THE EVOLUTION OF MY RESEARCH IN THE TREATMENT OF SCHIZOPHRENIA AND UNANSWERED QUESTIONS

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DISCLOSURES

I have an interest in relation with one or more organizations that could be perceived as a possible conflict of interest in the context of this presentation. The relationships for the past 5 years are summarized:

INTEREST	NAME OF ORGANIZATION
Grants	Lundbeck, Otsuka, Janssen, Sunovion
Shares	HealthRhythms (private/stock options), LB Pharmaceuticals, Inc. (private/stock options), North Shore Therapeutics (private/stock), Vanguard Research Group (private); NW Pharmatech (private/stock options), Saladax (private/stock options), Reviva (stock options); Terran (private/stock options)
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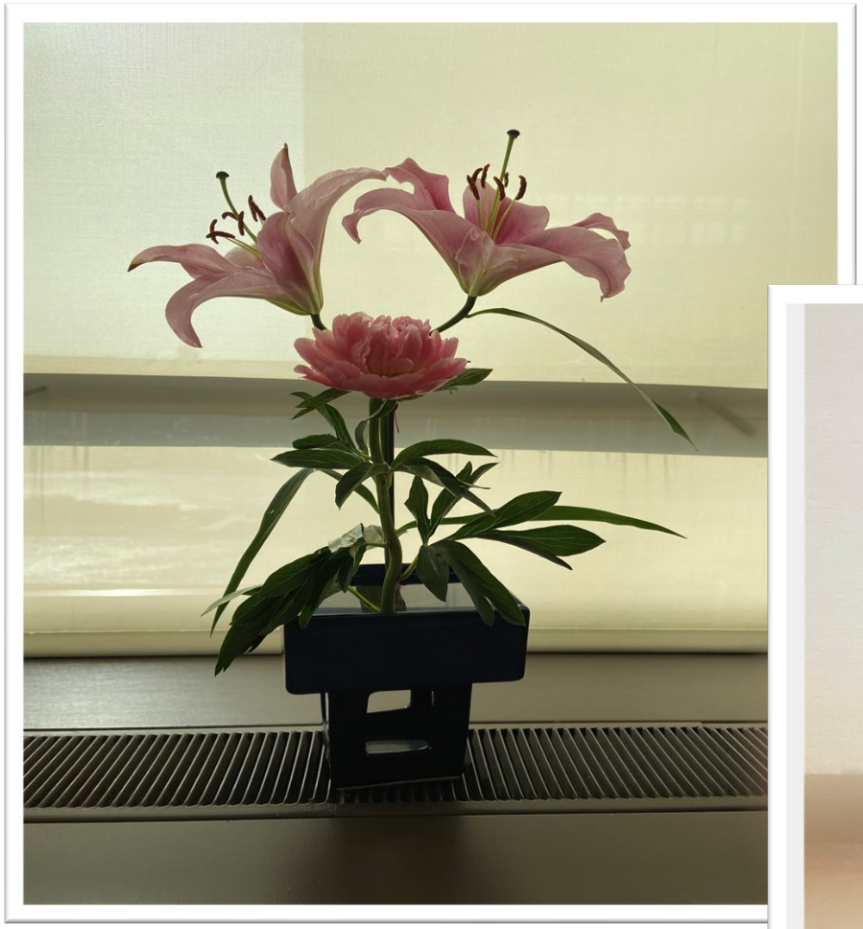
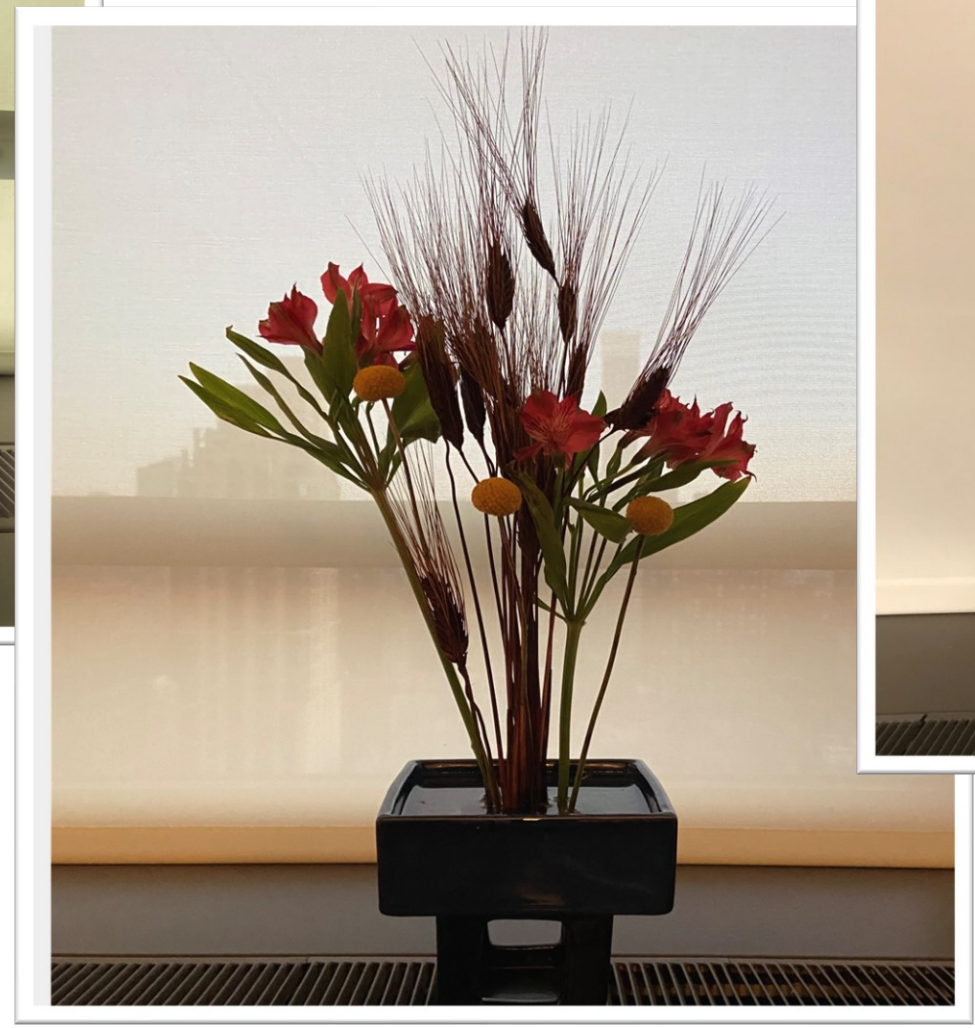
K2
K2

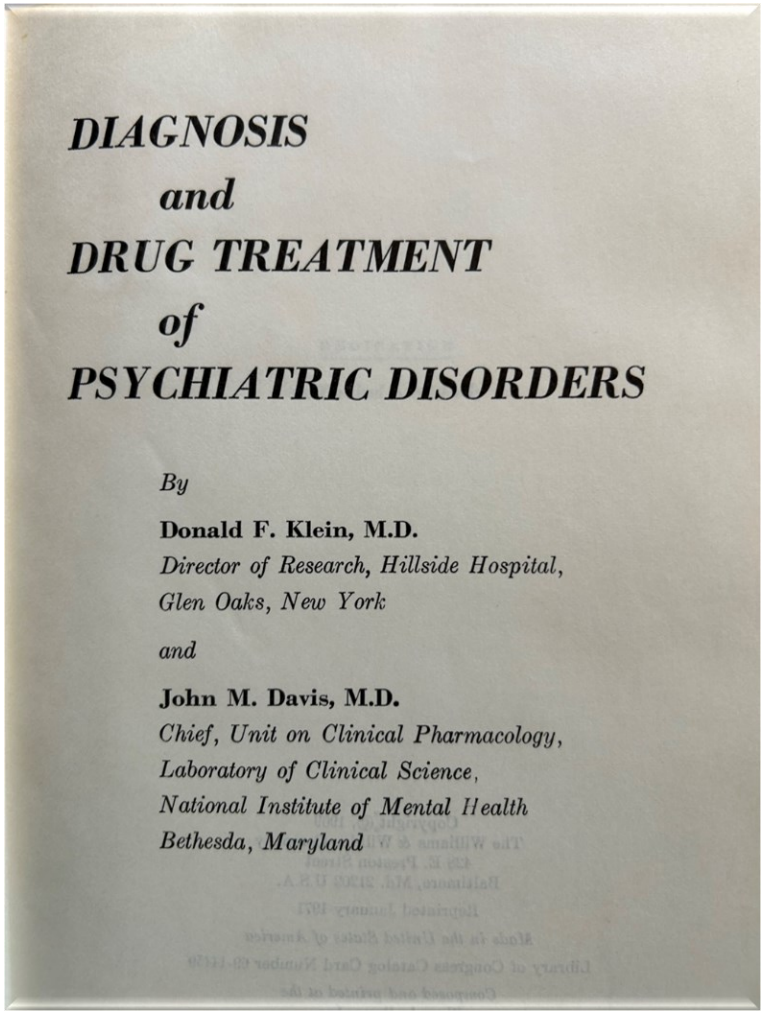
Perfection is achieved, not when there is nothing more to add, but when there is nothing left to take away.

Antoine de Saint-Exupery





THE BOOK THAT STARTED IT ALL…



DIAGNOSIS
and
DRUG TREATMENT
of
PSYCHIATRIC DISORDERS

By

Donald F. Klein, M.D.
Director of Research, Hillside Hospital,
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and

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Somewhere between reality and delusion lies the unconquerable world of uncertainty.

John Kane

Clinical Trial > Arch Gen Psychiatry. 1982 Jan;39(1):70-3.
doi: 10.1001/archpsyc.1982.04290010048009.

Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia

J M Kane, A Rifkin, F Quitkin, D Nayak, J Ramos-Lorenzi

PMID: 6275811 DOI: 10.1001/archpsyc.1982.04290010048009

Abstract

Twenty-eight patients who had recently recovered from an acute-onset, first-episode schizophrenic illness were randomly given fluphenazine hydrochloride or decanoate or placebo for a one-year period in a double-blind study. Seven of 17 patients(14%) receiving placebo experienced a psychotic relapse, whereas none of 11 drug-treated patients experienced a relapse. Eighteen (69%) of the 26 patients available for follow-up (mean interval, 3.5 years) experienced a second psychotic relapse either during the study or afterward, and 50% (14/28) of the original sample experienced a third episode.

Review > Arch Gen Psychiatry. 1982 Apr;39(4):473-81.
doi: 10.1001/archpsyc.1982.04290040069010.

Tardive dyskinesia: prevalence and risk factors, 1959 to 1979

J M Kane, J M Smith

PMID: 6121548 DOI: 10.1001/archpsyc.1982.04290040069010

Abstract

Fifty-six prevalence surveys of tardive dyskinesia (TD) in neuroleptic-treated patients are reviewed, yielding an average prevalence of 20% as compared with 5% prevalence of "spontaneous" dyskinesia in 19 samples of untreated individuals. Reported prevalence has increased during the past two decades and is not attributable simply to the more widespread use of rating scales. Controlled studies of a variety of risk factors are reviewed and suggest that advancing age and, to a lesser extent, female sex are the two variables most consistently associated with increased prevalence. There are relatively few data supporting the assumption that the risk of TD development continues to increase with increasing neuroleptic exposure, CNS dysfunction, or exposure to antiparkinsonism medication.

Research Diagnoses for Tardive Dyskinesia

Nina R. Schooler, PhD; John M. Kane, MD

» Author Affiliations

Arch Gen Psychiatry. 1982;39(4):486-487. doi:10.1001/archpsyc.1982.04290040080014

Abstract

To the Editor —The recent publication by the American Psychiatric Association of its Task Force report on tardive dyskinesia (TD)[1] provides a summary of the state of the art in both clinical practice and research-based knowledge that addresses issues of both phenomenology of the disorder and differential diagnosis. However, there has not yet been a systematic effort to reduce the diagnostic heterogeneity that is found within the range of patients who are identified as having TD. The diagnosis reported in the literature frequently represents nothing more than a score on a rating scale. Furthermore, investigators use a variety of terms to modify the primary diagnosis (eg, covert dyskinesia, masked dyskinesia, presumptive TD, withdrawal emergent symptoms, or widhrawal dyskinesia), making communication and comparison of results among investigators difficult.

Tardive Dyskinesia

Prevalence, Incidence, and Risk Factors

KANE, JOHN M. MD; WOERNER, MARGARET PhD; LIEBERMAN, JEFFREY MD

Author Information

Journal of Clinical Psychopharmacology 8(4):p 57S, August 1988.

Abstract

Despite increased attention to the problem of tardive dyskinesia (TD), many questions remain unresolved. There is a consensus that neuroleptics play a substantial role in its development, but other variables must also contribute. Prevalence surveys have helped to define the scope of the problem and suggest risk factors for further study. Their usefulness has been limited by methodological problems including the difficulty of estimating false-negative (masked) dyskinesia and false-positive (movements caused by other neuromedical conditions) rates. A recent large scale survey reported an overall rate of abnormal involuntary movements of 23.4% among neuroleptic-treated psychiatric patients; the range was from 12.3% among outpatients at a Veterans Administration hospital to 37.4% among state hospital inpatients. Rates of covert dyskinesia, obtained by withdrawing medication from 70 TD negative cases, ranged from 17% for the Veterans Administration to 67% at the state hospital (overall rate, 34%). Very few clear false-positive cases were found. The incidence of TD, based on a large prospective study of young adult patients, is 19% after 4 years of cumulative neuroleptic exposure. Higher incidence rates have been found in prospective studies of older patient samples. Age remains the risk factor most consistently associated with TD development; it may also relate to increased persistence. Female sex among older populations, diagnosis of affective disorder, and evidence of neuroleptic-induced pseudoparkinsonism also relate to increased risk. Further work is needed to elucidate the role of dosage and length of neuroleptic treatment, as well as other potential contributory factors.

Incidence of Tardive Dyskinesia with Risperidone or Olanzapine in the Elderly: Results from a 2-Year, Prospective Study in Antipsychotic-Naïve Patients

Margaret G Woerner, Christoph U Correll, Jose Ma J Alvir, Blaine Greenwald, Howard Delman & John M Kane

Neuropsychopharmacology **36**, 1738–1746 (2011) | Cite this article

Abstract

Tardive dyskinesia (TD) rates with second-generation antipsychotics (SGAs) are considered to be low relative to first-generation antipsychotics (FGAs), even in the particularly vulnerable elderly population. However, risk estimates are unavailable for patients naïve to FGAs. Therefore, we aimed to determine the TD incidence in particularly vulnerable, antipsychotic-naïve elderly patients treated with the SGA risperidone or olanzapine. The present work describes a prospective inception cohort study of antipsychotic-naïve elderly patients aged ⩾55 years identified at New York Metropolitan area in-patient and out-patient geriatric psychiatry facilities and nursing homes at the time of risperidone or olanzapine initiation. At baseline, 4 weeks, and at quarterly periods, patients underwent assessments of medical and medication history, abnormal involuntary movements, and extra-pyramidal signs. TD was classified using Schooler–Kane criteria. Included in the analyses were 207 subjects (age: 79.8 years, 70.0% female, 86.5% White), predominantly diagnosed with dementia (58.9%) or a

Low-Dose Neuroleptic Treatment of Outpatient Schizophrenics

I. Preliminary Results for Relapse Rates

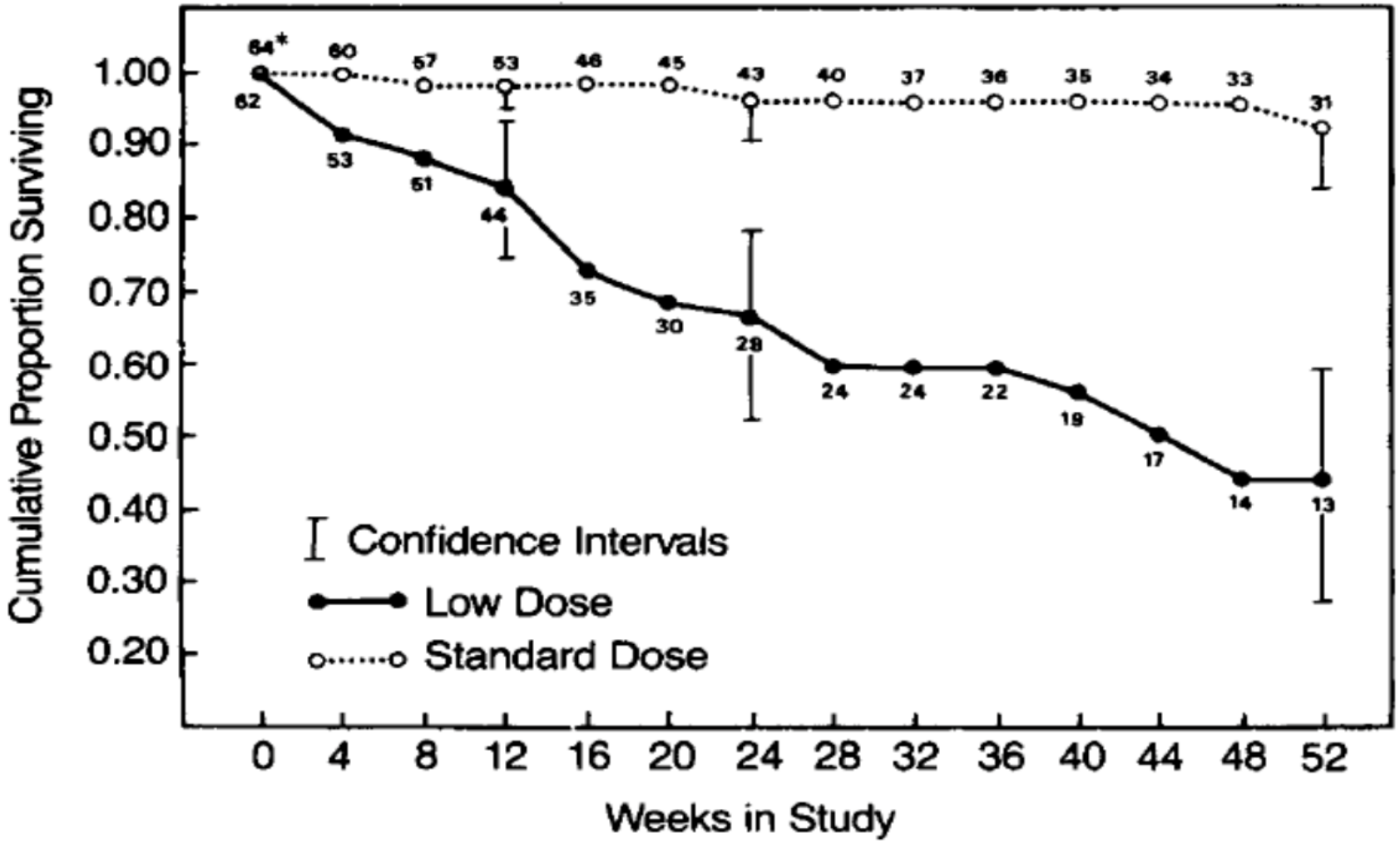
John M. Kane, MD; Arthur Rifkin, MD; Margaret Woerner, PhD; et al

» Author Affiliations

Arch Gen Psychiatry. 1983;40(8):893-896. doi:10.1001/archpsyc.1983.01790070083010

Abstract

• In an attempt to begin to establish minimum effective dosage requirements for the maintenance treatment of schizophrenia, we undertook a double-blind comparison of low-dose fluphenazine decanoate (1.25 to 5.0 mg/2 wk) with the standard-dose regimen (12.5 to 50.0 mg/2 wk) in outpatient schizophrenics. For the first 126 patients studied, cumulative relapse rates at one year for the low dose were 56% and for the standard dose 7%, a significant difference. Despite the fact that very little dyskinetic symptomatology developed in the sample as a whole, the low-dose treatment appeared to have a significant advantage in producing fewer early signs of tardive dyskinesia. Severity of relapse and total cumulative dosage were also considered.



Survival curves over 52-week period for patients receiving low-dose or standard-dose fluphenazine decanoate therapy. Asterisk indicates numbers referring to subjects entering each interval.

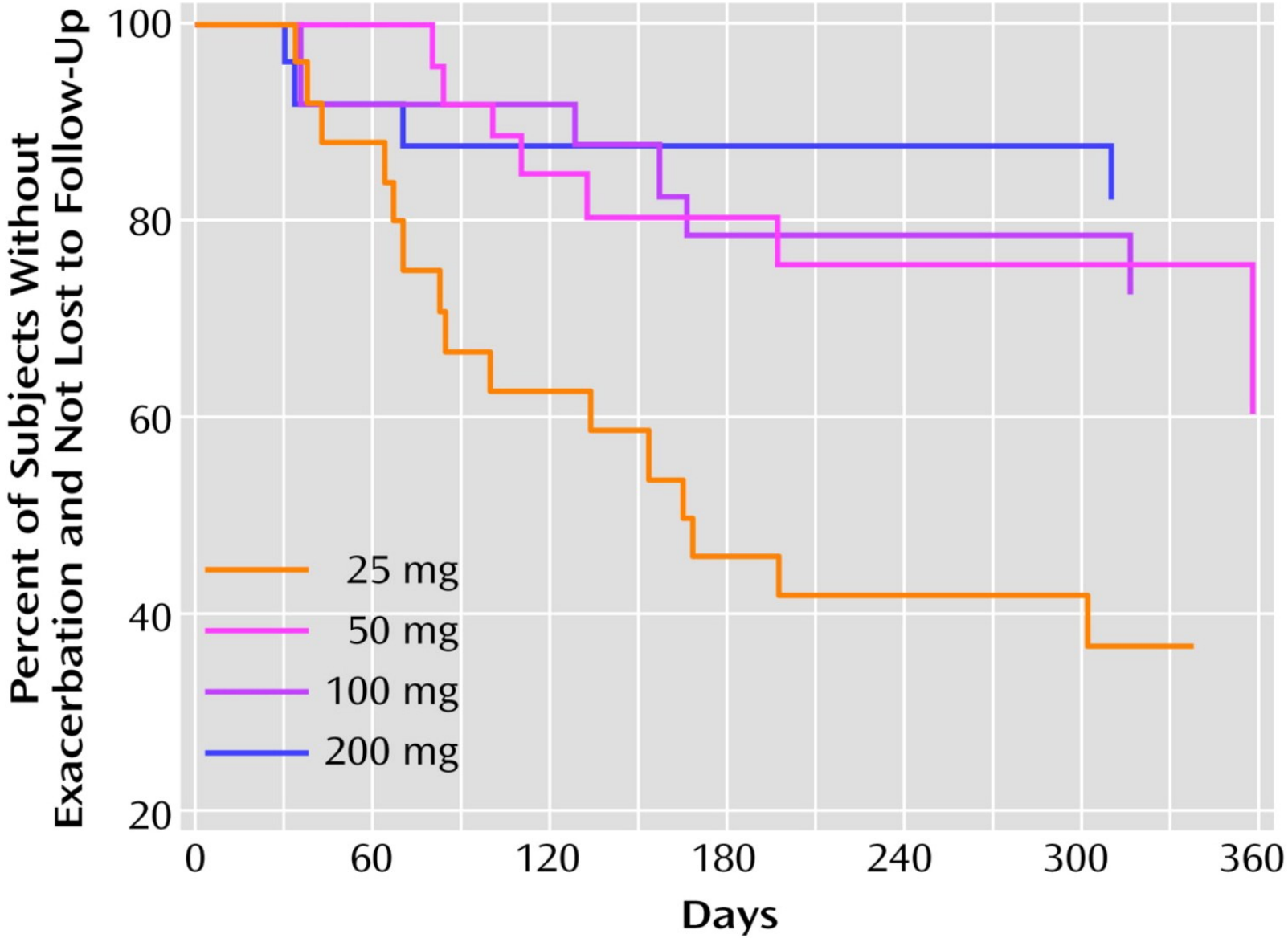
Kane, J. et. al. Arch Gen Psych 1983

FULL ACCESS | Article | Publication Date: 1 April 2002

A Multidose Study of Haloperidol Decanoate in the Maintenance Treatment of Schizophrenia

John M. Kane, M.D., John M. Davis, M.D., Nina Schooler, Ph.D., Stephen Marder, M.D., Daniel Casey, M.D., Benjamin Brauzer, M.D., Jim Mintz, Ph.D., and Robert Conley, M.D. | AUTHORS INFO & AFFILIATIONS

Publication: American Journal of Psychiatry • Volume 159, Number 4 • https://doi.org/10.1176/appi.ajp.159.4.554



Kane, J. et. al. Am J Psych 2002

Clozapine for the Treatment-Resistant Schizophrenic

A Double-blind Comparison With Chlorpromazine

John Kane, MD; Gilbert Honigfeld, PhD; Jack Singer, MD; Herbert Meltzer, MD; and the Clozaril Collaborative Study Group

• The treatment of schizophrenic patients who fail to respond to adequate trials of neuroleptics is a major challenge. Clozapine, an atypical antipsychotic drug, has long been of scientific interest, but its clinical development has been delayed because of an associated risk of agranulocytosis. This report describes a multicenter clinical trial to assess clozapine's efficacy in the treatment of patients who are refractory to neuroleptics. *DSM-III* schizophrenics who had failed to respond to at least three different neuroleptics underwent a prospective, single-blind trial of haloperidol (mean dosage, 61 ± 14 mg/d) for six weeks. Patients whose condition remained unimproved were then randomly assigned, in a double-blind manner, to clozapine (up to 900 mg/d) or chlorpromazine (up to 1800 mg/d) for six weeks. Two hundred sixty-eight patients were entered in the double-blind comparison. When a priori criteria were used, 30% of the clozapine-treated patients were categorized as responders compared with 4% of chlorpromazine-treated patients. Clozapine produced significantly greater improvement on the Brief Psychiatric Rating Scale, Clinical Global Impression Scale, and Nurses' Observation Scale for Inpatient Evaluation; this improvement included "negative" as well as positive symptom areas. Although no cases of agranulocytosis occurred during this relatively brief study, in our view, the apparently increased comparative risk requires that the use of clozapine be limited to selected treatment-resistant patients.

(*Arch Gen Psychiatry* 1988;45:789-796)

refractory subgroup remains a major public health problem—these individuals require more intensive care and are subject to the persistent disabilities associated with chronic schizophrenia. In addition, the continued presence of psychotic signs and symptoms makes these patients less available to psychosocial and vocational rehabilitation.

It is estimated that about 1 million Americans suffer from schizophrenia. While there are no definitive data available on how many do not respond to neuroleptics, extrapolations from clinical trial data suggest that there may be 100 000 to 200 000 such patients.

Data from maintenance medication trials indicate that even among patients initially responsive to antipsychotic drugs, 20% to 30% may relapse during the first year or two of maintenance drug treatment.[1] A proportion of these patients contributes to the number in the subgroup of patients refractory to treatment. Since many of these patients remain ill, there is a cumulative increase in the number of people in the treatment-refractory category.

See also p 865.

The recognition that some patients do not benefit from typical neuroleptics has resulted in research along two fronts: (1) to identify phenomenologic, demographic, and/or biologic factors that may be associated with poor treatment response and (2) to explore alternative treatment strategies that might be beneficial to this subgroup

PREVALENCE OF TREATMENT RESISTANCE WITHIN SCHIZOPHRENIA

More than 21 million people worldwide are affected by schizophrenia[1]

Over 60 different types of atypical and typical antipsychotic treatments for schizophrenia are used globally, with 15–40 being available in any single country[2]

Despite the variety of antipsychotics available, a considerable proportion of patients suffering from schizophrenia remain severely ill and resistant to treatment[3]

At the onset of illness, rates of primary treatment resistance have been shown to be up to 23%[4]

Overall, 10–30% of patients have little or no response to antipsychotic medications, and up to an additional 30% of patients have partial responses to treatment[3]

1. World Health Organization. who.int/mediacentre/factsheets/fs397/en/; 2. Bruijnzeel, D., et al. (2014). Antipsychotic treatment of schizophrenia: an update. Asian journal of psychiatry, 11, 3-7.; 3. Lehman, A. F., et al. (2004). American Journal of Psychiatry, 161(2 SUPPL.), i-iv+.; 4. Lally, J., et al. (2016). Psychological medicine, 46(15), 3231-3240.

Clinical Trial > Arch Gen Psychiatry. 2001 Oct;58(10):965-72. doi: 10.1001/archpsyc.58.10.965.

Clozapine and haloperidol in moderately refractory schizophrenia: a 6-month randomized and double-blind comparison

J M Kane [1], S R Marder, N R Schooler, W C Wirshing, D Umbricht, R W Baker, D A Wirshing, A Safferman, R Ganguli, M McMeniman, M Borenstein

Affiliations + expand

PMID: 11576036 DOI: 10.1001/archpsyc.58.10.965

Abstract

Background: Despite the demonstrated efficacy of clozapine in severely refractory schizophrenia, questions remain regarding its efficacy for primary negative symptoms, comparison with a moderate dose of a first-generation antipsychotic, and adverse effects during a longer-term trial. This study examined its efficacy in partially responsive, community-based patients, compared clozapine with moderate-dose haloperidol, and extended treatment to 6 months.

Methods: Randomized, double-blind, 29-week trial comparing clozapine (n = 37) with haloperidol (n = 34). Subjects with schizophrenia who were being treated in community settings at 3 collaborating clinical facilities were enrolled.

Results: Subjects treated with haloperidol were significantly more likely to discontinue treatment for lack of efficacy (51%) than were those treated with clozapine (12%). A higher proportion of clozapine-treated subjects met an a priori criterion of improvement (57%) compared with haloperidol-treated subjects (25%). Significantly greater improvement was seen in symptoms of psychosis, hostile-suspiciousness, anxiety-depression, thought disturbance, and total score measured on the Brief Psychiatric Rating Scale. No differences were detected in negative symptoms using the Brief Psychiatric Rating Scale or the Schedule for Assessment of Negative

Randomized Controlled Trial > J Clin Psychiatry. 2016 May;77(5):628-34.
doi: 10.4088/JCP.13m08351.

Clozapine and risperidone in moderately refractory schizophrenia: a 6-month randomized double-blind comparison

Nina R Schooler [1], Stephen R Marder, K N R Chengappa, Georgios Petrides, Donna Ames, William C Wirshing, Marjorie McMeniman, Robert W Baker, Haranath Parepally, Daniel Umbricht, John M Kane

Affiliations + expand

PMID: 27035871 DOI: 10.4088/JCP.13m08351

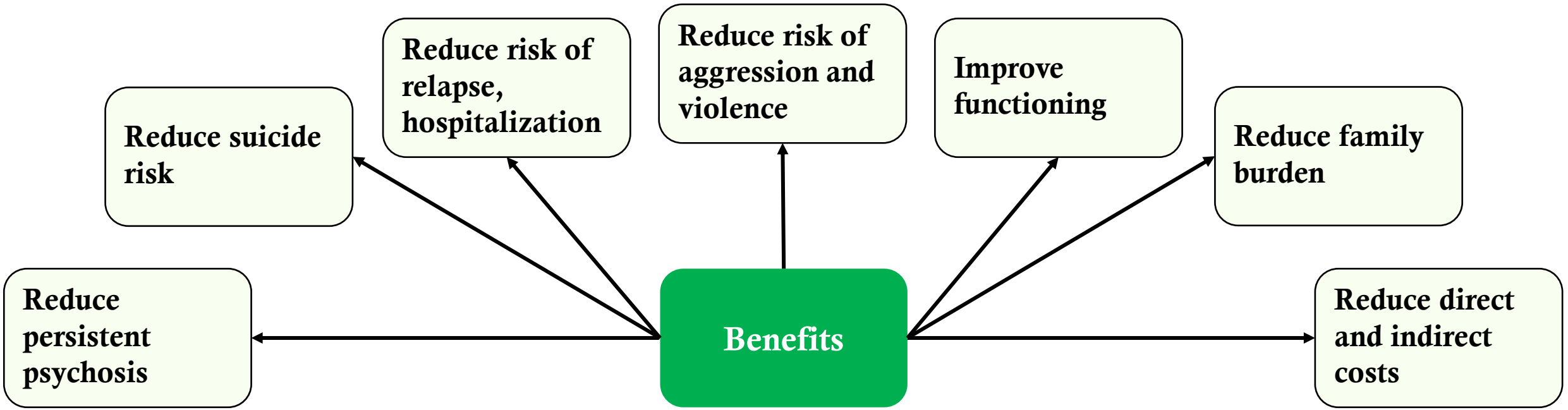
Abstract

Objective: Clozapine remains the only medication indicated for refractory schizophrenia. As new antipsychotic drugs become available, their efficacy compared to clozapine, particularly in moderately ill patients, is of great clinical interest. We compared risperidone, the first of these, to clozapine in partially responsive patients. Further, since participation of patients usually excluded from clinical trials is increasingly important, we broadened inclusion to a wider patient population.

Methods: We compared clozapine (n = 53) to risperidone (n = 54) in a randomized, double-blind, 29-week trial in schizophrenia patients (diagnosed using DSM-IV) at 3 research outpatient clinics. Randomization was stratified by "narrow" or "broad" inclusion criteria. The study was conducted between December 1995 and October 1999. Time to treatment discontinuation for lack of efficacy and time to 20% improvement in the Brief Psychiatric Rating Scale psychotic symptom cluster were the primary outcome measures.

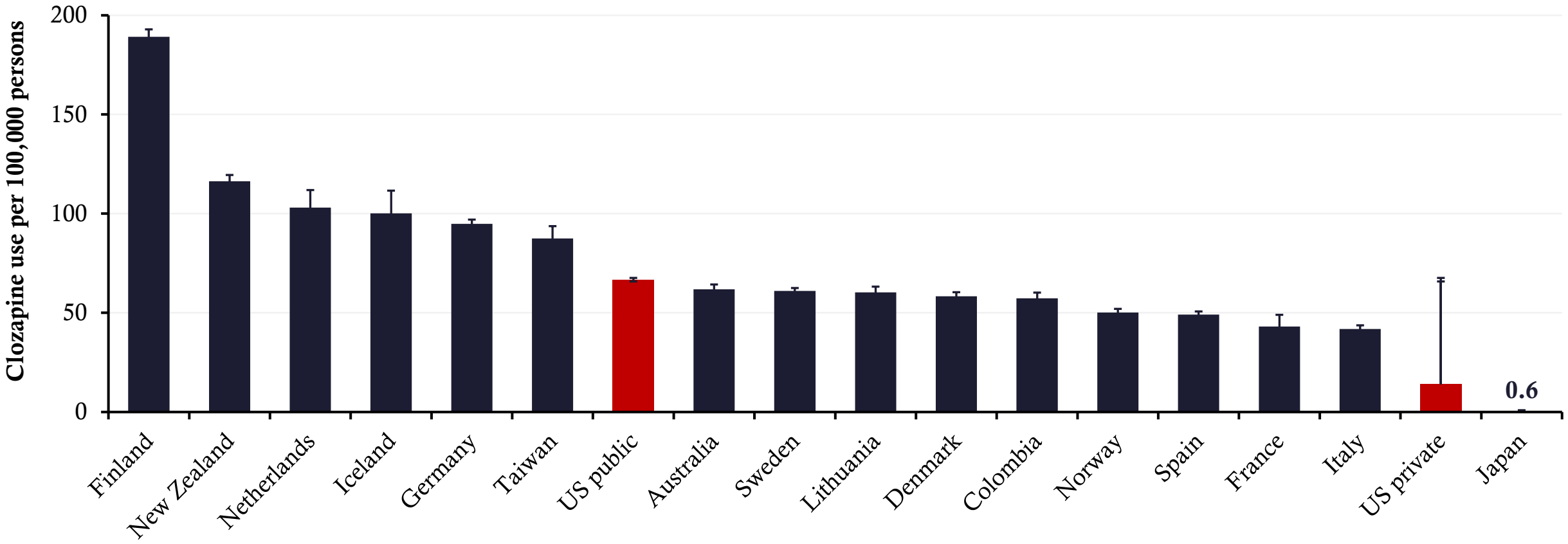
Results: There were no differences in all-cause discontinuation; clozapine-treated participants were significantly less likely to discontinue for lack of efficacy (15%) than risperidone-treated participants (38%) (Wilcoxon $\chi(2)1 = 6.10$, $P = .01$). Clozapine resulted in significantly more global

CLOZAPINE'S POTENTIAL ROLE IN IMPROVING PATIENTS' LIVES



For some patients, clozapine treatment can be life-changing
Benefit/Risk assessment individualized; requires therapeutic trial of clozapine

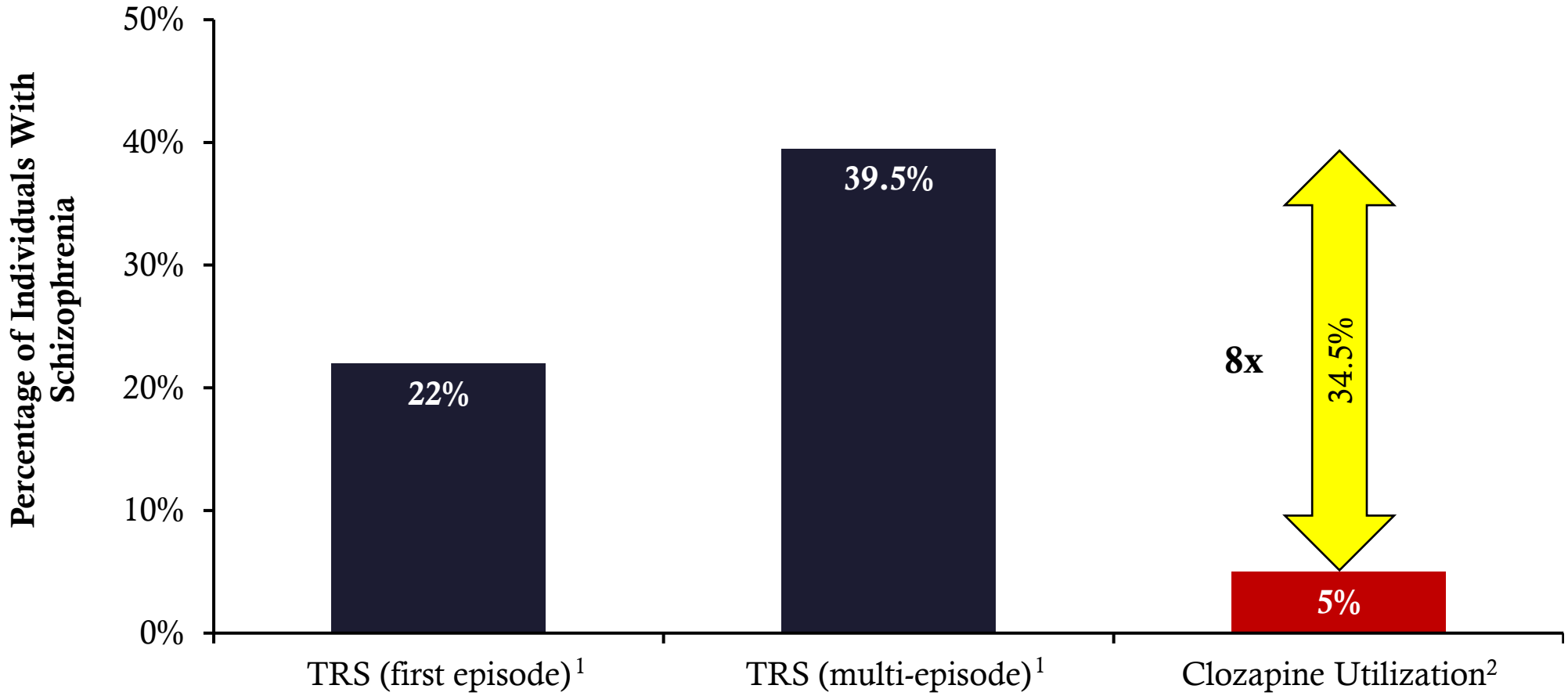
THE US LAGS BEHIND IN CLOZAPINE USE



Bachmann CJ, et al. *Acta Psychiatr Scand*. 2017;136(1):37-51

Prevalence of clozapine use in 2014 (or the most recent year available) with the following exceptions: Australia (2005–2013), Colombia (2006–2014), France (2006–2014), Italy (2005–2012), Japan (2009–2014), Spain (2011–2014), Sweden (2006–2014), Taiwan (2005–2013) and publicly insured US cohort (2005–2010).

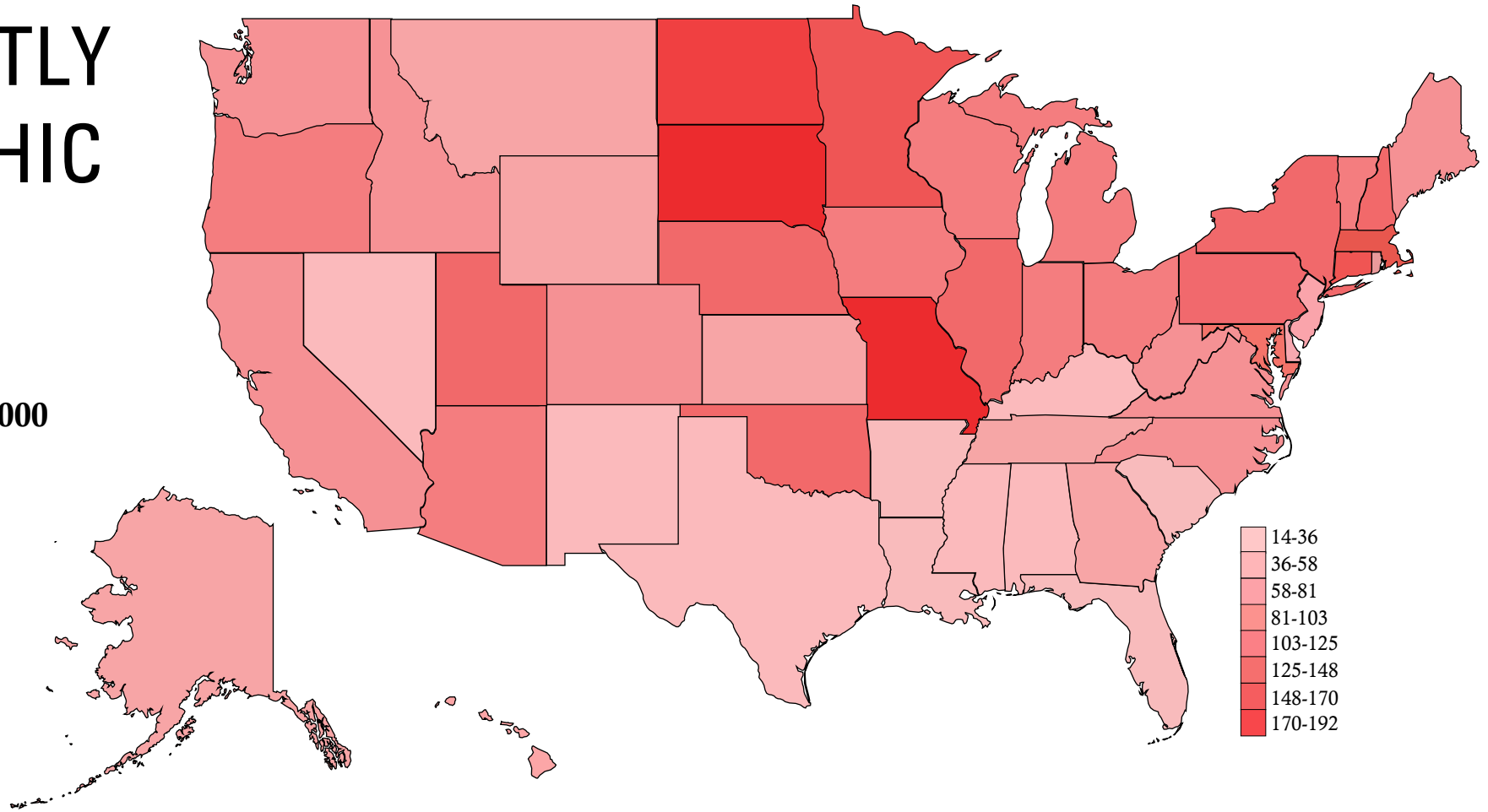
US CLOZAPINE UNDERUTILIZATION GAP



1. Diniz E, et al. *Braz J Psychiatry*. 2023;45(5):448-458; 2. Olfson M, et al. *Psychiatr Serv*. 2016;67(2):152.

CLOZAPINE USE VARIES GREATLY BY GEOGRAPHIC REGION

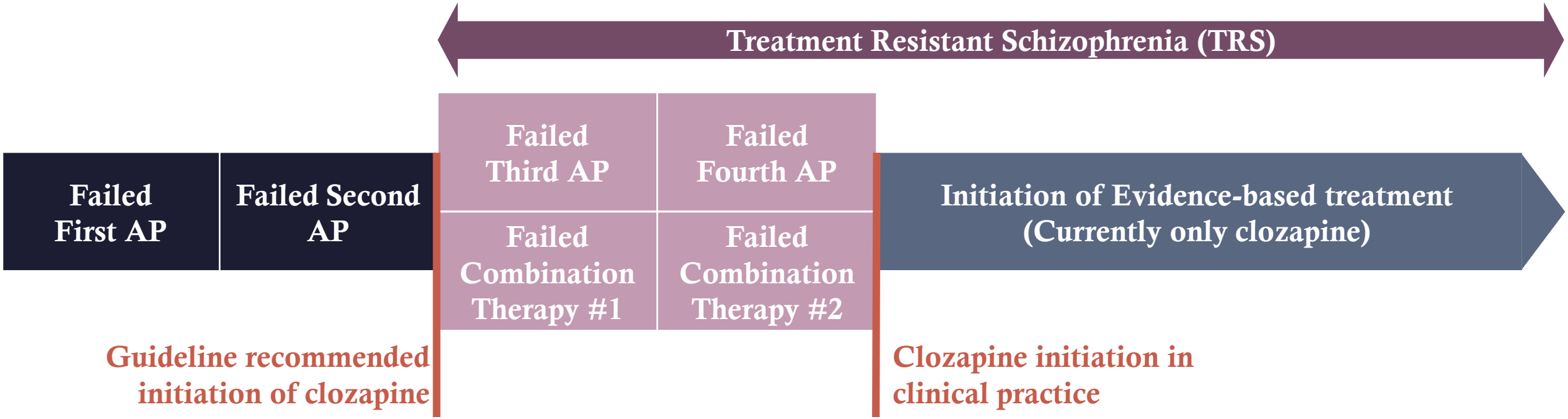
2019 Prescriptions per 100,000 Medicaid Enrollees



Adapted from *Schizophr Res*, 255, Benito RA, et al, Thirteen-fold variation between states in clozapine prescriptions to United States Medicaid patients, 79-81, Copyright 2023, with permission from Elsevier.

DELAYS IN PRESCRIBING CLOZAPINE ARE COMMON

Although guidelines recommend starting clozapine after two AP treatment failures, its introduction is often delayed by several years[1,2]



AP=antipsychotic; TRS=treatment-resistant schizophrenia.

Reprinted from Newron Pharmaceuticals — Moving Towards R&D Inflection Points. March 14, 2019; London UK. Edison Investment Research Ltd. Available at: https://www.edisongroup.com/research/moving-towards-rd-inflection-points-2/23649/. 1. Howes OD, et al. Br J Psychiatry. 2012;201(6):481-485; 2. Najim H, et al. Psytchiatry Danub. 2013;25(suppl 2):165-170. Image: https://www.edisongroup.com/research/moving-towards-rd-inflection-points-2/23649/

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., Sue E. Estroff, Ph.D., Patricia Marcy, B.S.N., James Robinson, M.Ed., Piper S. Meyer-Kalos, Ph.D., L.P., Jennifer D. Gottlieb, Ph.D., Shirley M. Glynn, Ph.D., David W. Lynde, M.S.W., Ronny Pipes, M.A., L.P.C.-S., Benji T. Kurian, M.D., M.P.H., Alexander L. Miller, M.D., Susan T. Azrin, Ph.D., Amy B. Goldstein, Ph.D., Joanne B. Severe, M.S., Haiqun Lin, M.D., Ph.D., Kyaw J. Sint, M.P.H., Majnu John, Ph.D., Robert K. Heinssen, Ph.D., A.B.P.P.

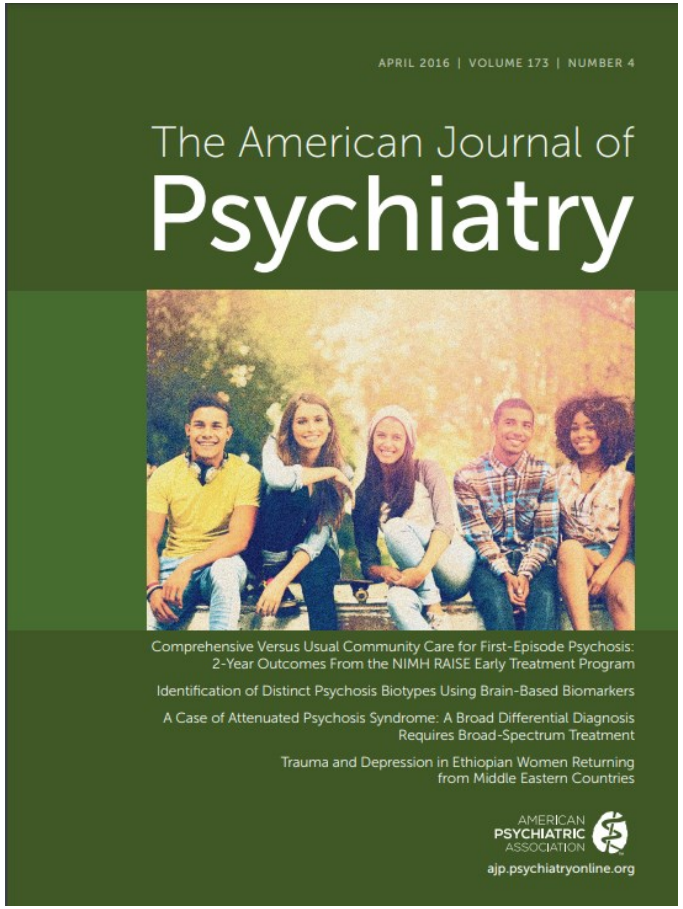
Objective: The primary aim of this study was to compare the impact of NAVIGATE, a comprehensive, multidisciplinary, team-based treatment approach for first-episode psychosis designed for implementation in the U.S. health care system, with community care on quality of life.

Method: Thirty-four clinics in 21 states were randomly assigned to NAVIGATE or community care. Diagnosis, duration of untreated psychosis, and clinical outcomes were assessed via live, two-way video by remote, centralized raters masked to study design and treatment. Participants (mean age, 23) with schizophrenia and related disorders and ≤6 months of antipsychotic treatment (N=404) were enrolled and followed for ≥2 years. The primary outcome was the total score of the Heinrichs-Carpenter Quality of Life Scale, a measure that includes sense of purpose, motivation, emotional and social interactions, role functioning, and engagement in regular activities.

Results: The 223 recipients of NAVIGATE remained in treatment longer, experienced greater improvement in quality of life and psychopathology, and experienced greater involvement in work and school compared with 181 participants in community care. The median duration of untreated psychosis was 74 weeks. NAVIGATE participants with duration of untreated psychosis of <74 weeks had greater improvement in quality of life and psychopathology compared with those with longer duration of untreated psychosis and those in community care. Rates of hospitalization were relatively low compared with other first-episode psychosis clinical trials and did not differ between groups.

Conclusions: Comprehensive care for first-episode psychosis can be implemented in U.S. community clinics and improves functional and clinical outcomes. Effects are more pronounced for those with shorter duration of untreated psychosis.

Am J Psychiatry 2016; 173:362–372; doi: 10.1176/appi.ajp.2015.15050632



Kane, J. M., et al. (2016). American Journal of Psychiatry, 173(4), 362-372.

Tread softly because you tread on my dreams.

W.B. Yeats

NAVIGATE

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 fewer side effects

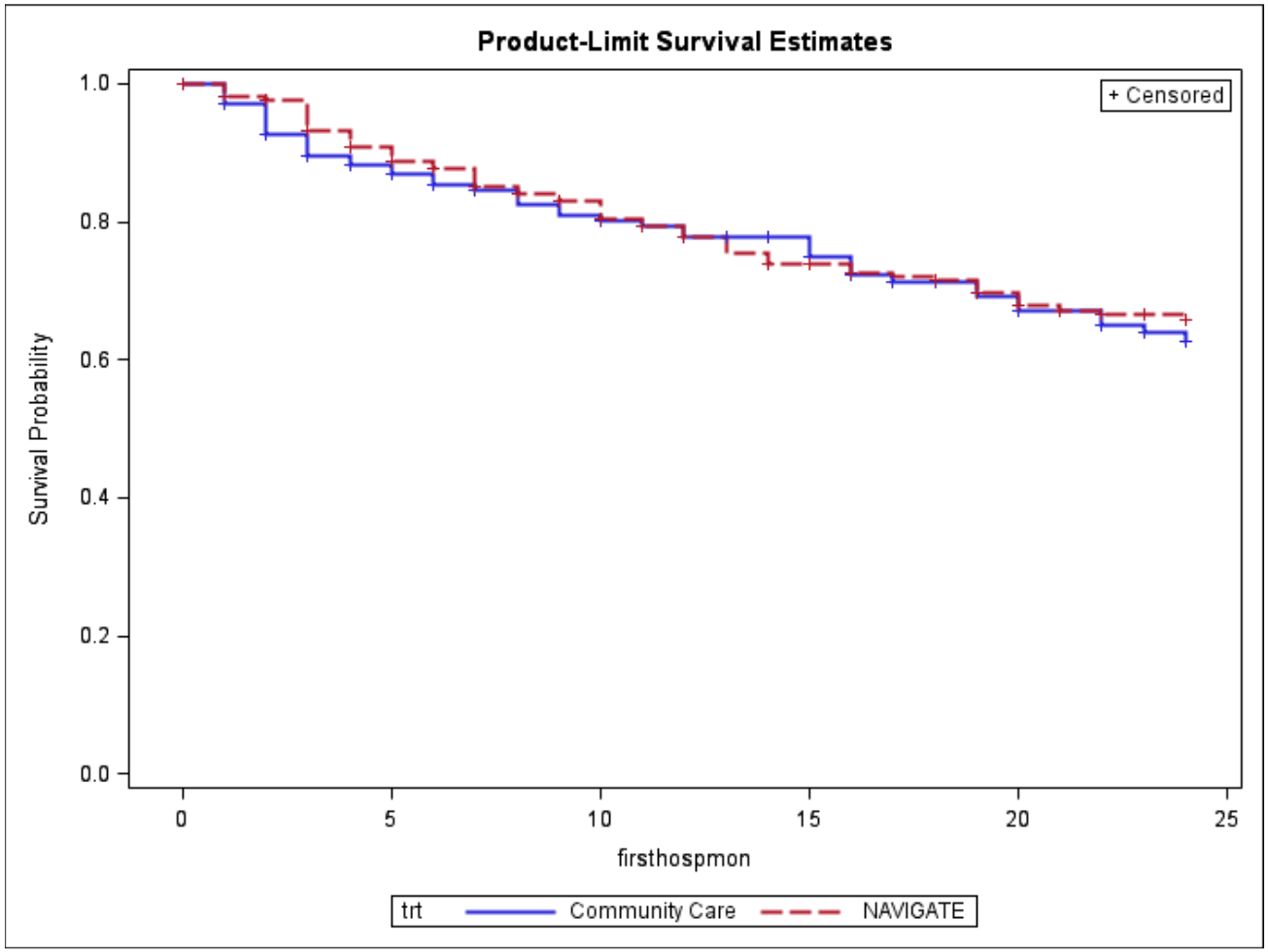
Duration of psychosis before treatment starts is an important moderator of initial NAVIGATE effectiveness.

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. (2016). American Journal of Psychiatry, 173(4), 362-372.

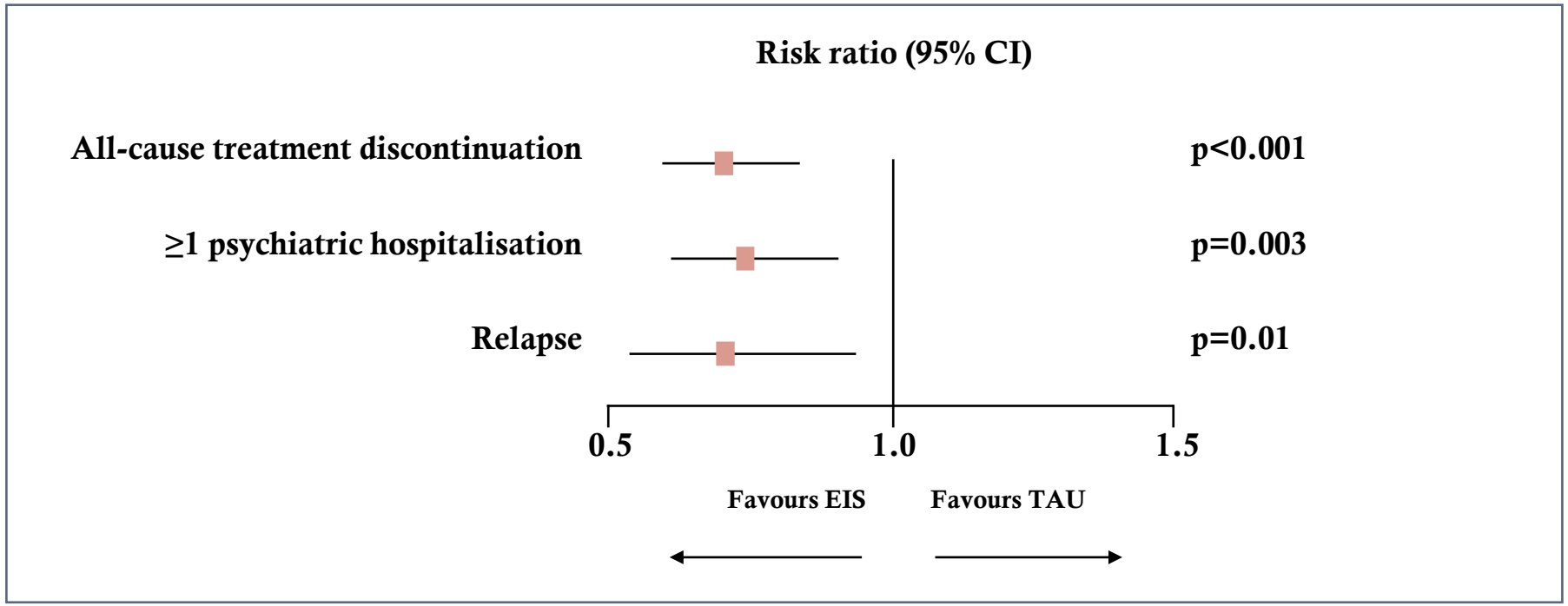
TIME TO FIRST PSYCHIATRIC HOSPITALIZATION

(DIFFERENCE BETWEEN TREATMENTS, P=0.75)



Kane, J. M., et al. (2016). American Journal of Psychiatry, 173(4), 362-372.

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, C. U., et al. (2018). JAMA Psychiatry, 75(6), 555-565.

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.

Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre–post studies

Taishiro Kishimoto, Katsuhiko Hagi, Shunya Kurokawa, John M Kane, Christoph U Correll

LAIs were associated with a lower risk of hospitalization or relapse than oral antipsychotics in each of the three study designs (RCTs: 29 studies, 7833 patients, RR 0·88 [95% CI 0·79–0·99], p=0·033; cohort studies: 44 studies, 106136 patients, RR 0·92 [0·88–0·98], p=0·0044; pre–post studies: 28 studies, 17876 patients, RR 0·44 [0·39–0·51], p<0·0001). This association was maintained across the study designs when we reversed the preferential order to risk of relapse over hospitalization, and in individual analysis of hospitalization risk.

Interpretation

Although study designs have strengths and weaknesses, including potential low quality of observational studies, we consistently identified significant benefit with LAIs versus oral antipsychotics in preventing hospitalisation or relapse, in settings ranging from restricted research (RCTs) to real-word application (cohort and pre–post studies). **Our findings suggest that increased clinical use of LAIs could improve outcomes in schizophrenia.**

Kishimoto, T., et al. (2021). The Lancet Psychiatry, 8(5), 387-404.

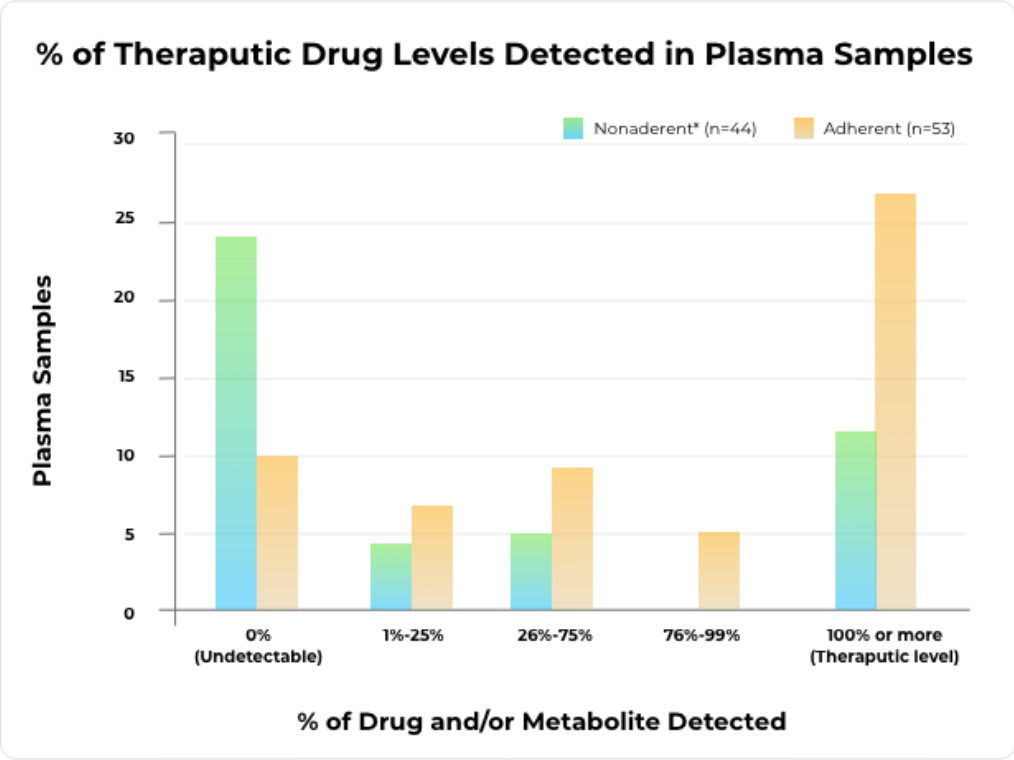
Indirect Measures of Adherence are Often *Inaccurate*

Study comparing clinician assessment of adherence and plasma levels in 97 patients presenting to ED

Adherence typically based on patient self-report or report of individuals involved in patient's care

Nearly 20% of patients (10 of 53) assessed as adherent had undetectable plasma levels (0%)

25% of patients (11 of 44) assessed as nonadherent had therapeutic levels (≥100%)



*As assessed by ED psychiatrist.
ED, emergency department.

Lopez LV, et al. J Clin Psychopharmacology. 2017;37(3):310-314.

Acta Psychiatr Scand 2018: 137: 39–46
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ACTA PSYCHIATRICA SCANDINAVICA

Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia

McCutcheon R, Beck K, D'Ambrosio E, Donocik J, Gobjila C, Jauhar S, Kaar S, Pillinger T, Reis Marques T, Rogdaki M, Howes OD. Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia.

Objective: Treatment resistance is a challenge for the management of schizophrenia. It is not always clear whether inadequate response is secondary to medication ineffectiveness, as opposed to medication underexposure due to non-adherence or pharmacokinetic factors. We investigated the prevalence of subtherapeutic antipsychotic plasma levels in patients identified as treatment-resistant by their treating clinician.

Method: Between January 2012 and April 2017, antipsychotic plasma levels were measured in 99 individuals provisionally diagnosed with treatment-resistant schizophrenia by their treating clinicians, but not prescribed clozapine. Patients were followed up to determine whether they were subsequently admitted to hospital.

Results: Thirty-five per cent of plasma levels were subtherapeutic, and of these, 34% were undetectable.

hospital ($P = 0.02$).

Conclusion: A significant proportion of patients considered treatment-resistant have subtherapeutic antipsychotic plasma levels, and this is associated with subsequent admission. The presence of subtherapeutic plasma levels may suggest a need to address adherence or pharmacokinetic factors as opposed to commencing clozapine treatment. While antipsychotic levels are not recommended for the routine adjustment of dosing, they may assist with the assessment of potential treatment resistance in schizophrenia.

R. McCutcheon[1,2,3,4], K. Beck[1,2,3], E. D'Ambrosio[1,4], J. Donocik[1,2,3,4], C. Gobjila[1,4], S. Jauhar[1,2,3,4], S. Kaar[1,2,3,4], T. Pillinger[1,2,3,4], T. Reis Marques[1,2,3,4], M. Rogdaki[1,2,3,4], O. D. Howes[1,2,3,4]

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monitoring; treatment-resistant; psychosis

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McCutcheon, R., et. (2018). Acta Psychiatrica Scandinavica, 137(1), 39-46.

LAIS:
PATIENTS STILL DO RELAPSE

Added value of this study

By use of precise participant-level inclusion criteria and a harmonised analytic approach across datasets, this study generated reliable estimates of the risk of relapse during assured antipsychotic exposure and its predictors. These results confirm that a sizeable proportion of individuals whose illness is stabilised on continuous antipsychotic treatment could experience subsequent relapse despite confirmed ongoing antipsychotic treatment.

Implications of all the available evidence

Antipsychotic drugs are highly efficacious in treating acute psychosis and preventing relapse compared with no treatment, but patients whose illness is stabilised on these drugs might subsequently have symptom exacerbations. Future research should investigate the role of dynamic changes in the dopaminergic system in relapse during antipsychotic treatment.

Psychosis relapse during treatment with long-acting injectable antipsychotics in individuals with schizophrenia-spectrum disorders: an individual participant data meta-analysis

Jose M Rubio, Georgios Schoretsanitis, Majnu John, Jari Tiihonen, Heidi Taipale, Daniel Guinart, Anil K Malhotra, Christoph U Correll, John M Kane

Summary

Background Most individuals with schizophrenia-spectrum disorders have relapses, which increase the risk of morbidity and mortality. Because non-adherence to antipsychotic maintenance treatment could affect more than half of individuals with schizophrenia-spectrum disorders, psychosis relapse can often be confounded by unnoticed treatment interruption. Research of relapse during confirmed antipsychotic exposure has basic clinical and neurobiological implications, but data are scarce. We aimed to generate reliable estimates of incidence and predictors of relapse during assured antipsychotic treatment.

Methods We did a systematic review and individual participant data (IPD) meta-analysis of clinical trials of long-acting injectable antipsychotics (LAIs) for psychosis relapse-prevention, following IPD-PRISMA guidelines. Datasets were identified by searching relevant repositories from inception to Aug 1, 2019. Each LAI group was reanalysed as a separate cohort, further identifying subcohorts of individuals with and without prospectively determined symptom remission (PSR). Summary incidence rate of relapse, incidence rate ratios (IRRs) of relapse between individuals with and without PSR, hazard ratios (HRs) of covariates on risk of relapse, and standardised mean difference (SMDs) in changes in overall functioning associated with relapse were generated by pooling results from the harmonised reanalysis of each study. This study is registered with PROSPERO, number CRD42019137439.

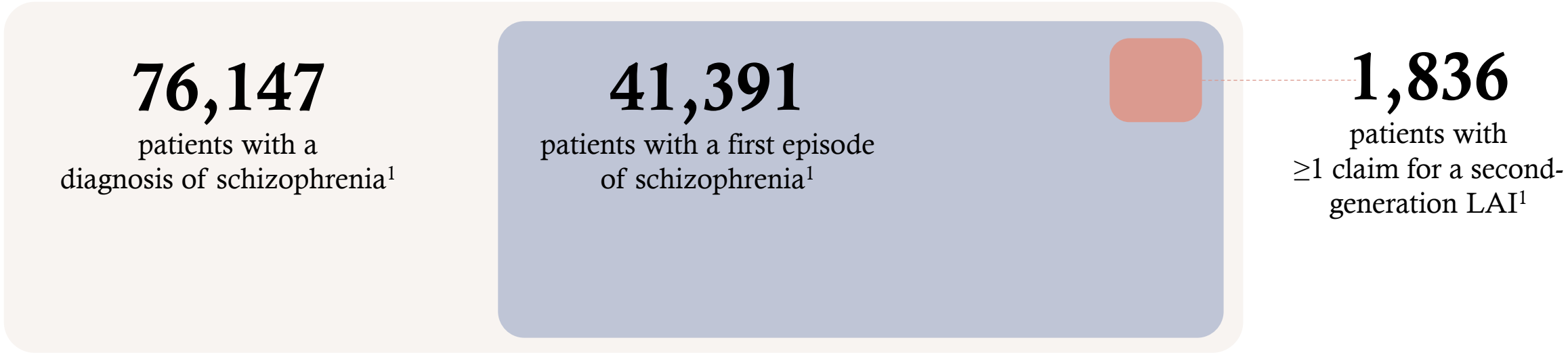
Findings 19 treatment cohorts consisting of 5130 individuals (2938 with PSR, 2192 without PSR), with 3959·53 observed participant-years, were meta-analysed. Pooled incidence of relapse was 22·97 per 100 participant-years (14·76 per 100 participant-years for the PSR subcohort, 31·51 per 100 participant-years for the non-PSR subcohort), with an IRR of 0·19 (95% CI 0·07 to 0·54). Relapse was associated with functional decline (overall SMD –0·76, 95% CI –1·14 to –0·37; PSR SMD –0·52, 95% CI –0·80 to –0·21; non-PSR SMD –0·72, 95% CI –1·18 to –0·26).The strongest predictor of relapse was tardive dyskinesia at treatment onset (HR 2·39, 95% CI 1·05 to 5·42).

Interpretation Despite the established efficacy of antipsychotics in preventing relapse, these data indicate that these drugs might not prevent subsequent exacerbations for a proportion of individuals whose illness is stabilised on continuous antipsychotic treatment. Tardive dyskinesia in particular might have pathophysiological implications for relapse.

Rubio, J. M., et al. (2020). The Lancet Psychiatry, 7(9), 749-761.

DESPITE EVIDENCE SHOWING THEIR BENEFITS, **LAI ANTIPSYCHOTICS ARE UNDERUTILISED IN NEWLY-DIAGNOSED PATIENTS**

In a US-based, real-world study, only 4.4% of young adults with a first episode of schizophrenia were treated with a second-generation LAI[1]



Patient claims data for young adults (aged 18–40 years) were obtained from the IBM® MarketScan® Commercial and Medicare Supplemental databases. Inclusion criteria included: a diagnosis of schizophrenia (according to ICD-9 or ICD-10 codes for schizophrenia) between 1 January 2013 and 30 September 2019; no schizophrenia diagnosis or LAI/oral antipsychotic claim within 12 months prior to the first diagnosis of schizophrenia (i.e., a first episode); claim for a second-generation LAI (aripiprazole, olanzapine, paliperidone, or risperidone) and continuous use (≥90 consecutive days, with 7-day gaps between refills permitted); continuous enrolment in commercial or Medicare supplemental medical and pharmacy benefits from ≥12 months prior to diagnosis to the end of continuous treatment with LAI; aged 18–40 years at diagnosis; and ≥1 claim for an oral antipsychotic (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, or ziprasidone) prior to the first LAI administration.1 In Europe and the UK, Abilify Maintena® 400 mg (aripiprazole once-monthly) is indicated for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole2

ICD-9/10=International Classification of Diseases, 9th/10th revision; LAI=long-acting injectable

1. Kane et al. J Clin Psychiatry 2023;84(3):22m14544; 2. Abilify Maintena® 400 mg (aripiprazole once-monthly). Summary of product characteristics. July 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/abilify-maintena-epar-product-information_en.pdf, accessed August 2023

Focused Ethnographic Examination of Barriers to Use of Long-Acting Injectable Antipsychotics

Objective: The authors designed this project to identify barriers to using long-acting formulations of antipsychotics.

Methods: The authors used a focused ethnographic approach. Patients, psychiatrists, nurses, therapists and administrators were interviewed about barriers to use of long-acting injectable (LAI) antipsychotics at six facilities in New York State, as were representatives from insurance firms, a pharmaceutical company, and a national professional organization. Interviews were conducted and analyzed by a central team not affiliated with the institutions.

Results: Interviews were obtained with 23 patients, 16 psychiatrists, three nurses, 23 therapists, 14 administrators, four insurers, one representative from a pharmaceutical industry, and one representative from a national organization. Major barriers identified from the interviews included restricting discussions about LAI medication to only patients with nonadherence or repeated hospitalizations; inadequate education efforts with patients about LAI antipsychotics; inadequate support for patients making medication decisions; lack of communication within the treatment team about issues relevant to use of LAI formulations by patients; therapists' limited knowledge about LAI antipsychotics, which restricted their role in supporting patients making treatment decisions; psychiatrist concerns about the pharmacologic properties of LAI formulations; lack of clinic infrastructure to support LAI prescriptions; and payer concerns about whether the immediate costs of LAI administration would translate into later potential cost benefits.

Conclusions: Effective shared decision making about use of LAI antipsychotics requires that patients receive accurate information and support for their decision making. The training needs and administrative support requirements for all team members should be considered to provide patients with the information and support required.

Psychiatric Services 2020; 71:337–342; doi: 10.1176/appi.ps.201900236

Robinson, D. G., et al. (2020). Psych Services, 71(4), 337-342.

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.

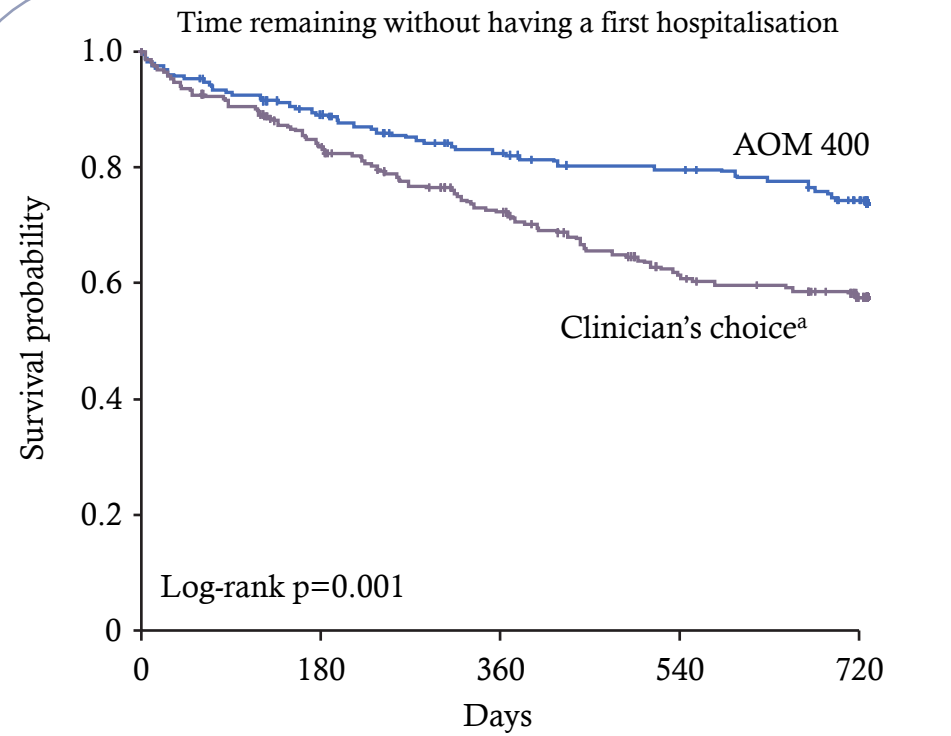
DESIGN, SETTING, AND PARTICIPANTS The Prevention of Relapse in Schizophrenia (PRELAPSE) trial was cluster randomized with a follow-up duration of 2 years. The study began in December 2014, was completed in March 2019, and was conducted in 39 mental health centers in 19 US states. Site randomization assigned 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.

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.

PRELAPSE

Time to first hospitalization (primary endpoint)



No. at risk:

234	183	157	147	127
255	186	148	116	93

For time to first hospitalization, HRb 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]

[a] Clinician's choice (CC) of medication, included (but not limited to):

- **Oral antipsychotics** (including but not limited to): aripiprazole, risperidone, lurasidone, quetiapine, olanzapine, ziprasidone
- **LAIs** (including but not limited to): risperidone, haloperidol, olanzapine, paliperidone, fluphenazine

AOM 400, aripiprazole once-monthly 400 mg; CC, clinician's choice, CI, confidence interval; HR, hazard ratio

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

PRELAPSE

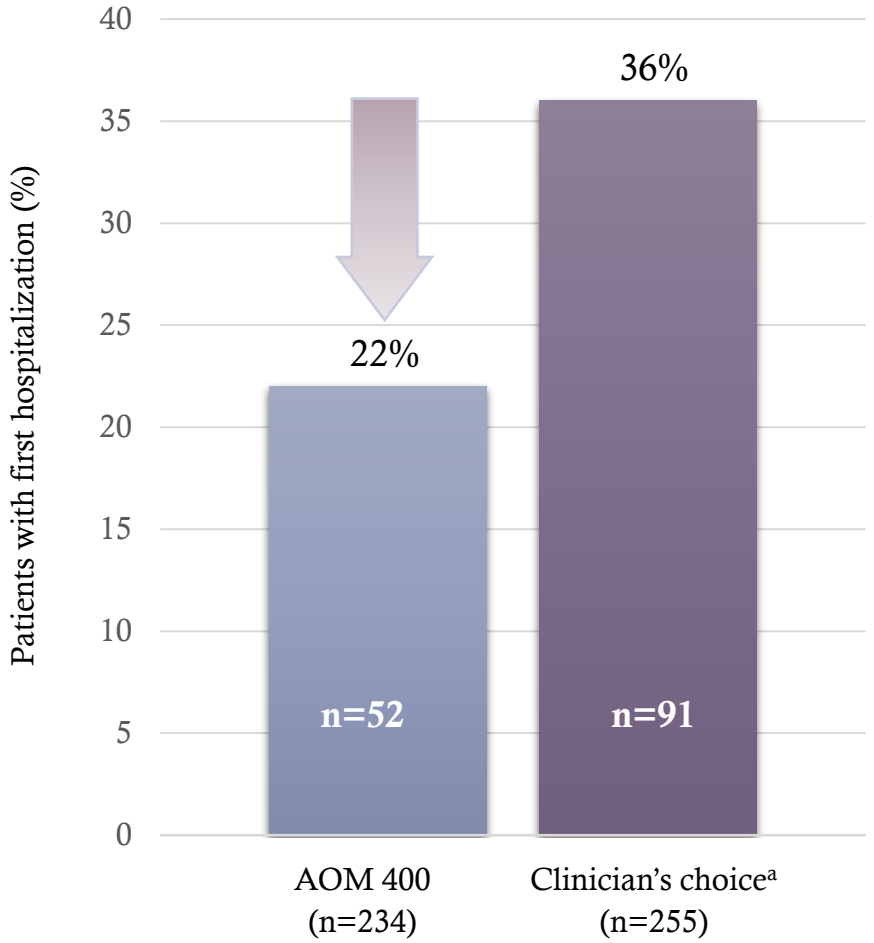
Hospitalization Rates

44%

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

NNT = **7**

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



AOM 400=aripiprazole once-monthly 400 mg; CI=confidence interval; LAI=long-acting injectable; RR=relative risk

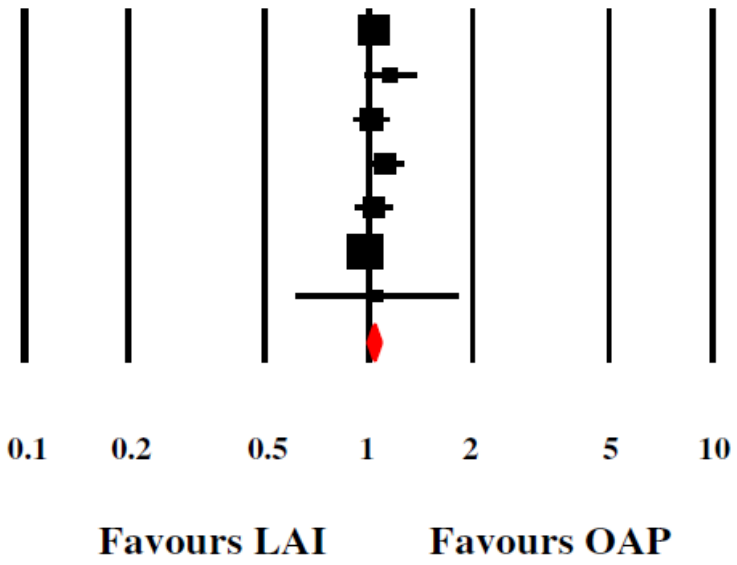
Adapted from: Kane, J. M., et al. (2020). JAMA Psychiatry, 77(12), 1217-1224.

ADVERSE EFFECTS WITH LAIS VS SAME ORAL ANTIPSYCHOTIC

(N=16, N=4,902)

No Difference in Frequency of At Least One Adverse Effect

Study name	Subgroup within study	Risk ratio	Lower limit	Upper limit	p-Value	Events / Total LAI	Events / Total 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 et al Schiz Res 2016; 176:220-230

Clozapine and Long Acting Injectable (LAI) Antipsychotic Use by EPINET Hub

Hub number	Number with medication data at any point	Number taking clozapine at any point	% taking clozapine at any point	Number taking a LAI at any point	% taking a LAI at any point
1	714	62	8.7%	157	22.0%
2	972	28	2.9%	192	19.8%
3	152	3	2.0%	12	7.9%
4	346	31	9.0%	66	19.1%
5	574	10	1.7%	128	22.3%
6	942	43	4.6%	353	37.5%
7	381	34	8.9%	19	5.0%
8	1252	86	6.9%	335	26.8%

Significant differences between EPINET Hubs exist for both LAI percentages ($p = 0.019$) and Clozapine percentages ($p = 0.016$) from testing for extra Poisson variation.

Kane, J. et al in preparation

First Experience With a Wireless System Incorporating Physiologic Assessments and Direct Confirmation of Digital Tablet Ingestions in Ambulatory Patients With Schizophrenia or Bipolar Disorder

John M. Kane, MD; Roy H. Perlis, MD, MSc; Lorenzo A. DiCarlo, MD; Kityee Au-Yeung, PhD; Jessie Duong, BA; Georgios Petrides, MD

J Clin Psychiatry 2013;74(6):e533-e540

Randomized Controlled Trial > Schizophr Res. 2019 Jun:208:167-172.

doi: 10.1016/j.schres.2019.03.014. Epub 2019 Mar 30.

Relationships between smartphone social behavior and relapse in schizophrenia: A preliminary report

Benjamin Buck [1], Emily Scherer [2], Rachel Brian [3], Rui Wang [4], Weichen Wang [4], Andrew Campbell [4], Tanzeem Choudhury [5], Marta Hauser [6], John M Kane [6], Dror Ben-Zeev [3]

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

A Collaborative Approach to Identifying Social Media Markers of Schizophrenia by Employing Machine Learning and Clinical Appraisals

Michael L Birnbaum[1, 2, 3]; Sindhu Kiranmai Ernala[4]; Asra F Rizvi[1, 2]; Munmun De Choudhury[4]; John M Kane[1, 2, 3]

Most people say that it is the intellect which makes a great scientist. They are wrong: It is character.

Albert Einstein

When people show you who they are, believe them the first time.

Maya Angelou

Collaboration is an unnatural act among two or more non-consenting adults.

Anonymous

Remember upon the conduct of each depends the fate of all.

Alexander the Great

I wouldn’t have seen it if I hadn’t believed it.

Marshall McLuhan (not Yogi Berra)

Ask yourself at every moment:
‘Is this necessary?’
You become what you give your attention to.

Marcus Aurelias