functioning as it is towards improving depressive symptoms. Finally, there were more widowed participants in the citalopram group *versus* the placebo group (12.5% *vs.* 1.1%). Although the absolute numbers of participants are not marked, we have recently demonstrated that married persons with schizophrenia rated their quality of life higher than those not married (Nyer *et al.*, in press). It is possible that this may have influenced the outcomes.

Despite these limitations, we believe this study is important as it is the first of which we are aware to study an SSRI's association with functional outcomes among middle aged and older adults with schizophrenia and SSDs. We were also able to assess the relationship between treatment response and these outcomes, and found that the effect of citalopram on mental health functioning was mediated by a significant reduction in severity of depressive symptoms. This suggests that in order to achieve improvement in mental health functioning in this group of patients with schizophrenia it is also likely important that clinicians focus on achieving a depressive symptom response (>50% reduction in symptoms).

It would be of interest in future studies to examine whether psychosocial augmentation strategies are able to further improve patients' functional outcomes. Granholm *et al.* (2005) recently demonstrated in a similar patient population that patients receiving cognitive behavioral and social skills training performed social functioning activities significantly better relative to subjects receiving "treatment as usual." Future studies could build on our findings by determining whether the addition of this or other psychosocial interventions improves the SSRI effect.

## Acknowledgments

This work was supported by RO1 MH 063931 citalopram augmentation of older patients with schizophrenia (S. Zisook, PI), and the department of veterans affairs. J. Kasckow was supported by RO 1MH6398, the VISN 4 MIRECC, and a VISN 4 CPPF award. The authors wish to thank the Cincinnati VAMC and University of Cincinnati for their support as well as Forest Pharmaceuticals, Inc for providing study drug.

The contents do not represent the views of the Department of Veterans Affairs of the United States Government.

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**Table 1**

Baseline demographic and clinical characteristics (N= 198)

Characteristic	Treatment				# F	p-value
	Citalopram (N = 104)		Placebo (N=94)			
	Mean	SD	Mean	SD		
Age (years)	53.14	7.68	51.70	6.33	2.032 (1,192)	0.156
Age at onset of first psychotic episode (years)	28.44	10.67	27.30	10.29	.484 (1,167)	0.488
Education level (years)	12.09	2.14	11.78	2.31	.938 (1,194)	0.334
Ham-17	13.59	4.39	13.38	4.08	.057(1,194)	0.812
CDRS	6.46	3.17	7.02	3.07	1957 (1,194)	0.163
	N	%	N	%	* $\chi^2$	P
Female gender	23	22.1	20	21.3	0.0149 (1)	0.903
Race					3.029 (3)	0.387
White	54	51.9	54	57.4		
Black	40	38.5	26	27.7		
Hispanic	5	4.8	9	5.3		
Other	5	4.8	5	9.6		
Marital status					15.169 (3)	0.002
Never (single)	32	30.8	48	51.1		
Married or cohabitating	18	17.3	10	10.6		
Divorced or separated	41	39.4	35	37.2		
Widowed	13	12.5	1	1.1		
Age < 18 years at onset of first psychotic episode	9	10.1	12	14.6	0.409 (1)	0.522
Diagnosed schizoaffective	48	46.2	33	35.1	1.521 (1)	0.218
Medications					0.036 (2)	0.982
Typical Antipsychotics	10	10.2	9	9.9		
Atypical Antipsychotics	69	70.4	65	71.4		
Both Typical and Atypical Antipsychotics	19	19.4	17	18.7		
Anticholinergics	30	30.6	26	28.6	0.035 (1)	0.853

#F values with degrees of freedom in parentheses derived from Analysis of Covariance adjusting for baseline values, site and site by treatment interactions.

\* Mantel-Haenszel  $\chi^2$  with degrees of freedom in parentheses.

**Table 2**

Changes in functional scales and quality of life with citalopram versus placebo treatment

Variable	N (Placebo, Citalopram)	Placebo		Citalopram		End-point Difference: ANCOVA		
		Baseline mean (SD)	Endpoint mean (SD)	Baseline mean (SD)	Endpoint mean (SD)	# F	df	p-value
SF-12 Mental	(73, 81)	41.8(11.1)	43.5 (9.8)	39.8 (10.7)	47.9(10.2)	13.2	1,149	0.001
SF-12 Physical	(73, 81)	43.6 (10.6)	43.8 (10.8)	43.7 (10.2)	42.9(10.3)	0.4	1,149	0.552
* SSFA	(65, 71)	31.1 (7.4)	30.4 (7.1)	33.1 (5.7)	33.7 (5.7)	5.6	1,134	0.019
* MMAA	(63, 73)	10.0 (7.6)	8.4 (7.1)	7.8 (5.9)	7.6 (6.6)	0.1	1,131	0.735
Quality of Life	(70, 70)	56.8(22.1)	57.5 (22.7)	58.8(21.5)	64.7 (24.5)	4	1,135	0.046

Values represent means with standard deviations in parentheses.

# F values with degrees of freedom (df) derived from analysis of covariance adjusting for baseline values, site and site by treatment interactions.

\* SSFA = social skills performance assessments; MMAA = total number of medication errors on the medication management ability assessment

**Table 3**

Relationship between treatment response and functional outcomes

Functional outcome scale*	Responders		Non-responders		** F	** df	p-value
	Baseline	Endpoint	Baseline	Endpoint			
* Physical SF-12	45.7 (±9.9)	44.3 (±10.0)	41.6 (±10.5)	42.2 (±10.9)	6.21	1,150	0.791
* Mental SF-12	42.3 (±11.1)	50.4 (±8.7)	39.1 (±10.7)	41.3 (±9.7)	33.22	1,149	0.000
* SSPA	32.6 (±6.6)	32.6 (±6.4)	31.7 (±6.7)	31.7 (±6.8)	0.23	1,134	0.632
* MMAA total errors	9.4 (±7.8)	8.4 (±7.7)	8.1 (±5.5)	7.5 (±5.8)	0.15	1,131	0.697
* QOLS	58.0 (±22.8)	64.5 (±23.2)	57.7 (±20.9)	57.8 (±24.2)	5.18	1,134	0.024

Values represent means with standard deviation in parentheses.

\* Physical SF-12 = physical component of the medical outcomes study short form SF-12; Mental SF-12 = mental component of the SF-12; SSPA = social skills performance assessments; MMAA total errors = total number of medication errors on the medication management ability assessments; QOLS = Quality of Life Scale.

\*\* F values with degrees of freedom (df) derived from analysis of covariance. Outcome at the study end point was the dependent variable. Treatment group, site, baseline severity, and treatment group by site interaction were included as independent variables.