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EVIDENCE ON SHORT- AND LONG-TERM OUTCOMES: RAISE-EARLY TREATMENT PROGRAM

Disclosures

Consultant to or receives honoraria
Alkermes, Allergan, Dainippon Sumitomo, H. Lundbeck, Indivior, Intracellular Therapies, Janssen Pharmaceutical, Johnson & Johnson, LB Pharmaceuticals, Merck, Minerva, Neurocrine, Newron, Novartis , Pharmaceuticals, Otsuka, Roche, Saladax, Sunovion, Teva

Grant Support
Otsuka, Lundbeck, Sunovion, Janssen

Shareholder
Vanguard Research Group, LB Pharmaceuticals, Inc., North Shore Therapeutics

Received royalties
Up to Date

Recovery After Initial Schizophrenia Episode Early Treatment Program

Studies of EIS Before RAISE-ETP

Study	Country
COAST	United Kingdom
LEO	United Kingdom
OPUS	Denmark
OTP	Norway

Specified Aims of RAISE From NIMH

Develop	Develop a comprehensive and integrated intervention to • promote symptomatic recovery • minimize disability • maximize social, academic, and vocational functioning • be capable of being delivered in real world settings utilizing current funding mechanisms
Assess	Assess the overall clinical impact and cost-effectiveness of the intervention as compared to currently prevailing treatment approaches • Conduct the comparison in non-academic, real world community treatment settings in the United States

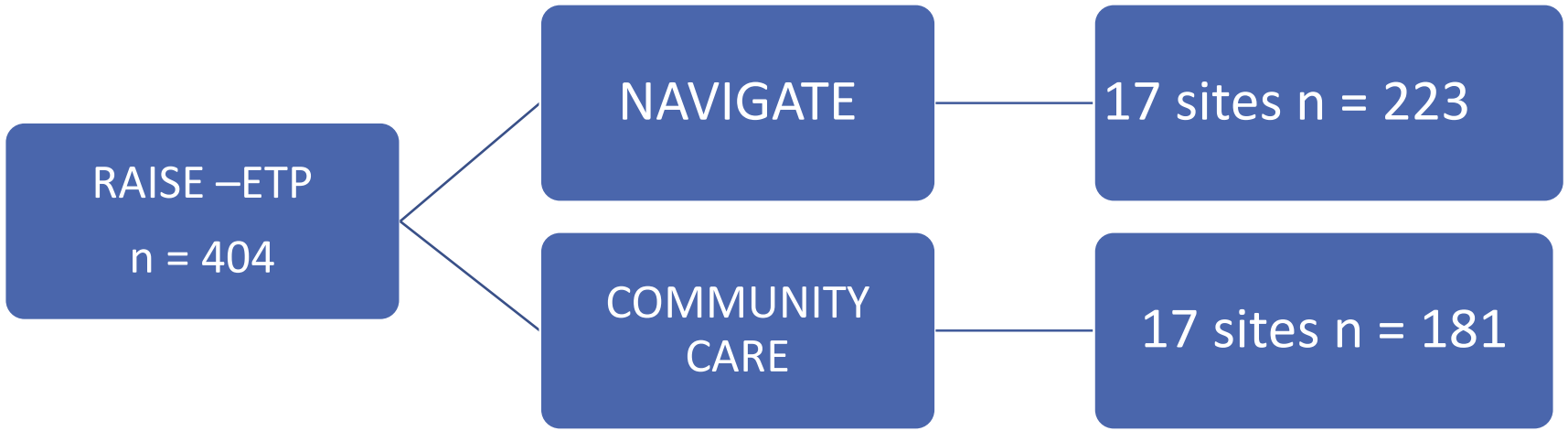
RAISE-ETP: Executive Committee

John Kane (PI)	Zucker Hillside Hospital (ZHH)
Delbert Robinson	ZHH
Nina Schooler	SUNY Downstate
Jean Addington	University of Calgary
Mary Brunette	Dartmouth
Christoph Correll	ZHH
Kim Mueser	Boston University
David Penn	UNC
Sue Estroff	UNC
Robert Rosenheck	Yale University
Patricia Marcy	ZHH – Project Director

Principal NIMH Collaborators

- Robert Heinssen
- Susan Azrin
- Amy Goldstein

404 First Episode Patients Were Recruited



RAISE – ETP Site Distribution

34 sites in 21 states

RAISE-ETP Inclusion Criteria

Age 15 – 40 years

Diagnosis

- Schizophrenia
- Schizophreniform disorder
- Schizoaffective disorder
- Brief Psychotic disorder
- Psychosis NOS

No more than six months of antipsychotic medication

First episode of psychosis

Kane, J.M. et. al. Am J Psychiatry 2016

Demographics

Adjusted for Cluster Design

	NAVIGATE	Community Care	p-value
Age and Gender			
Age (mean)	23.5	23.2	
Males (%)	77.6	66.2	.05
Race			
White (%)	65.9	49.9	
African American (%)	25.4	44.1	
Other (%)	8.7	6.0	
Role Functioning			
In school (%)	14.9	25.5	.03
Working (%)	12.6	16.6	
Prior Hospitalization (%)	76.2	81.6	.05

Kane, J.M. et. al. Am J Psychiatry 2016

Duration of Untreated Psychosis in Community Treatment Settings in the United States

Jean Addington, Ph.D., Robert K. Heinssen, Ph.D., Delbert G. Robinson, M.D., Nina R. Schooler, Ph.D., Patricia Marcy, B.S.N., Mary F. Brunette, M.D., Christoph U. Correll, M.D., Sue Estroff, Ph.D., Kim T. Mueser, Ph.D., David Penn, Ph.D., James A. Robinson, M.Ed., Robert A. Rosenheck, M.D., Susan T. Azrin, Ph.D., Amy B. Goldstein, Ph.D., Joanne Severe, M.S., John M. Kane, M.D.

Objective: This study is the first to examine duration of untreated psychosis (DUP) among persons receiving care in community mental health centers in the United States.

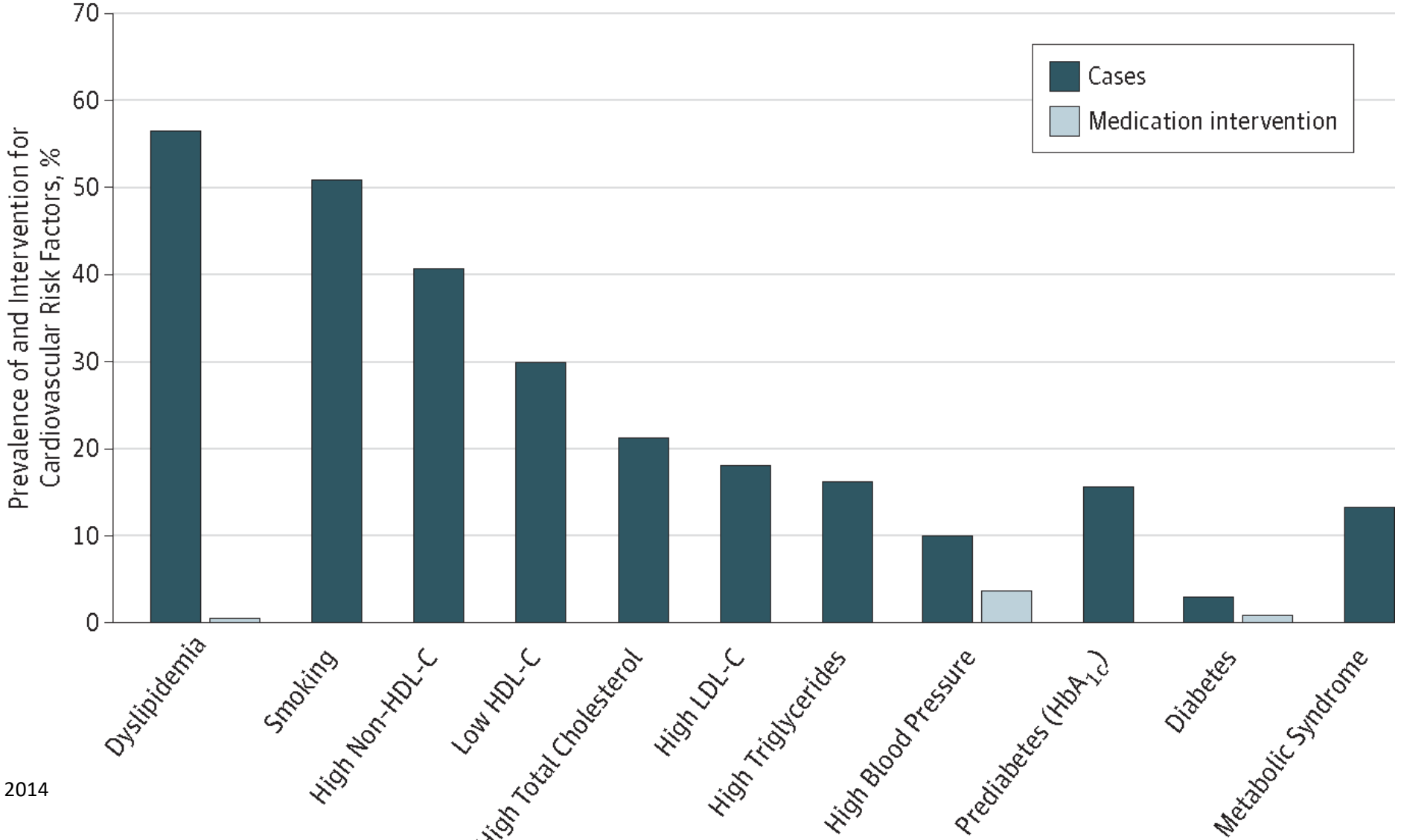
Methods: Participants were 404 individuals (ages 15–40) who presented for treatment for first-episode psychosis at 34 nonacademic clinics in 21 states. DUP and individual- and site-level variables were measured.

Results: Median DUP was 74 weeks (mean=193.5±262.2 weeks; 68% of participants had DUP of greater than six months). Correlates of longer DUP included earlier age at first psychotic symptoms, substance use disorder, positive and general symptom severity, poorer functioning, and referral from outpatient treatment settings.

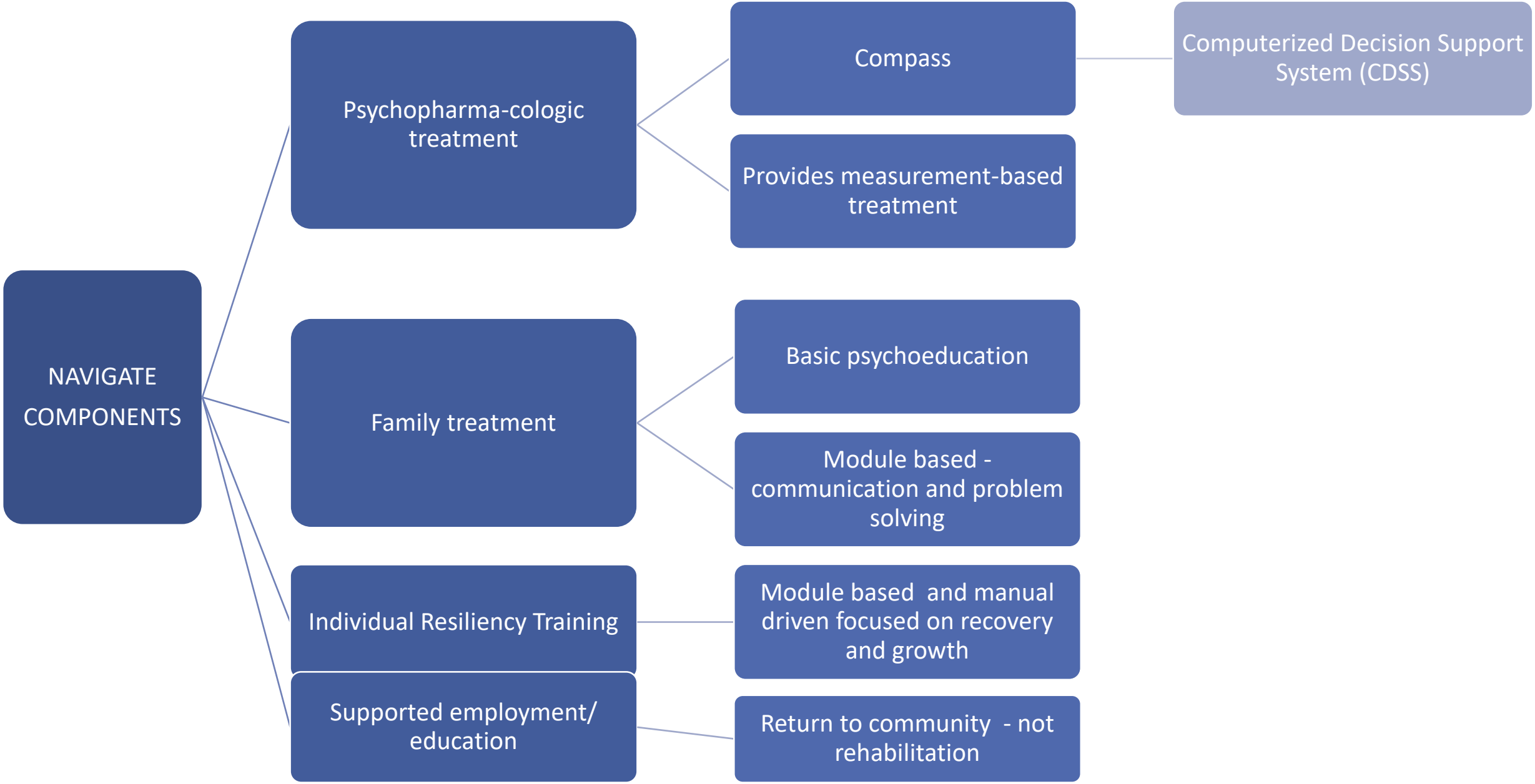
Conclusions: This study reported longer DUP than studies conducted in academic settings but found similar correlates of DUP. Reducing DUP in the United States will require examination of factors in treatment delay in local service settings and targeted strategies for closing gaps in pathways to specialty FEP care.

Psychiatric Services 2015; 66:753–756; doi: 10.1176/appi.ps.201400124

Many Patients Had Metabolic Abnormalities or Cardiovascular Risk Factors But Few Were Getting Treatment For These



Correll et al. JAMA Psychiatry 2014


NAVIGATE COMPONENTS
Psychopharma-cologic treatment
Compass
Computerized Decision Support System (CDSS)
Provides measurement-based treatment
Family treatment
Basic psychoeducation
Module based - communication and problem solving
Individual Resiliency Training
Module based and manual driven focused on recovery and growth
Supported employment/ education
Return to community - not rehabilitation

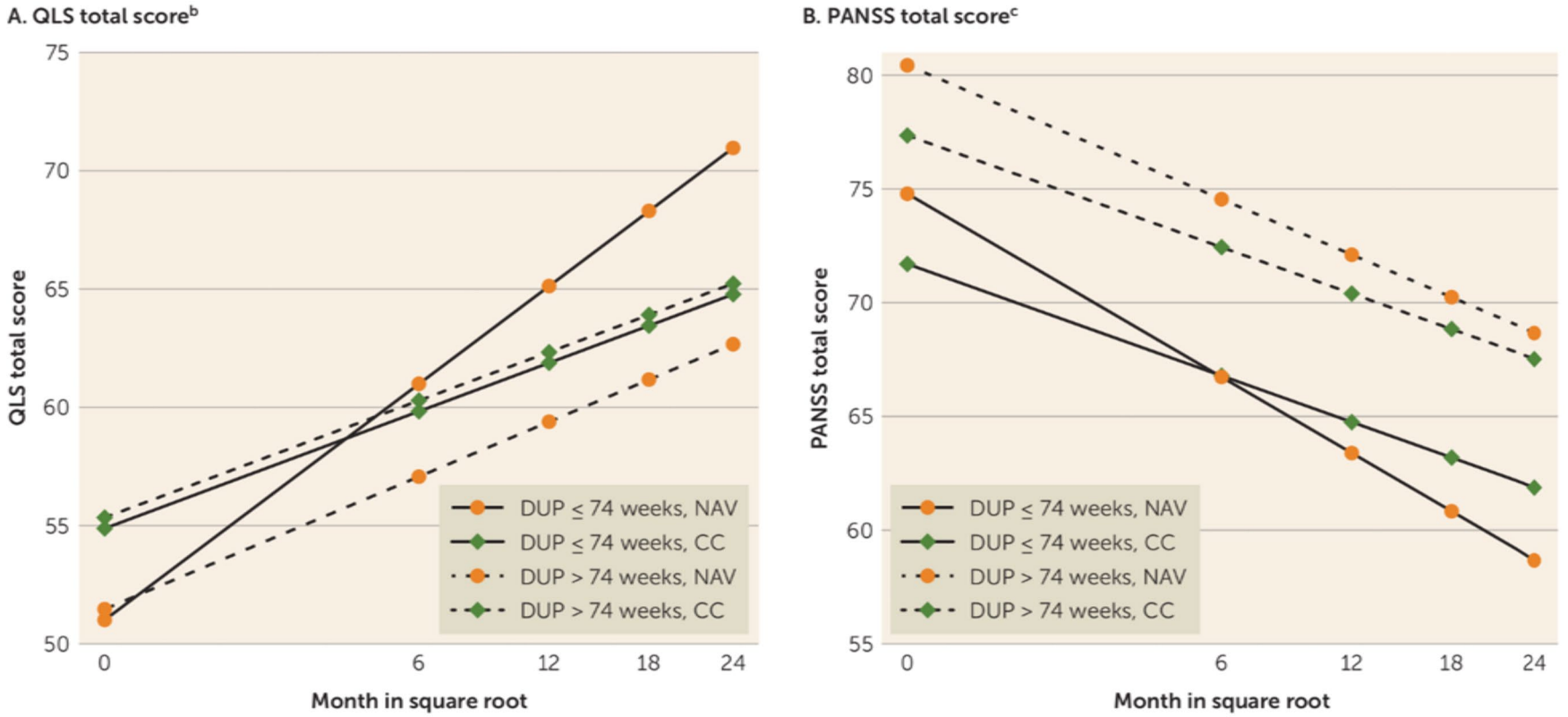
Outcome Measures

Primary Outcome Measure – Total Score on the Heinrichs Carpenter Quality of Life Scale (QLS). The QLS covers sense of purpose, motivation, emotional and social interaction, role functioning, and engagement in regular activities.

Secondary measures included the PANSS for symptom severity assessment, the Calgary Depression Scale for Schizophrenia, service utilization and a number of participant self-report measures.

Participants with Shorter Duration of Untreated Psychosis Gained More From NAVIGATE Treatment

FIGURE 3. Heinrichs-Carpenter Quality of Life (QLS) Total Score and PANSS Total Score: Effects of Shorter or Longer Duration of Untreated Psychosis (DUP) Based on a Model With Square Root Transformation of Months[a]



[a] In the model, DUP and DUP by square root of time by treatment terms were included as covariates in addition to the covariates listed in Table 2. The DUP by square root of time term was found not to be significant for either outcome. PANSS=Positive and Negative Syndrome Scale; CC=Community Care; NAV=NAVIGATE.
[b] DUP by treatment by square root of time interaction, p=0.003.
[c] DUP by treatment by square root of time interaction, p=0.043.

Kane, J.M. et. al. Am J Psychiatry 2016

Results

Compared with usual care, patients receiving NAVIGATE treatment were significantly more likely to remain in treatment and

- Had better quality of life
- Had less severe psychotic and depressive symptoms
- Had more gains in working or going to school
- Were more likely to receive a prescription that conformed to treatment guidelines
- Experienced less side effects

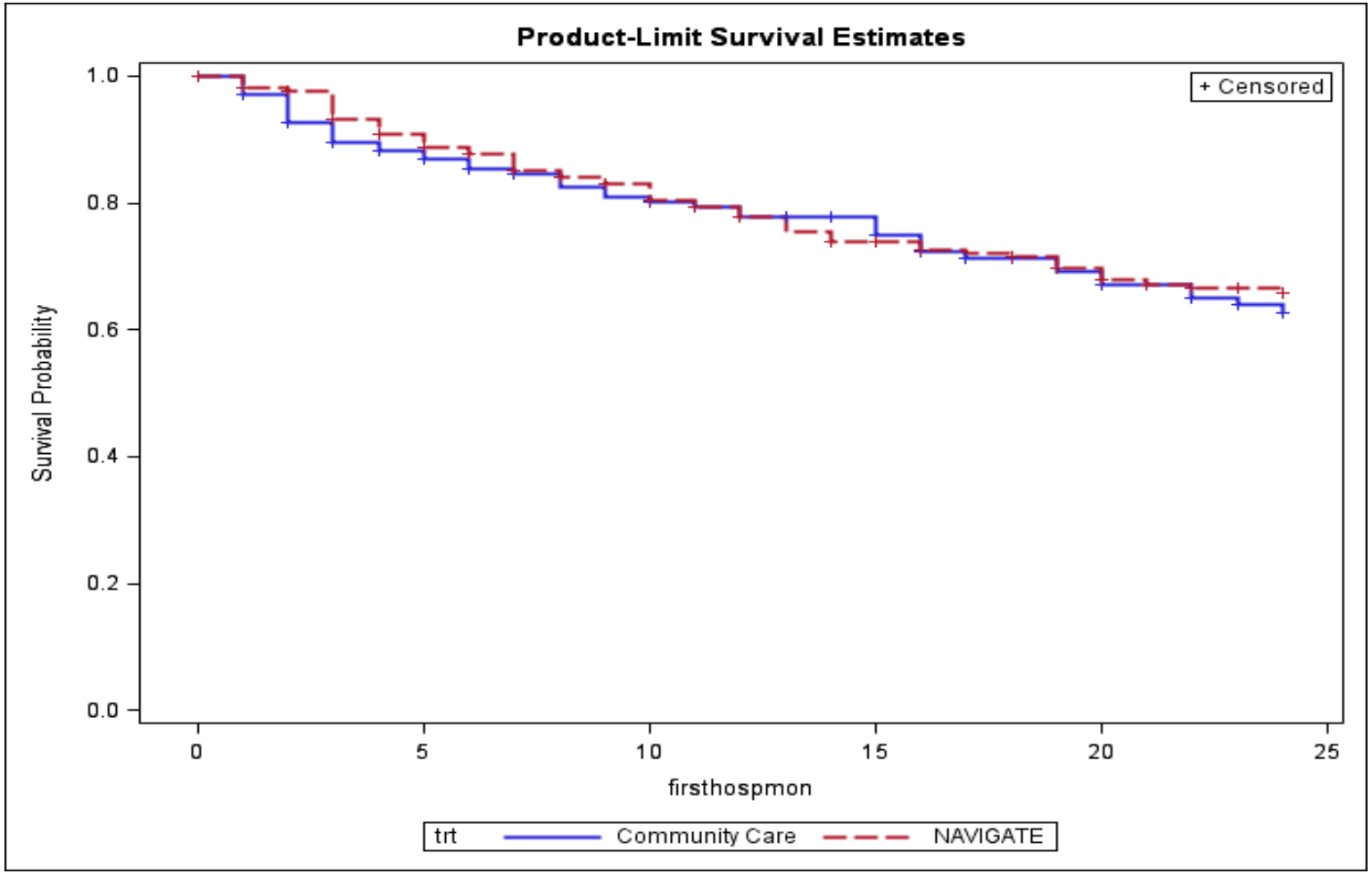
Duration of psychosis before treatment starts is an important moderator of initial NAVIGATE effectiveness

These results show that a coordinated specialty care model can be implemented in a diverse range of community clinics and that the quality of life of first episode patients can be improved

Kane, J.M. et. al. Am J Psychiatry 2016

Time to First Psychiatric Hospitalization

(Difference between treatments, p=0.75)



Kane, J.M. et. al. Am J Psychiatry 2016

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

Results

34% 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, time-varying days of substance misuse, presence of Positive and Negative Syndrome Scale 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 in medication taking. Addressing these factors could enhance the impact of first-episode early intervention treatment models, as well as enhance outcomes of first-episode psychosis treated with other models.

Robinson et al. Psychiatr Serv. 2019;70:569.

JAMA Psychiatry | Original Investigation

Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis

A Systematic Review, Meta-analysis, and Meta-regression

Christoph U. Correll, MD; Britta Galling, MD; Aditya Pawar, MD; Anastasia Krivko, MD; Chiara Bonetto, MD; Mirella Ruggeri, MD; Thomas J. Craig, PhD; Merete Nordentoft, MD; Vinod H. Srihari, MD; Sinan Guloksuz, MD; Christy L. M. Hui, PhD; Eric Y. H. Chen, MD; Marcelo Valencia, PhD; Francisco Juarez, PhD; Delbert G. Robinson, MD; Nina R. Schooler, PhD; Mary F. Brunette, MD; Kim T. Mueser, PhD; Robert A. Rosenheck, MD; Patricia Marcy, BSN; Jean Addington, PhD; Sue E. Estroff, PhD; James Robinson, MEd; David Penn, PhD; Joanne B. Severe, MS; John M. Kane, MD

IMPORTANCE The value of early intervention in psychosis and allocation of public resources has long been debated because outcomes in people with schizophrenia spectrum disorders have remained suboptimal.

OBJECTIVE To compare early intervention services (EIS) with treatment as usual (TAU) for early-phase psychosis.

DATA SOURCES Systematic literature search of PubMed, PsycINFO, EMBASE, and ClinicalTrials.gov without language restrictions through June 6, 2017.

STUDY SELECTION Randomized trials comparing EIS vs TAU in first-episode psychosis or early-phase schizophrenia spectrum disorders.

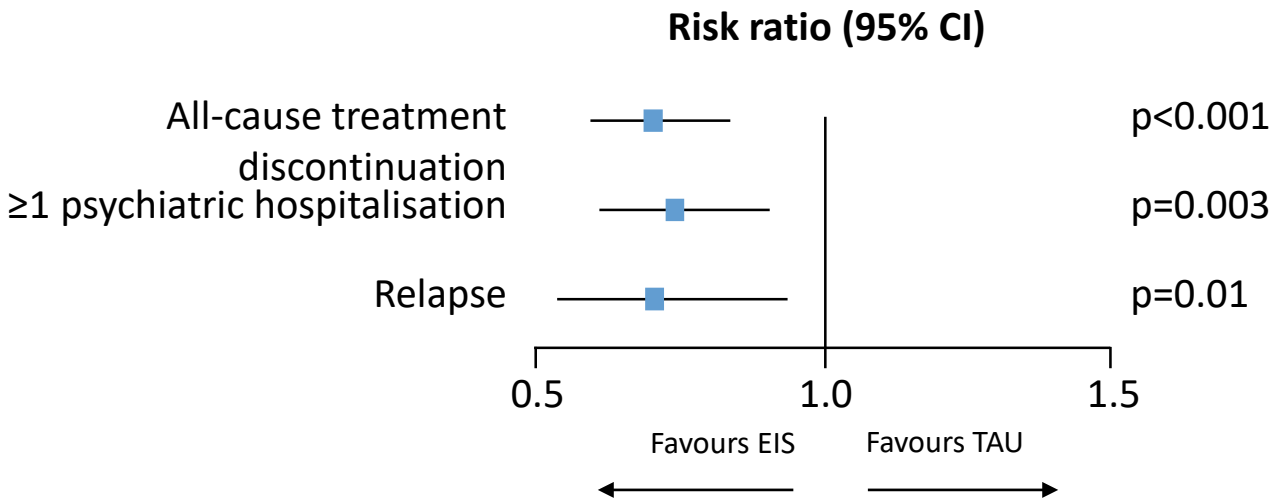
DATA EXTRACTION AND SYNTHESIS This systematic review was conducted according to PRISMA guidelines. Three independent investigators extracted data for a random-effects meta-analysis and prespecified subgroup and meta-regression analyses.

MAIN OUTCOMES AND MEASURES The coprimary outcomes were all-cause treatment discontinuation and at least 1 psychiatric hospitalization during the treatment period.

RESULTS Across 10 randomized clinical trials (mean [SD] trial duration, 16.2 [7.4] months; range, 9-24 months) among 2176 patients (mean [SD] age, 27.5 [4.6] years; 1355 [62.3%] male), EIS was associated with better outcomes than TAU at the end of treatment for all 13 meta-analyzable outcomes. These outcomes included the following: all-cause treatment discontinuation (risk ratio [RR], 0.70; 95% CI, 0.61-0.80; $P < .001$), at least 1 psychiatric hospitalization (RR, 0.74; 95% CI, 0.61-0.90; $P = .003$), involvement in school or work (RR, 1.13; 95% CI, 1.03-1.24; $P = .01$), total symptom severity (standardized mean difference [SMD] −0.32; 95% CI, −0.47 to −0.17; $P < .001$), positive symptom severity (SMD, −0.22; 95% CI, −0.32 to −0.11; $P < .001$), and negative symptom severity (SMD, −0.28; 95% CI, −0.42 to −0.14; $P < .001$). Superiority of EIS regarding all outcomes was evident at 6, 9 to 12, and 18 to 24 months of treatment (except for general symptom severity and depressive symptom severity at 18-24 months).

CONCLUSIONS AND RELEVANCE In early-phase psychosis, EIS are superior to TAU across all meta-analyzable outcomes. These results support the need for funding and use of EIS in patients with early-phase psychosis.

Comparison of early-intervention services vs treatment as usual for early-phase psychosis



The risk of ≥1 psychiatric hospitalisation in 10 studies among 2,105 patients was significantly lower with EIS than TAU (32.3% vs 42.4%; RR 0.74 [95% CI: 0.61, 0.90], p=0.003; NNT 10.1 [95% CI: 6.4, 23.9], p=0.001)

CI=confidence interval; EIS=early-intervention services; NNT=number-needed-to-treat; RR=relative risk; TAU=treatment as usual

Adapted from: Correll et al. JAMA Psychiatry 2018;75(6):555–565

IMPORTANCE Long-acting injectable antipsychotics (LAIs) can potentially reduce hospitalization risk by enhancing medication adherence but are rarely considered for early-phase schizophrenia treatment.

OBJECTIVE To determine whether encouraging use of a LAI compared with usual care delays the time to first hospitalization with patients with early-phase illness.

DESIGN, SETTING, AND PARTICIPANTS The Prevention of Relapse in Schizophrenia (PRELAPSE) trial was cluster randomized with a follow-up duration of 2 years. The study began in December 2014, was completed in March 2019, and was conducted in 39 mental health centers in 19 US states. Site randomization assigned 19 clinics to encourage treatment with long-acting aripiprazole monohydrate (aripiprazole once monthly [AOM] condition) and 20 to provide treatment as usual (clinician's choice [CC] condition). Participant eligibility criteria included (1) schizophrenia diagnosis confirmed by a structured clinical interview, (2) fewer than 5 years of lifetime antipsychotic use, and (3) age 18 to 35 years. The AOM sites identified 576 potentially eligible participants, of whom 234 (40.6%) enrolled; CC sites identified 685 potentially eligible participants, of whom 255 (37.2%) enrolled.

INTERVENTIONS There were no restrictions on treatment at CC sites (including using LAIs) or at A

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hospitalization was 613.7 days (95% CI, 582.3-645.1 days) for AOM participants and 530.6 days (95% CI, 497.3-563.9 days) for CC participants. For time to first hospitalization, the hazard ratio was 0.56 (95% CI, 0.34- 0.92; $P = .02$), favoring AOM. Survival probabilities were 0.73 (95% CI, 0.65-0.83) for AOM participants and 0.58 (95% CI, 0.50-0.67) for CC participants. The number needed to treat to prevent 1 additional hospitalization was 7 participants treated with AOM compared with CC.

CONCLUSIONS AND RELEVANCE Long-acting injectable antipsychotic use by patients with early-phase schizophrenia can significantly delay time to hospitalization, a personally and economically important outcome. Clinicians should more broadly consider LAI treatment fo patients with early-phase illness.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02360319

JAMA Psychiatry | Original Investigation

Effect of Long-Acting Injectable Antipsychotics vs Usual Care on Time to First Hospitalization in Early-Phase Schizophrenia

A Randomized Clinical Trial

John M. Kane, MD; Nina R. Schooler, PhD; Patricia Marcy, BSN; Christoph U. Correll, MD; Eric D. Achtyes, MD; Robert D. Gibbons, PhD; Delbert G. Robinson, MD

CONCLUSIONS AND RELEVANCE Long-acting injectable antipsychotic use by patients with early-phase schizophrenia can significantly delay time to hospitalization, a personally and economically important outcome. Clinicians should more broadly consider LAI treatment for patients with early-phase illness.

Kane, J. M., et. al. (2020) *JAMA psychiatry*, *77*(12), 1217-1224.

Five Year Outcomes

Includes periods of active EIS treatment and follow-up care

Over 5 years, NAVIGATE compared to CC treated participants:

- Better QLS scores. The estimate was 13.14 units favoring NAVIGATE ($p < 0.001$)
- Better PANSS scores. The estimate was 7.73 units favoring NAVIGATE ($p < 0.002$)
- Fewer days in hospital. Estimated days for Community Care was 5.97 for CC and 3.46 for NAVIGATE($p=0.02$)

Robinson D.G. et. al. Schiz Bull 2022

Conclusions #1

- RAISE-ETP provides compelling evidence of a lasting benefit in quality of life and in symptom outcomes with NAVIGATE during a period with EIS and post-EIS treatment
- For the PANSS total it is an 8 point greater gain for NAVIGATE treated patients and for the QLS Total Score the difference in gain is 13 points
- These benefits are substantial. For context the minimal clinically important difference with the QLS total score is 5.3 points

Robinson D.G. et. al. Schiz Bull 2022

Conclusions #2

- Further, these differential gains were in comparison to standard care treatment that was itself effective in improving QLS and PANSS scores.
- The finding of long-term benefit both during and after EIS ends is in contrast to prior studies
- Possible explanations
  - Longitudinal assessment model
  - US versus European setting
  - Statistical methodology employed

Robinson D.G. et. al. Schiz Bull 2022

Payment for Services When RAISE-ETP Ended

CSC Role	Coverage Status
Team Leadership	Not covered
Psychotherapy	Billable via CPT 90832; 90834; 90853
Case Management	Inconsistently covered*
Family Education and Support	Billable via CPT 90846; 90847; 90849
Supported Employment/ Education	Inconsistently covered*
Pharmacotherapy and Primary Care Coordination	Billable via CPT 99214
CSC Team-Level Activity	Not covered

*if covered, coverage is almost only provided by Medicaid

Source: NIMH white paper Evidence-Based Treatments for First Episode Psychosis: Components of Coordinated Specialty Care

Conclusions

Coordinated Specialty Care/Early Intervention Services have been shown to provide important benefits for those with early phase schizophrenia

The duration of untreated psychosis remains a target

Relapse and hospitalization rates should be reduced to the extent possible

Sustained implementation can be a challenge