Mid and Long-term Treatment of Schizophrenia

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Pre-Lecture Questions

- 1. T/F: All antipsychotics (old and new) are equal in efficacy for long-term treatment of schizophrenia
  a) True
  b) False

Ans: _____

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- 2. Based on meta-analaysis, which are the three most effective antipsychotics for long-term treatment of schizophrenia?
  - a) clozapine, aripiprazole, hpl
  - b) clozapine, quetiapine, risperidone
  - c) clozapine, ziprasidone, risperidone
  - d) clozapine, olanzapine, and risperidone
  - e) clozapine, risperidone,hpl

Ans: _____

Pre-Lecture Questions

- 3. Based on evidence-based data, which are effective interventions for long-term treatment of schizophrenia?
  - a) medication
  - b) psychotherapy (like CBT or supportive psychotherapy)
  - c) drug and psychotherapy combined
  - d) psychosocial rehabilitation, like vocational rehabilitation
  - e) all of the above

Ans: _____

Disclosures

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- He has equity in Johnson & Johnson

Outline

- Introduction
- Methods
- Results
- Discussion
- Summary and Conclusion

Introduction

- What are the best treatment interventions for long-term treatment of schizophrenia?
- Which are the most effective antipsychotic?
- Aims:
  - Compare mid to ***long-term*** data on efficacy to ***short-term*** RCTs
  - Use data to personalize treatment

Life Course of Schizophrenia

"…the illness takes a really bad toll on almost all the people almost all the time…"

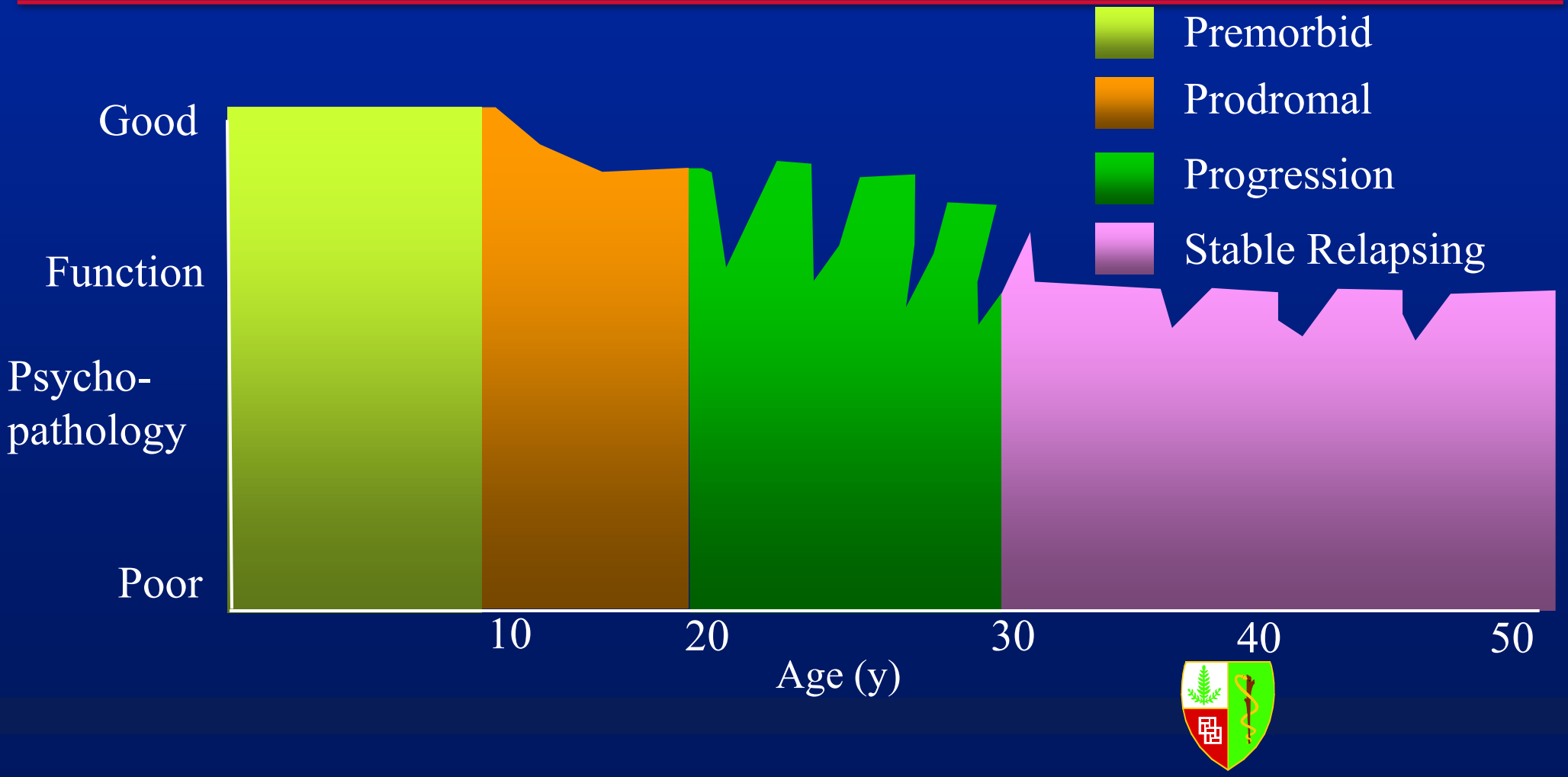
(Carpenter agreed, however, that) "the orthodox view of schizophrenia as a disease that always has an inexorably downward course is simply wrong. Moreover, even in the case of the sickest patients, there appears to be some natural improvement with aging."

Ref: Will Carpenter, MD,
Editor, Schizophrenia Bulletin, 1998

Outcome Goals

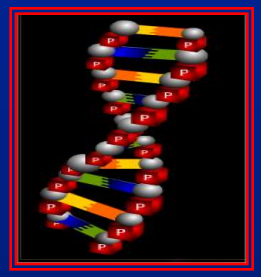
"Clinicians should assume that most patients have a chance for substantial stability and have a chance to regain much of their lost niche in society," Carpenter said. "Individuals will vary in how far they can go in accomplishing that."

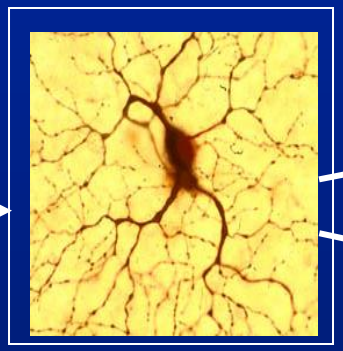
Natural History of Schizophrenia



Ref: Lewis et al, 2000

The path from here to there…





cognition

schizophrenia

temperament

Genes:

multiple susceptibility alleles each of small effect

Cells:

subtle molecular abnormalities

Systems:

abnormal information processing

Behavior:

complex functional interactions and emergent phenomena

Ref: D Weinderger

The Continuum of Care

Efficacy

Positive symptom relief
Hostility, aggression
Smooth IM to P0 transition
Alleviation of comorbid depressive/manic symptoms

Negative symptom relief
Improve mood and depressive symptoms
Cognitive improvement
Suicide prevention

Control Behavior (agitation)

Relapse Prevention
Reintegration
Quality of Life

1-3days | 7-14days | 6+months

Acute dystonia
Sedation
Orthostasis
QTc prolongation

EPS
Drug-drug interactions
QTc prolongation

TD
Hyperprolactinemia
Weight gain
Hyperglycemia
QTc prolongation

Safety

The Core Symptom Clusters of Schizophrenia and Their Influence on Occupational and Social Dysfunction

Positive Symptoms
- delusions
- hallucinations
- disorganized speech
- catatonia

Negative Symptoms
- affective flattening
- alogia
- avolition
- anhedonia

Social/Occupational Dysfunction
- work
- interpersonal relationships
- self care

Cognitive Symptoms
- attention
- memory
- executive functions

Mood Symptoms
- dysphoria
- suicidality
- hopelessness

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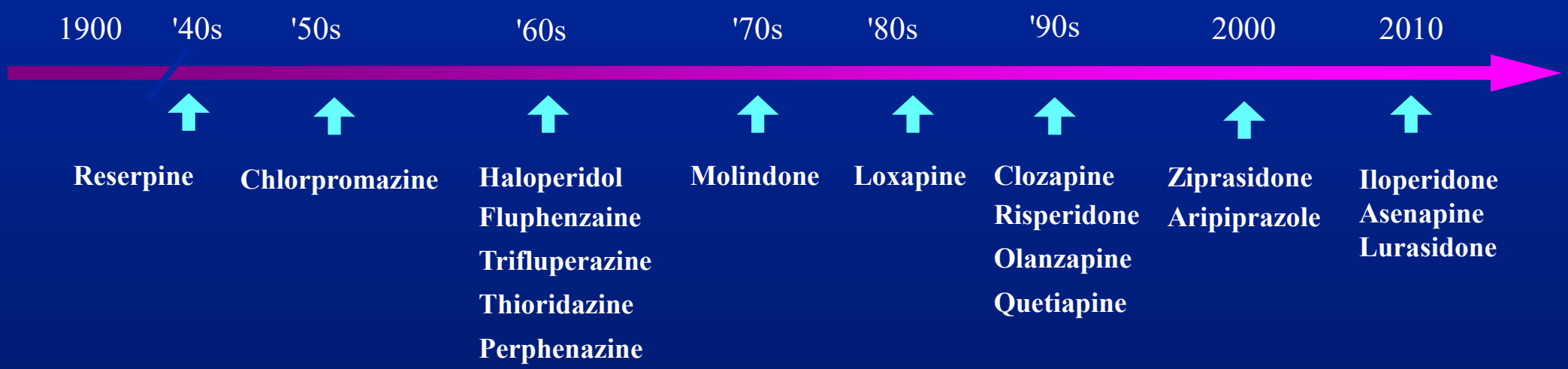
The Evolution of Antipsychotic Medications



Conventional or "Typical" Neuroleptics

Atypical Antipsychotics

"Atypical Atypicals"

Adapted from "Treating Psychotic Disorders: What is the State of the Art?," Jeffrey Lieberman, M.D., et al; APA Annual Meeting, May 2001

The New Model of Schizophrenia

- = a syndrome with multiple domains of dysfunction or "component symptom complexes"

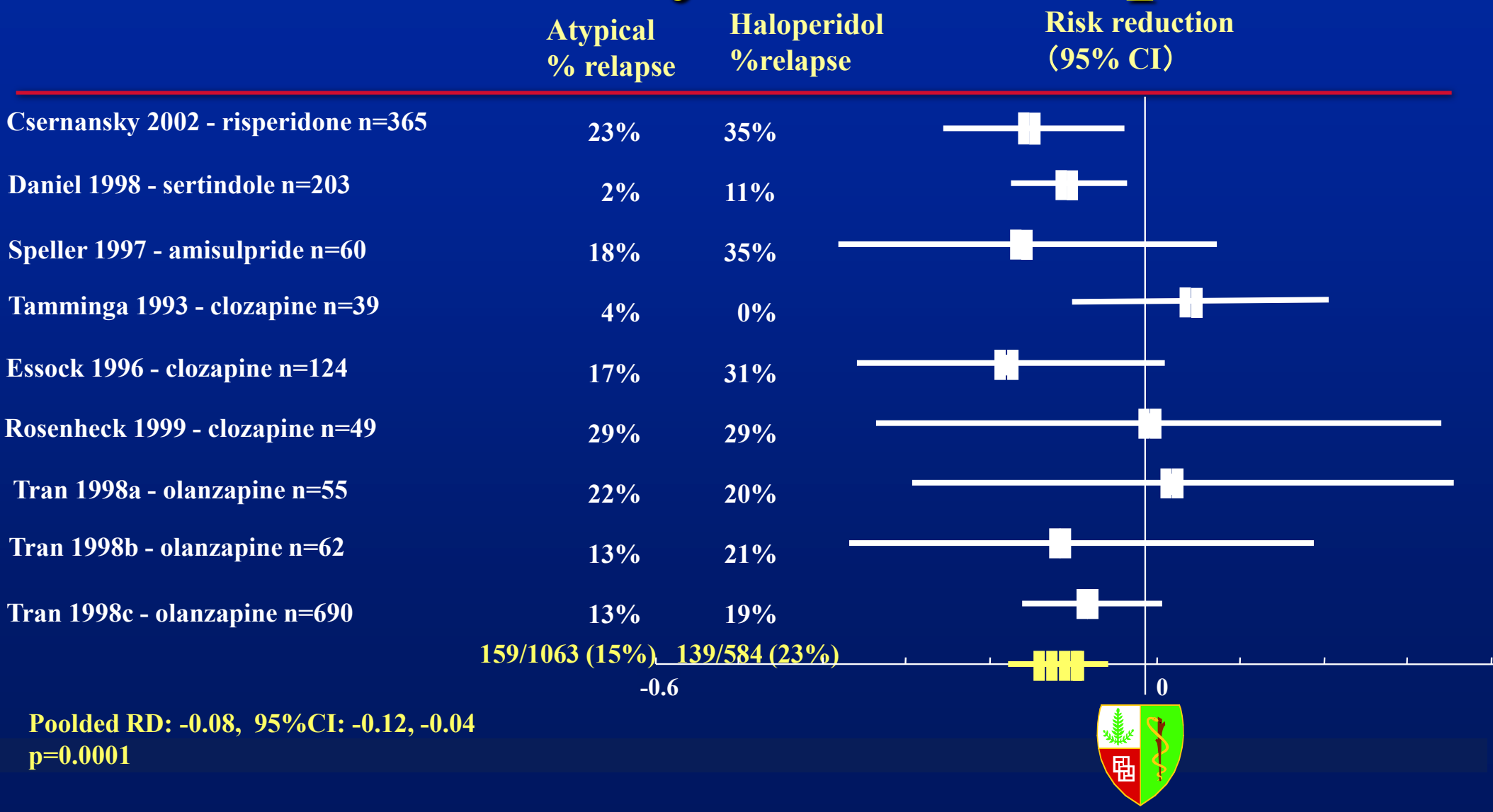
  Hyman & Fentan, 2003

- Components (genetics, developmental processes & disease) are separable and independent and command different mechanisms and treatment

Methodology

- Design issues
- Graphic display of our meta-analyses compared to longer term studies
- Efficacy, effectiveness and side effect comparisons
- Controlled studies vs. naturalistic studies vs. long-term extension phase of first-episode studies

Meta-Analyses - Relapse



Poolded RD: -0.08, 95%CI: -0.12, -0.04
p=0.0001

Leucht S, et al, Winter workshop on schizophrenia, 23 Feb-1 Mar, 2002, Davos

Schizophrenia & Cognition

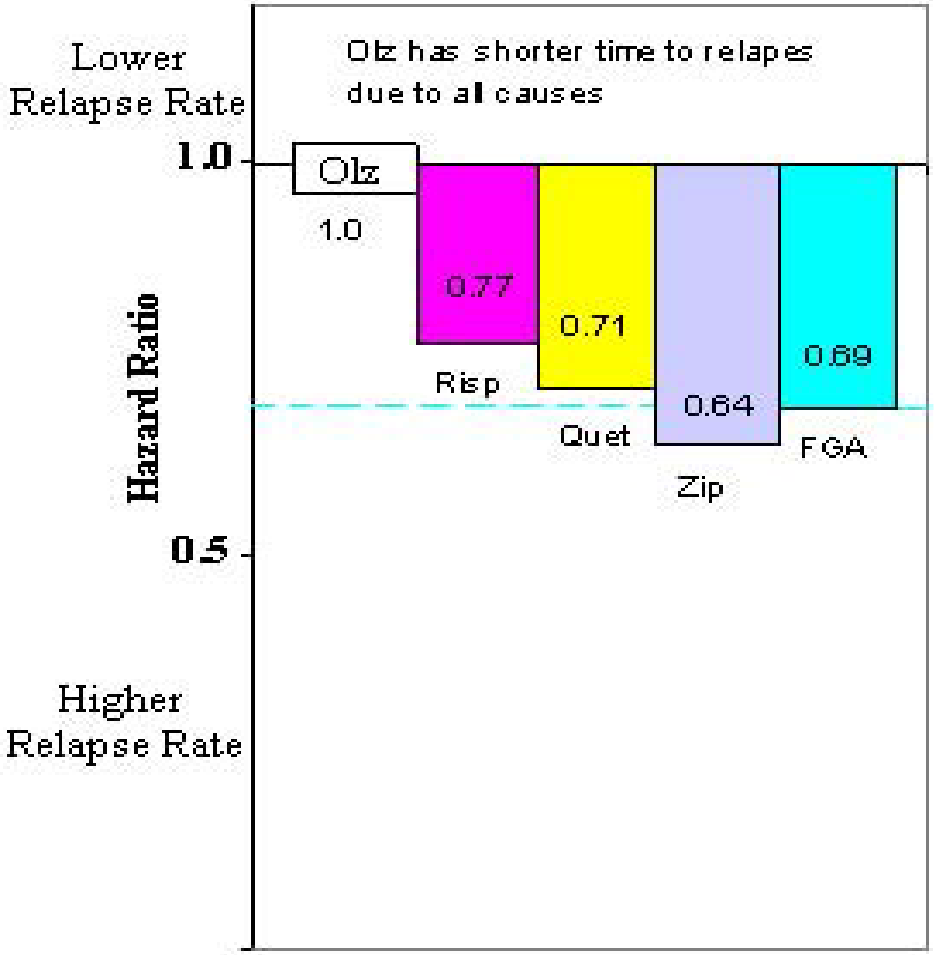
- The disease decreases cognitive abilities
- SGAs have modest, but limited effects on improving cognition, and even less on community function.
- "Cognitive Remediation" (CR) results in moderate improvement in cognitive performance
- When combined with psychosocial rehabilitation CR also, improves functional outcome

Results

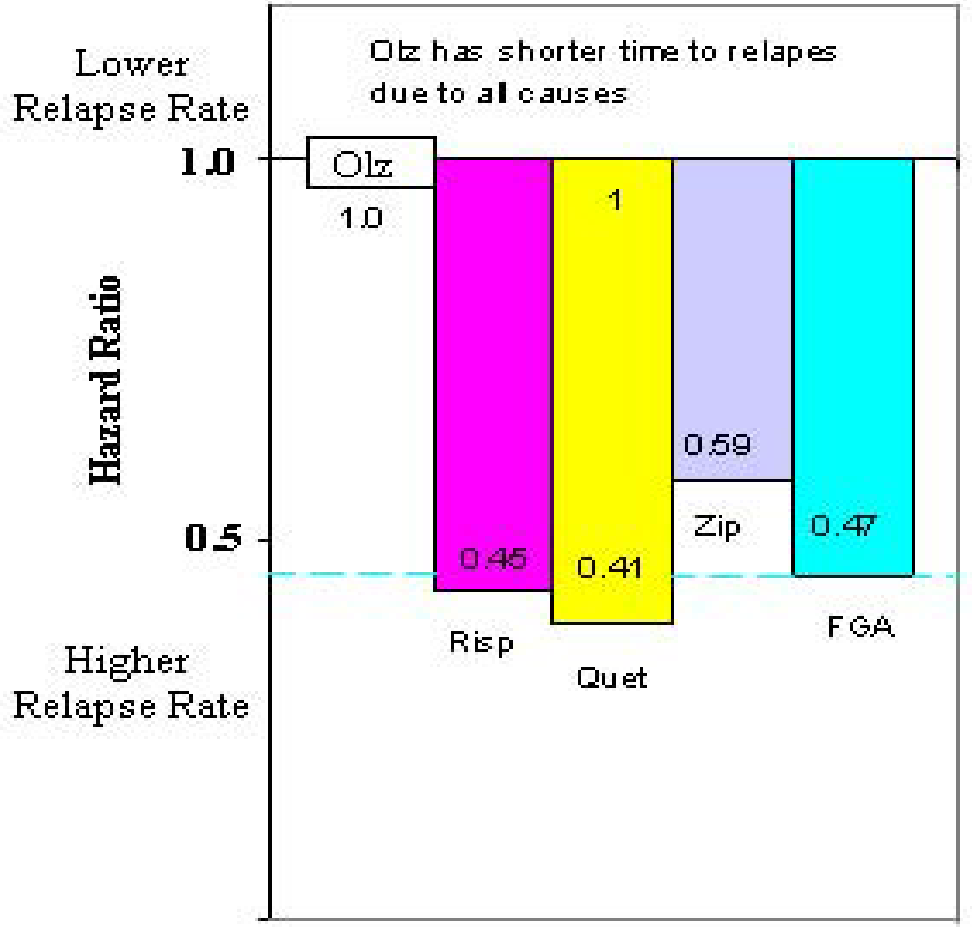
- Controlled studies
- Naturalistic studies
- Longer-term extension phase first-episode studies

Comparison with CATIE (Lieberman et al. 2005)

Our Meta-Analysis
Discontinuation for
All Cause

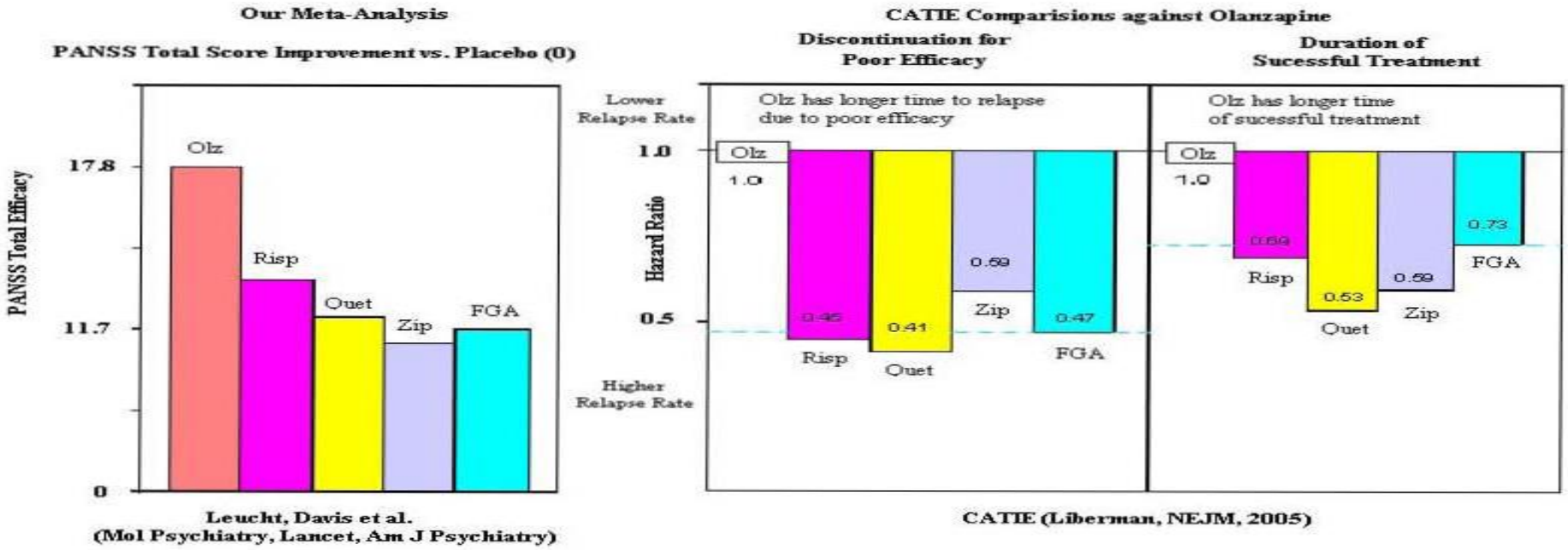


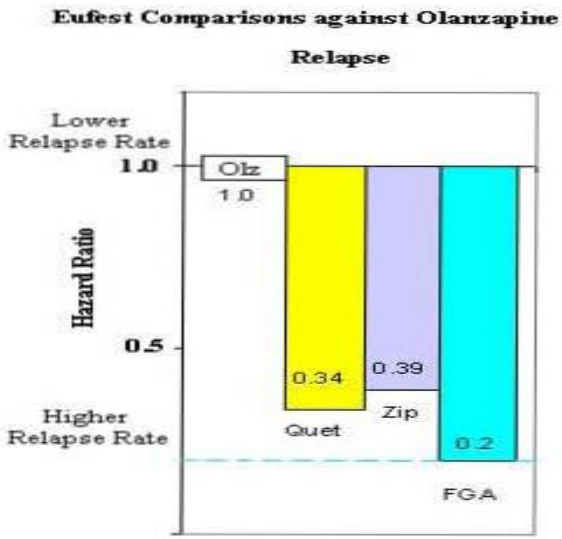
CATIE Comparisions against Olanzapine
Discontinuation for
All Cause

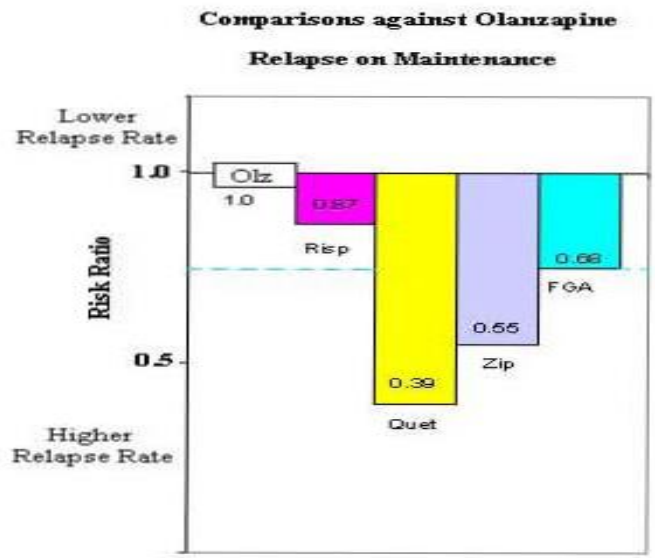


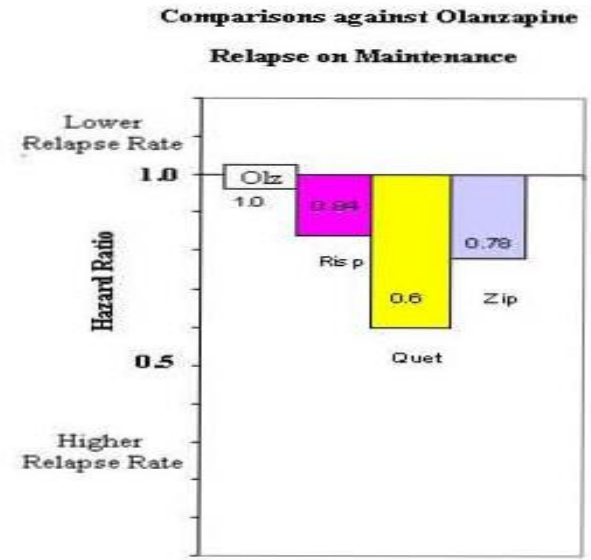
CATIE study (Lieberman et al. 2005)

Comparison to CATIE

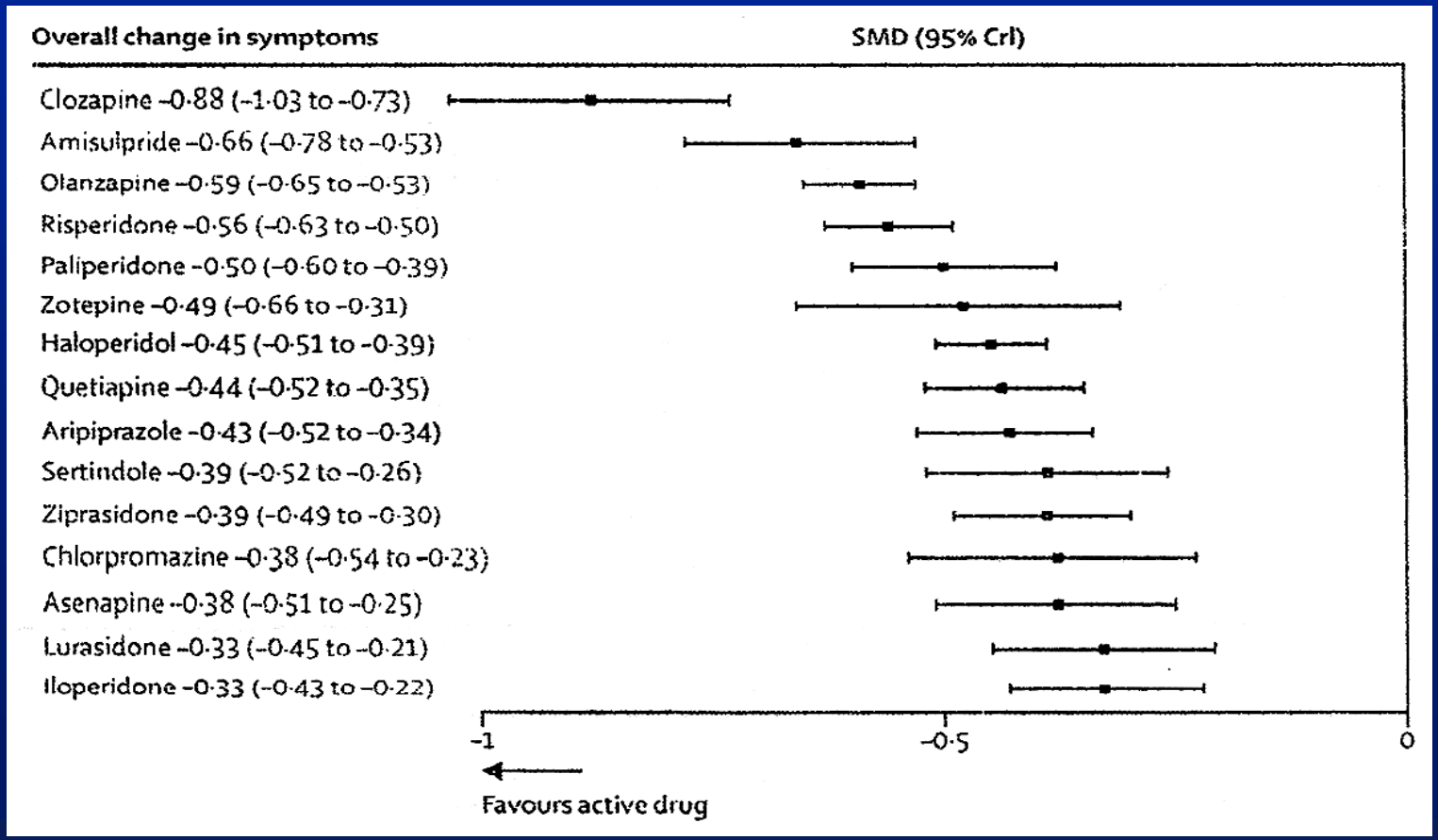








Relative Efficacy of Antipsychotics



Ref: L Eucht et al, 2012

Results: Side Effects

- EPS and akathisia: hpl and rsp
- Weight gain: clozapine and olanzapine
- Other issues

*

Side Effects - Overview

Atypical Medications

	EPS	Orthostatic Hypotension	Anticholinergic Symptoms	Prolactin Elevation
Aripiprazole	+/-	+/-	+/-	+/-
Asenapine	+	+/-	+/-	+/-
Iloperidone	+/-	+/-	+	+
Olanzapine	+/-	+/-	+	+/-
Paliperidone	+	+	+/-	++
Quetiapine	+/-	++	++	+/-
Risperidone	+	+	+/-	++
Ziprasidone	+/-	+/-	+/-	+/-

Discussion and Clinical Implications

- Summary of results
- Industry bias: not a factor

Shared Decision Making

- Who to involve: patient + SOs
- Patient experience crucial, re: efficacy and side effects

Schizophrenia Morbidity & Mortality

- Higher-Than-Expected Mortality*,**,***
  - Twice as much as normal controls without schizophrenia. No difference between FGAs and SGAs.
- Life expectancy: 20% shorter than general population**
  - Average age of death: 61 ys 76 years old
- Morbidity
  - Medical diseases are under-recognized and under-treated
  - Poverty, limited insight, lack of access to care

* Harris EC, Banaclough B. Br J Psychiatry. 1998: 173:11-53

** Newman SC, Bland RC. Can J Psych. 1991: 36:239-245

*** Brown S et al. Br J Psychiatry. 2000: 177:212-217

Clinical Recommendation for Long-Term Treatment

- Acute and stabilization phase
- Chronic phase

Goals of Long-Term Management in Schizophrenia

- Relapse prevention
- Improvements in long-term functional outcomes
- Minimization of residual psychopathology and cognitive deficits
- Prevention or reduction of suicidality and violence
- Minimization of adverse effects of medications
- Treatment adherence

Issues for Long-Term Recovery

- Natural course - most patients improve and stabilize after the initial, acute episodes
- What % look “normal” - about 10%

(*Jeste, 2001*)

Issue of Long-Term Recovery (cont'd)

- Provide appropriate psychopharmacologic intervention and support
- Provide appropriate psychosocial intervention and support
- Provide appropriate rehabilitative intervention and support
- Provide appropriate family intervention and support

Key Issues

- Compliance - to all of above
- Why - "penalty of each relapse," meaning each time a patient relapses, prognosis is worse, presumably because of brain damage associated with relapse

  (*Keith, 2001*)
- Solution -
  - "Consistent contact" with treatment team
  - Contract with patient/family (*Jeste, 2001*)

What Do Patients Want From Their Doctors?

- An ongoing relationship
- An explanation of what is wrong (Dx) and what to do about it (Rx)
- Delivery of cutting-edge treatment
- Modest improvement in Sx
- Help in dealing with side-effects

Evidence Based Practices

Current "Worst"

- FGAs = SGAs
- Polypharmacy and frequent switching
- Minimal individual & family support

Proposed "Best"

- TOC (treatment of choice): cloz, amisultpride, olanz, risp
- Monotherapy use of clozapine & LAIs
- Psychosoc, ind/family psychoeducation, support Rx & CBT

R_x Guideline: Efficacy

- Work best on pos sx
- For severe POS SX: OLZ or RISP
- For high denial: I-M
- Don't keep switching if partial response
- Don't use antipsychotic polypharmacy- use Cloz
- Minimize adjunct polypharmacy

R_x Guidelines: Side Effects

- Know thyself – familiarize yourself with side effects of most used drugs
- For patients apathetic: ZIP or ARI
- For patients with c-v risk: use lower c/m risk agents
- Evaluate c/m risk vs. efficacy
- If using CLZ or OLZ must monitor metabolic side effects
- SGAs and EPS: differences within class

Treatment Tips

- T.O.C – Monotherapy with minimal adjuncts
- Dose – ”Goldilocks” principle (meaning not too high, not too low, just right!)
- Individual Psychotherapy – support, encouragement and hope
- Family Intervention – education and support

R_x Guidelines: Cost

- If cost is an issue, use FGAs
- SGAs coming off-patent

Summary and Conclusion

- Antipsychotics are not a homogeneous group, either for efficacy or side effects; especially on an individual patient level
- Individualize treatment!
- Share decision making with patient and family

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Ans: _____

Post-Lecture Question and Answer

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  a) True
  b) False

Ans: b) False

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Ans: d) cloz, olanz, and risp

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Ans: e) all of the above