Assertive Community Treatment as Part of Integrated Care Versus Standard Care: A 12-Month Trial in Patients With First- and Multiple-Episode Schizophrenia Spectrum Disorders Treated With Quetiapine Immediate Release (ACCESS Trial)

Martin Lambert, MD; Thomas Bock, PhD; Daniel Schöttle, MD; Dietmar Golks, PhD; Klara Meister, PhD; Liz Rietschel, PhD; Alexandra Bussopulos, MD; Marietta Frieling; Michael Schödlbauer, PhD; Marc Burlon, MD; Christian G. Huber, MD; Gunda Ohm, MD; Manoshi Pakrasi, MD; Michael Sadre Chirazi-Stark, MD; Dieter Naber, MD; and Benno G. Schimmelmann, MD

Objective: The ACCESS trial examined the 12-month effectiveness of continuous therapeutic assertive community treatment (ACT) as part of integrated care compared to standard care in a catchment area comparison design in patients with schizophrenia spectrum disorders treated with quetiapine immediate release.

Method: Two catchment areas in Hamburg, Germany, with similar population size and health care structures were assigned to offer 12-month ACT as part of integrated care (n = 64) or standard care (n = 56) to 120 patients with first- or multiple-episode schizophrenia spectrum disorders (Structured Clinical Interview for *DSM-IV* Axis I Disorders criteria); multiple-episode patients were restricted to those with a history of relapse due to medication nonadherence. The primary outcome was time to service disengagement. Secondary outcomes comprised medication nonadherence, improvements of symptoms, functioning, quality of life, satisfaction with care from patients' and relatives' perspectives, and service use data. The study was conducted from April 2005 to December 2008.

Results: 17 of 120 patients (14.2%) disengaged with service, 4 patients (6.3%) in the ACT and 13 patients (23.2%) in the standard care group. The mean Kaplan-Meier estimated time in service was 50.7 weeks in the ACT group (95% CI, 49.1–52.0) and 44.1 weeks in the standard care group (95% CI, 40.1–48.1). This difference was statistically significant ($P = .0035$). Mixed models repeated measures indicated larger improvements for ACT compared to standard care regarding symptoms ($P < .01$), illness severity ($P < .001$), global functioning ($P < .05$), quality of life ($P < .05$), and client satisfaction as perceived by patients and family (both $P < .05$). Logistic regression analyses revealed that ACT was associated with a higher likelihood of being employed/occupied ($P = .001$), of living independently ($P = .007$), and of being adherent with medication ($P < .001$) and a lower likelihood of persistent substance misuse ($P = .027$).

Conclusions: Compared to standard care, intensive therapeutic ACT as part of integrated care could improve 1-year outcome. Future studies need to address in which settings these improvements can be sustained.

Trial Registration: clinicaltrials.gov Identifier: NCT01081418

J Clin Psychiatry 2010;71(10):1313–1323

Submitted: *February 9, 2009; accepted June 9, 2009.*
Online ahead of print: *March 23, 2010 (doi:10.4088/JCP.09m05113yel).*
Corresponding author: *Martin Lambert, MD, Psychosis Centre, Department for Psychiatry and Psychotherapy, Centre for Psychosocial Medicine, University Medical Center Hamburg-Eppendorf, Martinistr 52, 20246 Hamburg, Germany (lambert@uke.uni-hamburg.de).*

An effective intervention for patients with severe mental illness is assertive community treatment (ACT).[1–4] Key features mediating the effectiveness of ACT are the multidisciplinary team approach with a small client/staff ratio, high-frequent treatment contacts with 60%–70% of interventions provided in the community setting, a "no drop-out policy," and the 24 hours a day availability including crises intervention.[5,6]

Since the initial demonstration study,[1] ACT has proven to be a robust model of community-based treatment for people with severe mental illness.[2] A Cochrane review,[2] based on 17 randomized trials, mostly conducted in the United States, concluded that ACT is a clinically effective approach to managing the care of people with severe mental illness in the community. ACT can substantially reduce the costs of hospital care while improving outcome and patient satisfaction.[2] However, recent trials in the United Kingdom[7–9] and other countries[3,10] did not fully confirm these positive results of earlier US trials. Explanations for these conflicting results include that standard care, being the control condition, has significantly improved in recent years and that the general reduction of psychiatric hospital beds contributed to the reduction of admission days within ACT studies.[3,11]

The ACCESS trial was initiated for the following reasons. First, most previous ACT studies solely focused on patients with severe mental illness comprising various psychiatric disorders. This approach, however, may reduce the fidelity and specialization of the ACT team and thereby the quality of care.[6] As such, there is a need for ACT studies focusing specifically on patients with psychotic disorders where treatment is offered by psychosis experts.[3] Second, there are only a few studies in which ACT was embedded into a specialized integrated care program and in which the ACT therapist offered frequent psychotherapeutic contacts. This approach

© Copyright 2010 Physicians Postgraduate Press, Inc.

Table 1. Characteristics of Assertive Community Treatment (ACT) as Part of Integrated Care Versus Standard Care

Characteristic	ACT as Part of Integrated Care	Standard Care
Catchment area	Department of Psychiatry and Psychotherapy of the UKE	Department of Psychiatry and Psychotherapy of the AWR
Population size of the catchment area	300,000	300,000
Health care facilities	Inpatient unit, day clinics, outpatient center,[a] 8 private psychiatrists,[b] ACT	Inpatient unit, day clinics, outpatient center,[a] 8 private psychiatrists[b]
Maximum full-time equivalent caseload	15	30–50
Staff fidelity and skills	Consultant psychiatrist, psychiatrist, psychologist, psychiatric nurse, social worker	Consultant psychiatrist, psychiatrist, psychologist, psychiatric nurse, social worker
Staff skills	Training in cognitive-behavioral therapy, dynamic psychotherapy, family therapy, psychoeducation	Training in cognitive-behavioral therapy, dynamic psychotherapy, family therapy, psychoeducation
Work style	Shared caseload. Patients are discussed in weekly team meetings and on a daily basis if needed	Individual caseload
Location	60%–80% in own environment, 20%–40% office based (outpatient center, inpatient if needed)	100% office based (outpatient center or private psychiatrists)
Availability	Extended hours (0800 to 1800 Monday–Friday) and 24-hour crisis telephone and 24-hour service of the UKE	Office hours only (0900 to 1700 Monday–Friday) and 24-hour service of the AWR
Contact with clients	Assertive engagement: multiple attempts, flexible and various approaches, "no dropout" policy	Offer appointment at office, discharge if unable to make or maintain contact
Main interventions	Psychotherapy, pharmacotherapy	Pharmacotherapy, supportive therapy

[a]Outpatient center with psychiatrists, psychologists, and social worker, group program available.
[b]Private psychiatrists offered one-to-one counseling for less severe patients.
Abbreviations: AWR = Asklepios Westhospital Rissen, UKE = University Medical Center Hamburg-Eppendorf.

may be of great importance as other studies without such integrated care found no (major) differences between ACT and standard care[3,9] nor sustained improvements after discontinuation.[12] Third, all previous ACT studies allowed the use of different antipsychotic agents without controlling for this important confounding factor.[2] Finally, the randomized controlled design of many ACT studies may hamper the inclusion of severely ill patients for which ACT was originally designed.[3,9]

AIMS OF THE STUDY

This study examined the 12-month effectiveness of therapeutic assertive community treatment (ACT) as part of integrated care compared to standard care in a catchment area comparison design in patients with schizophrenia spectrum disorders treated with quetiapine immediate release (IR). The primary outcome of the study was the time to service disengagement. Secondary outcomes comprised medication nonadherence, improvements of symptoms, functioning, quality of life, and satisfaction with care from patients' and relatives' perspectives.

METHOD

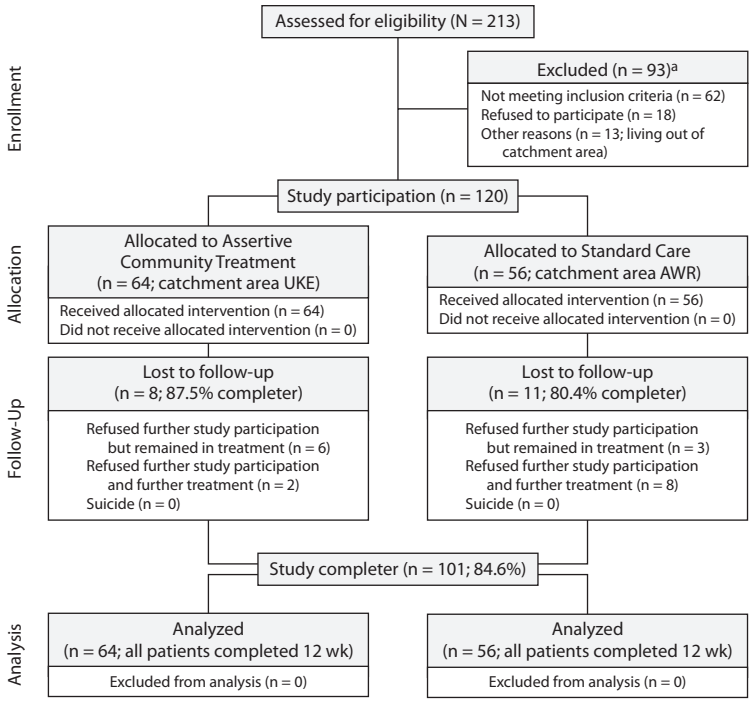
Context and Sample

The trial was carried out in 2 catchment areas in Hamburg, Germany (ie, University Medical Center Hamburg-Eppendorf [UKE] and Asklepios Westhospital Rissen [AWR]), with similar catchment area sizes of approximately 300,000 inhabitants and similar health care structure (Table 1). In the UKE catchment, ACT was implemented as part of integrated care. As such, ACT was offered to study participants within the UKE and not in the AWR area (ie, AWR = standard care). The study was conducted from April 2005 through December 2008.

Participants were recruited from January 2006 to November 2007 within the 2 catchment areas and included in the study if they met the following inclusion criteria: (1) aged 18–65 years; (2) met the diagnostic criteria for first- or multiple-episode schizophrenia spectrum disorders, ie, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, or psychotic disorder NOS[13] as assessed by the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I)[14]; and (3) newly initiated or on current treatment with quetiapine IR. *First-episode psychosis* was defined as experiencing symptoms of a psychotic illness that has not been treated for more than 6 months.[15] Multiple-episode patients had to meet the following additional inclusion criterion: at least one psychotic relapse with subsequent hospitalization caused by medication nonadherence within the last 24 months.[15] The selection of first-episode and previously nonadherent multiple-episode patients was chosen because they represent a key population with high risk of service disengagement, medication nonadherence, and incomplete remission.[16–18] This selection was chosen to mirror the severe mental illness definition of ACT within a group of patients with psychotic disorders. Exclusion criteria included (1) other psychotic disorders (eg, due to medical condition) and (2) mental retardation (IQ lower than 70 points). The local institutional review board approved the study (registration number: 2515).

Out of 213 patients screened, 138 patients fulfilled the inclusion criteria. One hundred twenty of those provided informed consent. Sixty-four patients were assigned to ACT (53.3%) and 56 to standard care (46.7%) due to catchment affiliation. See the CONSORT flowchart in Figure 1 for details regarding ascertainment and lost to follow-up.

Figure 1. CONSORT Flowchart of the Patients Through the Study



[a]Multiple exclusion reasons possible.
Abbreviations: AWR = Asklepios Westhospital Rissen, UKE = University Medical Center Hamburg-Eppendorf.

Treatment Groups

ACT as part of integrated care. Participants in the UKE intervention group received ACT, which was implemented as part of a specialized psychosis integrated care treatment program. On a structural level this program comprises a specialized psychosis inpatient unit, 2 day clinics (1 only for first-episode patients), a psychosis outpatient center with specialized treatment offers, an occupational therapy center, and a network of 8 private psychiatrists. Within this treatment program, each study participant was designated to a team consisting of 1 ACT therapist and 1 psychiatrist (from the ACT team or a private psychiatrist) who offered 12 months continuous treatment.

ACT was structured and implemented according to guidelines of the Assertive Community Treatment Association (ACTA [see Table 1]).[6] Team members were highly educated psychosis experts consisting of a consultant psychiatrist, a psychiatrist, 2 psychologists, and a nurse, all of whom received training in cognitive-behavioral therapy (CBT), dynamic psychotherapy, and/or family psychotherapy. The caseload ratio was 15 patients per ACT therapist. According to personal preferences and needs, patients were visited at home or at other places in the community, or seen at the therapist's office. During hospitalization, responsibility for the patient was transferred to the psychiatrist on the ward, but the ACT therapist participated in each important visit (eg, family meetings) and maintained contact with the patient at least weekly. Office hours were Monday to Friday, from 8 AM to 6 PM. Each participant received 2 (emergency) telephone numbers: the number of his ACT therapist for all contacts within office hours and a 24 hours crisis number for all emergencies outside office hours. The primary ACT therapist was responsible for maintaining contact, coordinating treatment, and offering intensive need-adapted psychotherapy. The allocation of a patient to a specific ACT therapist was among others driven by her/his individual clinical problems and the need for a specific psychotherapy. Additionally, study participants could use all treatment options within the integrated care program such as psychoeducation groups, social skills training, family groups, motivational addiction therapy, and meta-cognitive training (see: http://www.uke.uni-hamburg.de/kliniken/psychiatrie/index_ENG_40441.php).

Fidelity of the model was assessed with the Dartmouth Assertive Community Treatment Scale (DACTS).[5] The DACTS has 28 criteria and 3 subscales ([1] human resources: structure and composition, [2] organizational boundaries, and [3] nature of services).[5] The maximal score on the DACTS is 5, representing a perfect implementation of all ACT principles.

Standard care. Comparably structured as within the OPUS trial,[12] participants in the AWR control group received standard care (see Table 1). Comparable to the UKE area, standard care comprised a treatment network consisting of open and closed inpatient wards, day clinics, an outpatient center, and 8 private psychiatrists. Each patient was treated by a private psychiatrist or by a psychiatrist in the outpatient center. Most of these psychiatrists have completed a 5-year hospital-based training and most of them long-term training in either CBT or dynamic psychotherapy. Home visits were possible, but office visits were the general rule. Patients were allowed to use all treatment offers in the outpatient center. Outside office hours, patients could refer themselves to the psychiatric hospital. Psychosocial treatments as supportive therapy, psychoeducation, psychotherapy, and family intervention were provided infrequently and in a less intensive and unsystematic way, and only in the minority of cases. This standard of care definition is in accordance with other studies.[9,12] The mean number of treatment contacts in the SC group was 15.6 (SD = 6.3) within 12 months.

Antipsychotics and Psychotropic Medications

All participants were treated with quetiapine IR at study entry, regardless of whether newly initiated or already treated. Allowed concomitant medications included all other indicated psychotropic medications (eg, other antipsychotics,

© Copyright 2010 Physicians Postgraduate Press, Inc.

benzodiazepines, mood stabilizer, antidepressants). Switching of quetiapine IR to other antipsychotics or antipsychotic augmentation therapy was allowed and did *not* cause study termination. Dose of antipsychotic augmentation therapy was assessed in chlorpromazine equivalents according to Woods.[19]

Assessments and Measures

Assessments were carried out at baseline and at 4, 12, 26, 38, and 52 weeks' follow-ups. At baseline, the following variables were assessed: (1) diagnosis of the psychotic disorder and comorbid Axis I psychiatric disorder(s) confirmed by the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I).[14] In case of clinical evidence for a comorbid Axis II disorder, a SCID-II interview for *DSM-IV* personality disorder was applied[14]; (2) demographic characteristics including age, gender, marital status, and years of education; (3) illness characteristics including premorbid functioning with the Global Assessment of Functioning Scale (GAF),[13] duration of untreated prodrome, psychosis, and illness with the Duration of Untreated Psychosis Scale,[20] traumatic events, family history and suicide attempts in the past with the respective assessment parts of the Early Psychosis File Questionnaire.[21–23] Medication nonadherence was assessed according to Robinson et al.[24] Accordingly, *nonadherence* was defined as failure to take medication for 1 week or longer. This definition was chosen because stopping medication for a week clearly indicates a problem with acceptance of pharmacologic treatment (as opposed of just forgetting a dose).

At baseline and all follow-up time points the following structured assessments were applied:

1. Psychopathology with the Positive and Negative Syndrome Scale (PANSS).[25]
2. Severity of illness with the Clinical Global Impressions-Severity of Illness scale (CGI-S).[26]
3. Level of functioning with the Global Assessment of Functioning Scale (GAF),[13] the Modified Vocational Status Index (MVSI),[27] and the Modified Location Code Index (MLCI).[27] The MVSI and MLCI are scales rated from 1 to 7, with lower scores indicating a better vocational status and a better ability to live independently. The criterion "employed/occupied" comprised paid or unpaid full- or part-time employment, being an active student in university, or full- or part-time volunteer; the criterion "independent living" comprised living alone, with partner, or with peers.
4. Quality of life with the 18-item Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-18).[28] The Q-LES-Q-18 is a self-report instrument scored on a 5-point scale ("not at all or never" to "frequently or all the time"), with higher scores indicating better enjoyment and satisfaction with specific life domains. The global quality of life index is the mean score of all 18 items; a score of 4.1 points characterizes a quality of life comparable with healthy controls.
5. Subjective well-being with the Subjective Well-being under Neuroleptic Treatment Scale (SWN-K).[29] The SWN-K is a self-rating Likert scale with 6 response categories ("absent" to "very much") and covers 20 statements (10 positive and 10 negative) with a minimum total score of 20 and a maximum total score of 120 points; higher scores indicate better well-being.
6. Satisfaction with antipsychotic medication with the Satisfaction with Antipsychotic Medication scale (SWAM).[30] The SWAM is a 33-item questionnaire; items are rated on a 5-point Likert scale from "strongly disagree" to "strongly agree." The total score ranges from 33 to 165 with higher scores reflecting a higher level of satisfaction.
7. Level of service engagement with the Service Engagement Scale (SES).[31] The SES is a 14-item scale were a client's engagement is rated on a 4-point Likert scale from 0 ("not at all or rarely") to 3 ("most of the time"). Higher scores reflected clients' greater levels of difficulty engaging with services.
8. Patients' and relatives' satisfaction with care with the Client Satisfaction Questionnaire (patient version [CSQ-8 P] and relative version [CSQ-8 R]).[32] The CSQ-8 is a 8-item instrument that is scored from 1 to 4. The total score ranges from 8 to 32; the mean satisfaction score is computed with a minimum score of 1 and a maximum of 4.

Outcome of a comorbid substance use disorder (SUD) was rated according to Lambert et al.[33] Accordingly, the course of SUD was categorized into (1) remitted SUD (stopped substance use completely during the study period), (2) reduced SUD (≥ 50% reduction in quantity and frequency), and (3) persistent SUD (no change or less than 50% decrease in quantity and frequency, or increase).

Assessment of Service Use Data

Within each treatment arm, service use data were assessed from the respective official patient hospital database, which covers inpatient admissions, day clinic admissions, and treatment contacts in the outpatient center. Additionally, treatment contacts were collected from each participating private psychiatrist. The service use data were available for all patients and directly retrieved from the above-mentioned sources.

Interrater Reliability

All investigators were trained in conducting SCID interviews and conducting PANSS, CGI-S, and GAF. The intraclass correlation coefficient was 0.88 for the PANSS total score, 0.91 for the CGI-S score, and 0.89 for the GAF score.

Outcome Measures

The primary outcome of the study was the time to service disengagement. This primary aim was chosen because the assertive approach of ACT is to prevent service disengagement[3] and because service disengagement is a major predictor for relapse and thereby a poor long-term outcome.[16,17] Service disengagement was present if a patient repeatedly refused further treatment despite need and several attempts of reengagement (phone calls of patient and family in both treatment arms and potentially home visits in the ACT group). Secondary outcomes comprised medication nonadherence, improvements of symptoms, functioning, quality of life, and satisfaction with care from patients' and relatives' perspectives.

Statistical Analysis

Preliminary analyses of the distribution for continuous predictor variables showed that duration of untreated psychosis was significantly positively skewed, which normalized with logarithmic transformation. Baseline differences between treatment arms (ACT and standard care) were assessed using *t* test for independent samples when the dependent variable was continuous and normally distributed or Mann-Whitney *U* test for continuous and nonnormally distributed variables; categorical variables were assessed with χ^2 tests.

To assess differences between ACT and standard care regarding service disengagement (primary outcome), preliminary Cox regression analyses[34] were specified in order to check whether baseline differences between the treatment arms affected service disengagement. Assumption of proportionality of the hazard function over time was checked prior to each Cox regression analysis.[35] When predictors were nonproportional over time, a second analysis that included a predictor-by-time interaction term were specified. The Cox model estimates regression weights for the main independent variable (treatment arm) and potential baseline covariates to test whether they improve the fit of the hazard function to the observed data in a manner analogous to multiple regression; hazard ratios derived from these coefficients are analogous to odds ratios in logistic regression. Only baseline covariates whose hazard ratios had *P* values less than or equal to .1 were selected for multivariate analyses to derive a parsimonious model that weighted the predictors appropriately. Note that refusal of further study participation did not necessarily mean service disengagement (see CONSORT flowchart, Figure 1), accordingly analyses assessed time to disengagement with treatment and not with study participation over the 12-month period.

For statistical analysis of treatment arm differences regarding continuous secondary outcome measures over time, mixed models repeated-measures (MMRM) analyses were specified controlling for relevant baseline differences between the treatment arms.[36,37] This likelihood-based repeated-measures approach, which is similar to a repeated-measure analysis of variance (ANOVA), has proven to be superior to, eg, last-observation-carried-forward ANOVA in simulation scenarios patterned after acute-phase neuropsychiatric clinical trials[35,36] and is actively employed in schizophrenia research.[38] Linear models like MMRM report 2 main results: a "main effect" and an "interaction with time effect" of a given independent variable (eg, treatment arm) on the dependent variable (eg, PANSS total score over time). In the latter example, the main effect describes the mean difference between treatment arms across all postbaseline time points regarding PANSS total score. The interaction with time effect detects whether or not the difference in PANSS total scores between treatment arms varies with time. Dividing the differences of adjusted mean scores by the standard deviation of residuals produced the effect sizes (*d*) reported. Treatment arm differences regarding categorical secondary outcome measures (such as vocation status at discharge or lost to follow-up) were assessed by means of sequential logistic regression models. Covariates, ie, variables with baseline differences between treatment groups as well as time in treatment were entered in the first step, and the variable of interest, ie, treatment arm, in the second step. All analyses were carried out using SPSS (version 14.0; SPSS Inc., Chicago, Illinois).

RESULTS

Sixty-four patients (53.3%) were assigned to ACT and 56 (46.7%) to standard care due to catchment affiliation. Fifty-six patients (87.5%) completed the study in the ACT group and 45 (80.4%) in the standard care group (completer in total: n = 101, 84.6%; see CONSORT flowchart in Figure 1).

Patients in both treatment arms had similar demographic and clinical characteristics at baseline (Table 2). The only exceptions were that patients in the ACT group were significantly younger ($P = .002$), had a higher rate of first or second-degree family history of any psychiatric disorder ($P = .048$), displayed a higher prevalence of comorbid substance use disorders at baseline ($P = .019$), and were significantly more often employed/occupied ($P = .011$). Overall, mean test scores showed that patients displayed a high severity of illness (PANSS total: 95.7; CGI-S: 5.1), a low functioning level (GAF: 44.8), and low to medium quality of life (Q-LES-Q-18: 3.0). The CSQ-8 scores at baseline point to a "fair" overall satisfaction with care by patients and relatives (CSQ-8 P: 2.0; CSQ-8 R: 1.9), with significantly higher scores in the ACT group ($P < .001$). The representativeness of the study sample was satisfactory when the baseline characteristics were compared to those of a consecutively admitted unselected sample of 95 patients, who met the same diagnostic inclusion criteria. Yet, the latter sample had a higher proportion of older multiple-episode patients (87.2%, mean age = 41.3 years, SD = 12.8) but comparable illness severity (CGI-S = 5.5, SD = 1.0; BPRS total score = 71.9, SD = 20.9) and global functioning (GAF = 40.7, SD = 13.9). With regard to number and duration of inpatient as well as day treatment prior to the study period, no statistically significant differences were detected.

Treatment details are displayed in Table 3. Patients were treated with a mean quetiapine IR dose of 582.8 mg per day (SD = 293.5); no statistically significant between-group

© Copyright 2010 Physicians Postgraduate Press, Inc.

Table 2. Baseline Variables of the Comparison Groups of Assertive Community Treatment (ACT) and Standard Care

Variable	ACT (n = 64)	Standard Care (n = 56)	*P* Value (ACT vs standard care)
Demographic details			
Age, mean (SD), y	31.4 (9.9)	37.6 (11.7)	.002
Male sex, n (%)	36 (56.3)	32 (57.1)	NS
Single partnership, n (%)	49 (76.6)	43 (76.8)	NS
Education, median (quartiles), years in school[a]	10.0 (10–13)	10.0 (9–12)	.031
Illness details			
Diagnostic distribution, n (%)			NS
Schizophrenia	34 (53.1)	32 (57.1)	
Schizoaffective disorder	14 (21.9)	9 (16.1)	
Schizophreniform disorder	8 (12.5)	9 (16.1)	
Delusional disorder	4 (6.3)	3 (5.4)	
Psychotic disorder NOS	4 (6.3)	3 (5.4)	
First-episode psychosis, n (%)	28 (43.8)	21 (37.5)	NS
Comorbid psychiatric disorder at entry, n (%)			
Comorbid disorder (without SUD)	23 (35.9)	21 (37.5)	NS
Substance use disorder	33 (51.6)	17 (30.4)	.019
Premorbid GAF score, mean (SD)	77.4 (10.1)	76.1 (7.6)	NS
Suicide attempts in the past, n (%)	21 (32.8)	15 (26.8)	NS
No. of suicide attempts in the past, median (quartiles)[a]	2 (1–2)	1 (1–2)	NS
Family history of any psychiatric disorder, n (%)[b]	39 (60.9)	24 (42.9)	.048
Family history of psychotic disorder, n (%)[b]	16 (25.0)	11 (19.6)	NS
Traumatic events in the past, n (%)	55 (85.9)	40 (71.4)	.051
Duration of untreated illness, median (quartiles), wk[c,a]	167.4 (64.4–265.3)	182.5 (79.5–341.1)	NS
Duration of untreated prodrome, median (quartiles), wk[c,a]	112.8 (31.5–212.0)	153.2 (52.1–217.3)	NS
Duration of untreated psychosis, median (quartiles), wk[c,a]	21.9 (8.3–65.3)	27.6 (8.7–52.1)	NS
Medication nonadherence			
Nonadherence with last medication, n (%)[d]	45 (70.3)	38 (67.9)	NS
Baseline scores on assessment scales[c]			
PANSS score, mean (SD)			
Total	97.0 (20.7)	94.3 (18.1)	NS
Positive	23.1 (7.5)	21.3 (4.8)	NS
Negative	25.2 (6.7)	24.0 (4.7)	NS
General	48.7 (9.2)	49.0 (10.6)	NS
CGI-S score, mean (SD)	5.2 (1.0)	5.0 (0.8)	NS
GAF score, mean (SD)	45.0 (12.0)	44.5 (11.7)	NS
Employment/occupation, n (%)	22 (34.4)	8 (14.3)	.011
Independent living, n (%)	41 (64.1)	30 (53.6)	NS
Q-LES-Q-18 score, mean (SD)	3.1 (0.2)	3.0 (0.2)	.067
SWN-K score , mean (SD)	76.5 (16.5)	73.4 (15.6)	NS
SWAM score, mean (SD)	84.1 (12.6)	79.6 (15.4)	.082
SES score, mean (SD)	15.9 (9.2)	14.5 (9.1)	NS
CSQ-8 P score, mean (SD)	2.2 (0.4)	1.8 (0.5)	< .001
CSQ-8 R score, mean (SD)	2.2 (0.4)	1.6 (0.5)	< .001

[a]Mann-Whitney *U* test for nonnormal distributed data was used.
[b]First- and second-degree relatives.
[c]Duration of untreated psychosis, prodrome, and illness were log transformed for statistical tests.
[d]*Nonadherence* was defined as failure to take medication for 1 week or longer.
Abbreviations: CGI-S = Global Clinical Impressions-Severity of Illness scale, CSQ-8 P = Client Satisfaction Questionnaire-8 (patient version), CSQ-8 R = Client Satisfaction Questionnaire-8 (relative version), GAF = Global Assessment of Functioning scale, NOS = not otherwise specified, NS = not significant, PANSS = Positive and Negative Syndrome Scale, Q-LES-Q-18 = 18-item Quality of Life Enjoyment and Satisfaction Questionnaire, SES = Service Engagement Scale, SUD = substance use disorder, SWAM = Satisfaction with Antipsychotic Medication scale, SWN-K = Subjective Well-being under Neuroleptic Treatment Scale.

differences were found. Of those who received quetiapine IR monotherapy throughout the complete study period, 65.6% were in the ACT group and 55.4% were in the standard care group. After a mean duration of 10.7 weeks (SD = 13.5) of quetiapine IR monotherapy, antipsychotic augmentation was initiated in 39.2% of the patients with a mean chlorpromazine equivalent dose of 276.5 mg/d (SD = 187.5) over a mean period of 30.8 weeks (SD = 20.0). Within the 12-month follow-up period, patients in the ACT group had a significantly higher mean number of treatment contacts (78.7, SD = 24.7) compared to the standard care group (15.6, SD = 6.3; $P < .001$). The DACTS was assessed twice within the study period (at 1- and 6-month follow-up). At 1 month, the mean subscale scores were 4.3 (human resources: structure and composition), 5 (organizational boundaries), and 4.3 (nature of services). At 6 months, the mean subscale scores were 4.3 (human resources: structure and composition), 5 (organizational boundaries), and 4.4 (nature of services). The total scores at 1- and 6-month follow-up were 4.5 points. This score indicates that the fidelity of the ACT model was good.

Service Disengagement

Preliminary Cox regression analyses revealed no relevant associations of the above-mentioned baseline differences between the treatment arms with service disengagement (all

Table 3. Treatment Variables of the Comparison Groups of Assertive Community Treatment (ACT) and Standard Care

Treatment Variable	ACT (n = 64)	Standard Care (n = 56)	*P* Value (ACT vs standard care)
Treatment with medication			
Quetiapine IR, mean (SD), mg/d	576.1 (298.4)	590.4 (290.2)	NS
Patients taking quetiapine IR monotherapy throughout the study, n (%)	42 (65.6)	31 (55.4)	NS
Switching of quetiapine IR to other antipsychotic medication, n (%)	1 (1.6)	3 (5.4)	NS
Duration of quetiapine IR treatment before switching, mean (SD), wk	7 (NA)[a]	23.7 (18.2)	NA[a]
Patients with antipsychotic augmentation, n (%)	22 (34.4)	25 (44.6)	NS
Duration of quetiapine IR monotherapy before augmentation, mean (SD), wk	9.5 (11.5)	11.8 (15.2)	NS
Duration of augmentation therapy, mean (SD), wk	36.7 (14.8)	25.8 (22.6)	.056
Chlorpromazine equivalents of antipsychotic augmentation, mean (SD), mg/d	278.0 (244.1)	275.2 (123.3)	NS
Concurrent treatment with other medication, n (%)	25 (39.1)	15 (26.8)	NS
Mood stabilizer[b]	8 (12.5)	6 (10.7)	NS
Antidepressants[c]	20 (31.3)	12 (21.4)	NS
Service use data			
Service use data in the 2 years before study entry[d,e]			
No. of inpatient admissions, median (range)	2 (1–6)	1 (0–8)	NS
No. of day clinic admissions, median (range)	0 (0–7)	0 (0–3)	.088
No. of days in inpatient treatment, mean (SD)	63.3 (51.3)	51.2 (44.6)	NS
No. of days in day clinic treatment, mean (SD)	23.7 (47.2)	11.2 (30.2)	NS
Service use data during the 1-year study period			
No. of treatment contacts, mean (SD)	78.7 (24.7)	15.6 (6.3)	< .001
Any admission, n (%)	25 (39.1)	39 (69.6)	.001
Inpatient admissions, n (%)	23 (35.9)	31 (55.4)	.033
Day clinic admissions, n (%)	5 (7.8)	14 (25.0)	.010
No. of inpatient admissions, median (range)[e]	0 (0–3)	1 (0–5)	.022
No. of day clinic admissions, median (range)[e]	0 (0–2)	1 (0–2)	.012
No. of days inpatient treatment, mean (SD)[e]	11.3 (20.1)	28.2 (44.9)	.028
No. of days day clinic treatment, mean (SD)[e]	2.4 (10.9)	16.4 (33.7)	.007

[a]Not computable due to low patient numbers.
[b]Including lithium, sodium valproate, lamotrigine.
[c]Including serotonin reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, and noradrenergic and specific serotonergic antidepressants.
[d]Service use data before study entry apply only to multiple-episode patients (n = 36 in ACT and n = 35 in standard care).
[e]Mann-Whitney *U* test was used for comparison of treatment arms regarding dimensional nonnormally distributed variables.
Abbreviations: IR = immediate release, NA = not applicable, NS = not significant

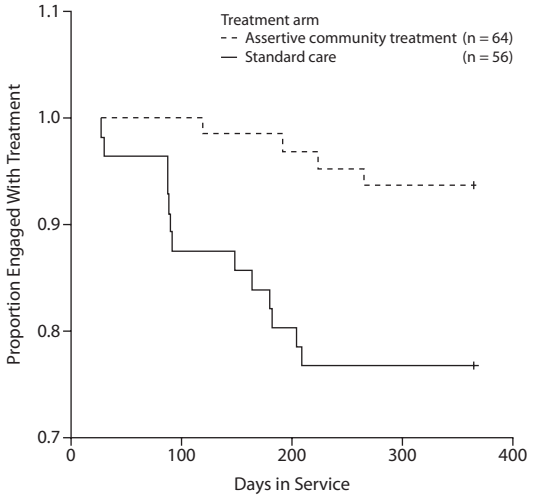
P values > .1). Accordingly, a simple Kaplan-Meier survival function with treatment arm as factor was specified and is displayed in Figure 2. Seventeen of 120 patients (14.2%) disengaged with service during the 12-month treatment period, 4 patients (6.3%) in the ACT group, and 13 patients (23.2%) in the standard care group. Over the 12-month period, the mean Kaplan-Meier estimated time in service was 50.7 weeks in the ACT group (95% CI, 49.1–52.0) and 44.1 weeks in the standard care group (95% CI, 40.1–48.1). Those, who disengaged with service did so after a median time of 29.6 weeks (range, 17.0–38.0) in ACT and 13.1 weeks (range, 4.0–29.9) in standard care. Accordingly, the patients disengaged with service more often and earlier in the standard care group compared to the ACT group. This effect was statistically significant (log rank test, $P = .0035$). The hazard ratio, derived from Cox regression, with treatment group as independent and time to service disengagement as the dependent variable, was 0.24 (95% CI, 0.08–0.73; $\chi^2 = 6.3$; $P = .012$). In other words, the risk to become service disengaged was about 4 times higher in the standard care group compared to the ACT group. Exploratory analyses on first-episode patients (n = 49) revealed that, based on the raw data, 10 first-episode patients (20.4%) disengaged with service, 7.1% (n = 2) in the ACT and 38.1% (n = 8) in the standard care group. As in the complete sample, patients receiving standard care compared to those receiving ACT disengaged earlier and more often (time in service, 39.4 weeks [95% CI, 32.0–46.7] in standard care vs 50.8 weeks [95% CI, 48.8–52.7] in ACT; hazard ratio = 0.15 [95% CI, 0.03–0.70; $\chi^2 = 5.8$; $P = .016$]). Note that these results reveal more pronounced treatment arm differences, yet the confidence intervals are slightly wider due to the small size of the first-episode patients subsample.

Secondary Outcomes

Table 4 displays the MMRM results for continuous secondary outcome measures controlled for baseline differences (adjusted means, confidence intervals, and statistics). Overall, larger improvements for ACT compared to standard care were observed regarding symptoms, illness severity, global functioning, quality of life, and client satisfaction as perceived by patients and family. The effect sizes indicate medium to large effects and were largest for improvements in illness severity, negative and general symptoms, global functioning, and relative's satisfaction with care. No significant differences were found regarding subjective well-being under and satisfaction with antipsychotic medication (SWN-K and SWAM-K scores). This was to be expected as patients in both treatment arms received the same main antipsychotic in comparable doses.

In the ACT group, 53.1% of the patients (n = 34) were employed/occupied at 12 months or lost to follow-up (vs 12.5%, n = 7, in the standard care group), 71.9% were living independently (vs 50% in the standard care group). Two

Figure 2. Time to Service Disengagement in Both Treatment Arms (Kaplan-Meier survival curve)



logistic regression analyses revealed that ACT was associated with a higher likelihood of being employed/occupied at 12 months or lost to follow-up (OR, 8.1; 95% CI, 2.4–28.0; $\chi^2 = 11.0$; $P = .001$) and of living independently (OR, 3.3; 95% CI, 1.4–8.0; $\chi^2 = 7.3$; $P = .007$). These analyses controlled for effects of age, first (vs multiple) episode status, substance use at baseline, time in treatment, and baseline vocation or location status, respectively. Over the treatment period, 39.1% of the patients in the ACT group stopped or reduced substance use compared to 12.5% in the standard care group (note that SUD was more prevalent at baseline in the ACT group). Treatment arm predicted persistent SUD (OR, 0.24; 95% CI, 0.07–0.85; $\chi^2 = 4.9$; $P = .027$) when SUD at baseline and time in treatment were controlled for. In other words, compared to patients in the ACT group, patients in the standard care group were 4.2 times more likely to keep using substances persistently at the same level or more. Similar results were found for nonadherence with medication (ACT, 23.4%; standard care, 60.7% [OR, 0.20; 95% CI, 0.09–0.44; $\chi^2 = 16.2$; $P < .001$]). In other words, standard care patients were about 5 times more likely to become nonadherent with medication throughout the study period. As displayed in Table 3, patients in ACT were significantly less often and shorter in need for inpatient and day treatment compared to standard care.

DISCUSSION

The present ACT study has some important methodological differences compared to previous trials: (1) the strict focus on patients with schizophrenia spectrum disorders instead of severe mental illness was chosen because it allows more specialized staff composition of the ACT team, which possibly increases the fidelity of the team (DACTS score of 4.5 points) and thereby the quality of care; (2) the present study population comprised first-episode and previously nonadherent multiple-episode patients with high levels of psychopathology at entry, while other studies tended to include patients with lower symptom scores (ie, baseline BPRS mean scores of 42[3] or 36.4[9]); (3) contrary to many previous ACT studies, as far as the information was published, the ACT staff in the present trial applied individual and family therapy explaining the high mean number of contacts in the intervention group (78.7 per year); and, finally, (4) the present trial used more homogeneous antipsychotic therapy.

Key Findings

One principal goal of ACT is to maintain contact with patients and thereby reduce the risk of service disengagement.[3] This is of great importance as service disengagement is related to a high risk of relapse and thereby poor long-term outcome.[13] In this study, ACT as part of integrated care had a significant advantage over standard care in reducing the rate of and time to service disengagement. This advantage of ACT is in line with other studies.[2,3,9] The positive effect of ACT on sustained service engagement may be explained by the lower and shared caseload, the higher contact frequency, the no drop-out policy, the 24-hour-a-day availability, and by the possibility to visit patients in the community, especially if at risk for disengagement.[2,3,9] Beyond the brokerage model, the psychotherapeutic orientation of the ACT team in this study may have strengthened the therapeutic alliance and thereby engagement with the service.

Overall, larger improvements for ACT compared to standard care were observed regarding symptoms, illness severity, global functioning, quality of life, and client satisfaction as perceived by patients and relatives. The effect sizes indicate medium to large effects and were largest for improvements in illness severity, negative and general symptoms, global functioning, and relatives' satisfaction with care. Patients in the ACT group were more likely to be employed/occupied at endpoint (OR, 8.1), to live independently (OR, 3.3), and to be adherent with medication (OR, 3.5) and were less likely to continue substance abuse (OR, 4.2). While previous studies on ACT have consistently found an advantage over standard care regarding service engagement and satisfaction with care in patients with severe mental illness[2,3,9] and in psychotic disorders,[39] the findings regarding improvement of symptoms, functioning, and quality of life are less consistent. The latter inconsistencies may be explained by the fact that models of ACT and standard care vary largely from study to study. The initial US studies compared ACT to relatively low level standard care and found symptomatic and functional advantages.[2,11] In the subsequent studies, mainly conducted in the United Kingdom, standard care models had improved and the symptomatic and functional advantages of ACT over standard care were not replicated.[3,8,9,11] More recent studies such as the OPUS trial applied models of ACT embedded in integrated care and targeted the model to specific diagnostic groups such as psychotic disorders and found the same advantages over standard care as in the present trial, particularly regarding negative symptoms, social functioning including employment/occupation and independent living, as well as substance use and adherence to medication.[12,39–41]

Table 4. Secondary Outcome Measures of Clients With Schizophrenia Spectrum Disorders Assigned to Assertive Community Treatment (ACT) or to Standard Care

	12-Month Endpoint		Mixed Models Repeated Measurements			
Measure	ACT (n = 64), Mean (95% CI)	Standard Care (n = 56), Mean (95% CI)	Time Effect, *F*	Treatment Effect, *F*	Time × Treatment Effect, *F*	Effect Size, *d*
PANSS score						
Total	59.6 (53.5–65.7)	72.6 (66.3–78.8)	6.5***	8.1**	1.6	0.68
Positive	12.4 (11.0–13.8)	14.4 (13.0–15.9)	5.2**	4.3*	1.4	0.46
Negative	15.4 (13.6–17.3)	19.9 (18.0–21.8)	6.6***	9.6**	1.4	0.77
General	31.8 (28.4–35.2)	38.0 (34.5–41.5)	5.0**	5.8*	1.6	0.56
CGI-S score	3.4 (3.1–3.7)	4.2 (3.9–4.5)	5.5**	13.9***	3.3*	0.87
GAF score	67.9 (63.8–72.0)	60.7 (56.5–65.0)	3.3*	6.9*	2.9*	0.57
Q-LES-Q-18 score	3.7 (3.6–3.9)	3.4 (3.3–3.6)	27.3***	5.0*	1.6	0.42
SWN-K score	81.3 (76.0–86.5)	81.9 (76.5–87.4)	2.1	0.7	0.6	0.19
SWAM score	78.2 (72.6–83.7)	85.9 (80.0–91.7)	1.5	1.1	1.8	0.23
SES score	11.3 (8.2–14.4)	14.3 (11.2–17.5)	1.0	2.5	1.1	0.36
CSQ-8 P score	2.1 (2.0–2.3)	1.9 (1.7–2.1)	1.0	5.4*	0.4	0.49
CSQ-8 R score	2.1 (1.9–2.3)	1.8 (1.6–2.0)	1.1	6.8*	0.5	0.58

*$P < .05$.
**$P < .01$.
***$P < .001$.
Abbreviations: CGI-S = Global Clinical Impressions-Severity of Illness scale, CSQ-8 P = Client Satisfaction Questionnaire-8 (patient version), CSQ-8 R = Client Satisfaction Questionnaire-8 (relative version), GAF = Global Assessment of Functioning scale, PANSS = Positive and Negative Syndrome Scale, Q-LES-Q-18 = 18-item Quality of Life Enjoyment and Satisfaction Questionnaire, SES = Service Engagement Scale, SWAM = Satisfaction with Antipsychotic Medication scale, SWN-K = Subjective Well-being under Neuroleptic Treatment Scale.

Limitations and Strengths

A nonrandomized design was chosen because severely ill patients and those at risk for service disengagement tend to refuse study participation if randomization to the potentially worse treatment arm is an integral part of the design. Since a broad range of baseline variables were assessed, potential differences between the 2 treatment arms were controlled. However, it cannot be excluded that important confounders were not assessed resulting in potential selection bias. Also, as in other controlled studies, the ACT team was most likely more motivated and knowledgeable in the treatment of patients with schizophrenia spectrum disorders. Accordingly, the advantage of ACT over standard care in this study must be interpreted with caution. Additionally, the magnitude of an ACT advantage over standard care depends on the sample selection. More severely ill and first-episode patients have a greater chance to improve compared to mildly to moderately ill patients with multiple episodes; therefore, generalizability to other schizophrenia spectrum samples is limited. Further, while data on the representativeness of the ACT sample for the general psychotic patients in the university hospital were available, we have no such information on the standard care sample compared to the general psychotic patients of the community hospital. The fact that raters were not blind to treatment arm may have introduced additional bias in favor of ACT, at least regarding the observer-rated scales. The latter bias, however, was not relevant for service disengagement, the primary outcome, and subjective measures such as subjective quality of life and well-being or satisfaction with care.

CONCLUSIONS

In line with the few similar recent studies, our results provide evidence that ACT embedded in integrative care program compared to standard care and applied to severely ill patients with first- and multiple-episode schizophrenia spectrum disorders may be related to better service engagement, the primary outcome of this study. Regarding secondary findings, ACT was associated with larger symptomatic and functional improvements, particularly in negative symptoms and employment/occupation rate as well as better quality of life and satisfaction with care. Of note, these advantages of ACT were achieved despite homogenous antipsychotic therapy, indicating that quality of psychosocial treatments matters.

However, it remains unclear how stable these improvements are and what happens after discontinuation of such an intensive treatment program. As such, there are several important questions that have to be addressed in future research: What are the key interventions within a specialized integrated care service including ACT that offer the greatest chance of long-lasting positive outcome? How long should intensive care be offered to maintain good clinical and social outcomes? How to make the transition as gentle as possible for patients who no longer need treatment? Who need a less intensive treatment program, and what are the key long-term interventions for patients who develop a chronic course of illness to remain stable on the best achievable psychosocial level?[12]

In our clinical experience, 3 key elements together, above the standard ACT characteristics, contributed to the superior effectiveness of this ACT intervention: continuity of care provided by the ACT team across all treatment settings (as opposed to just time-limited interventions), embedment of ACT in an integrated care program allowing need-adapted treatment (psychoeducation, supported employment, social skills training, and addiction therapy), and the quality of the ACT team (experts in the treatment of psychosis with psychotherapeutic training delivering individual psychotherapy, family interventions, and pharmacotherapy).

© Copyright 2010 Physicians Postgraduate Press, Inc.

Drug names: quetiapine (Seroquel), lithium (Eskalith, Lithobid, and others), lamotrigine (Lamictal and others).

Author affiliations: Psychosis Centre, Department of Psychiatry and Psychotherapy, University Centre for Psychosocial Medicine (Drs Lambert, Bock, Schöttle, Golks, Meister, Rietschel, Bussopulos, Schödlbauer, Burlon, Huber, and Naber and Ms Frieling) and Corporate Development and Strategic Planning (Dr Ohm), Medical Center Hamburg-Eppendorf; Department of Psychiatry and Psychotherapy, Asklepios Westklinikum Rissen, (Drs Pakrasi and Chirazi-Stark), Hamburg, Germany; and University Hospital of Child and Adolescent Psychiatry, University of Bern, Switzerland (Dr Schimmelmann).

Author contributions: The study was conducted as an investigator-initiated trial in collaboration of the Psychosis Centre of University Medical Center Hamburg-Eppendorf (Drs Lambert, Bock, Schimmelmann, and Naber) and the Department of Psychiatry of the Asklepius Westklinikum Hamburg (Drs Chirazi-Stark and Pakrasi). The first and senior authors (Drs Lambert and Schimmelmann) developed the research question, the study design, and conducted the study together with the ACCESS study group (Drs Bock, Schöttle, Golks, Meister, Rietschel, Bussopulos, Schödlbauer, Pakrasi, Chirazi-Stark, and Naber and Ms Frieling). Drs Lambert and Schimmelmann conducted all data analyses, interpreted the data, and wrote the manuscript. All authors have read and contributed to the final version of the manuscript.

Potential conflicts of interest: **Dr Lambert** has received grant/research support from AstraZeneca; has received honoraria from AstraZeneca, Eli Lilly, Janssen-Cilag, and Bristol-Myers Squibb; and has served on speakers boards for AstraZeneca and Eli Lilly. **Drs Bock, Schöttle**, **Schödlbauer**, and **Huber** have served on speakers boards for AstraZeneca. **Dr Naber** has received grant/research support and honoraria from and has served on speakers or advisory boards for AstraZeneca. **Dr Schimmelmann** has been a consultant to Bristol-Myers Squibb; has received grant/research support from AstraZeneca, Eli Lilly, Novartis, and UCB Pharma; and has served on speakers or advisory boards for AstraZeneca, Eli Lilly, Bristol-Myers Squibb, and Novartis. **Drs Golks**, **Meister**, **Rietschel**, **Bussopulos**, **Burlon**, **Ohm**, **Pakrasi**, and **Chirazi-Stark** and **Ms Frieling** report no financial or other relationship relevant to the subject of the article.

Funding/support: This study was conducted as an investigator-initiated trial funded by an educational grant from AstraZeneca Germany.

Role of sponsor: AstraZeneca had no role in developing the research question and data analysis strategy, analyzing the raw data, interpreting the data, or writing the manuscript. AstraZeneca had the right to comment on the final draft of this article before submission to the Journal. AstraZeneca approved the manuscript unchanged.

***Previous presentation*:** Poster presentation at the Congress of the German Association of Psychiatry, Psychotherapy, and Neurology; November 26–28, 2008; Berlin, Germany.

Acknowledgments: The authors express their gratitude to all participating patients and following private psychiatrists who were involved in the integrated care of the participating patients: (catchment area Asklepios Westhospital Rissen) Christine Berenbek, MD; Christiane Biehl, MD; Doris Folkerts, MD; Ralf Schnedler, MD; Hans-Jürgen Schrum, MD; Farhad Showgi, MD; Oktay Yagdiran, MD; (catchment area University Medical Center Hamburg-Eppendorf) Friedrich Chaban, MD; Gabriele Gade, MD; Sonja Fischer, MD; Mauricio Dessauer, MD; Christian Perro, MD; and Ludger Wiethaup, MD.

REFERENCES

1. Stein LI, Test MA. Alternative to mental hospital treatment. I. Conceptual model, treatment program, and clinical evaluation. *Arch Gen Psychiatry.* 1980;37(4):392–397.
2. Marshall M, Lockwood A. Assertive community treatment for people with severe mental disorders. (review) *Cochrane Database Syst Rev.* 2000;2(2):CD001089.
3. Sytema S, Wunderink L, Bloemers W, et al. Assertive community treatment in the Netherlands: a randomized controlled trial. *Acta Psychiatr Scand.* 2007;116(2):105–112.
4. Sytema S, Burgess P, Tansella M. Does community care decrease length of stay and risk of rehospitalization in new patients with schizophrenia disorders? A comparative case register study in Groningen, The Netherlands; Victoria, Australia; and South-Verona, Italy. *Schizophr Bull.* 2002;28(2):73–281.
5. Teague GB, Bond GR, Drake RE. Program fidelity in assertive community treatment: development and use of a measure. *Am J Orthopsychiatry.* 1998;68(2):216–232.
6. Assertive Community Treatment Association (ACTA). Assertive Community Treatment Association Web site. http://www.actassociation.org/. Accessed February 1, 2010.
7. Burns T, Creed F, Fahy T, et al. Intensive versus standard case management for severe psychotic illness: a randomised trial. UK 700 Group. *Lancet*. 1999;353(9171):2185–2189.
8. Harrison-Read P, Lucas B, Tyrer P, et al. Heavy users of acute psychiatric beds: randomized controlled trial of enhanced community management in an outer London borough. *Psychol Med.* 2002;32(3):403–416.
9. Killaspy H, Bebbington P, Blizard R, et al. The REACT study: randomised evaluation of assertive community treatment in north London. *BMJ.* 2006;332(7545):815–820.
10. Essock SM, Mueser KT, Drake RE, et al. Comparison of ACT and standard case management for delivering integrated treatment for co-occurring disorders. *Psychiatr Serv.* 2006;57(2):185–196.
11. McHugo GJ, Hargreaves W, Drake RE, et al. Methodological issues in assertive community treatment studies. *Am J Orthopsychiatry.* 1998; 68(2):246–260.
12. Bertelsen M, Jeppesen P, Petersen L, et al. Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. *Arch Gen Psychiatry.* 2008;65(7):762–771.
13. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association, 2000.
14. Ventura J, Liberman RP, Green MF, et al. Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I/P). *Psychiatry Res.* 1998;79(2):163–173.
15. McGorry PD, Edwards J, Mihalopoulos C, et al. EPPIC: an evolving system of early detection and optimal management. *Schizophr Bull.* 1996;22(2):305–326.
16. Ruggeri M, Salvi G, Bonetto C, et al. Outcome of patients dropping out from community-based mental health care: a 6-year multiwave follow-up study. *Acta Psychiatr Scand.* 2007;116(437):42–52.
17. Schimmelmann BG, Conus P, Schacht M, et al. Predictors of service disengagement in first-admitted adolescents with psychosis. *J Am Acad Child Adolesc Psychiatry.* 2006;45(8):990–999.
18. Lacro JP, Dunn LB, Dolder CR, et al. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry.* 2002;63(10):892–909.
19. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry.* 2003;64(6):663–667.
20. Schimmelmann BG, Huber CG, Lambert M, et al. Impact of duration of untreated psychosis on pre-treatment, baseline, and outcome characteristics in an epidemiological first-episode psychosis cohort. *J Psychiatr Res.* 2008;42(12):982–990.
21. Conus P, Cotton S, Schimmelmann B, et al. First Episode Psychosis Outcome Study (FEPOS): pre-morbid and baseline characteristics of 786 first episode psychosis patients treated in EPPIC between 1998 and 2000. *Early Interv Psychiatry*. 2007;1:191–200.
22. Morley KI, Cotton SM, Conus P, et al. Familial psychopathology in the First Episode Psychosis Outcome Study. *Aust N Z J Psychiatry.* 2008; 42(7):617–626.
23. Robinson J, Cotton S, Conus P, et al. Prevalence and predictors of suicide attempt in an incidence cohort of 661 young people with first-episode psychosis. *Aust N Z J Psychiatry.* 2009;43(2):149–157.
24. Robinson DG, Woerner MG, Alvir JM, et al. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. *Schizophr Res.* 2002;57(2-3):209–219.
25. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13(2):261–276.
26. Guy W. Clinical global impression. In: Guy W, ed. *ECDEU Assessment Manual for Psychopharmacology, revised*. Rockville, MD: National Institute of Mental Health; 1976:217–222.
27. Tohen M, Hennen J, Zarate CM Jr, et al. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. *Am J Psychiatry.* 2000;157(2):220–228.
28. Ritsner M, Kurs R, Gibel A, et al. Validity of an abbreviated quality of life enjoyment and satisfaction questionnaire (Q-LES-Q-18) for schizophrenia, schizoaffective, and mood disorder patients. *Qual Life Res.* 2005; 14(7):1693–1703.
29. Naber D, Moritz S, Lambert M, et al. Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. *Schizophr Res.* 2001;50(1-2):79–88.
30. Rofail D, Gray R, Gournay K. The development and internal consistency of the satisfaction with Antipsychotic Medication Scale. *Psychol Med.* 2005;35(7):1063–1072.
31. Tait L, Birchwood M, Trower P. A new scale (SES) to measure engagement with community mental health services. *J Ment Health.* 2002;11: 191–198.

32. Nguyen TD, Attkisson CC, Stegner BL. Assessment of patient satisfaction: development and refinement of a service evaluation questionnaire. *Eval Program Plann.* 1983;6(3-4):299–313.
33. Lambert M, Conus P, Lubman DI, et al. The impact of substance use disorders on clinical outcome in 643 patients with first-episode psychosis. *Acta Psychiatr Scand.* 2005;112(2):141–148.
34. Cox DR, Snell DJ. *The Analysis of Binary Data*. 2nd ed. London, England: Chapman & Hall; 1989.
35. Tabachnick BG, Fidell LS. *Using Multivariate Statistics*. 4th ed. Needham Heights, MA: Allyn & Bacon; 2001.
36. Mallinckrodt CH, Clark WS, David SR. Accounting for dropout bias using mixed-effects models. *J Biopharm Stat.* 2001;11(1-2):9–21.
37. Mallinckrodt CH, Kaiser CJ, Watkin JG, et al. The effect of correlation structure on treatment contrasts estimated from incomplete clinical trial data with likelihood-based repeated measures compared with last observation carried forward ANOVA. *Clin Trials.* 2004;1(6):477–489.
38. Lambert M, Huber CG, Naber D, et al. Treatment of severe agitation with olanzapine in 166 patients with schizophrenia, schizoaffective, or bipolar I disorder. *Pharmacopsychiatry.* 2008;41(5):182–189.
39. Petersen L, Nordentoft M, Jeppesen P, et al. Improving 1-year outcome in first-episode psychosis: OPUS trial. *Br J Psychiatry Suppl.* 2005;48: s98–s103.
40. Thorup A, Petersen L, Jeppesen P, et al. Integrated treatment ameliorates negative symptoms in first episode psychosis—results from the Danish OPUS trial. *Schizophr Res.* 2005;79(1):95–105.
41. Lehman AF, Kreyenbuhl J, Buchanan RW, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. *Schizophr Bull.* 2004;30(2):193–217.

© Copyright 2010 Physicians Postgraduate Press, Inc.