



National Academy of Science
July 17-18, 2018
Washington DC
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RESTRICTION OF TREATMENT QUALITY IN PRAGMATIC CLINICAL TRIALS

Key Points for RWE in Randomized Clinical Trials

Transforming minds,
bringing hope
for a meaningful life.

- What is the question?
 - Who
 - What
 - How
 - When
- What is real world evidence?
 - Everything
 - Nothing

RESTRICTION OF TREATMENT QUALITY IN PRAGMATIC CLINICAL TRIALS

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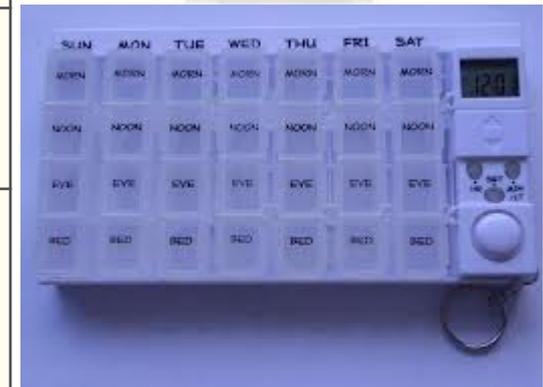
- Whose treatment is restricted?
 - **What are their vulnerabilities?**
- Specifically what is to be restricted?
 - **What is impact of the treatment elements restricted?**
- Where will restrictions be applied?
 - **Are treatment practice and ethical considerations similar in all areas?**
- How long are the restrictions in place?
 - **Will the treatment restrictions have enduring impact on morbidity and mortality?**
- What is the value of the restrictions?
 - **What are the risk benefit considerations of imposing the restrictions?**



Considerations for Study Design Restrictions

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DOMAIN	DEFINITION OF DOMAIN TERMINOLOGY
Participant eligibility criteria	Considerations include the intended treatment population of interest as identified by the study's authors
Intervention flexibility	Considerations include posology, dose, dosing interval, windows allowed for dosing; permitted concomitant treatments. The domain should be considered separately for experimental and comparisons treatment interventions
Medical practice setting/practitioner expertise	Considerations include experience, skills and resources of the practitioner and the treatment team; the healthcare delivery system; standards of care at the site, and local cultural practices that may influence medical delivery or outcomes. The domain should be considered separately for experimental and comparisons treatment interventions.
Follow-up intensity and duration	Considerations include frequency and length of visits and the number and the scope of the assessments.
Outcome(s)	Considerations include evaluation of measure(s) by which the interventions' effects are assessed and how well they reflect outcomes that are used and considered important to real world practice.
Participant adherence	Considerations include the degree to which the subjects are encouraged and tracked for adherence to study-related procedures.





CASE # 1 InterSePT

International Suicide Prevention Trial

Goal

- Demonstrate that clozapine is better than olanzapine for reducing the risk for suicidal behavior in patients with schizophrenia or schizoaffective disorder who are known to be at high risk for suicide.



The Public Health Problem

- Patients with schizophrenia and schizoaffective disorder exhibit high rates of suicide behavior (suicide attempts and deaths by suicide)
 - Lifetime risk of death by suicide is approximately 5%.
 - Lifetime risk of suicide attempts is 25-50%
- This outcome represents a under-treated life-threatening mental health condition.

InterSePT Study Null Hypothesis

Suicide behavior or perceived risk for imminent suicide is similar during 2-year follow up treatment with clozapine or olanzapine in patients with schizophrenia or schizoaffective disorder known to be at high risk for suicide.

Design

- A 2-year, multicenter, international, randomized, open-label, rater-/suicide monitoring board-blinded study comparing the risk for suicidal behavior in patients with schizophrenia or schizoaffective disorder treated with clozapine vs olanzapine
- 980 high risk patients enrolled

Randomization	Clozapine		
	12.5 mg BID	300-900 mg/day (26 weekly visits)	300-900 mg/day (Biweekly visits)
	Olanzapine		
	5mg QD	5-30 mg/day (26 weekly visits)	5-30 mg/day (Biweekly visits)
	4 Wk	26 Weeks	74 Weeks

- Endpoints
 - suicide attempts (including those that led to death),
 - hospitalizations to prevent suicide
 - rating of "much worsening of suicidality" from baseline

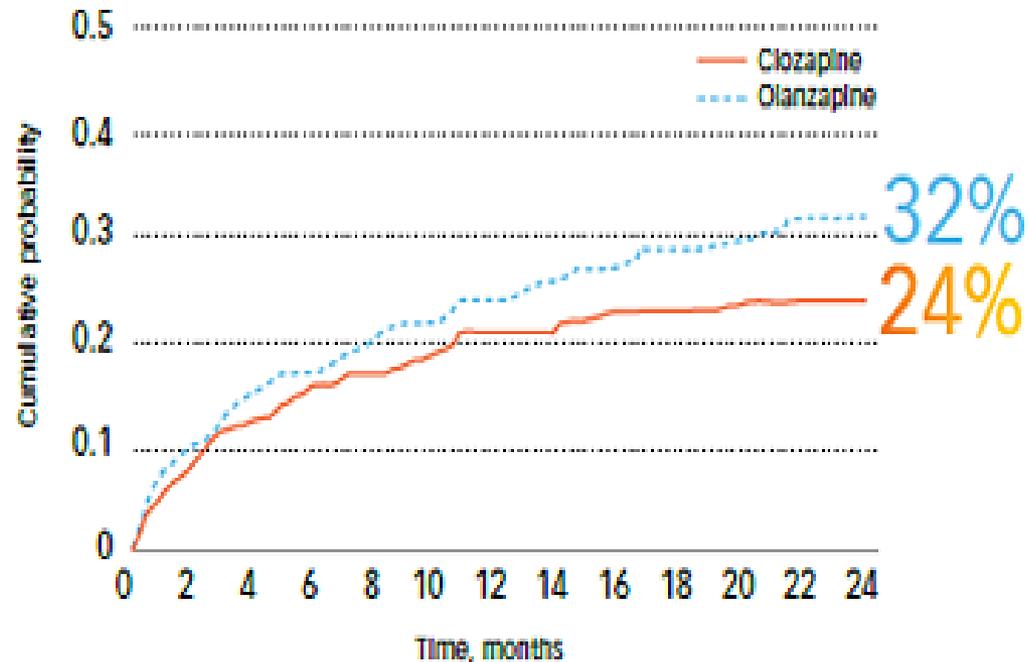
Key Considerations

- Ethical considerations required that the design minimize suicide attempts and deaths
 - After randomization, unblinded clinicians at each site could make any interventions necessary to prevent the occurrence of suicide attempts.
 - Suicidal behavior was assessed at each visit.
- Defining suicidal behavior in patients with psychosis
- Endpoint selection
- Determination of analytic strategy
- Development of scales to assess suicidal behavior
- Differential monitoring requirements for clozapine vs olanzapine

Results

- Significantly fewer patients treated with clozapine exhibited **any suicidal behavior endpoint** ($P = .03$; HR = 0.76; CI = 0.58 – 0.97).
 - Significantly fewer patients treated with clozapine exhibited **attempted suicide** ($P = .03$; 34 vs 55).
 - Significantly fewer patients treated with clozapine exhibited **required hospitalizations** ($P = .05$; 82 vs 107).
 - Significantly fewer patients treated with clozapine exhibited **required rescue interventions** ($P = .01$; 118 vs 155)
 - Significantly fewer patients treated with clozapine exhibited **required concomitant antidepressants** ($P = .01$; 221 vs 258)
 - Significantly fewer patients treated with clozapine exhibited **required concomitant anxiolytics/soporifics** ($P = .03$; 301 vs 331)
 - Similar numbers **died by suicide** (5 clozapine vs 3 olanzapine-treated patients; $P = .73$)

Cumulative probability
of experiencing a
significant suicide
attempt or
hospitalization to
prevent suicide¹



InterSePT Summary Finding

Suicide behavior and/or perceived risk for **imminent suicide is NOT similar** during 2-year follow up treatment with clozapine or olanzapine in patients with schizophrenia or schizoaffective disorder known to be at high risk for suicide.



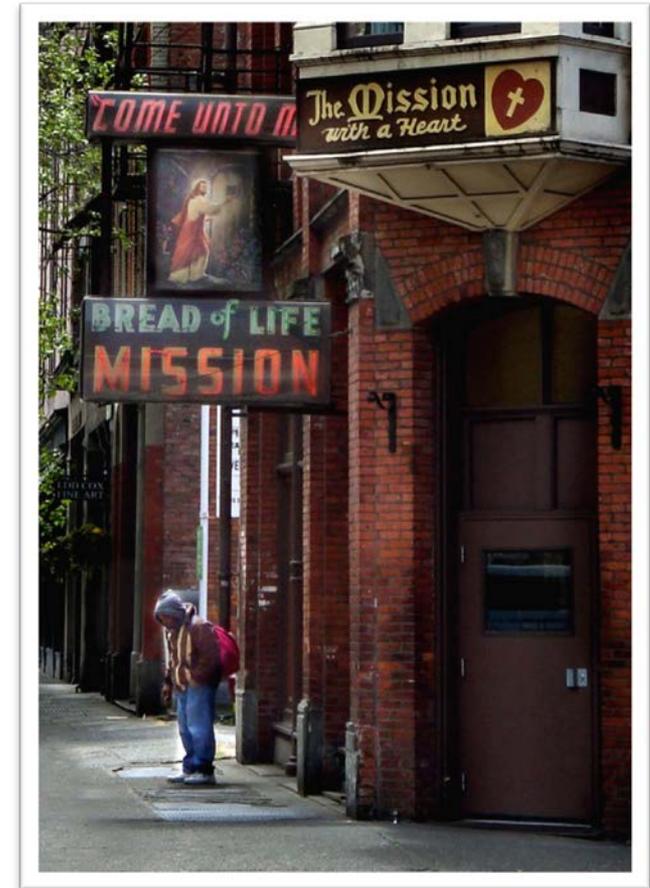
CASE # 2 PRIDE



Treating Schizophrenia in Real World Settings with Paliperidone Palmitate Once Monthly vs Oral Antipsychotics

PRIDE Study Goal

To determine if treatment with long acting injectable antipsychotic paliperidone palmitate has clinical and economic advantages over oral antipsychotic treatments provided to persons with schizophrenia who had recently been released from incarceration.



Public Health Problem

- **Deinstitutionalization** of the mentally ill over the past 50 years and changes in health policy have **shifted the burden** of care for mental illness **to jails and prisons**
- The **largest facilities** for psychiatric patients in the United States are **not hospitals but jails**
- It is **more costly** to provide mental health care in the correctional system

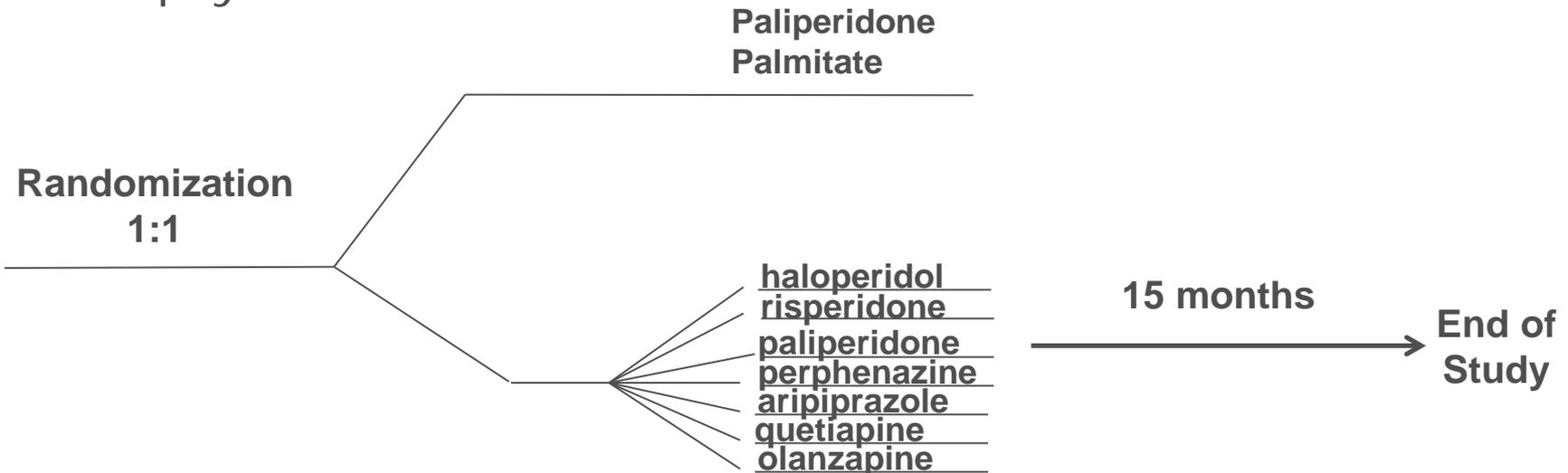


PRIDE Study Null Hypothesis

Treatment failure (hospitalization, re-incarceration, adding antipsychotic to prevent a treatment failure) is similar during 15-month follow up treatment with paliperidone palmitate once monthly or one of 7 commonly used oral antipsychotic treatments in patients with schizophrenia who have recently been incarcerated and/or arrested.

PRIDE Study Design

A 15-month, multicenter, US-based, randomized, open-label, event monitoring board-blinded study comparing the risk for treatment failure in patients with schizophrenia treated with paliperidone palmitate once monthly vs oral antipsychotics



Endpoints

- Time to hospitalization or suicide
- Time to arrest/incarceration
- Time to intervention to prevent hospitalization or arrest

Key Considerations

- Ethical considerations required that the design minimize incarcerations and psychotic relapses
 - Completely open label, events were determined by a blinded event monitoring board
 - Patients could not be incarcerated at the time of entry into study
- Endpoint selection
 - Hospitalization, reincarceration/arrest, suicide, intervention to prevent treatment failure
- Determination of analytic strategy

Results

- 442 patients at 51 US sites
- Paliperidone palmitate delayed time to treatment failure compared to the most commonly used daily oral antipsychotic treatments
 - Risk of treatment failure was **1.4 times higher** with oral antipsychotics (95% CI: 1.09, 1.88, P=0.011)
 - Median days to treatment failure **416 days** for paliperidone palmitate vs. **226 days** for oral antipsychotics
 - **Arrest/incarceration** and **psychiatric hospitalization** were the most common reasons for treatment failure in the paliperidone palmitate and oral antipsychotic groups (21.2% vs 29.4% and 8.0% vs 11.9%, respectively)

Modeled Results

- Decision modeling of PRIDE study results were used to predict outcomes in stable schizophrenic Medicaid patients
- Primary outcome for decision model study was PSYCH hospitalizations.
- Final target real-world Medicaid sample size: $n = 4,609$.
- Compared to oral antipsychotic treatment, paliperidone palmitate produced a per-patient decrease:
 - PSYCH-related hospitalizations of 0.27 (95% confidence interval [CI]: – 0.43, 0.97)
 - All Cause-related hospitalizations 0.28 (95% CI: –0.28, 0.84)
- Validation exercises assured that the reweighting methodology used could replicate observed outcomes in the Medicaid sample.
- These incremental reductions in hospitalization rates are worth about \$3.4 to \$3.8 billion over an 18-month period in patients with schizophrenia receiving Medicaid.

PRIDE Study Findings

- Treatment failure (hospitalization, re-incarceration, adding antipsychotic to prevent a treatment failure) **is not similar** during 15-month follow up treatment with paliperidone palmitate once monthly or one of 7 commonly used oral antipsychotic treatments in patients with schizophrenia who have recently been incarcerated and/or arrested.
 - Application of state of the art epidemiology matching methodology suggests that that this data can be mapped to a large Medicare data set and **may save \$3.4 to \$3.8 billion over an 18-month** period in patients with schizophrenia receiving Medicaid.

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THANK YOU