The Good, the Bad and the Uncertain in the Treatment of Schizophrenia

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UNMET NEEDS IN TREATING SCHIZOPHRENIA

RESIDUAL POSITIVE SYMPTOMS

NEGATIVE SYMPTOMS

RECOVERY

ADHERENCE

COGNITIVE DYSFUNCTION

SUBSTANCE ABUSE

COMORBID MEDICAL CONDITIONS

BREAKTHROUGH ON ANTIPSYCHOTIC MEDICATION

A Systematic Review and Meta-analysis of Recovery in Schizophrenia

Erika Jääskeläinen[*,1,6], Pauliina Juola[1], Noora Hirvonen[1,2], John J. McGrath[3,4], Sukanta Saha[3], Matti Isohanni[1], Juha Veijola[1], and Jouko Miettunen[1,5,6]

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[6]These authors contributed equally to the article.

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Conclusions:

Based on the best available data, approximately, 1 in 7 individuals with schizophrenia met our criteria for recovery. Despite major changes in treatment options in recent decades, the proportion of recovered cases has not increased

Jääskeläinen E et al. Schizophr Bull 2013;39(6):1296–1306

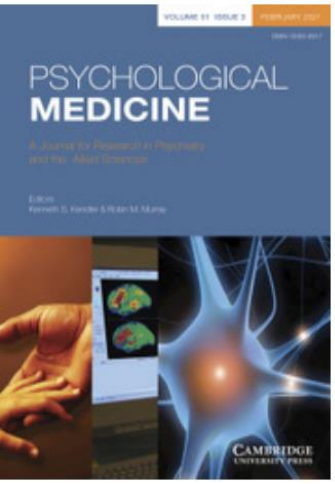
The Effect of Family Interventions on Relapse and Rehospitalization in Schizophrenia—A Meta-analysis FREE

Gabi Pitschel-Walz ✉, Stefan Leucht, M.D., Josef Bäuml, Werner Kissling, Rolf R. Engel

Schizophrenia Bulletin, Volume 27, Issue 1, 2001, Pages 73–92,
https://doi.org/10.1093/oxfordjournals.schbul.a006861
Published: 01 January 2001

Abstract
Twenty-five intervention studies were meta-analytically examined regarding the effect of including relatives in schizophrenia treatment… The main result of the meta-analysis was that the relapse rate can be reduced by 20 percent if relatives of schizophrenia patients are included in the treatment.

Schizophr Bull 2001;27(1):73-92



Psychological treatments in schizophrenia: I. Meta-analysis of family intervention and cognitive behaviour therapy

Published online by Cambridge University Press: **15 August 2002**

S. PILLING, P. BEBBINGTON, E. KUIPERS, P. GARETY, J. GEDDES, G. ORBACH and C. MORGAN

Show author details

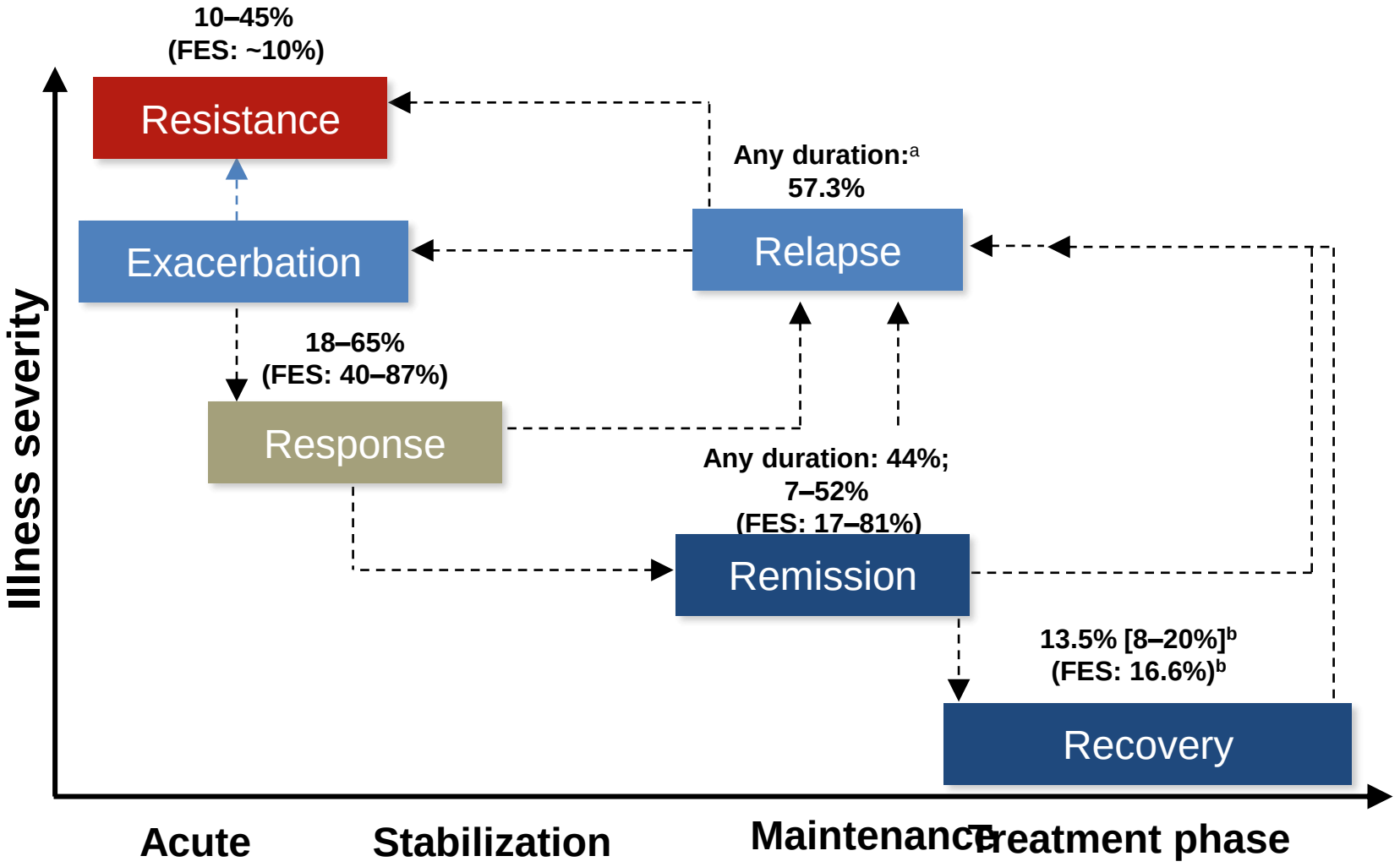
Family therapy can reduce risk of relapse and hospitalization as well as facilitate adherence

Cognitive behavior therapy (CBT) can improve mental state and reduce dropouts

CBT can be helpful in some treatment resistant patients

Psychol Med 2002 Jul;32(5):763-82.

Medication Efficacy in Different Disease Phases in Schizophrenia

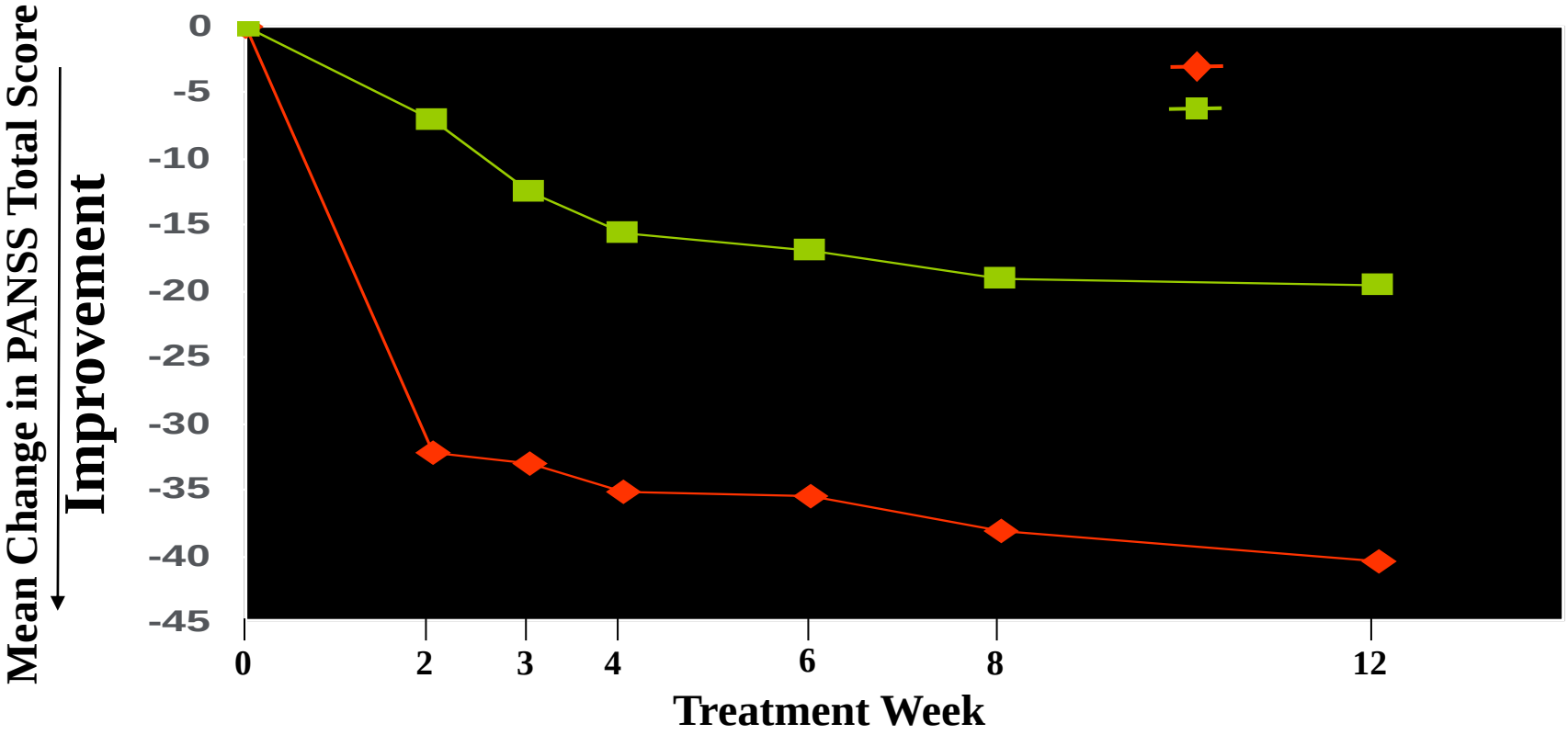


[a]In antipsychotic discontinuation studies; [b]median (interquartile range)
FES=first-episode schizophrenia

Carbon & Correll. Dialogues Clin Neurosci 2014;16(4):505–524

Early Treatment Responders On Risperidone Demonstrated Better Symptom Improvement Than Early Non-Responders On Risperidone

Early Responders Showed Significantly More Improvement on PANSS Total Score Than Early Non-Responders at All Time Points from Week 1 to Week 12



- **Response was defined as ≥ 20% improvement in PANSS Total Score at 2 weeks.**

Kinon B et al. Neuropsychopharm 2010

Early Improvement As a Predictor of Later Response to Antipsychotics in Schizophrenia: A Diagnostic Test Review

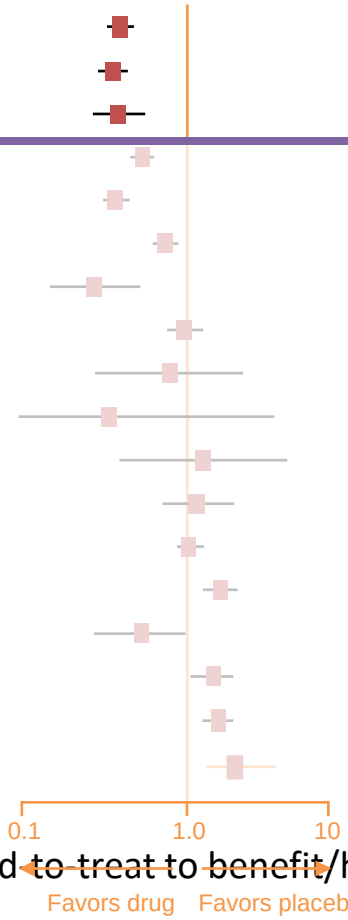
Those patients experiencing a psychotic relapse who receive adequate treatment for two weeks and do not achieve minimal improvement (i.e. 20% from baseline) are not likely to experience the desired level of further improvement and a change in treatment should be considered

Samara M et al. Am J Psychiatry 2015 Jul; 172(7):617-29

Relapse prevention – antipsychotic drugs vs placebo

Summary of pooled results from randomized trials of antipsychotic drugs compared with placebo as maintenance treatment in patients with schizophrenia

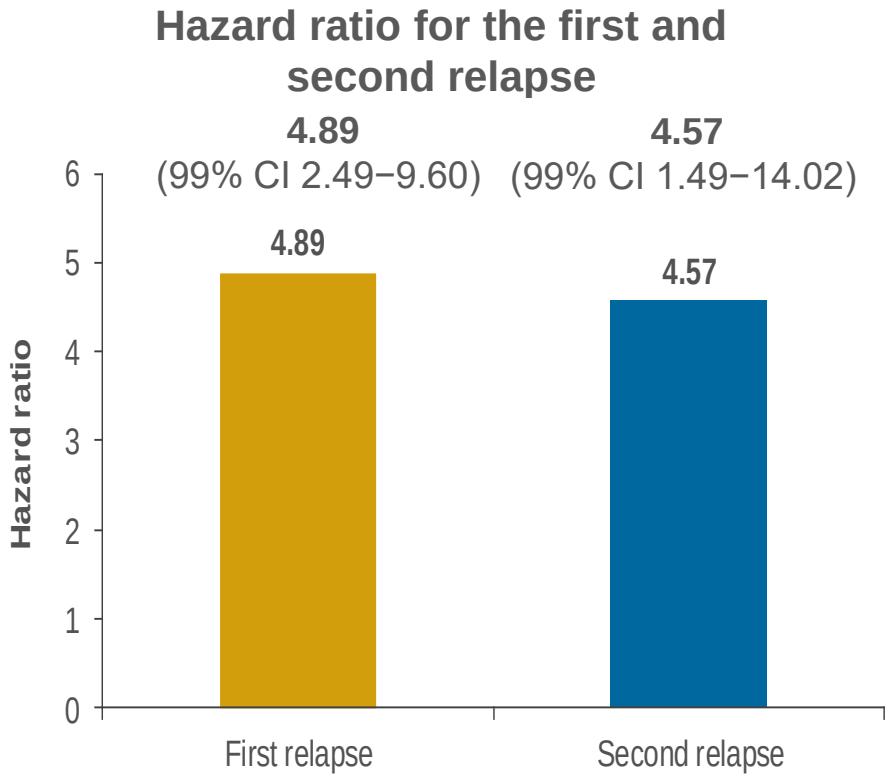
Outcome	Number of studies	Drug group	Control group	Mean study duration (months)	Risk ratio (95% CI)	Absolute difference (95% CI)	NNTB/H
Relapse 7–12 months	24	392/1,465 (27%)	773/1,204 (64%)	11		-0·39 (-0·46, -0·32)	3
Relapse independent of duration	62	744/3,395 (22%)	1,718/2,997 (57%)	9		-0·38 (-0·43, -0·33)	3
Participants readmitted to hospital	16	112/1,132 (10%)	245/958 (26%)	13		-0·19 (-0·27, -0·11)	5
Dropout for any reason	57	802/2,642 (30%)	1,130/2,076 (54%)	9		-0·24 (-0·30, -0·17)	4
Dropout because of inefficacy	46	412/2,539 (16%)	830/2,007 (41%)	8		-0·27 (-0·34, -0·19)	4
Participants unimproved/worse	14	614/880 (70%)	569/644 (88%)	5		-0·25 (-0·35, -0·14)	4
Violent/aggressive behavior	5	9/403 (2%)	34/277 (12%)	8		-0·09 (-0·17, -0·01)	11
Participants employed	2	63/130 (48%)	65/129 (50%)	11		-0·02 (-0·14, 0·10)	50
Death (any)	14	5/1,240 (<1%)	7/1,116 (1%)	7		0·00 (-0·01, 0·00)	∞
Suicide	8	0/1,021 (0%)	2/920 (<1%)	6		0·00 (-0·01, 0·00)	∞
Death from natural causes	14	5/1,272 (1%)	3/1,129 (<1%)	7		0·00 (0·00, 0·01)	∞
Dropout because of AE	43	129/2,437 (5%)	78/1,896 (4%)	8		0·00 (-0·01, 0·02)	∞
At least one AE	10	575/1,188 (48%)	450/996 (45%)	7		0·01 (-0·06, 0·08)	100
At least one movement disorder	22	304/1,901 (16%)	134/1,510 (9%)	7		0·06 (0·03, 0·10)	17
Dyskinesia	13	18/1,051 (2%)	37/769 (5%)	9		-0·01 (-0·02, 0·01)	100
Use of antiparkinsonian medication	7	182/748 (24%)	90/569 (16%)	7		0·09 (0·02, 0·16)	11
Sedation	10	158/1,174 (13%)	85/972 (9%)	6		0·05 (0·00, 0·10)	20
Weight gain	10	128/1,231 (10%)	61/1,090 (6%)	7		0·05 (0·03, 0·07)	20



- AE=adverse event; CI=confidence interval; NNTB/H=number-needed-to-treat-to-benefit/harm
- Adapted from: Leucht et al. Lancet 2012;379(9831):2063–2071

Stopping medication is a powerful predictor of relapse

Survival analysis: risk of a first or second relapse when not taking medication is **~5 times** greater than when taking it

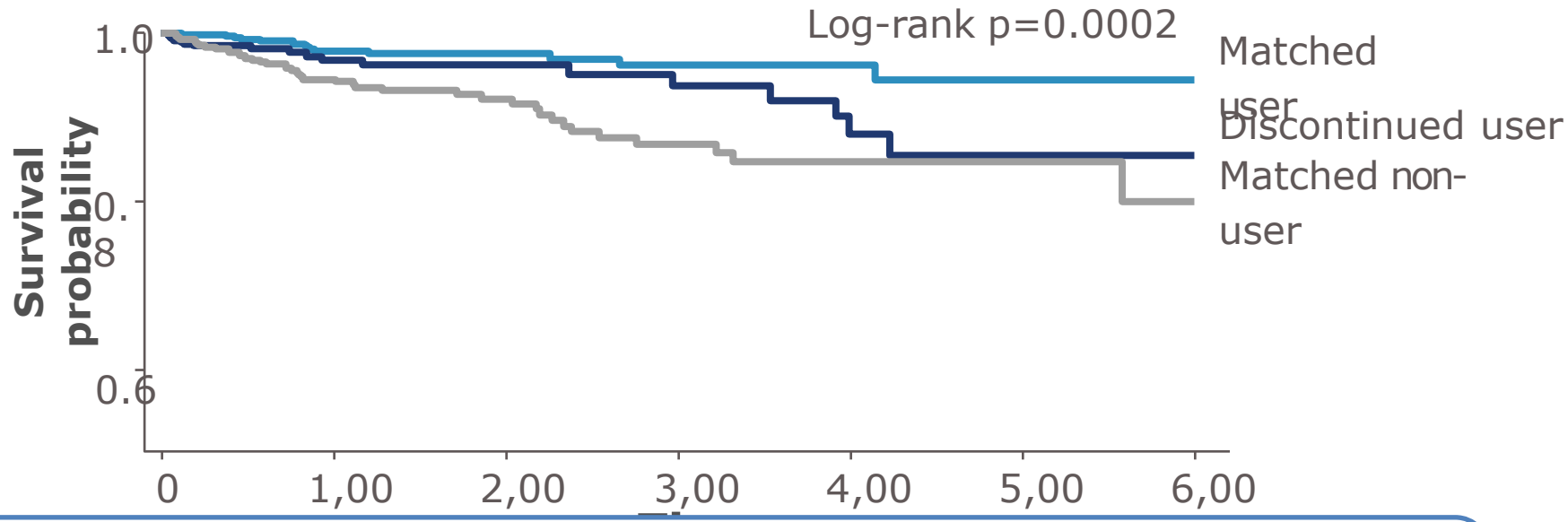


First relapse, n=104; second relapse, n=63. CI=confidence intervals.

Adapted from: Robinson et al. Arch Gen Psychiatry 1999;56(3):241–247.

Continuation of antipsychotics in patients with first episode schizophrenia increases the chance of survival

This prospective study investigated the risk of treatment failure (psychiatric rehospitalization or death) after discontinuation of antipsychotic treatment. Outcomes data were collected from Finnish nationwide register data for all patients hospitalized for the first time with a schizophrenia diagnosis between 1996–2014 (N=8,719)



Compared with the continuous users of antipsychotics:

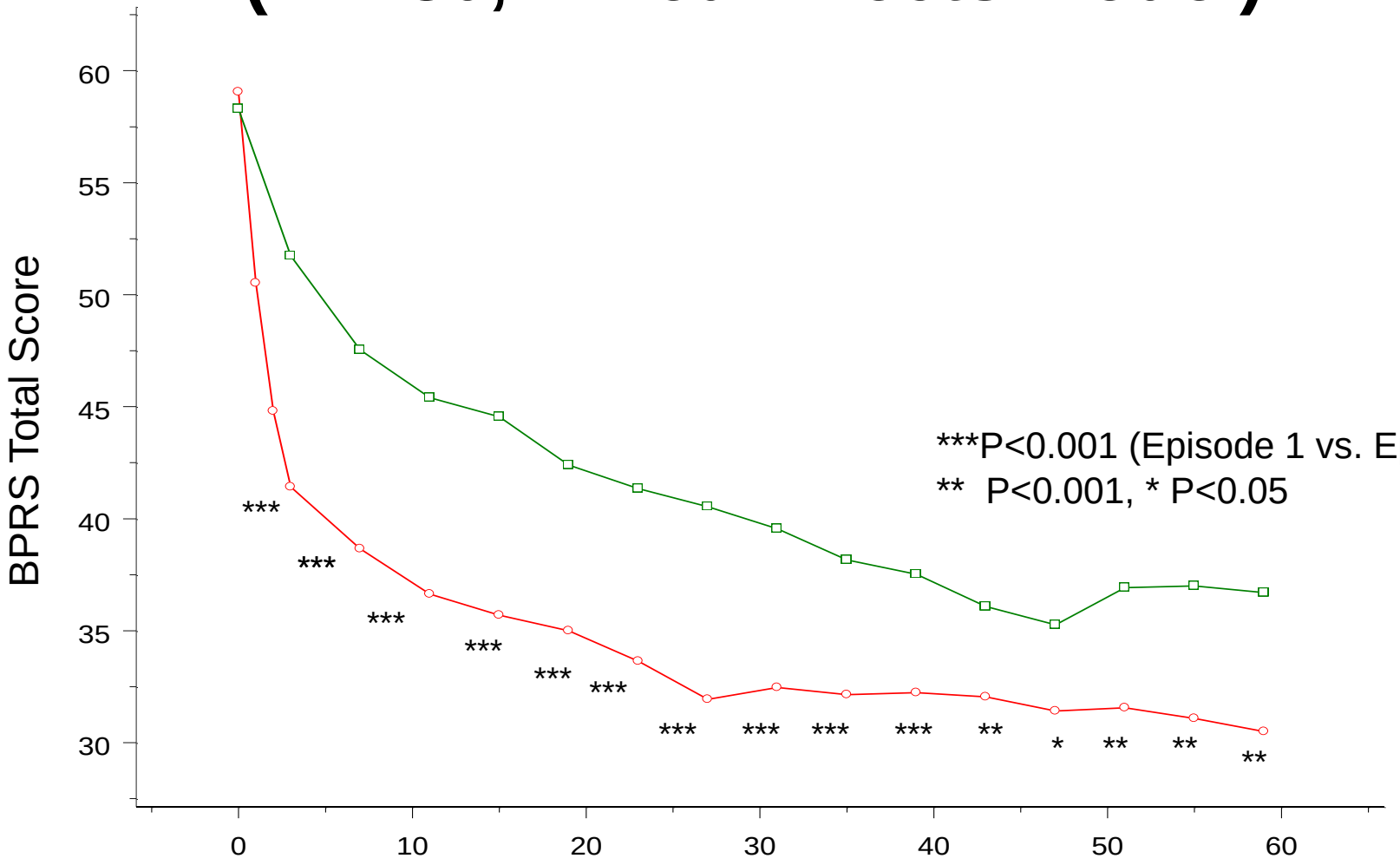
- No antipsychotic use: 214% higher risk of death (HR=3.14, 95% CI: 1.29–7.68)
- Early discontinuation: 174% higher risk of death (HR=2.74, 95% CI: 1.09–6.89)

non-user).

CI, confidence interval; HR, hazard ratio.

Tiihonen J et al. *Am J Psychiatry* 2018; 175: 765–773.

BPRS Total Trajectory in Phases 1 and 2 (N=130, Mixed Effects Model)



P-value 0.230
Baseline

Takeuchi H et al, Neuropsychopharmacology 2019

The American Journal of Psychiatry

Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program

John M. Kane, M.D., Delbert G. Robinson, M.D., Nina R. Schooler, Ph.D., Kim T. Mueser, Ph.D., David L. Penn, Ph.D., Robert A. Rosenheck, M.D., Jean Addington, Ph.D., Mary F. Brunette, M.D., Christoph U. Correll, M.D., **... See all authors**

Coordinated Specialty Care: Early Intervention Services

Psychosocial interventions should be tailored to the goals, needs, abilities and circumstances of the individual patient

NAVIGATE

Team based

- Shared decision-making
- Strength & resiliency focus
- Psychoeducational teaching skills
- Motivational enhancement teaching skills
- Collaboration with natural supports

Four components

- **Psychopharmacology**
- **Individual Resiliency Training (IRT)**
- **Family psychoeducation**
- **Supported employment/education**

Kane, J. et. al. Am J Psych 2016 Apr1;173(4):362-72; https://pubmed.ncbi.nim.nih.gov/25772766/

Psychopharmacological Treatment in the RAISE-ETP Study: Outcomes of a Manual and Computer Decision Support System Based Intervention

Delbert G. Robinson, M.D., Nina R. Schooler, Ph.D., Christoph U. Correll, M.D., Majnu John, Ph.D., Benji T. Kurian, M.D., M.P.H., Patricia Marcy, B.S.N., Alexander L. Miller, M.D., Ronny Pipes, M.A., L.P.C.-S., Madhukar H. Trivedi, M.D., John M. Kane, M.D.

Objective: The Recovery After an Initial Schizophrenia Episode–Early Treatment Program compared NAVIGATE, a comprehensive program for first-episode psychosis, to clinician-choice community care over 2 years. Quality of life and psychotic and depressive symptom outcomes were found to be better with NAVIGATE. Compared with previous comprehensive first-episode psychosis interventions, NAVIGATE medication treatment included unique elements of detailed first-episode-specific psychotropic medication guidelines and a computerized decision support system to facilitate shared decision making regarding prescriptions. In the present study, the authors compared NAVIGATE and community care on the psychotropic medications prescribed, side effects experienced, metabolic outcomes, and scores on the Adherence Estimator scale, which assesses beliefs related to nonadherence.

Method: Prescription data were obtained monthly. At baseline and at 3, 6, 12, 18, and 24 months, participants reported whether they were experiencing any of 21 common antipsychotic side effects, vital signs were obtained, fasting blood samples were collected, and the Adherence Estimator scale was completed.

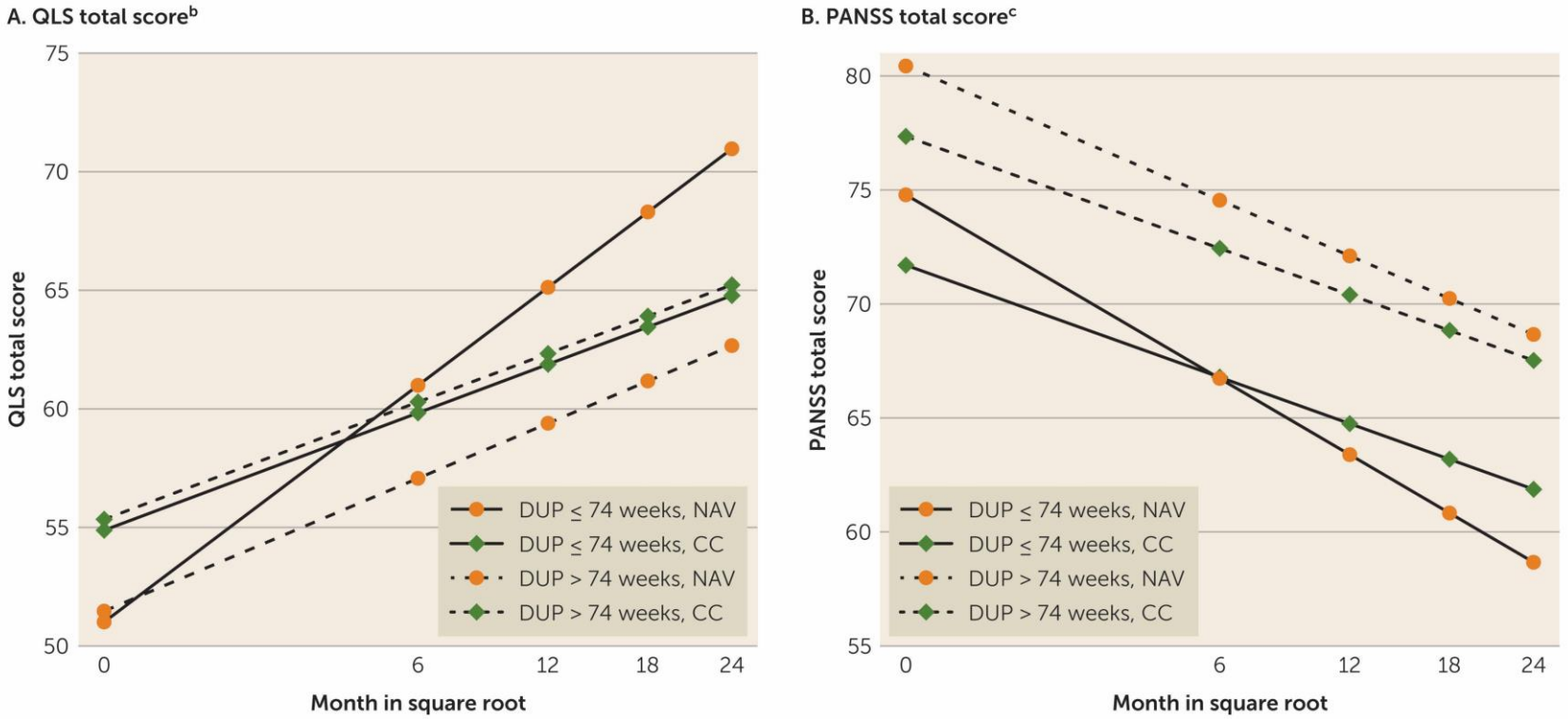
Results: Over the 2-year study period, compared with the 181 community care participants, the 223 NAVIGATE participants had more medication visits, were more likely to receive a prescription for an antipsychotic and more likely to receive one conforming to NAVIGATE prescribing principles, and were less likely to receive a prescription for an antidepressant. NAVIGATE participants experienced fewer side effects and gained less weight; other vital signs and cardiometabolic laboratory findings did not differ between groups. Adherence Estimator scores improved in the NAVIGATE group but not in the community care group.

Conclusions: As part of comprehensive care services, medication prescription can be optimized for first-episode psychosis, contributing to better outcomes with a lower side effect burden than standard care.

AJP in Advance (doi: 10.1176/appi.ajp.2017.16080919)

DUP and QLS and PANSS Outcomes

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]

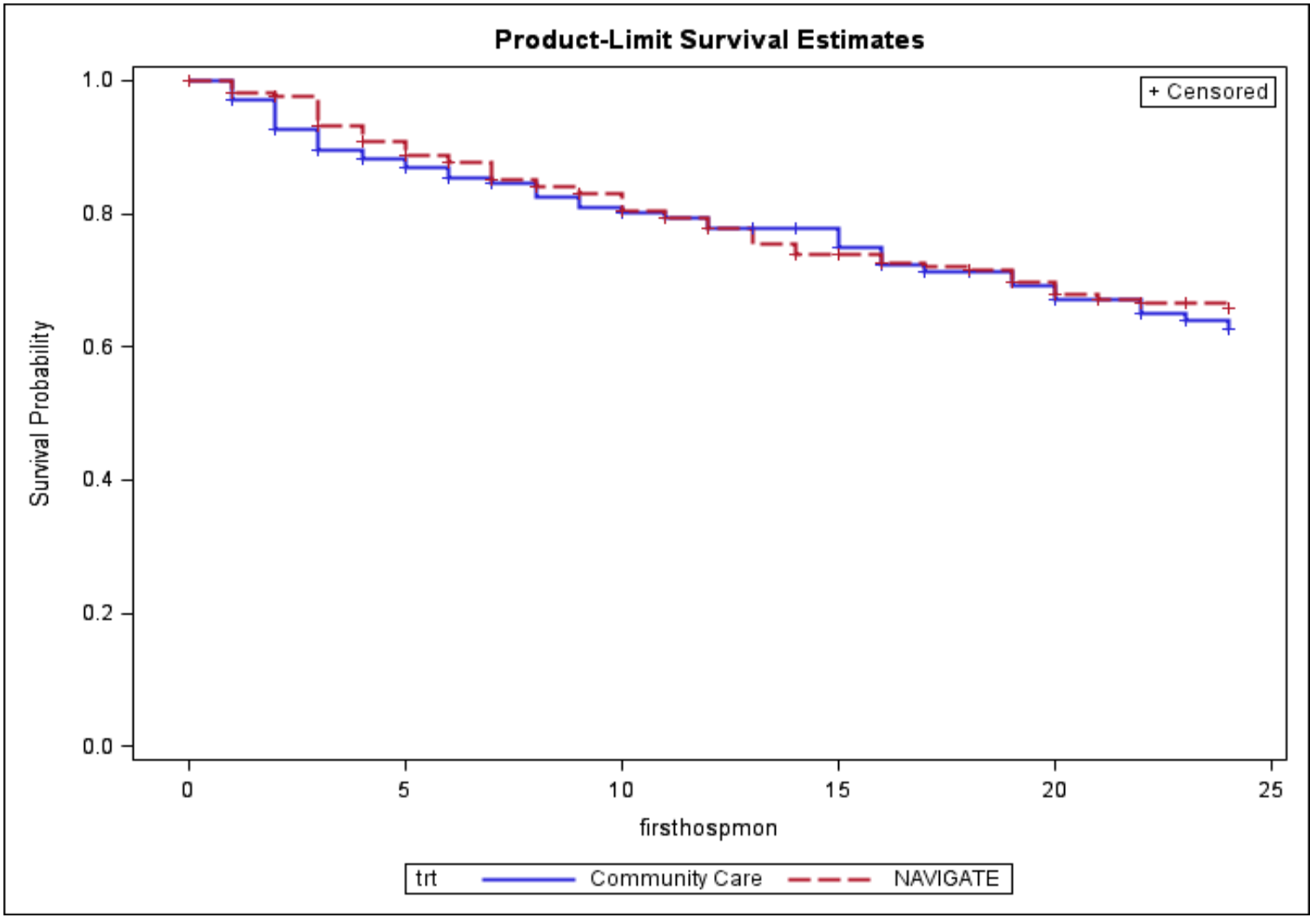


[a] In the model, DUP and DUP by square root of time by treatment terms were included as covariates in addition to the covariates listed in Table 2. The DUP by square root of time term was found not to be significant for either outcome. PANSS=Positive and Negative Syndrome Scale; CC=Community Care; NAV=NAVIGATE.
[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 JM et al. AJP 2016

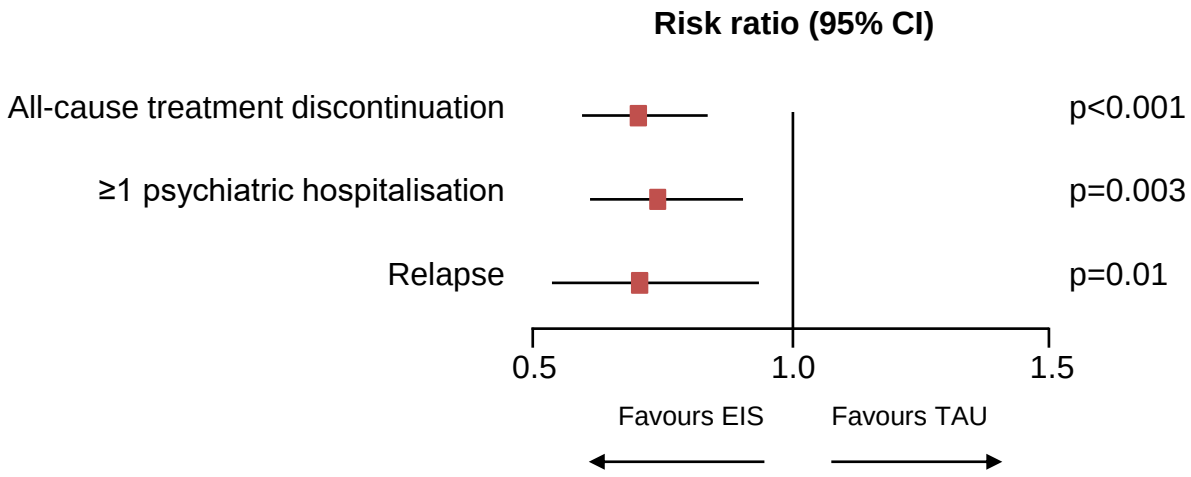
Time to First Psychiatric Hospitalization

(Difference between treatments, p=0.75)



Kane JM et al. AJP 2016

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

Psychiatr Serv. Author manuscript; available in PMC 2020 Jul 1.
Published in final edited form as:
Psychiatr Serv. 2019 Jul 1; 70(7): 569–577.
Published online 2019 May 14. doi: 10.1176/appi.ps.201800511

PMCID: PMC6602852
NIHMSID: NIHMS1525105
PMID: 31084291

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

Delbert G. Robinson, M.D.,[a,b] Nina R. Schooler, Ph.D.,[c] Robert A. Rosenheck, M.D.,[d] Haiqun Lin, Ph.D.,[e] Kyaw J. Sint, M.P.H.,[e] Patricia Marcy, B.S.N.,[f] and John M. Kane, M.D.[a,b]

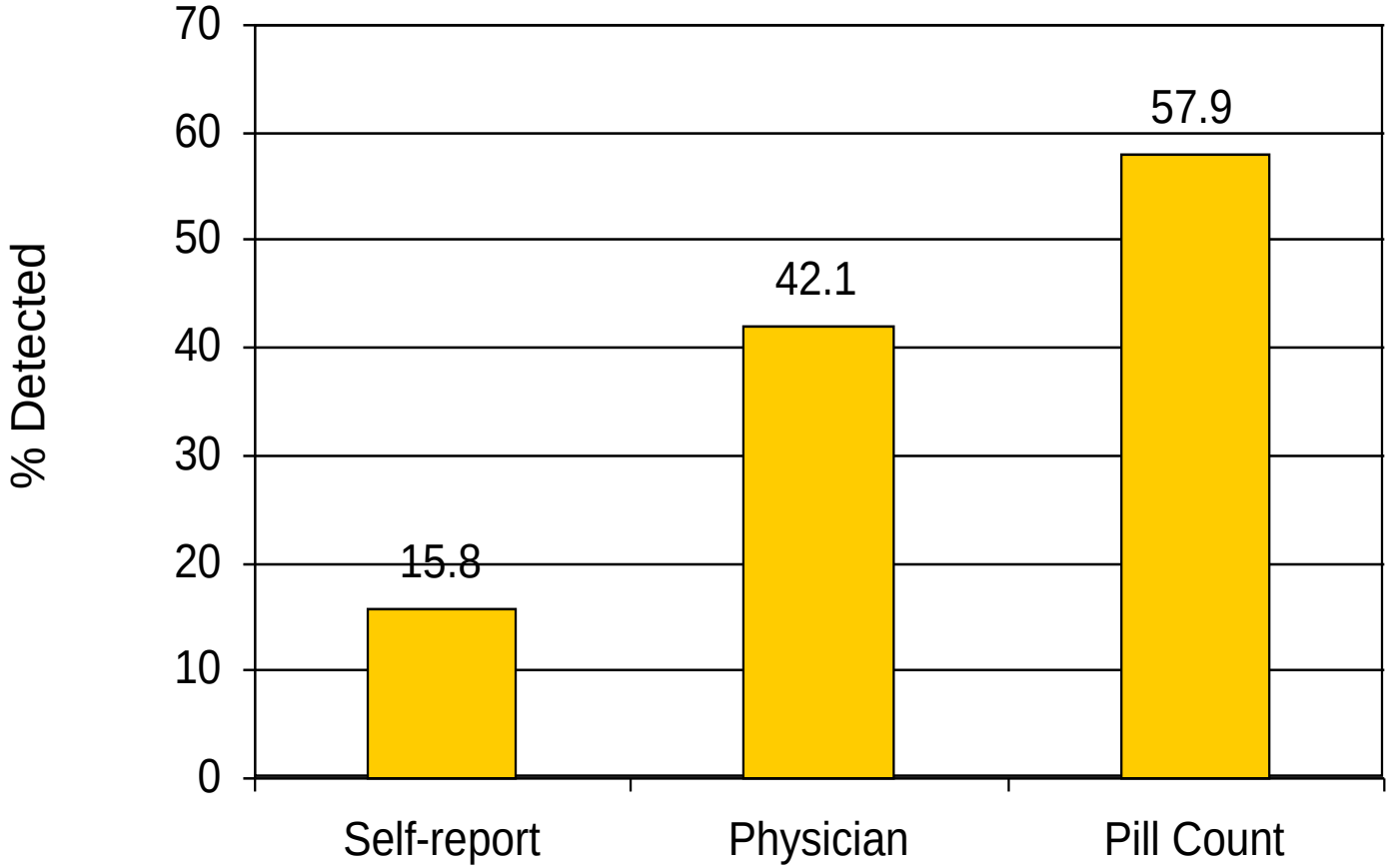
One third of first episode patients are hospitalized within two years

Duration of untreated psychosis (DUP), substance misuse, and residual positive symptoms are risk factors

Negative beliefs about the value of medication (a proxy for nonadherence) also predict hospitalization

Reducing DUP, minimizing residual symptoms, preventing substance misuse and facilitating adherence in medication taking should be treatment goals to improve outcomes in early phase illness

Detection of Antipsychotic Non-adherence



Criterion standard (n=19) is MEMS MPR ≤.80 over 12 wks, compared with patient self-report, physician impressions, and unannounced in home pill counts. Patient and physician reports correlated with BPRS.

BPRS=Brief Psychiatric Rating Scale; MPR=medication possession ratio.

Velligen et al. *Psych Serv.* 2007Sep;58(9):1187-92

Potential Clinical Consequences of Undetected Medication Non-adherence

- Unidentified non-adherence may lead to unnecessary:
  - Antipsychotic medication changes[1]
  - Dosage increases[1,2]
  - Concomitant antipsychotic medications[1]
  - Labeling of patients as "treatment resistant"[1]
- Identify patient adherence patterns then find the best treatment option[2,3]

1. Velligan DI, et al. *Psychiatric Services*. 2007;58:1187-1192. 2. Velligan DI, et al. *Schizophr Bull.* 2006;32:724-742.
3. Byerly M, et al. *Psychiatry Res.* 2005;133:129-133.

Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology

Objective: Research and clinical translation in schizophrenia is limited by inconsistent definitions of treatment resistance and response. To address this issue, the authors evaluated current approaches and then developed consensus criteria and guidelines.

Method: A systematic review of randomized antipsychotic clinical trials in treatment-resistant schizophrenia was performed, and definitions of treatment resistance were extracted. Subsequently, consensus operationalized criteria were developed through 1) a multiphase, mixed methods approach, 2) identification of key criteria via an online survey, and 3) meetings to achieve consensus.

Results: Of 2,808 studies identified, 42 met inclusion criteria. Of these, 21 studies (50%) did not provide operationalized criteria. In the remaining studies, criteria varied considerably, particularly regarding symptom severity, prior treatment duration, and antipsychotic dosage thresholds; only two studies (5%) utilized the same criteria. The consensus group identified minimum and optimal criteria, employing the following principles: 1) current symptoms of a minimum duration and severity determined by a standardized rating scale; 2) moderate or worse functional impairment; 3) prior treatment consisting of at least two different antipsychotic trials, each for a minimum duration and dosage; 4) systematic monitoring of adherence and meeting of minimum adherence criteria; 5) ideally at least one prospective treatment trial; and 6) criteria that clearly separate responsive from treatment-resistant patients.

Conclusions: There is considerable variation in current approaches to defining treatment resistance in schizophrenia. The authors present consensus guidelines that operationalize criteria for determining and reporting treatment resistance, adequate treatment, and treatment response, providing a benchmark for research and clinical translation.

AJP in Advance (doi: 10.1176/appi.ajp.2016.16050503)

Howes OD et al. AJP 2017 Mar 1;174(3):216-229.

CLOZAPINE

Clozapine remains the only medication with regulatory approval for treatment resistant schizophrenia[1]

Most guidelines suggest implementing clozapine after two failures of antipsychotic medications given in adequate doses with adequate adherence for six weeks[2]

To rule out “pseudo-resistance” due to inadequate treatment adherence, the optimal definition of treatment resistance would include at least one failed trial with a long-acting injectable antipsychotic, given for at least 6 weeks after it has achieved steady state (generally at least 4 months from commencing treatment).[2]

Clozapine remains grossly underutilized, especially in early phase patients, 15-20% of whom are already treatment resistant.[3]

Delaying the implementation of clozapine for more than a year or two is associated with poorer ultimate response.[4, 5]

1. Kane J et al. Arch Gen Psychiatry 1988 Sep;45(9):789-96
2. Howes OD, et al. Am J Psychiatry. 2017 Mar 1;174(3):216-229
3. Demjaha A, et al. Psychol Med. 2017 Aug;47(11):1981-1989
4. Chan SKW, et al. Schizophr Bull. 2021 Mar 16;47(2):485-494.
5. Shah P, et al. Psychiatry Res. 2018 Oct;268:114-122.

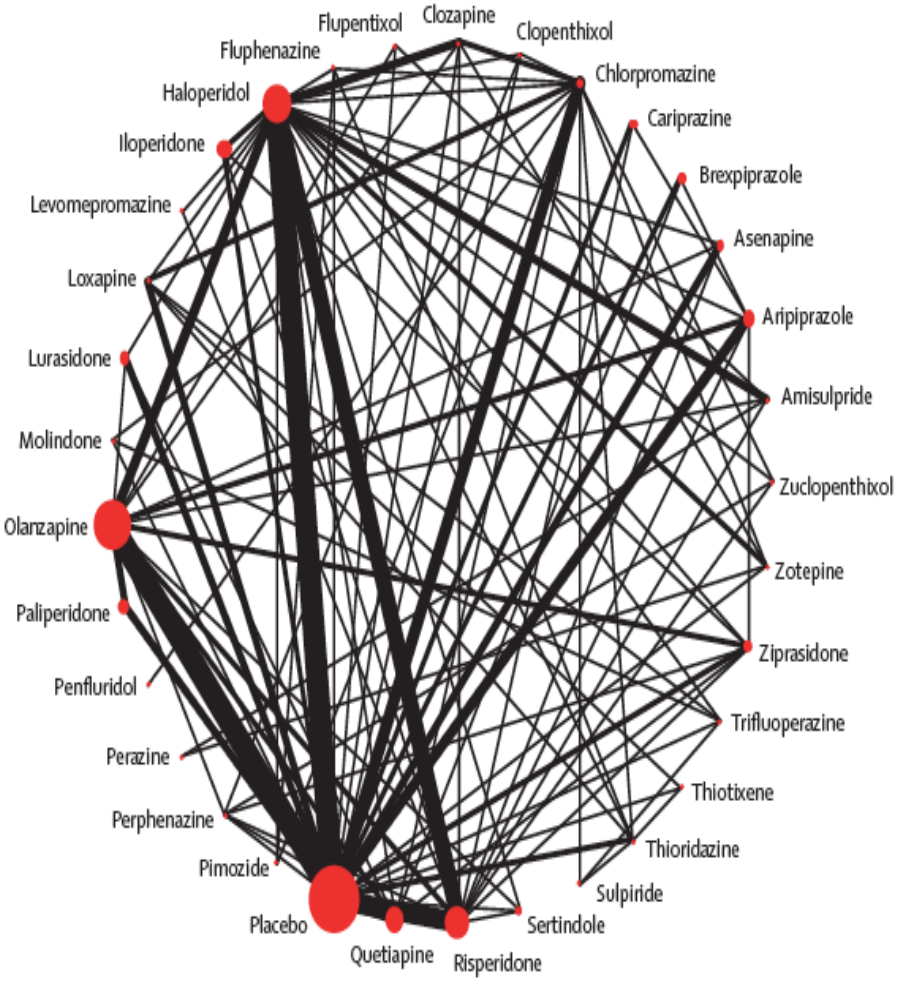
Antipsychotic Network Meta-analysis

Aim

- Create hierarchy for 32 antipsychotics
- Efficacy and major side effects
- Direct and indirect comparisons

Data set

- 402 RCTs for acute schizophrenia
- 53,463 participants
- Mean illness duration: 11.9 years
- Mean age: 37.4 years
- 56.02% male



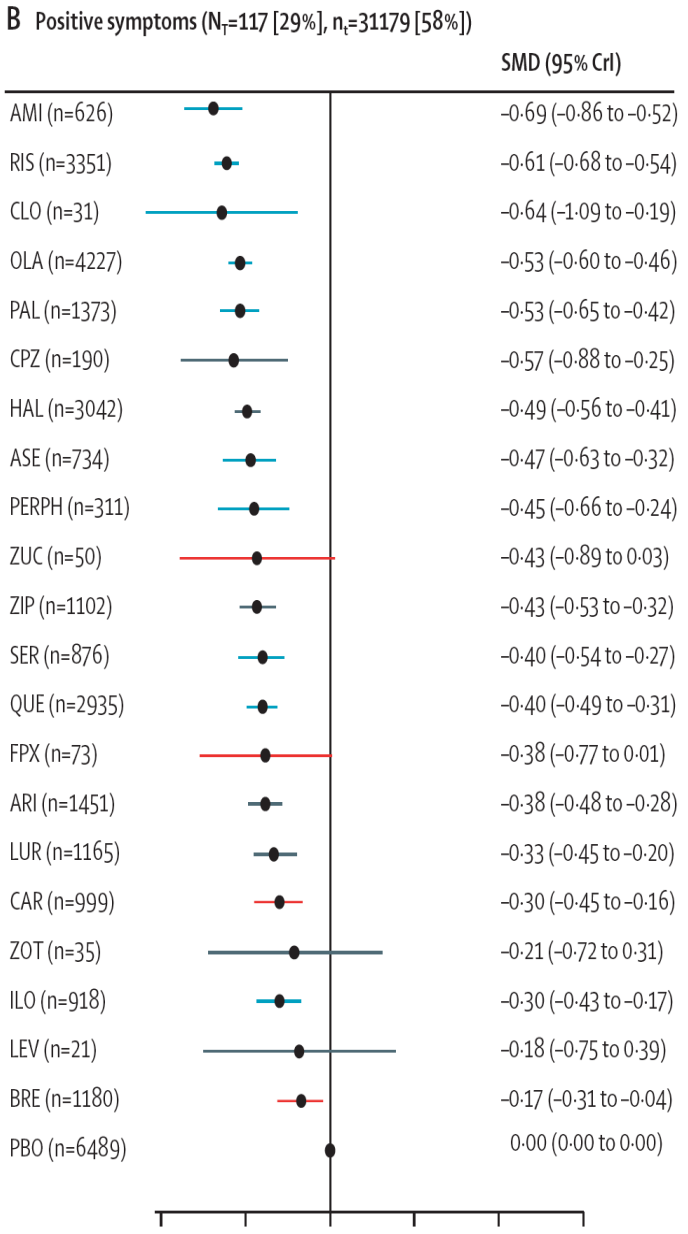
Network of comparisons

RCT = randomized controlled trial.

Huhn M, et al. *Lancet*. 2019;394(10202):939-951.

Key Findings

"There are some efficacy differences between antipsychotics, but most of them are gradual rather than discrete. Differences in side effects are more marked."



Huhn M, et al. *Lancet*. 2019;394(10202):939-951.

Schizophrenia Bulletin
doi:10.1093/schbul/sbab016

EDITORIAL

Antipsychotic Medications: Enhancing Use to Improve Outcomes

Hiroyoshi Takeuchi[*,1,2], **Stefan Leucht**[3], **John M. Kane**[4,5], **Ofer Agid**[2,6,7], **and Gary Remington**[2,6–8,]

Increased efficacy dramatically diminishes above risperidone equivalent 3.7 mg/day, corresponding to 2-fold MED. Accordingly, evidence supports prescribing 2-fold MED in the acute treatment of schizophrenia if response is insufficient at MED.

Given that relapse, even one, contributes to attenuated response, maintenance antipsychotic treatment represents the safest strategy in terms of clinical outcome.

Schizophr Bull 2021 Mar 22;sbab016. doi: 10.1093/schbul/sbab016. Online ahead of print.

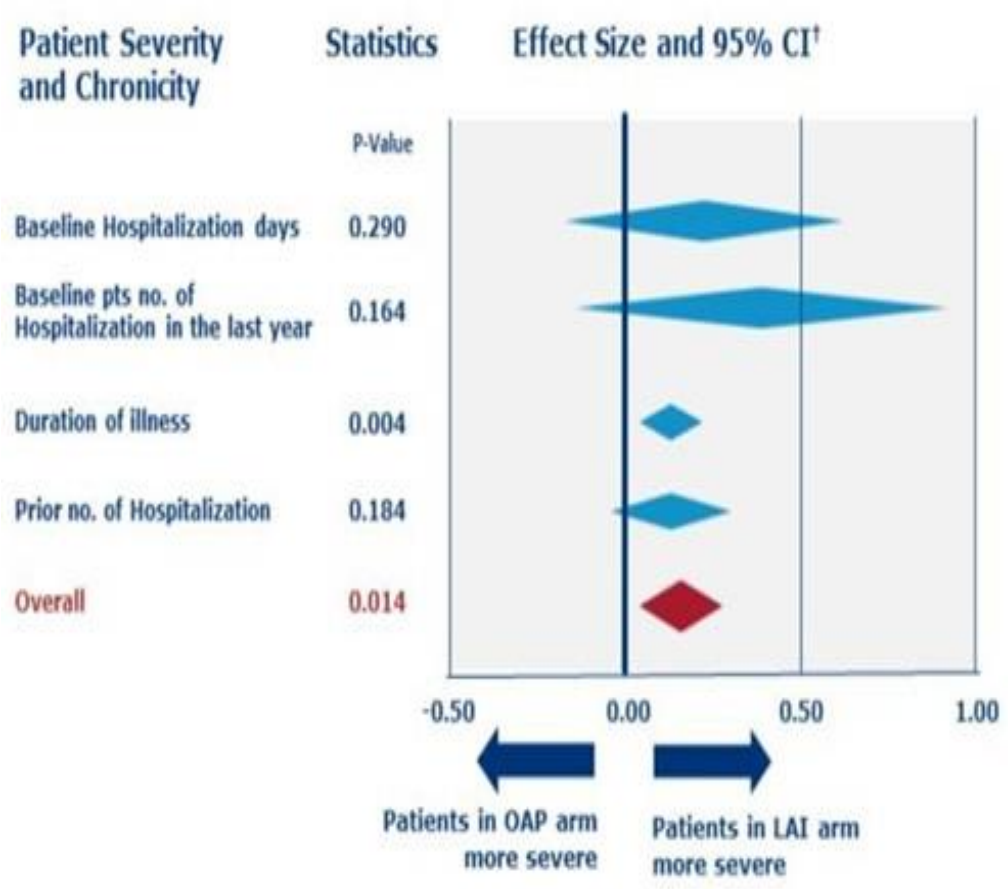
Clinicians Primarily Use LAIs for Patients Later in Their Illness in Early Phase Illness

A meta-analysis of cohort studies found that adult patients with schizophrenia given an LAI had:

-- Significantly longer duration of illness

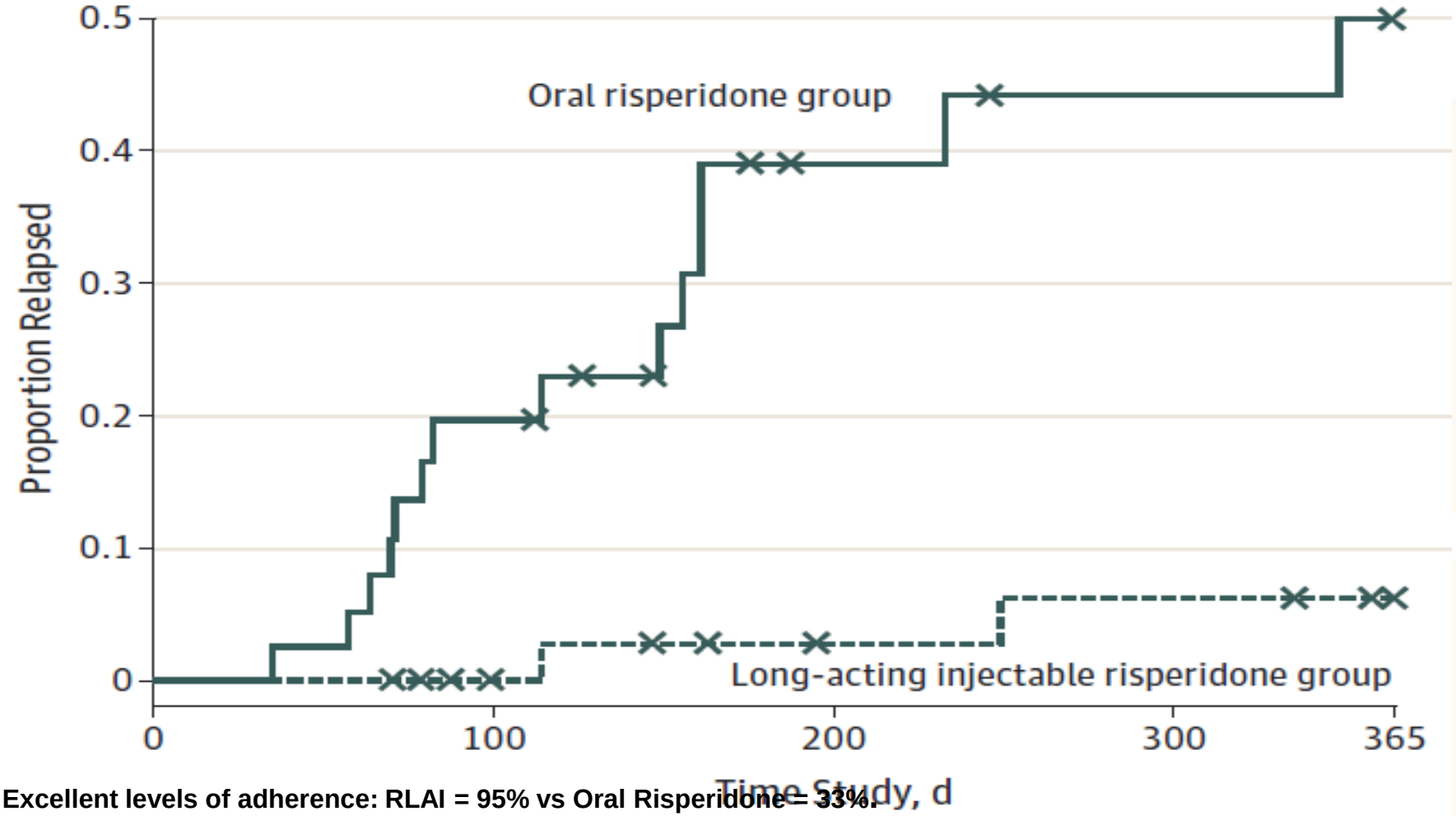
-- Significantly greater illness severity

Limitations: Cohort studies were nonrandomized and therefore prone to expectation bias; study design and methodology were heterogeneous between studies; and the indicators used for illness severity may not have captured the actual severity of each patient's symptoms.



- Kishimoto T, et al. *Schizophr Bull.* 2018;44:603-619

33% vs 5% Relapse in 86 First-Episode Schizophrenia Patients Randomized to Oral Risperidone vs Risperidone LAI

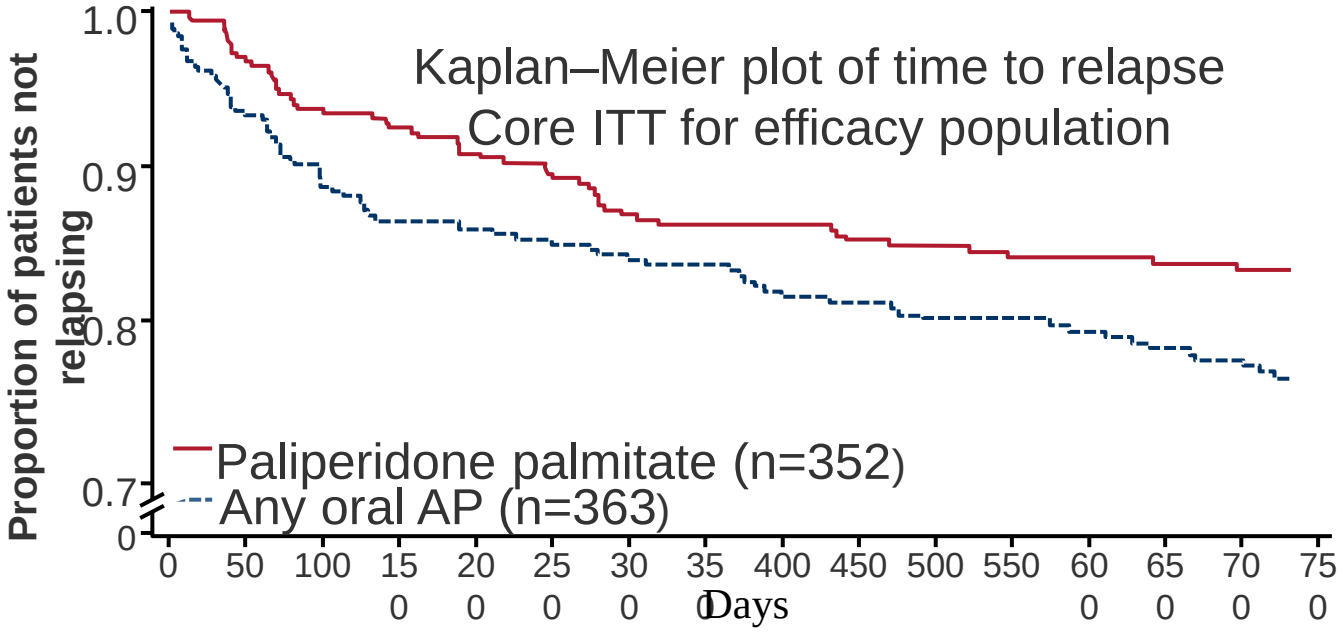


Excellent levels of adherence: RLAI = 95% vs Oral Risperidone = 33%.

Subotnik KL, et al. *JAMA Psychiatry*. 2015;72(8):822-829**.**

PROSIPAL: PP Once Monthly vs oral Aps in Recently Diagnosed SCZ: Time to relapse

- Time to relapse* was significantly longer in the PP group compared to the oral AP group (p=0.0191, HR [95% CI] 1.5 [1.1; 2.2])†
- The 85th percentile for time to relapse was 469 days in the PP group vs 249 days in the oral AP group



Patients in the treatment phase																
PP	352	326	306	292	278	272	260	256	252	244	237	233	230	225	221	0
Oral AP	363	323	297	280	265	258	246	242	230	227	216	212	207	201	198	0

By the end of the 24-month treatment phase, 52 (14.8%) patients met relapse criteria in the PP group versus 76 (20.9%) patients in the oral AP group (p=0.0323)

This represents a 29.4% relative risk reduction in favour of PP

*According to Csernansky criteria †log-rank test AP, antipsychotic; HR, hazard ratio; ITT, intent-to-treat; PP, paliperidone palmitate;

Schreiner A et al. Schizophr Res 2015 Dec;169(1-3):393-9.

A nationwide cohort study of oral and depot antipsychotics after first hospitalisation for schizophrenia

Objective: Data on the effectiveness of antipsychotics in the early phase of schizophrenia are limited. The authors examined the risk of rehospitalization and drug discontinuation in a nationwide cohort of 2,588 consecutive patients hospitalized for the first time with a diagnosis of schizophrenia between 2000 and 2007 in Finland.

Method: The authors linked national databases of hospitalization, mortality, and antipsychotic prescriptions and computed hazard ratios, adjusting for the effects of sociodemographic and clinical variables, the temporal sequence of the antipsychotics used, and the choice of the initial antipsychotic for each patient.

Results: Of 2,588 patients, 1,507 (58.2%) collected a prescription for an antipsychotic during the first 30 days after hospital discharge, and 1,182 (45.7%, 95% confidence interval [CI]=43.7–47.6) continued their initial treatment for 30 days or longer. In a pairwise comparison between depot injections and their equivalent oral formulations, the risk of rehospitalization for patients receiving depot medications was about one-third of that for patients receiving oral medications (adjusted hazard ratio=0.36, 95% CI=0.17–0.75). Compared with oral risperidone, clozapine (adjusted hazard ratio=0.48, 95% CI=0.31–0.76) and olanzapine (adjusted hazard ratio=0.54, 95% CI=0.40–0.73) were each associated with a significantly lower rehospitalization risk. Use of any antipsychotic compared with no antipsychotic was associated with lower mortality (adjusted hazard ratio=0.45, 95% CI=0.31–0.67).

Conclusions: In Finland, only a minority of patients adhere to their initial antipsychotic during the first 60 days after discharge from their first hospitalization for schizophrenia. Use of depot antipsychotics was associated with a significantly lower risk of rehospitalization than use of oral formulations of the same compounds. Among oral antipsychotics, clozapine and olanzapine were associated with more favorable outcomes. Use of any antipsychotic was associated with lower mortality.

Conclusions: In Finland, only a minority of patients adhere to their initial antipsychotic during the first 60 days after discharge from their first hospitalization for schizophrenia. Use of depot antipsychotics was associated with a significantly lower risk of rehospitalization than use of oral formulations of the same compounds. Among oral antipsychotics, clozapine and olanzapine were associated with more favorable outcomes. Use of any antipsychotic was associated with lower mortality.

Tiihonen J, et al. Am J Psychiatry. 2011;168:603–609.

11 possible reasons why LAIs are not widely used in early-phase schizophrenia

1. **Clinician overestimation of patients' degree of adherence**
2. **Bias against injections as being invasive, punitive, or overly painful**
3. Perception that including LAIs in the discussion about treatment options would take inordinate time
4. **Belief that offering LAIs means that the clinician does not trust the patient and, therefore, LAIs will disrupt the therapeutic alliance**
5. Difficulties in interpreting the mixed results of research studies assessing the benefits of LAIs over orals in chronic patients
6. **Insufficient involvement of family members and peer counselors**
7. Lack of appreciation of the advantages of LAIs for patients, families, and healthcare providers in the context of guidelines that relegate LAIs to a last resort approach
8. Lack of training in the use of LAIs, including the best approaches for switching, administration, dose adjustments, and managing AEs
9. **Inadequate training in effective shared decision-making approaches and anticipating/answering frequently asked questions**
10. Inadequate discussion or implementation of LAIs by referring inpatient units
11. **Belief that LAIs are inappropriate for early-phase schizophrenia patients who have not clearly demonstrated patterns of non-adherence leading to relapse**

- AE=adverse event; LAI=long-acting injectable
- Kane et al. J Clin Psychiatry 2019;80(3):18m12546

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

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 AOM sites with the exception that aripiprazole monohydrate had to be prescribed within US Food and Drug Administration–approved guidelines.

MAIN OUTCOMES AND MEASURES The primary outcome was time to first psychiatric hospitalization based on participant interviews every 2 months, the service use resource form administered every 4 months, and other sources (eg, health records) as available. Potential events were adjudicated by an independent committee masked to treatment assignment.

RESULTS The 489 participants (368 men [55.3%]) had a mean (SD) age of 25.2 (4.2) years and 225 (46.0%) had 1 year or less lifetime antipsychotic use. Fifty-two AOM (22%) and 91 CC participants (36%) had at least 1 hospitalization. The mean survival time until first 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 for patients with early-phase illness.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02360319

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2020.2076
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PRELAPSE – objective and design

Primary research question

- Compared with usual care, does the use of a long-acting formulation of aripiprazole medication reduce the risk of hospitalization in early-phase schizophrenia?

Primary outcome	• Time to first hospitalization
Secondary outcomes	• Total number of days of psychiatric hospitalization during the 2-year follow-up • Change from baseline in BPRS, CGI-S, QLS • Change from baseline in neuropsychological functioning (RBANS)

Challenge

- To conduct a study with the rigor of a randomized trial within a real-world clinical setting

Solution

- Cluster-randomized study

AOM 400[a] (19 sites, n=234)
vs
Clinician's choice[b] (20 sites, n=255)

- [a]LAI AOM 400 treated according to FDA-approved guidelines; [b]clinician's choice – oral antipsychotics (including but not limited to): aripiprazole, risperidone, lurasidone HCl, quetiapine fumarate, olanzapine, ziprasidone HCl; LAIs (including but not limited to): risperidone, haloperidol decanoate, olanzapine, paliperidone palmitate, fluphenazine decanoate. Products may have different indications and availability in different countries. Number of patients per product is not available. No direct comparison has been made with individual products. The PRELAPSE study is an investigator-sponsor initiated, multicenter, cluster randomized, controlled clinical trial with a follow-up duration of 2 years. The objective was to document the acceptability of treatment with LAI antipsychotic medication to early-phase schizophrenia patients. All sites were community ('real world') mental health clinics that are very representative of where most patients receive ambulatory services. It was designed as a large simple trial, which is less likely to influence adherence as it is embedded in the delivery of care and demands little extra effort from physicians and patients
- AOM 400=aripiprazole once-monthly 400 mg; BPRS=Brief Psychiatric Rating Scale; CGI-S=Clinical Global Impression – Severity; FDA=US Food and Drug Association; LAI=long-acting injectable;
QLS=Heinrichs–Carpenter Quality of Life Scale; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status
- Kane et al. JAMA Psychiatry 2020; doi: 10.1001/jamapsychiatry.2020.2076

Rationale for the choice of aripiprazole once-monthly

Adverse events

- The safety and tolerability profile of AOM 400 during long-term treatment was similar to that observed in patients during the lead-in studies[a,1]
- The most frequently observed ADRs reported in ≥5% of patients in two double-blind, long-term trials of AOM 400 were:[2]

9.0%
Weight increase

7.9%
Akathisia

5.8%
Insomnia

5.1%
Injection site pain

Previous experience

- A 52-week open-label study evaluating AOM 400 established long-term therapeutic effect[1]
  - PANSS, CGI-S and CGI-I scores remained relatively stable[1]
  - 92% of patients initiated or

Data presented as mean (SD)	Oral stabilisation phase (N=1144)	AOM 400 maintenance phase (N=1081)			
		Enrolled from 52-week study (n=464)	Enrolled from 38-week study (n=474)	De novo (n=143)	All patients (N=1081)
PANNS total score	57.9 (15.5)	55.6 (12.9)	53.4 (13.1)	54.9 (12.2)	54.5 (12.9)
CGI-S score	3.1 (1.0)	3.0 (0.9)	2.9 (0.9)	3.3 (0.8)	3.0 (0.8)
CGI-I score*	n/a	3.4 (0.9)	3.6 (0.7)	3.2 (0.8)	3.5 (0.8)
CGI-SS score	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)

*CGI-I was relative to end of oral stabilisation
Adapted from Peters-Strickland, 2015

[a]Lead-in studies were a 52-week placebo-controlled study (ASPIRE-US) and a 38-week active-controlled study (ASPIRE-EU) that assessed AOM 400 as maintenance treatment of schizophrenia[3,4]

ADR=adverse drug reaction; AOM 400=aripiprazole once-monthly 400 mg; ADR=adverse reactions; PANSS=Positive and Negative Syndrome Scale; CGI-S=Clinical Global Impression-Severity; CGI-I=Clinical Global Impression-Improvement.

1. Peters-Strickland et al. NPJ Schizophr 2015;1:15039; 2. Abilify Maintena® (aripiprazole once-monthly). Summary of product characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/abilify-maintena-epar-product-information_en.pdf) [Accessed on: October 2020]; 3. Kane J, et al. J Clin Psych. 2012;73(5):617-624; 4. Fleischhacker WW, et al. B J Psychiatry. 2014;205:135-144.

Randomized Controlled Trial > Schizophr Bull. 2015 Nov;41(6):1227-36.
doi: 10.1093/schbul/sbv125. Epub 2015 Sep 3.

A Randomized Comparison of Aripiprazole and Risperidone for the Acute Treatment of First-Episode Schizophrenia and Related Disorders: 3-Month Outcomes

Delbert G Robinson [1], Juan A Gallego, Majnu John [2], Georgios Petrides, Youssef Hassoun [3], Jian-Ping Zhang, Leonardo Lopez [3], Raphael J Braga [3], Serge M Sevy [4], Jean Addington [5], Charles H Kellner [6], Mauricio Tohen [7], Melissa Naraine [8], Natasha Bennett [8], Jessica Greenberg [8], Todd Lencz, Christoph U Correll [9], John M Kane [10], Anil K Malhotra [11]

Abstract

Research findings are particularly important for medication choice for first-episode patients as individual prior medication response to guide treatment decisions is unavailable. We describe the first large-scale double-masked randomized comparison with first-episode patients of aripiprazole and risperidone, 2 commonly used first-episode treatment agents. One hundred ninety-eight participants aged 15-40 years with schizophrenia, schizophreniform disorder, schizoaffective disorder or psychotic disorder Not Otherwise Specified, and who had been treated in their lifetime with antipsychotics for 2 weeks or less were randomly assigned to double-masked aripiprazole (5-30 mg/d) or risperidone (1-6 mg/d) and followed for 12 weeks. Positive symptom response rates did not differ (62.8% vs 56.8%) nor did time to response. Aripiprazole-treated participants had better negative symptom outcomes but experienced more akathisia. Body mass index change did not differ between treatments but advantages were found for aripiprazole treatment for total and low-density lipoprotein cholesterol, fasting glucose, and prolactin levels. Post hoc analyses suggested advantages for aripiprazole on depressed mood. Overall, if the potential for akathisia is a concern, low-dose risperidone as used in this trial maybe a preferred choice over aripiprazole. Otherwise, aripiprazole would be the preferred choice over risperidone in most situations based upon metabolic outcome advantages and some symptom advantages within the context of similar positive symptom response between medications.

PRELAPSE – target patient population

‘Early phase’ schizophrenia

- Schizophrenia diagnosis confirmed by SCID-5RV
- 18–35 years of age
- Ability to provide informed consent

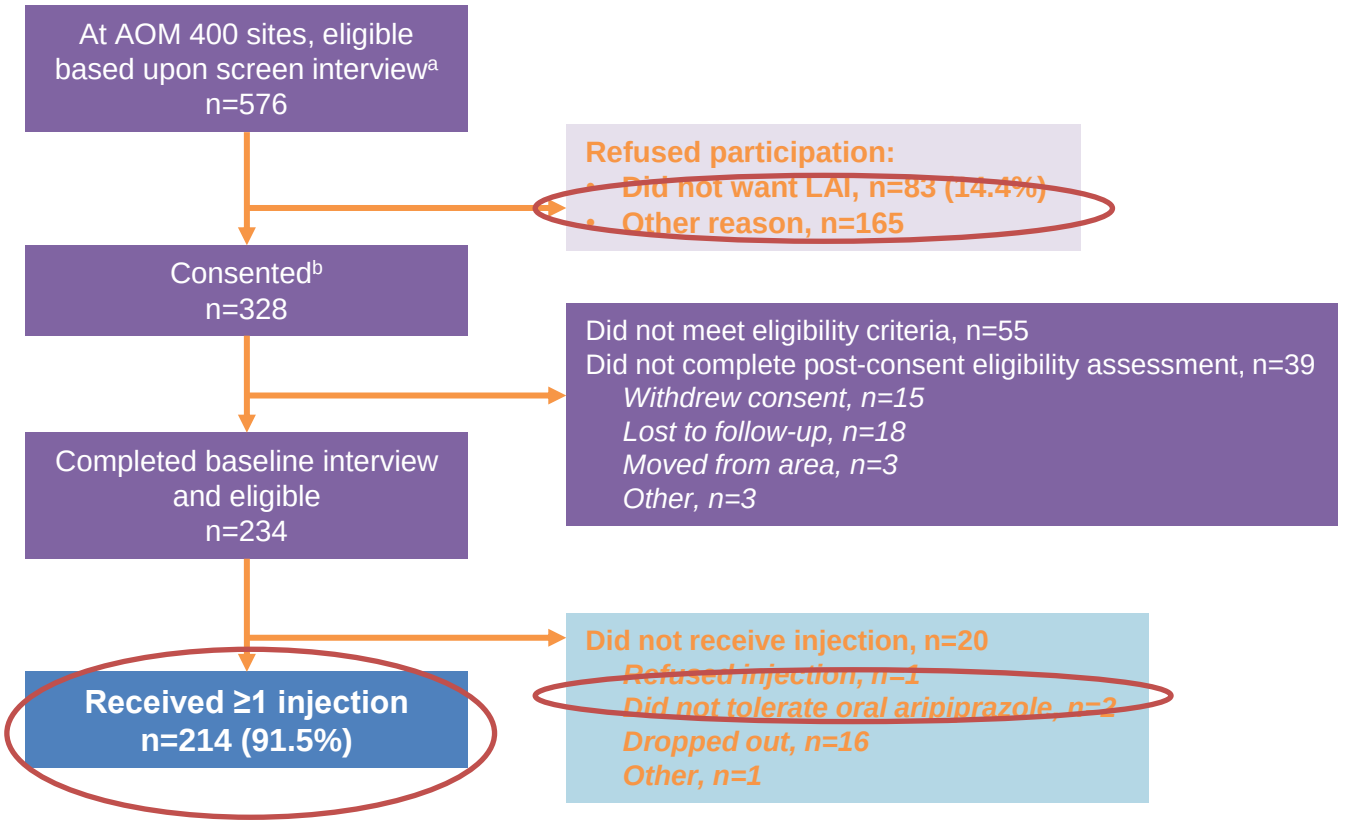
First-episode patients
with <1 year of lifetime exposure to antipsychotics

OR

Early-phase patients
with >1 episode of psychosis and ≤5 years lifetime exposure to antipsychotics

- Exclusion criteria: primary DSM-5 diagnosis other than schizophrenia; being pregnant or lactating (women); unstable medical condition making trial participation unwise; prior clozapine use; and history of intolerance to aripiprazole (AOM 400 sites only)
- The PRELAPSE study is an investigator-sponsor initiated, multicenter, cluster randomized, controlled clinical trial with a follow-up duration of 2 years. The objective was to document the acceptability of treatment with LAI antipsychotic medication to early-phase schizophrenia patients. All sites were community (‘real world’) mental health clinics that are very representative of where most patients receive ambulatory services. It was designed as a large simple trial, which is less likely to influence adherence as it is embedded in the delivery of care and demands little extra effort from physicians and patients
- AOM 400=aripiprazole once-monthly 400 mg; SCID-5RV=Structured Clinical Interview for DSM-5, Research Version
- Kane et al. JAMA Psychiatry 2020; doi: 10.1001/jamapsychiatry.2020.2076

PRELAPSE – number of patients who received ≥1 injection with aripiprazole monohydrate once monthly (AOM) 400 mg



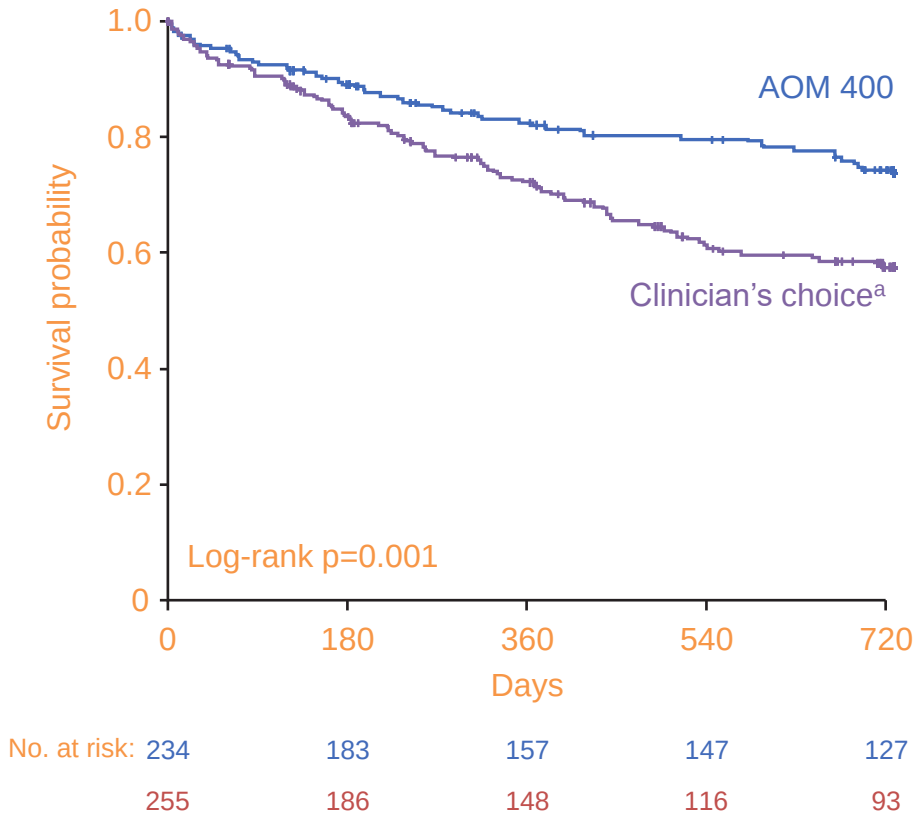
- [a]Potential subjects meeting brief (pre-consent) checklist; [b]potential subjects who signed informed consent form and agreed to participate in study if eligibility criteria were met. The PRELAPSE study is an investigator-sponsor initiated, multicenter, cluster randomized, controlled clinical trial with a follow-up duration of 2 years. The objective was to document the acceptability of treatment with LAI antipsychotic medication to early-phase schizophrenia patients. All sites were community ('real world') mental health clinics that are very representative of where most patients receive ambulatory services. It was designed as a large simple trial, which is less likely to influence adherence as it is embedded in the delivery of care and demands little extra effort from physicians and patients
- AOM 400=aripiprazole once-monthly 400 mg; LAI=long-acting injectable
- Adapted from: Kane et al. J Clin Psychiatry 2019;80(3):18m12546; Kane et al. JAMA Psychiatry 2020; doi: 10.1001/jamapsychiatry.2020.2076

PRELAPSE – baseline demographics and patient characteristics

Characteristic	AOM (n=234)	Clinician's choice[a] (n=255)
Age, years, mean (SD)	25.7 (4.3)	24.7 (4.1)
Sex, male, n (%)	172 (73.5)	196 (76.9)
Race, n (%)		
White	80 (34.2)	91 (35.7)
Black	109 (46.6)	104 (40.8)
Other	45 (19.2)	58 (22.7)
Unknown	0 (0.0)	2 (0.8)
≤1-year lifetime antipsychotic exposure, n (%)	102 (43.6)	123 (48.2)
Receiving LAI at time of consent, n (%)	72 (30.8)	70 (27.4)
AOM	36 (15.4)	10 (3.9)
Other LAI	36 (15.4)	60 (23.5)
Hospitalizations for psychiatric illness, mean (SD)	3 (2.5)	3.4 (2.9)
Hospitalizations for psychiatric illness, n (%)		
0	29 (12.4)	32 (12.5)
1	68 (29.1)	62 (24.3)
2	38 (16.2)	41 (16.1)
≥3	97 (41.5)	115 (45.1)

- [a]Clinician's choice – oral antipsychotics (including but not limited to): aripiprazole, risperidone, lurasidone HCl, quetiapine fumarate, olanzapine, ziprasidone HCl; LAIs (including but not limited to): risperidone, haloperidol decanoate, olanzapine, paliperidone palmitate, fluphenazine decanoate. Products may have different indications and availability in different countries. Number of patients per product is not available. No direct comparison has been made with individual products. The PRELAPSE study is an investigator-sponsor initiated, multicenter, cluster randomized, controlled clinical trial with a follow-up duration of 2 years. The objective was to document the acceptability of treatment with LAI antipsychotic medication to early-phase schizophrenia patients. All sites were community ('real world') mental health clinics that are very representative of where most patients receive ambulatory services. It was designed as a large simple trial, which is less likely to influence adherence as it is embedded in the delivery of care and demands little extra effort from physicians and patients
- AOM=aripiprazole once-monthly; LAI=long-acting injectable; SD=standard deviation
- Adapted from: Kane et al. JAMA Psychiatry 2020; doi: 10.1001/jamapsychiatry.2020.2076

PRELAPSE – time to first hospitalization (primary endpoint)

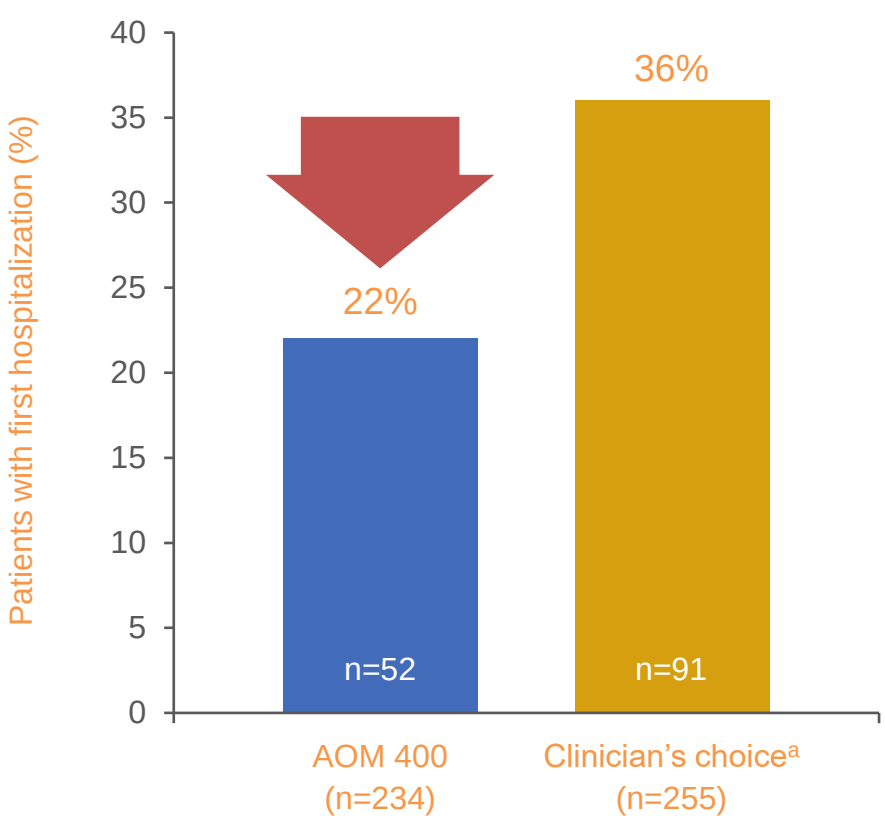


- For time to first hospitalization, HR[b] favored AOM 400: 0.56 (95% CI: 0.34, 0.92; p=0.02)
- Mean (95% CI) time to first hospitalization:
  - AOM 400, 613.7 days (582.3, 645.1)
  - Clinician's choice, 530.6 days (497.3, 563.9)

7 patients[c] needed to receive AOM 400 treatment to prevent one additional hospitalization, compared with clinician's choice[a]

- Log rank test χ^2=11.373; df=1; p<0.001. [a]Clinician's choice – oral antipsychotics (including but not limited to): aripiprazole, risperidone, lurasidone HCl, quetiapine fumarate, olanzapine, ziprasidone HCl; LAIs (including but not limited to): risperidone, haloperidol decanoate, olanzapine, paliperidone palmitate, fluphenazine decanoate. Products may have different indications and availability in different countries. Number of patients per product is not available. No direct comparison has been made with individual products. [b]Proportional hazards assumption. [c]Number-needed-to-treat=6.67. The PRELAPSE study is an investigator-sponsor initiated, multicenter, cluster randomized, controlled clinical trial with a follow-up duration of 2 years. The objective was to document the acceptability of treatment with LAI antipsychotic medication to early-phase schizophrenia patients. All sites were community ('real world') mental health clinics that are very representative of where most patients receive ambulatory services. It was designed as a large simple trial, which is less likely to influence adherence as it is embedded in the delivery of care and demands little extra effort from physicians and patients
- AOM 400=aripiprazole once-monthly 400 mg; CI=confidence interval; HR=hazard ratio
- Adapted from: Kane et al. JAMA Psychiatry 2020; doi: 10.1001/jamapsychiatry.2020.2076

PRELAPSE – hospitalization rates



44% reduction in incidence rate of first hospitalization with AOM 400 treatment[b]

- 40/52 patients in the AOM group were receiving aripiprazole monohydrate at the time of first hospitalization and 22/91 patients in the clinician's choice group were receiving any LAI
- [a]Clinician's choice – oral antipsychotics (including but not limited to): aripiprazole, risperidone, lurasidone HCl, quetiapine fumarate, olanzapine, ziprasidone HCl; LAIs (including but not limited to): risperidone, haloperidol decanoate, olanzapine, paliperidone palmitate, fluphenazine decanoate. Products may have different indications and availability in different countries. Number of patients per product is not available. No direct comparison has been made with individual products; [b]compared with clinician's choice. The PRELAPSE study is an investigator-sponsor initiated, multicenter, cluster randomized, controlled clinical trial with a follow-up duration of 2 years. The objective was to document the acceptability of treatment with LAI antipsychotic medication to early-phase schizophrenia patients. All sites were community ('real world') mental health clinics that are very representative of where most patients receive ambulatory services. It was designed as a large simple trial, which is less likely to influence adherence as it is embedded in the delivery of care and demands little extra effort from physicians and patients
- AOM 400=aripiprazole once-monthly 400 mg; CI=confidence interval; LAI=long-acting injectable; RR=relative risk
- Adapted from: Kane et al. JAMA Psychiatry 2020; doi: 10.1001/jamapsychiatry.2020.2076

Study limitations

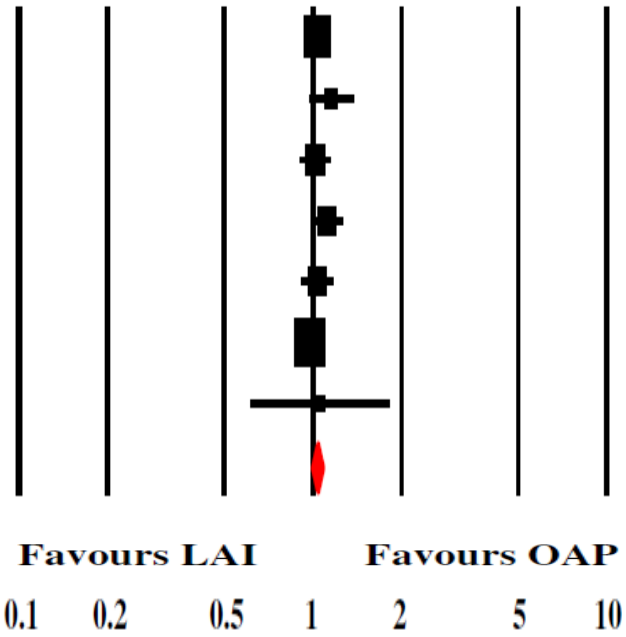
- Study sites were required to have the capability to provide AOM treatment; thus these sites likely had more interest in, and more infrastructure for, LAI antipsychotic treatment than typical treatment sites
- Clinicians in the AOM treatment arm were trained in methods for discussing earlier use of LAI antipsychotics with patients; thus they were equipped to offer this treatment and address concerns of patients and family members
  - This kind of specialized training may not currently be available at most community treatment sites, limiting the generalizability of this approach
- Although participant groups had very similar baseline characteristics (e.g., baseline use of LAIs, hospitalization, and antipsychotic treatment history), selection effects may have occurred with cluster randomization design
- Results might have underestimated the effects of LAIs on hospitalization because of the relatively high LAI use rates for patients with first-episode/early-phase illness in the clinician's choice group

- The PRELAPSE study is an investigator-sponsor initiated, multicenter, cluster randomized, controlled clinical trial with a follow-up duration of 2 years. The objective was to document the acceptability of treatment with LAI antipsychotic medication to early-phase schizophrenia patients. All sites were community ('real world') mental health clinics that are very representative of where most patients receive ambulatory services. It was designed as a large simple trial, which is less likely to influence adherence as it is embedded in the delivery of care and demands little extra effort from physicians and patients
- AOM=aripiprazole once-monthly; LAI=long-acting injectable
- Kane et al. J Clin Psychiatry 2019;80(3):18m12546; Kane et al. JAMA Psychiatry 2020; doi: 10.1001/jamapsychiatry.2020.2076

Adverse Effects with LAI vs Same Oral Antipsychotics (N=16, n=4,902)

No Difference in Frequency of At Least One Adverse Effect

Study name	Subgroup within study	Statistics for each study				Events / Total	
		Risk ratio	Lower limit	Upper limit	p-Value	LAI	OAP
Fleischhacker, 2014	ARI LAI vs ARI	1.032	0.951	1.120	0.448	219 / 265	213 / 266
Ishigooka, 2015	ARI LAI vs ARI	1.156	0.972	1.374	0.102	130 / 228	112 / 227
Detke, 2011	OLA LAI vs OLA	1.018	0.906	1.144	0.759	182 / 264	176 / 260
Starr, 2014 PP vs PAL/RIS	PAL LAI vs PAL/RIS	1.121	0.988	1.271	0.075	181 / 208	66 / 85
Chue, 2005	RLAI vs RIS	1.038	0.915	1.178	0.561	195 / 319	189 / 321
Kamijima, 2009	RLAI vs RIS	0.970	0.904	1.041	0.398	137 / 147	49 / 51
NCT00992407	RLAI vs RIS	1.058	0.612	1.827	0.841	11 / 20	13 / 25
Overall		1.026	0.984	1.071	0.231	1055 / 1451	818 / 1235



- **Out of all 119 adverse events, LAIs and OAPs did not differ significantly regarding 115 (96.6%).**
- **LAIs were associated with more akinesia, low-density lipoprotein cholesterol change and anxiety.**
- **LAIs were associated with significantly lower prolactin change.**

Misawa F, Kishimoto T, Hagi K, Kane KM, Correll CU et al. Schizophr Res 2016 Oct;176(2-3):220-30.

Neuroleptic Malignant Syndrome on Long-Acting vs. Oral Formulations

- 662 reported cases with NMS (age=36, males=61.2%)
- 122 (18.4%) involved LAIs (second-generation antipsychotic (SGA)-LAIs=10, 1.5%)
- 540 (81.6%) involved OAPs (SGA-OAPs=159, 24.0%).

The two groups **did not differ** on

- age
- illness duration
- comorbidities
- presence of NMS symptoms
- presence and severity of NMS symptoms (Francis-Yacoub score: LAI=26 vs. OAP=23, p=0.83)

Guinart D et al J Clin Psych 2020

Outcome of NMS on Long-Acting vs. Oral Formulations

LAI formulation was associated with

- longer median **duration of NMS** vs. OAPs
- (2.0 vs. 1.4 weeks, p=0.03),
- but not for **SGA**-LAIs vs. **SGA**-OAPs
- (1.6 vs. 1.3 weeks, p=0.98).

Antipsychotic formulation was **not** associated with:

- longer **duration of hospitalization** associated with NMS (LAIs=5.0 vs. OAPs=3.8 weeks, p=0.83),
- **post-NMS sequalae** (LAI=8.8% vs. OAP=7.0%, p=0.74)
- **death** (LAI=12.8% vs. OAP=7.6%, p=0.08, full adj. p=0.13)

Guinart, D et al J Clin Psych 2020

Duration of Untreated Illness of Major Mental Disorders in the US

Table 1. Proportional Treatment Contact in the Year of Disorder Onset and Median Duration of Delay Among Cases That Subsequently Made Treatment Contact

	Treatment Contact Made in Year of Onset, %	Median Duration of Delay, y*	No.†
Anxiety disorders			
Panic disorder	33.6	10	269
Agoraphobia	15.1	12	137
pecific phobia	1.6	20	720
Social phobia	3.4	16	694
Generalized anxiety disorder	33.3	9	444
Posttraumatic stress disorder	7.1	12	389
Separation anxiety disorder	1.0	23	234
Mood disorders			
Major depressive episode	37.4	8	1092
Dysthymia	41.6	7	229
Bipolar disorder I and II	39.1	6	224
Impulse control disorders			
Attention-deficit/hyperactivity disorder	7.0	13	253
Oppositional defiant disorder	6.6	4	324
Intermittent explosive disorder	6.8	13	447
Substance disorders			
Alcohol abuse	12.4	9	751
Alcohol dependence	20.7	6	307
Drug abuse	12.5	6	450
Drug dependence	26.5	5	174

Wang PS. Arch Gen Psychiatry. 2005 Jun;62(6):603-13.

But what is Digital Health anyway?

Use of information and communication technologies

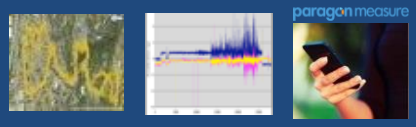
to **improve human health, healthcare and wellness**

for individuals and across populations

Kostova P. Front Public Health. 2015;3:134.

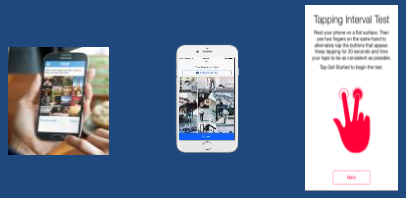
Diverse data sources can be used to measure established clinical symptoms, side effects, behaviors

Passively-recorded activity, location



"Real" Sensors, wearables, IoT

Self-report, Active tasks

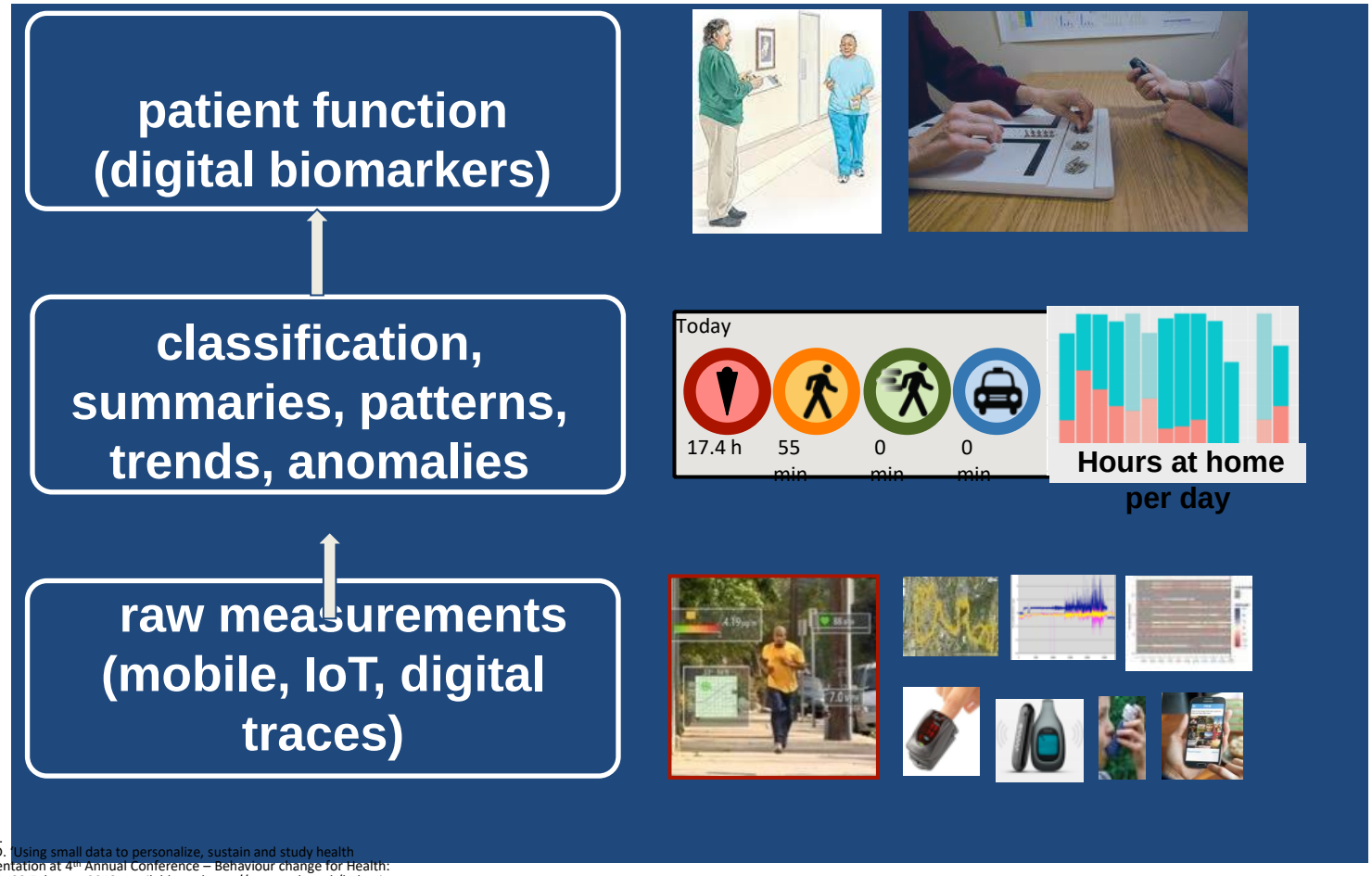


Digital traces: purchases, me

IoT=internet of things.

Adapted from Estrin D. 'Using small data to personalize, sustain and study health behaviour.' Oral presentation at 4th Annual Conference – Behaviour change for Health: Digital and Beyond, 21–22 February 2018. Available at: https://www.ucl.ac.uk/behaviour-change/events/conf-18/presentations/K.2_-_Estrin.pdf.

Opportunity and challenge across all novel data sources: extract biomarkers from multiple, noisy data streams



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Enlight: A Comprehensive Quality and Therapeutic Potential Evaluation Tool for Mobile and Web-Based eHealth Interventions

Monitoring Editor: Gunther Eysenbach

Reviewed by Obinna Anya and John Torous

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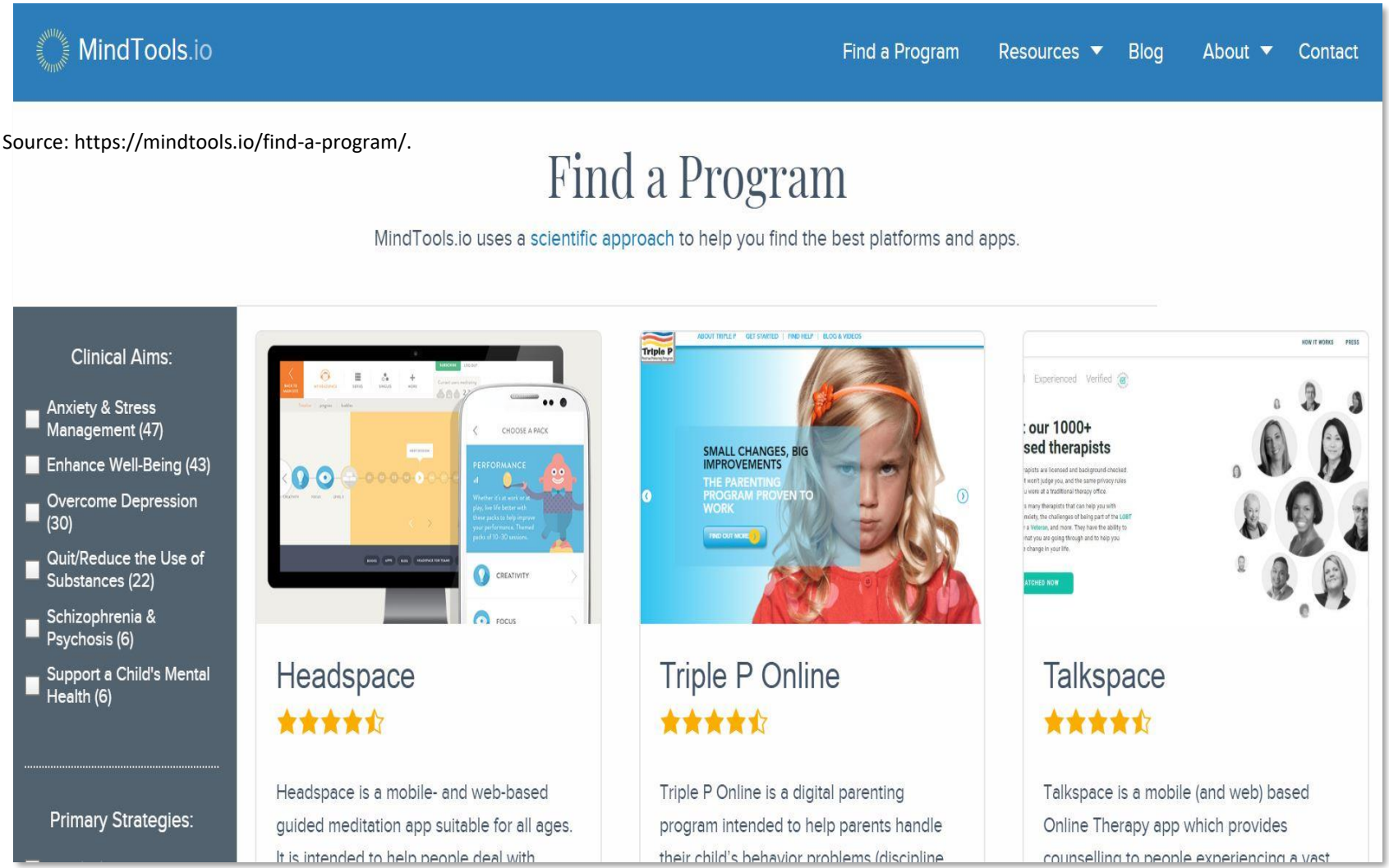
Corresponding Author: Amit Baumel llun@ved:otliam

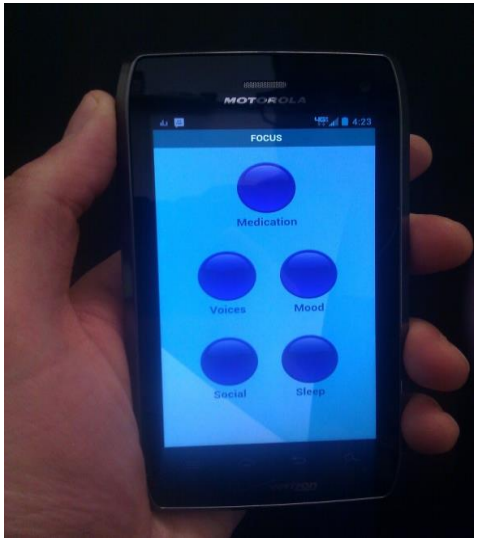
Source: https://mindtools.io/find-a-program/.

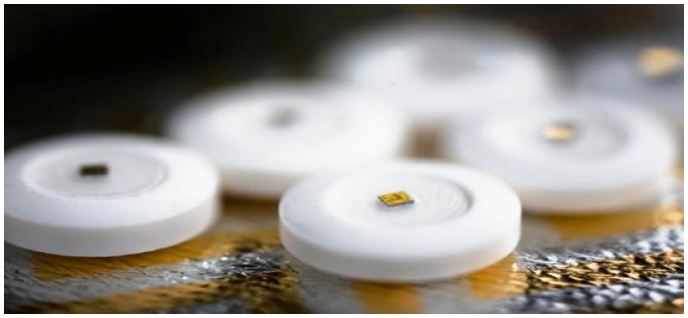


Improving Outcomes/Reducing Costs

Health Technology Coach and Case Manager

- 3 Daily prompts
- “On-demand” resources
- Native app
- 5 targets: voices, social, meds, sleep, mood
- Online clinician dashboard
- Tailored: target selection, prompting schedule





Ingestible Event Marker

Web-based therapy for patients and families

Computerized Decision Support System

Ben-Zeev et al. JMIR Mental Health 2016

Health Technology Intervention After Hospitalization for Schizophrenia: Service Utilization and User Satisfaction

Amit Baumel, Ph.D., Christoph U. Correll, M.D., Marta Hauser, Ph.D., Mary Brunette, M.D., Armando Rotondi, Ph.D., Dror Ben-Zeev, Ph.D., Jennifer D. Gottlieb, Ph.D., Kim T. Mueser, Ph.D., Eric D. Achtyes, M.D., Nina R. Schooler, Ph.D., Delbert G. Robinson, M.D., Susan Gingerich, M.S.W., Patricia Marcy, B.S.N., Piper Meyer-Kalos, Ph.D., John M. Kane, M.D.

Objective: The authors examined patients' acceptance of the Health Technology Program (HTP), an integrative approach to relapse prevention after hospitalization of adults with schizophrenia or related disorders. The program combines use of digital tools with support from a mental health technology coach (MHTC).

Methods: Patients with schizophrenia spectrum disorders received six months of treatment that began within 60 days of a psychiatric hospitalization and included the development of a personalized relapse prevention plan, three digital tools, and contacts with MHTCs.

Results: A total of 200 patients (mean±SD age=34.6±10.6 years) had 28.2±2.0 contacts with the MHTC that lasted 38.3±14.2 minutes. The most discussed topic was case management (52%), and digital tools were discussed in 45% of meetings. Altogether, 87% of patients used at least one of the digital tools, with 96% of patients rating the HTP as satisfying to at least some extent.

Conclusions: These data suggest very high acceptance of the HTP, a program that integrates available human support with digital tools.

Psychiatric Services in Advance (doi: 10.1176/appi.ps.201500317)

Baumel A, et al. Psychiatr Serv. 2016;67(9):1035–1038.

National Institute of Mental Health

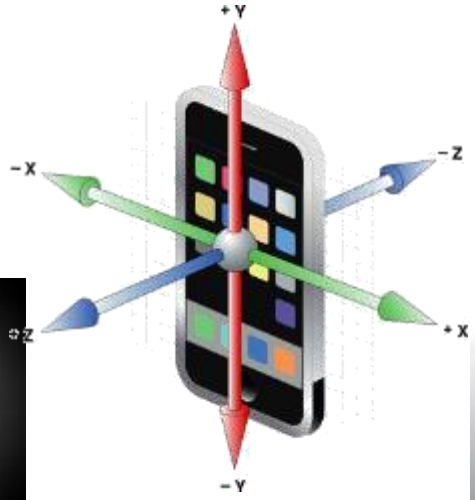
Northwell Health

Dartmouth

CORNELL TECH

CrossCheck
A new Paradigm for Illness Monitoring and Relapse Prevention

Multi-Modal Sensing



Ben-Zeev, Choudhury, Campbell, & Kane. *CrossCheck*

Smartphones for Schizophrenia SXS, Relapse

- 61 outpts with Scz
- CrossCheck app on phone
  - Passively collected digital socialization data (call logs, text messages, microphone)
- Tracked over 1 year

Found that reductions in the number and duration of outgoing calls, as well as number of text messages were associated with relapses

Buck et al. Schizophrenia Res 2019;208:167-72.

- 26 outpts with Scz
- ”CrossCheck” app on phone
  - Passively collected data on physical activities, sleep, sociability, other app use, calls
- Tracked between 2-12 months

App able to predict BPRS score within ±1.6 purely passive sensing from phones without any self-reported information from the participants

*BPRS=Brief Psychiatric Rating Scale

Wang et al. PACM Interact Mob Wearable Ubiquitouq Technol 2017;1(3).

Article | Open Access | Published: 03 December 2020

Identifying signals associated with psychiatric illness utilizing language and images posted to Facebook

Michael L. Birnbaum ✉, Raquel Norel, Anna Van Meter, Asra F. Ali, Elizabeth Arenare, Elif Eyigoz, Carla Agurto, Nicole Germano, John M. Kane & Guillermo A. Cecchi

npj Schizophrenia **6**, Article number: 38 (2020) | Cite this article

Abstract

Classification achieved AUC of 0.77 (HV vs. MD), 0.76 (HV vs. SSD), and 0.72 (SSD vs. MD). SSD used more ($P < 0.01$) perception words (hear, see, feel) than MD or HV. SSD and MD used more ($P < 0.01$) swear words compared to HV. SSD were more likely to express negative emotions compared to HV ($P < 0.01$). MD used more words related to biological processes (blood/pain) compared to HV ($P < 0.01$). The height and width of photos posted by SSD and MD were smaller ($P < 0.01$) than HV. MD photos contained more blues and less yellows ($P < 0.01$). Closer to hospitalization, use of punctuation increased (SSD vs HV), use of negative emotion words increased (MD vs. HV), and use of swear words increased ($P < 0.01$) for SSD and MD compared to HV. Machine-learning algorithms are capable of differentiating SSD and MD using Facebook activity alone over a year in advance of hospitalization. Integrating Facebook data with clinical information could one day serve to inform clinical decision-making.

Using Digital Media Advertising in Early Psychosis Intervention

Michael L. Birnbaum, M.D., Chantel Garrett, B.S., Amit Baumel, Ph.D., Maria Scovel, Asra F. Rizvi, M.A., Whitney Muscat, B.S., John M. Kane, M.D.

Objective: Identifying and engaging youth with early-stage psychotic disorders in order to facilitate timely treatment initiation remains a major public health challenge. Although advertisers routinely use the Internet to directly target consumers, limited efforts have focused on applying available technology to proactively encourage help-seeking in the mental health community. This study explores how one might take advantage of Google AdWords in order to reach prospective patients with early psychosis.

Methods: A landing page was developed with the primary goal of encouraging help-seeking individuals in New York City to contact their local early psychosis intervention clinic. In order to provide the best opportunity to reach the intended audience, Google AdWords was utilized to link more than 2,000 selected search terms to strategically placed landing page advertisements. The campaign ran for 14 weeks between April 11 and July 18, 2016 and had a total budget of $1,427.

Results: The ads appeared 191,313 times and were clicked on 4,350 times, at a per-click cost of $.33. Many users took additional help-seeking steps, including obtaining psychosis-specific information/education (44%), completing a psychosis self-screener (15%), and contacting the local early treatment program (1%).

Conclusions: Digital ads appear to be a reasonable and cost-effective method to reach individuals who are searching for behavioral health information online. More research is needed to better understand the many complex steps between online search inquiries and making first clinical contact.

Psychiatric Services in Advance (doi: 10.1176/appi.ps.201600571)

Mental illness and vulnerability

Regulators and Institutional Review Boards tend to view people with psychiatric conditions as more vulnerable than people with medical disorders[1]

Some in the general public perceive people with mental illnesses as having diminished decision-making capacity[2]

Subjecting such concerns to empirical investigations is critical – helps to ensure that principle of justice is met[3]

1. Bracken-Roche D, et al. Can J Psychiatry. 2016;61:335–339; 2. Muroff JR, et al. Schizophr Bull. 2006;32(1):129–136. 3. Roberts LW. Compr Psychiatry. 1998;39(3):99−110.

Conclusions

- Medication must not be given in a vacuum
- When efficacy is similar tolerability is key
- We still need to use all medications wisely
- LAIs and clozapine should be considered more frequently, especially in early phase patients
- Digital technology shows promise for providing better access and disease management