Predictors of Hospitalization of Individuals With First-Episode Psychosis: Data From a 2-Year Follow-Up of the RAISE-ETP

Delbert G. Robinson, M.D., Nina R. Schooler, Ph.D., Robert A. Rosenheck, M.D., Haiqun Lin, M.D., Ph.D., Kyaw J. Sint, Ph.D., Patricia Marcy, B.S.N., John M. Kane, M.D.

Objective: Despite treatment advances in other domains, inpatient psychiatric hospitalization rates for individuals with first-episode psychosis remain high. Even with early intervention services, a third or more of individuals are hospitalized over the first 2 years of treatment. Reducing hospitalization is desirable from the individual's perspective and for public health reasons because hospitalization costs are a major component of treatment costs.

Methods: Univariate and multivariate baseline and time-varying covariate analyses were conducted to identify predictors of hospitalization in the Recovery After an Initial Schizophrenia Episode–Early Treatment Program (RAISE-ETP) study, a 2-year cluster randomized trial for participants experiencing a first episode of psychosis who were outpatients at study entry. The trial compared an early intervention treatment model (NAVIGATE) with usual community care at 34 clinics across the United States.

Results: RAISE-ETP enrolled 404 participants of whom 382 had one or more postbaseline assessments that included hospitalization data. Thirty-four percent of NAVIGATE and 37% of usual-care participants were hospitalized during the trial. Risk analyses revealed significant predictors of hospitalization to be the number of hospitalizations before study entry; duration of untreated psychosis; and time-varying days of substance misuse, presence of positive symptoms, and beliefs about the value of medication.

Conclusions: These results indicate that hospital use may be decreased by reducing the duration of untreated psychosis and prior hospitalizations, minimizing residual symptoms, preventing substance misuse, and facilitating adherence to medication taking. Addressing these factors could enhance the impact of first-episode early intervention treatment models and also enhance outcomes of people with first-episode psychosis treated using other models.

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Inpatient hospitalization can be very disruptive to the goals (e.g., schooling) of young people with first-episode psychosis (FEP), and it is often experienced as traumatic (1, 2). Caregivers frequently experience distress and negative outcomes (e.g., stigma, changes in relationships) associated with their family member's hospitalization (3, 4), in addition to the positive changes that hospitalization can foster (4). From a services perspective, hospitalization costs are a major component of the cost of first-episode care in early intervention services (EIS). The mean cumulative cost for psychiatric inpatient treatment over five years for the OPUS intervention in Denmark was €58,502 of the total treatment cost of €123,683 (5) and, over 18 months in the British Lambeth Early Onset trial, £6,103 of the total cost of £11,685 (6). In the United States, the average cost of EIS NAVIGATE treatment every six months in the Recovery After an Initial Schizophrenia Episode–Early Treatment Program (RAISE-ETP)

HIGHLIGHTS

- Even with current evidence-based treatment, a third or more of individuals with first-episode psychosis (FEP) will be hospitalized during the first 2 years of treatment.
- Baseline characteristics of participants in the RAISE-ETP FEP study who were hospitalized during their first 2 years of participation were higher number of hospitalizations before study entry and longer duration of untreated psychosis.
- Factors assessed while participants were in the trial that predicted hospitalization were days of substance misuse, presence of positive symptoms, and less belief about the value of medication.
- These results provide targets for future intervention development to decrease the need for hospitalization of individuals with FEP.

study was $9,018, of which $4,709 was hospitalization costs (7). Further decreasing hospitalization costs could bolster the cost-effectiveness and thus the sustainability of EIS.

A meta-analysis (8) of EIS trials (9–17) found that compared with usual care, EIS were associated with a reduced risk of hospitalization (rates presented in Table 1). Hospitalization utilization varied by follow-up duration and health system. Over a two-year period, the lowest percentage of participants hospitalized even with EIS is 33%. Hospitalization rates with EIS treatment provided outside of a randomized treatment trial context (18, 19) have also been reported, and these are similar to the rates found in the randomized trials.

To identify targets for the development of interventions to decrease the risk of hospitalization for individuals with FEP, we examined data from the RAISE-ETP study (ClinicalTrials.gov registration NCT01321177). RAISE-ETP compared a multielement treatment model (20) for FEP with usual care. RAISE-ETP's background, rationale, and design have been published (21), as have its CONSORT flow diagram, participant characteristics, and two-year outcomes (16). The advantage of using RAISE-ETP data to find hospitalization predictors for a population with an already relatively low hospitalization rate is that the data cover a 2-year follow-up of a population with a low hospitalization rate compared with that observed in other studies of similar duration.

METHODS

Participants

RAISE-ETP enrolled English-speaking individuals between ages 15 and 40 years with a *DSM-IV* diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, or psychotic disorder not otherwise specified. Individuals were excluded if they had affective psychosis, substance-induced psychotic disorder, psychosis resulting from a general medical condition, clinically significant head trauma, or a serious general medical condition. All participants had experienced only one episode of psychosis (although this episode might have resulted in multiple hospitalizations) and had taken six or fewer months of lifetime antipsychotics.

Written informed consent was obtained from adult participants and from legal guardians of participants younger than age 18, who provided written assent. The institutional review boards of the coordinating center and the participating sites approved the study. The National Institute of Mental Health Data and Safety Monitoring Board provided study oversight.

Clinical Sites

Thirty-four outpatient community mental health centers in 21 states were selected via a national search. Site eligibility criteria included experience treating individuals with schizophrenia; interest in offering EIS for FEP; sufficient staff to implement the experimental intervention; ability to recruit an adequate number of participants; and institutional assurance that research assessments would be completed. Academic centers or sites with existing first-episode programs were excluded. All participants were outpatients at the time of their baseline assessment.

RAISE-ETP used cluster randomization (i.e., randomization by clinic rather than individual participant; 22). The study statisticians randomly assigned 17 of the clinics to the experimental intervention and 17 to standard care.

Interventions

NAVIGATE (20), the experimental EIS, is team based and includes four interventions: personalized medication management, family psychoeducation, resilience-focused individual therapy, and supported education and employment (manuals available at www.raiseetp.org). The primary outcome measure and therefore the goal of RAISE-ETP was improved quality of life, not the prevention of hospitalization per se. These goals are not mutually exclusive in that hospitalization impedes progress toward improving quality of life. With respect to factors that might influence hospitalization risk, personalized medication management included assessment of symptoms, side effects, adherence, and substance use at each visit. The psychosocial interventions included illness management strategies and modules on adherence and making decisions about substance use. The control condition, community care, was psychosis treatment determined by individual and clinician choice and service availability.

Trial Duration

Enrollment occurred between July 2010 and July 2012. The minimum potential trial duration for each participant was two years (longer for early enrollees); these two years are the focus of this report. Study assessments were suspended during periods of incarceration or hospitalization but resumed after release or discharge. Research assessments continued even if participants discontinued NAVIGATE or community care treatment.

Assessment Strategy and Measures

Centralized assessors, masked both to individual treatment assignments and to the overall study design, administered the following measures via live, two-way video conferencing: the Structured Clinical Interview for DSM-IV (SCID-IV; 23) for diagnosis and to obtain the information required to determine the duration of untreated psychosis (DUP), the Positive and Negative Syndrome Scale (PANSS; 24), the Clinical Global Impressions Severity Scale (CGI-severity; 25), the Calgary Depression Scale for Schizophrenia (CDSS; 26), and the Heinrichs-Carpenter Quality of Life Scale (QLS; 27), which was the primary outcome measure. Remote assessment via two-way video conferencing is comparable to face-to-face assessment in patient acceptability and reliability

TABLE 1. Hospitalization rates in controlled trials of early intervention treatment of first-episode psychosis

Study	Country	Number of participants	Length of treatment (months)	Hospitalization rates (%) during follow-up interval	
				Experimental intervention	Treatment as usual
Sample size >100					
OPUS (year 2 of trial[a]; 11)	Denmark	243 intervention; 193 control[b]	13–24	26	39
PIANO[c] (15)	Italy	272 intervention; 172 control	9	17	16
Valencia et al., study 1 (14)	Mexico	60 intervention; 60 control	6	6	10
LEO[d] (10)	United Kingdom	71 intervention; 73 control	15	33	51
RAISE-ETP[e] (16)	United States	223 intervention; 181 control	24	34	37
STEP[f] (17)	United States	60 intervention; 57 control	12	23	44
Sample size <100					
Grawe et al. (12)	Norway	30 intervention; 20 control	24	33	50
Valencia et al., study 2 (13)	Mexico	44 intervention; 44 control	12	5	11
COAST[g] (9)	United Kingdom	32 intervention; 27 control	12	22[h]	41[i]

[a] Rates of hospitalization in OPUS for year 1 were 59% with the intervention and 71% with treatment as usual. These rates include hospitalization at the time of recruitment for participants recruited as inpatients.
[b] Participants with 2-year follow-up; baseline sample included 263 participants assigned to the intervention and 244 assigned to treatment as usual.
[c] Psychosis: early intervention and assessment of needs and outcome.
[d] Lambeth Early Onset.
[e] Recovery After an Initial Schizophrenia Episode-Early Treatment Program.
[f] STEP, Specialized Treatment Early in Psychosis.
[g] COAST, Croydon Outreach and Assertive Support Team.
[h] 7 total admissions for 32 participants.
[i] 11 total admissions for 27 participants.

(28). The SCID-IV was completed at baseline; the other measures were completed every six months.

Site research assistants interviewed participants monthly with the Service Use and Resource Form (SURF; 29, 30) to capture psychiatric inpatient and emergency services use and self-reported days of alcohol or drug use. Emergency department visits that lasted more than 24 hours were considered hospitalizations. Participant-reported assessments allowed us to obtain information not only about treatment that participants received at their study site but also about treatment they received outside the site (e.g., inpatient admission at another agency). Participant self-report has proven to be generally accurate (29). The outcome of interest for this article was mental health hospitalization occurring after study entry (all participants were outpatients at this time point). We obtained data on hospitalizations before study entry through individual and family interviews and medical record search; these data were examined as predictors of hospitalization during the study.

At baseline, 3-month follow-up, 6-month follow-up, and every 6 months thereafter, participants completed the Intent to Attend measure (31), the Adherence Estimator (32), Brief Evaluation of Medication Influences and Beliefs (BEMIB) scale (33), seven items from the Stigma Scale (34), a subset of the Perceived Well-Being Scale (35), the six-item Autonomy Support Scale short-form version of the Health Care Climate Questionnaire (36), and an abbreviated version of the Mental Health Recovery Measure (37). They also rated their current state of mental and emotional health on a scale ranging from 1, worst possible, to 100, perfect health, and how they felt about their life as a whole on a scale ranging from 1, terrible, to 7, delighted.

Statistical Analysis

We used time-to-event analysis for hospitalization. The Cox proportional hazard model was used with site included as a frailty term to account for clustering of individuals within site. Clustered randomized trials often have a limited number of clusters, and this can result in an imbalance on baseline measures between the randomized treatment conditions. Such imbalances may confound the relationship between treatment and individual-level outcomes. Therefore, significant baseline differences between the treatment conditions were included as adjustment variables. We assessed whether the two treatment conditions differed in hospitalization and adjusted for the baseline covariates of gender, student status at entry, and total PANSS score, which were found to be significantly associated with treatment condition in previously reported analyses (16).

For analysis of the longitudinal assessments, we constructed time-varying predictor variables that consisted of the results of the assessment concurrent with or, if not concurrent with, the assessment closest in time to an individual's first hospitalization. The severity and intensity of a factor often change over time. The use of time-varying predictor variables allowed us to examine the effects of a variable of interest assessed at the time closest to a hospitalization, when it might have had the greatest impact on hospitalization. For example, if an individual had a hospitalization at month 18, we used the month 18 assessment; if those results were not available, we used the closest preceding assessment to month 18. For individuals with no hospitalizations, we used the results from the last assessment.

To determine hospitalization predictors, we first performed univariate analyses using a Cox proportional model

TABLE 2. Univariate associations between baseline variables and later hospitalization among 382 participants in RAISE-ETP

Variable	Hazard ratio	95% CI	p
Categorical			
Duration of untreated psychosis >74 weeks	1.45	.99–2.11	.055
Male sex	.80	.54–1.2	.284
Race (reference: white)			.983
African American	.98	.66–1.45	
Other	.94	.48–1.84	
Hispanic	.89	.54–1.46	.649
Marital status (reference: never married)			.623
Presently married	.91	.42–1.96	
Widowed, divorced, or separated	.62	.23–1.67	
Current residence (reference: independent living)			.641
Supported or structured	.80	.24–2.66	
Family, parents, grandparents, sibling	.77	.49–1.22	
Homeless, shelter, or other	1.02	.49–2.14	
Patient's education (reference: some or completed grade school)			.903
Some college or higher	.87	.36–2.06	
Completed high school	1.03	.44–2.44	
Some high school	.94	.40–2.24	
Mother's education (reference: no school or unknown)			.290
Some college or higher	.76	.47–1.24	
Completed high school	.70	.41–1.21	
Some high school or grade school	.51	.25–1.04	
Current student	.77	.46–1.27	.304
Currently working	.54	.29–1.01	.055
Student or worker	.71	.46–1.09	.116
Type of insurance (reference: private)			.453
Public	.95	.58–1.55	
Uninsured	.76	.48–1.22	
SCID-IV[a] diagnosis (reference: schizophrenia)			.586
Schizoaffective bipolar	1.30	.62–2.71	
Schizoaffective depressive	.85	.47–1.51	
Schizophreniform provisional or definite	.67	.38–1.20	
Brief psychotic disorder or psychotic disorder NOS[b]	.96	.51–1.82	
Lifetime alcohol use disorder (reference: does not meet criteria)			.117
Met abuse criteria	.71	.37–1.39	
Met dependence criteria	1.39	.92–2.1	
Lifetime cannabis use disorder (reference: does not meet criteria)			.395
Met abuse criteria	1.01	.59–1.74	
Met dependence criteria	1.35	.87–2.10	
Prior hospitalizations (reference: no prior hospitalization)			.002
1	1.30	.75–2.26	
2	1.92	1.04–3.54	
≥3	2.77	1.52–5.06	
Prescribed ≥1 antipsychotic at consent	1.10	.65–1.87	.724
Medication compliance by SURF[c] interview			
Days in the past month not taking a prescribed antipsychotic (reference: few if any, <7)			.949
7–13	.88	.32–2.41	
14–20	1.17	.43–3.19	
Most, >20	.69	.25–1.88	
Not prescribed antipsychotic	.95	.59–1.55	
Days in the past month taking less than prescribed antipsychotic dose (reference: never or almost never, 0%–25%)			.938
Always or almost always, 76%–100%	.78	.31–1.92	
Usually, 51%–75%	.96	.24–3.91	
Sometimes, 26%–50%	1.32	.57–3.03	
Not prescribed antipsychotic	.97	.6–1.58	
Adherence Estimator risk category (reference: low risk)			.143
Medium	.89	.49–1.64	
High	.54	.28–1.04	
Continuous			
Age	.98	.94–1.01	.188
Duration of untreated psychosis (weeks)	1.00	1.00–1.00	.102
Heinrichs-Carpenter QLS[d]			
Total score	.99	.98–1.00	.116
Interpersonal relations	.99	.97–1.01	.394
Instrumental role	.97	.94–1.00	.069
Intrapsychic foundations	.98	.96–1.01	.244
Common objects and activities	.96	.88–1.04	.270
PANSS[e]			
Total score	1.01	1.00–1.03	.067
Wallwork factor scores			
Positive	1.07	1.02–1.12	.007
Negative	.97	.94–1.01	.169
Disorganized-concrete	.97	.91–1.04	.388
Excited	1.10	1.03–1.17	.005
Depressed	1.09	1.02–1.15	.006
CDSS total score[f]	1.05	1.01–1.1	.014
CGI–Severity Scale[g]	1.41	1.11–1.78	.004
Autonomy Support Scale mean score	1.02	.87–1.19	.828
BEMIB mean score[h]	.97	.81–1.16	.726
Mental Health Recovery Measure mean score	.88	.77–1.01	.079
Stigma Scale mean score	1.04	.89–1.22	.633
Perceived Well-Being Scale mean score	.79	.63–.99	.044
Current state of mental health	.99	.98–1.00	.032
Life as a whole	.94	.83–1.08	.382
No. of days of alcohol intoxication past month	.98	.89–1.07	.584
No. of days of illegal drugs past month	1.00	.98–1.03	.940
Duration of lifetime antipsychotic medication at consent (days)	1.00	1.00–1.00	.669
How likely to complete study[i]	1.06	.95–1.18	.326
How likely to attend next visit[i]	1.12	.98–1.28	.110
Adherence Estimator risk numeric ordinal	.96	.69–1.35	.829

[a] Structured Clinical Interview for DSM-IV.
[b] NOS, not otherwise specified.
[c] Service Use and Resource Form.
[d] QLS, Quality of Life Scale.
[e] Positive and Negative Syndrome Scale.
[f] CDSS, Calgary Depression Scale for Schizophrenia.
[g] Clinical Global Impressions.
[h] BEMIB, Brief Evaluation of Medication Influences and Beliefs.
[i] Intent to Attend measure.

with frailty of site for each candidate of the baseline and time-varying covariates. In developing the multivariate model for baseline predictors, the variables we screened for entry into the analysis were those with significant or trend-level associations in the univariate analyses of baseline predictors. Because inclusion of correlated variables can

result in unstable multivariate correlations, we used several criteria to determine which correlated variables to enter. We gave preference to variables that would provide more clinically meaningful information if associations with hospitalization were found (e.g., we preferred factor scores over total scores because the former describe more circumscribed symptoms than the latter and could provide more precise targets for intervention development). The final set of baseline variables for model entry included DUP longer than 74 weeks, number of prior hospitalizations, PANSS positive and excited factors, CDSS, and the Perceived Well-Being Scale.

TABLE 3. Multivariate model of associations between baseline variables and hospitalization among 382 participants in RAISE-ETP[a]

Parameter	Hazard ratio	95% CI	χ^{2b}	p
Duration of untreated psychosis>74 weeks	1.51	1.02–2.23	4.13	.042
1 prior hospitalization vs. none	1.73	.97–3.08	3.46	.063
2 prior hospitalizations vs. none	2.43	1.29–4.58	7.57	.006
≥3 prior hospitalizations vs. none	3.78	2.00–7.15	16.67	<.001
Positive and Negative Syndrome Scale excited factor	1.11	1.03–1.18	8.19	.004
Perceived Well-Being Scale mean score	.79	.63–1.00	3.85	<.050

[a] Model from backward selection of variables (frailty model with site). Variables entered into the analysis were duration of untreated psychosis greater than 74 weeks, number of prior hospitalizations, and scores on the Positive and Negative Syndrome Scale positive and excited factors, Calgary Depression Scale for Schizophrenia, and the Perceived Well-Being Scale.
[b] df=1.

The strategy for developing the final multivariate models that integrate both baseline and time-varying variables was to consider for entry first, the baseline variables with significant associations with hospitalization in the multivariate baseline analysis and second, the time-varying variables with significant associations with hospitalization from the univariate analyses of time-varying variables and hospitalization. By examining the correlations among variables and using our strategy of considering clinical meaningfulness in variable selection, we developed two groups of variables for entry into the analyses. Both groups included the baseline predictors DUP and number of prior hospitalizations and the time-varying predictors of days of illegal drug use and being a student or working. In addition, in analysis 1 we added time-varying variables rated by the central assessors—the PANSS positive and excited factors and the CDSS—plus the self-rated Adherence Estimator. In analysis 2, we added time-varying variables rated by the participant, the BEMIB, and the Perceived Well-Being Scale total score. The participant-rated Adherence Estimator and BEMIB measures were highly correlated (r= −.43). Thus, we could include only one of them in analysis 2, which focused on participant-rated assessment. We chose to include the BEMIB in analysis 2 because it taps participants' beliefs about the value of medication for themselves. The Adherence Estimator taps general attitudes toward medication and was not significantly correlated with any of the central assessor-rated variables; it was included in analysis 1.

For each analysis, we checked proportional hazard assumptions by dividing time into 6-month intervals and assessing whether the coefficients were statistically different across time intervals.

RESULTS

Participants

Characteristics of the full RAISE-ETP sample of 404 individuals have been published (16). Some participants did not have any postbaseline assessments. Supplemental Table 1, which presents the characteristics of the 382 participants who had at least one postbaseline assessment and thus have postbaseline hospitalization data, is available as an online supplement to this article. Overall, the 382 participants were young (mean±SD age =23.2±5.1 years), mostly male (73%, N=279), and of diverse racial background. Outpatient community center sites typically receive most of their FEP referrals from inpatient units. Consistent with this pattern, only 84 participants had never had an inpatient psychiatric hospitalization.

Psychiatric Hospitalization

Of the participants, 112 had at least one psychiatric hospitalization during the two-year observation period. On the basis of a survival analysis, 34% of NAVIGATE and 37% of community care participants had a hospitalization (this estimate is the same as that previously reported [16] for the sample of 404 individuals as a result of censoring effects with survival analysis of individuals who did not have postbaseline assessments). Hospitalization rates did not differ between participants receiving NAVIGATE and those receiving community care treatment (hazard ratio=0.892, χ^2=0.35, df=1, p=.557).

Factors Associated With Hospitalization

Baseline variables. Table 2 presents the associations between baseline characteristics and psychiatric hospitalization during the follow-up, based on univariate analyses. We found significant associations for having had a hospitalization before study entry; scores on the Wallwork (38); positive, excited, and depressed factors of the PANSS; CDSS total score; CGI-severity; and participants' ratings of the Perceived Well-Being Scale and their current state of mental health. Other variables with trend-level associations (p<.1) were DUP (dichotomized at the median value of 74 weeks [16, 39]), working at the time of study entry, Heinrichs-Carpenter QLS Instrumental Role, PANSS total score, and the Mental Health Recovery Measure.

Table 3 presents the results of multivariate analyses of the association between baseline variables and subsequent hospitalization. DUP, prior hospitalizations, the PANSS excited factor, and Perceived Well-Being Scale mean score were all significant predictors of subsequent hospitalization.

TABLE 4. Univariate associations between time-varying variables and hospitalization among 382 participants in RAISE-ETP

Variable	Hazard ratio	95% CI	p
Categorical			
Current residence (reference: independent living)			.093
Supported or structured	.44	.11–1.86	
Family, parents, grandparents, sibling	1.02	.65–1.59	
Homeless, shelter, or other	2.2	1.02–4.72	
Current student	.93	.59–1.47	.757
Currently working	.42	.24–.73	.002
Student or worker	.62	.42–.93	.022
Type of insurance (reference: private insurance)			.873
Public	.88	.54–1.44	
Uninsured	.90	.54–1.48	
Days in the past month not taking a prescribed antipsychotic (reference: few if any, <7)			.254
7–13	1.33	.61–2.91	
14–20	2.47	1.07–5.72	
Most, >20	1.06	.49–2.32	
Not prescribed antipsychotic	.92	.59–1.45	
Days in the past month taking less than prescribed antipsychotic dose (reference: always/almost always, 76%–100%)			.058
Usually, 51%–75%	1.50	.72–3.12	
Sometimes, 26%–50%	3.04	1.39–6.65	
Never or almost never, 0%–25%	1.24	.50–3.09	
Not prescribed antipsychotic	.95	.61–1.50	
Adherence Estimator risk category (reference: low risk)			.070
Medium	1.87	1.08–3.22	
High	1.30	.73–2.31	
Continuous			
Heinrichs-Carpenter QLS[a]			
Total score	.99	.98–1.00	.014
Interpersonal Relations	.98	.96–1.00	.116
Instrumental Role	.95	.92–.98	<.001
Intrapsychic Foundations	.98	.96–1.01	.116
Common Objects and Activities	.94	.87–1.01	.09
PANSS[b]			
Total score	1.02	1.01–1.03	.001
Wallwork factor scores			
Positive	1.09	1.04–1.14	<.001
Negative	.98	.94–1.01	.186
Disorganized–concrete	1.04	.97–1.11	.294
Excited	1.14	1.07–1.22	<.001
Depressed	1.13	1.07–1.20	<.001
CDSS[c]	1.07	1.02–1.11	.003
CGI severity scale[d]	1.54	1.24–1.90	<.001
Autonomy Support Scale mean score	.89	.77–1.02	.100
BEMIB mean score[e]	.81	.68–.96	.017
Mental Health Recovery Measure mean score	.81	.70–.93	.003
Stigma Scale mean score	1.07	.92–1.25	.365
Perceived Well-Being Scale mean score	.73	.58–.91	.005
Current state of mental health	.99	.98–1.00	.009
Life as a whole	.86	.76–.98	.027
No. of days of alcohol intoxication	1.03	.95–1.10	.518
No. of days of illegal drugs	1.02	1.00–1.04	.029
How likely to complete study[f]	1.05	.93–1.19	.402
How likely to attend next visit[f]	1.02	.91–1.15	.708
Adherence Estimator risk numeric ordinal	1.37	1.05–1.80	.023

[a] QLS, Quality of Life Scale.
[b] Positive and Negative Syndrome Scale.
[c] Calgary Depression Scale for Schizophrenia.
[d] CGI, Clinical Global Impressions.
[e] BEMIB, Brief Evaluation of Medication Influences and Beliefs.
[f] Intent to Attend measure.

Time-varying variables. Table 4 presents the univariate analyses of the associations between the time-varying variables and hospitalization. We found significant associations among currently working; being a student or worker; QLS total and Instrumental Role scores; PANSS total and positive, excited, and depressed factor scores; CDSS; CGI-severity; BEMIB; Mental Health Recovery Measure scores; Perceived Well-Being Scale scores; current state of mental health; life as a whole; number of days of illegal drugs; and Adherence Estimator risk scores and subsequent hospitalization.

Multivariate models integrating baseline and time-varying variables. As described in the Statistical Analysis section, we tested two analysis models. As presented in Table 5, both analyses found significant associations between hospitalization during the study and having had multiple hospitalizations before study entry and time-varying days of illegal drug use. We found additional significant associations with PANSS positive symptoms in analysis 1 and with DUP of more than 74 weeks and BEMIB scores in analysis 2.

DISCUSSION

Even though RAISE-ETP participants experienced a relatively low hospitalization rate, we were able to identify predictors of hospitalization. At study baseline, those with longer DUP, more hospitalizations before study entry, symptoms of excitement, and lower reported well-being were more likely to be hospitalized during the two-year treatment period. When we added information gathered across the trial to our multivariate analyses, longer DUP and history of hospitalization before study entry continued to influence risk of hospitalization, but positive psychosis

symptoms closer to the time of hospitalization, use of illegal drugs, and beliefs about medication were now predictive.

Our results are generally consistent with the predictors of hospitalization found in other first-episode trials or longitudinal follow-up studies with the exception of the findings regarding DUP. Our finding that individuals with prior hospitalizations were at increased risk for hospitalization during the trial is consistent with the results of other studies of first-episode populations over the first years of treatment (18, 40). This vulnerability may persist for longer periods; Mortensen and Eaton (41) found that, over the first 10 years after a first admission for schizophrenia, time to readmission became shorter as the number of admissions increased. As with our study, other first-episode studies have identified psychosis (18, 42–44), excitement symptoms (45), use of illegal drugs (11, 46–50), and poor medication adherence (48, 51–54) as hospitalization risk factors. In our study, individual self-report of adherence over time predicted hospitalization at a trend level in univariate analyses, and its association with beliefs about medication was significant in the multivariate analyses.

TABLE 5. Multivariate models of associations between baseline and time-varying variables and hospitalization among 382 participants in RAISE-ETP

Variable	Hazard ratio	95% CI	χ^{2a}	p
Model 1[b]				
1 prior hospitalization before baseline vs. none	2.02	.97–4.22	3.51	.061
2 prior hospitalizations before baseline vs. none	2.55	1.11–5.86	4.84	.028
≥3 prior hospitalizations before baseline vs. none	4.42	2.03–9.59	14.09	<.001
Time-varying Positive and Negative Syndrome Scale positive factor	1.08	1.02–1.14	7.87	.005
Time-varying days of illegal drug use	1.03	1.00–1.05	4.74	.029
Model 2[c]				
Duration of untreated psychosis>74 weeks	1.78	1.14–2.79	6.41	.011
1 prior hospitalization before baseline vs. none	2.59	1.18–5.67	5.67	.017
2 prior hospitalizations before baseline vs. none	3.42	1.42–8.21	7.53	.006
≥3 prior hospitalizations before baseline vs. none	5.67	2.51–12.83	17.35	<.001
Time-varying days of illegal drug use	1.03	1.01–1.05	5.96	.015
Time-varying Brief Evaluation of Medication Influences and Beliefs	.82	.67–.99	4.15	.042

[a] df=1.
[b] Model from backward selection of variables (frailty model with site). Baseline variables entered into the analysis were duration of untreated psychosis greater than 74 weeks and number of prior hospitalizations; time-varying variables were Positive and Negative Syndrome Scale positive and excited factors, Calgary Depression Scale for Schizophrenia, days of illegal drug use, Adherence Estimator risk scores, and being a student or worker.
[c] Model from backward selection of variables (frailty model with site). Baseline variables entered into the analysis were duration of untreated psychosis greater than 74 weeks and number of prior hospitalizations; time-varying variables were days of illegal drug use, longitudinal Brief Evaluation of Medication Influences and Beliefs, Perceived Well-Being Scale total score, and being a student or worker.

DUP is a predictor of several outcome domains of FEP (55, 56). In contrast, no association between DUP and hospitalization risk has been found among several first-episode populations (18, 43, 44, 57), although we and Sipos and colleagues (45) have found an association. These studies come from a variety of countries with different health systems and pathways to care that may have contributed to the variability of results. Moreover, comparison across studies is complicated by the often skewed distribution of DUP. For example, although the median duration in RAISE-ETP was 74 weeks, 23.8% of participants had a DUP duration of 3 months or less, the target DUP in the consensus statement (58) of the World Health Organization and the International Early Psychosis Association. Nevertheless, the DUP in all of the studies that did not find an association with hospitalization risk was shorter than the median 74 weeks in RAISE-ETP. It is possible that once DUP is shortened to a particular degree, further DUP shortening does not decrease hospitalization risk. Research is needed to clarify the effect of DUP on first-episode hospitalization risk and determine what, if any, is the minimum DUP associated with increased hospitalization risk.

Our findings have implications for future efforts to enhance EIS. Individuals enter outpatient treatment with an already fixed number of prior hospitalizations and DUP. Changing these factors will require public health initiatives and innovative outreach strategies (59) to facilitate earlier entry into treatment. These baseline characteristics can also be used to identify individuals at increased hospitalization risk who might be candidates for interventions specifically targeted to decrease that risk, such as individualized relapse prevention plans. Current EIS models include interventions to help individuals decrease substance misuse, achieve symptom reduction, and understand medications and adherence. Some of these interventions have low participation by individuals who would benefit from them (e.g., substance misuse interventions [60]), suggesting that more effort may be needed to motivate individuals to use available services. Further direct development or refinement of the interventions, such as innovative strategies to support medication adherence (61–63), also should be considered.

To be a RAISE-ETP site, facilities had to have an interest in participating in such a study and the clinical and administrative infrastructure to provide NAVIGATE treatment if the site was randomly assigned to provide it. A limitation to generalization of our finding to the entire range of community clinics is that the site inclusion criteria may have resulted in the selection of clinics with above-average

motivation and resources to serve individuals with FEP. Our study sites were outpatient facilities. Our data do not address predictors of hospitalization for individuals experiencing FEP who never receive outpatient treatment (e.g., those whose treatment occurs only on inpatient units).

CONCLUSIONS

Current treatment practices can reduce the risk of hospitalization of individuals with FEP, but further efforts at reducing hospitalization risk are needed. Potential targets for further intervention development include reducing the length of DUP and the number of hospitalizations before EIS care commences, decreasing substance misuse and symptoms, and enhancing adherence. Better intervention could enhance the impact of first-episode EIS treatment models and enhance outcomes for people with FEP treated through the use of other models.

AUTHOR AND ARTICLE INFORMATION

Department of Psychiatry, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, Feinstein Institute for Medical Research, Manhasset, New York (Robinson, Kane); Department of Psychiatry, SUNY Downstate Medical Center, Brooklyn, New York (Schooler); Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut (Rosenheck); Yale School of Public Health, New Haven (Lin, Sint); Vanguard Research Group, Glen Oaks, New York (Marcy). Send correspondence to Dr. Robinson (drobinso@northwell.edu).

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