Managing first episodes of psychosis: The role of medications

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Consultation for Boeringer-Ingelheim, Lundbeck, Otsuka, Takeda, Teva, Roche, Genentech, Targacept, Forum, Allergan

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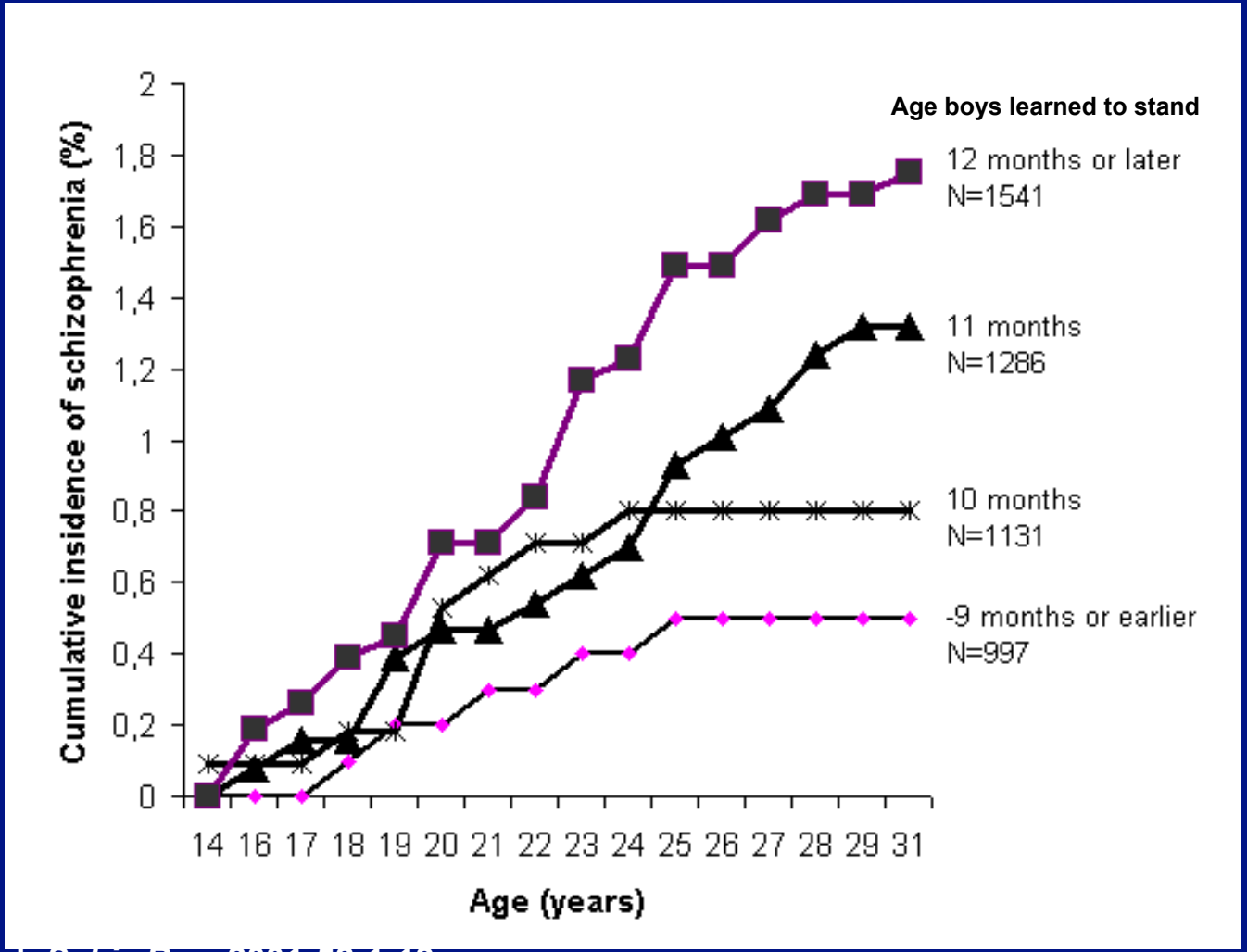
Management of Recent Onset Psychosis

- Neurobiology in recent onset patients
- Clinical considerations
- Pharmacological and non pharmacological treatment
- Summary of management recommendations

Developmental antecedents are well established

The later boys stand during the first year of life, the greater the risk of schizophrenia



Isohanni M, et al. *Schiz Res*. 2001;52:1-19.

Premorbid Cognitive Decline?

- **Reichenberg et al (2005)**
  - **Population-based cohort of 555,326 adolescents from Israel.**
  - **Assessed the discrepancy between actual and expected IQ at 17**
  - **Estimated IQ based on reading and spelling skills.**

Reichenberg et al

Arch Gen Psychiatry 2005;62:1297-1304

Table 2. Estimated and Actual Standardized IQ Scores

Population	Standardized Score*
Cohort†	
Estimated IQ	0.00
Actual IQ	0.00
Schizophrenia cases	
Estimated IQ	−0.18
Actual IQ	−0.49

Important facts about first episodes

- There is often cognitive decline
- Biomarkers of stress and inflammation are elevated at the onset of psychosis
- First-episode psychosis patients display progressive brain morphological abnormalities during the first years after illness onset, particularly regional grey matter volume reduction and lateral ventricle enlargement

Schizophrenia risk from complex variation of complement component 4

Aswin Sekar[1,2,3], Allison R. Bialas[4,5], Heather de Rivera[1,2], Avery Davis[1,2], Timothy R. Hammond[4], Nolan Kamitaki[1,2], Katherine Tooley[1,2], Jessy Presumey[5], Matthew Baum[1,2,3,4], Vanessa Van Doren[1], Giulio Genovese[1,2], Samuel A. Rose[2], Robert E. Handsaker[1,2], Schizophrenia Working Group of the Psychiatric Genomics Consortium*, Mark J. Daly[2,6], Michael C. Carroll[5], Beth Stevens[2,4] & Steven A. McCarroll[1,2]

Schizophrenia is a heritable brain illness with unknown pathogenic mechanisms. Schizophrenia's strongest genetic association at a population level involves variation in the major histocompatibility complex (MHC) locus, but the genes and molecular mechanisms accounting for this have been challenging to identify. Here we show that this association arises in part from many structurally diverse alleles of the complement component 4 (*C4*) genes. We found that these alleles generated widely varying levels of *C4A* and *C4B* expression in the brain, with each common *C4* allele associating with schizophrenia in proportion to its tendency to generate greater expression of *C4A*. Human C4 protein localized to neuronal synapses, dendrites, axons, and cell bodies. In mice, C4 mediated synapse elimination during postnatal development. These results implicate excessive complement activity in the development of schizophrenia and may help explain the reduced numbers of synapses in the brains of individuals with schizophrenia.

- Different structural forms of C4 gene lead to different levels of expression
- Abnormal forms more likely to occur in schizophrenia
- C4 is related to synaptic pruning

Special issues in first-episode patients

- Diagnostic uncertainty
- Concerns about delaying treatment
- How long to treat
- High rates of suicide
- Resistance to settings that serve chronically mentally ill

Schizophrenia Bulletin
doi:10.1093/schbul/sbv154

Cannabis Use Is Associated With Increased Psychotic Symptoms and Poorer Psychosocial Functioning in First-Episode Psychosis: A Report From the UK National EDEN Study

Table 2. Current Substance Use at Baseline (n = 1027)

Substance	n
Cannabis	279
Stimulants (eg, amphetamine, ecstasy, crack or cocaine)	110
Sedatives or sleeping tablets (eg, valium)	67
Other drugs	53
Opiates (eg, heroin, morphine, methadone)	19
LSD	17
Inhalants (eg, petrol or glue)	8

Cannabis users were more psychotic and had lower GAF scores

Early Predictors of Ten-Year Course in First-Episode Psychosis

Svein Friis, M.D., Ph.D., Ingrid Melle, M.D., Ph.D., Jan Olav Johannessen, M.D., Ph.D., Jan Ivar Røssberg, M.D., Ph.D., Helene Eidsmo Barder, Ph.D., Julie Horgen Evensen, M.D., Ph.D., Ulrik Haahr, M.D., Wenche ten Velden Hegelstad, M.Sc., Ph.D., Inge Joa, Ph.D., Johannes Langeveld, Ph.D., Tor Ketil Larsen, M.D., Ph.D., Stein Opjordsmoen, M.D., Ph.D., Bjørn Rishovd Rund, Ph.D., Erik Simonsen, M.D., Ph.D., Per Wiggen Vaglum, M.D., Ph.D., Thomas H. McGlashan, M.D.

TABLE 3. Mixed-model analysis of estimated fixed effects of risk factors for follow-up time in psychosis among 286 patients with *DSM-IV* nonorganic, nonaffective first-episode psychosis[a]

Parameter	Estimate	SE	t	df	p	95% CI
Time	.94	.28	3.32	192	.001	.38 to 1.49
Premorbid social deterioration	3.90	1.98	1.97	229	.050	.00 to 7.81
Core schizophrenia spectrum disorder	5.43	2.04	2.67	228	.008	1.42 to 9.45
Duration of untreated psychosis ≥26 weeks	4.37	2.08	2.10	230	.037	.27 to 8.48
No remission within first 3 months	22.41	2.32	9.65	181	<.001	17.83 to 26.99
No remission within first 3 months × time	−1.35	.44	−3,08	196	.002	−2.22 to −.49

[a] Estimates indicate the reduction of weeks in psychosis per year among those for whom the risk factor was absent compared with those for whom the factor was present.

Psychiatric Services in Advance (doi: 10.1176/appi.ps.201400558)

First-episode psychosis patients should be followed carefully after the start of treatment. Findings indicate that if symptoms do not remit within three months with adequate treatment, there is a considerable risk of a poor long-term outcome, particularly for patients with a deterioration in premorbid social functioning, a DUP of at least half a year, and a diagnosis within the core schizophrenia spectrum.

Management of Recent Onset Psychosis

- Neurobiology in recent onset patients
- Clinical considerations
- **Pharmacological and non pharmacological treatment**
- Summary of management recommendations

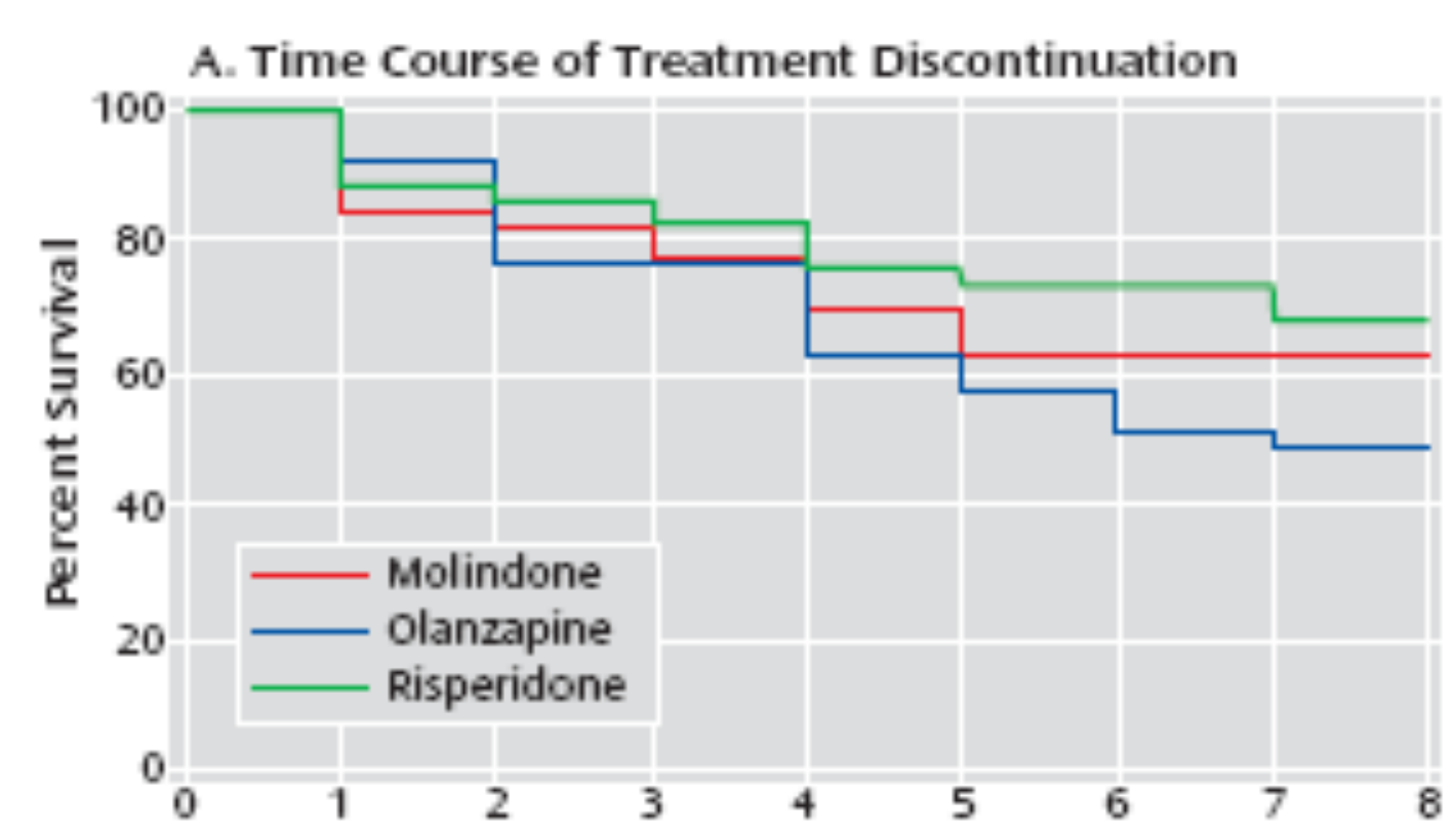
Schizophrenia PORT 2009

Recommendation. People with first-episode schizophrenia exhibit increased treatment responsiveness and an increased sensitivity to adverse effects compared with people with multiepisode schizophrenia. Therefore, antipsychotic treatment should be started with doses lower than those recommended for multiepisode patients (first-generation antipsychotics: 300–500 mg CPZ equivalents; risperidone and olanzapine: lower half of recommended dosage range for multiepisode patients). An important exception is with quetiapine, which often requires titration to 500–600 mg/day. The therapeutic efficacy of low-dose aripiprazole or ziprasidone has not been evaluated in people with first-episode schizophrenia.

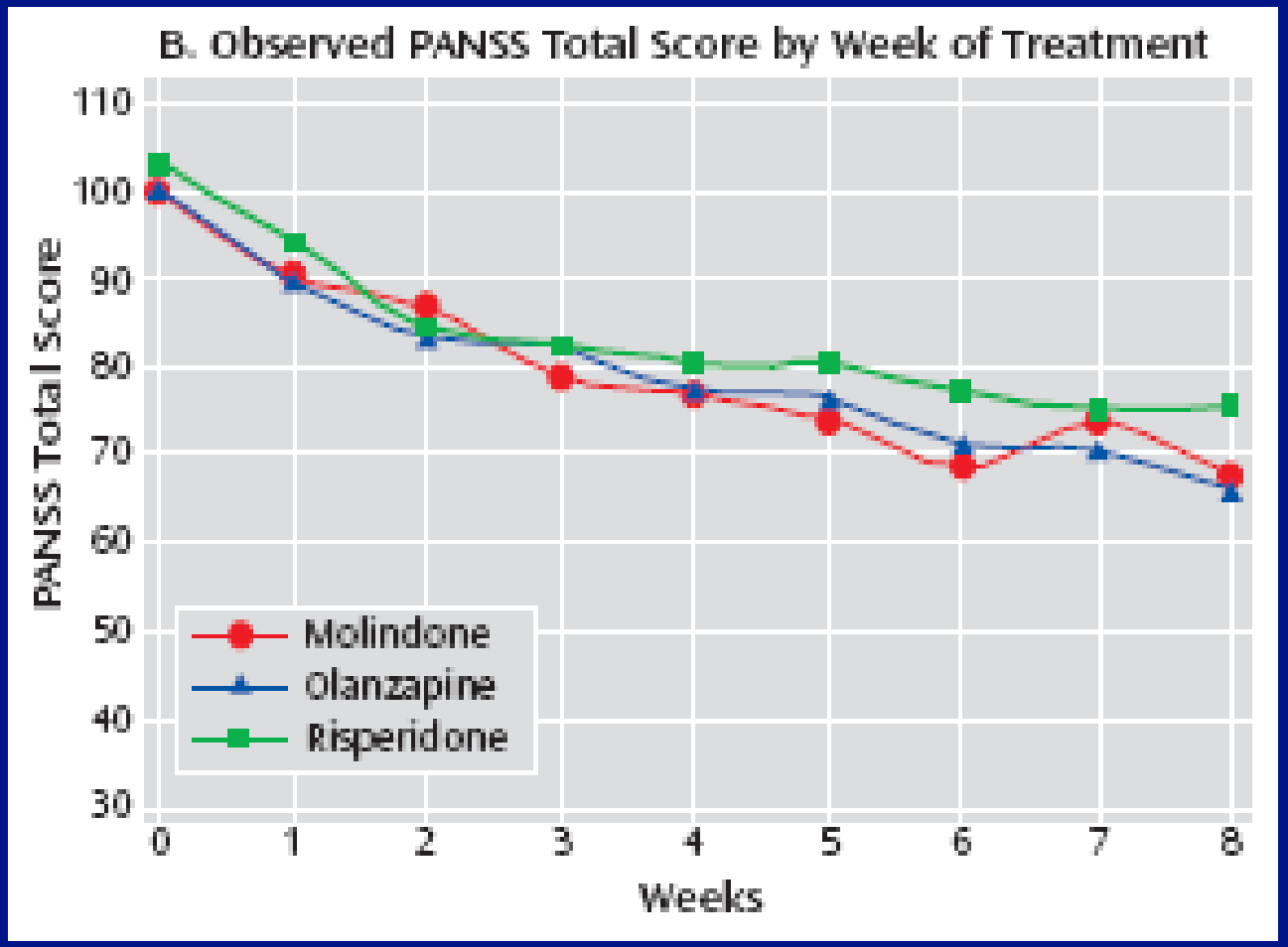
Treatment of early-onset schizophrenia spectrum disorders (TEOSS)
Sikich et al Am J Psychiatry 2008

- 8-19 yo pts w schizophrenia were randomly assigned to double-blind molindone 10-140 mg, olanzapine 2.5-20 mg, or risperidone 0.5-6 mg for 8 weeks
- Primary outcome was responder status defined as much or very much improved on CGI; ≥20% reduction in total PANSS; and tolerating treatment

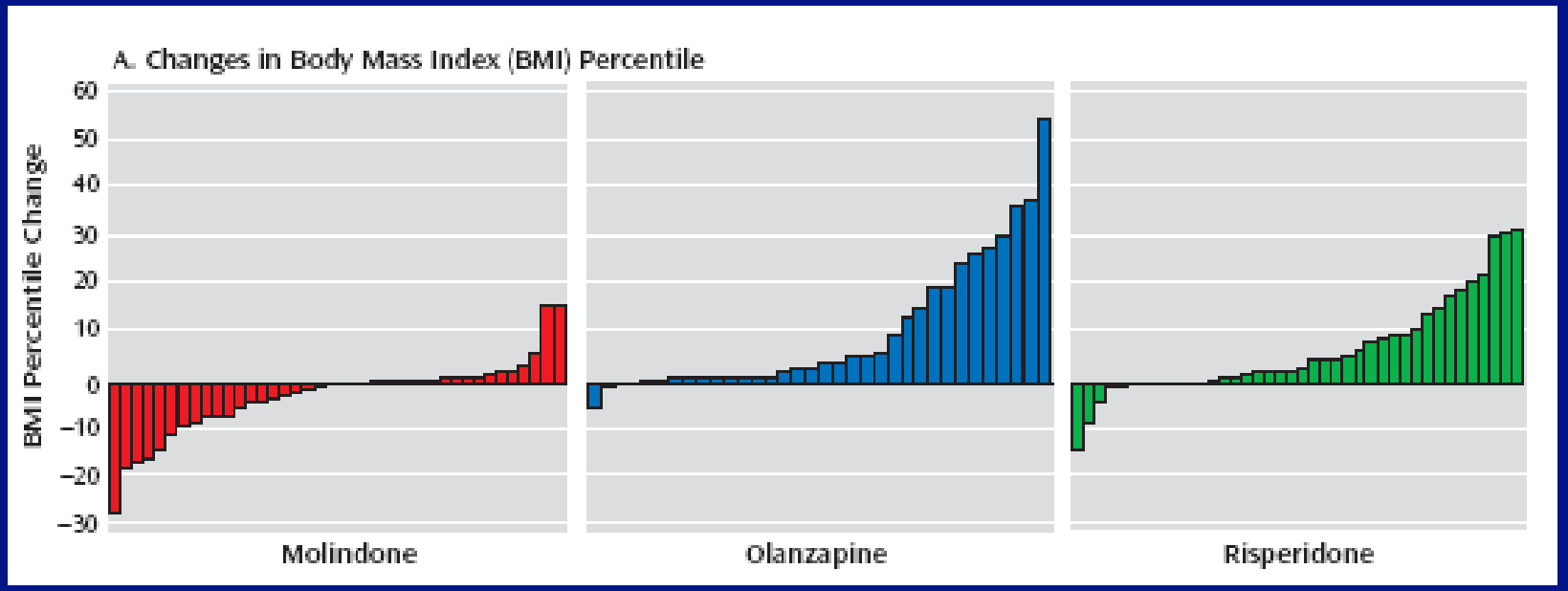
TEOSS Treatment Discontinuation



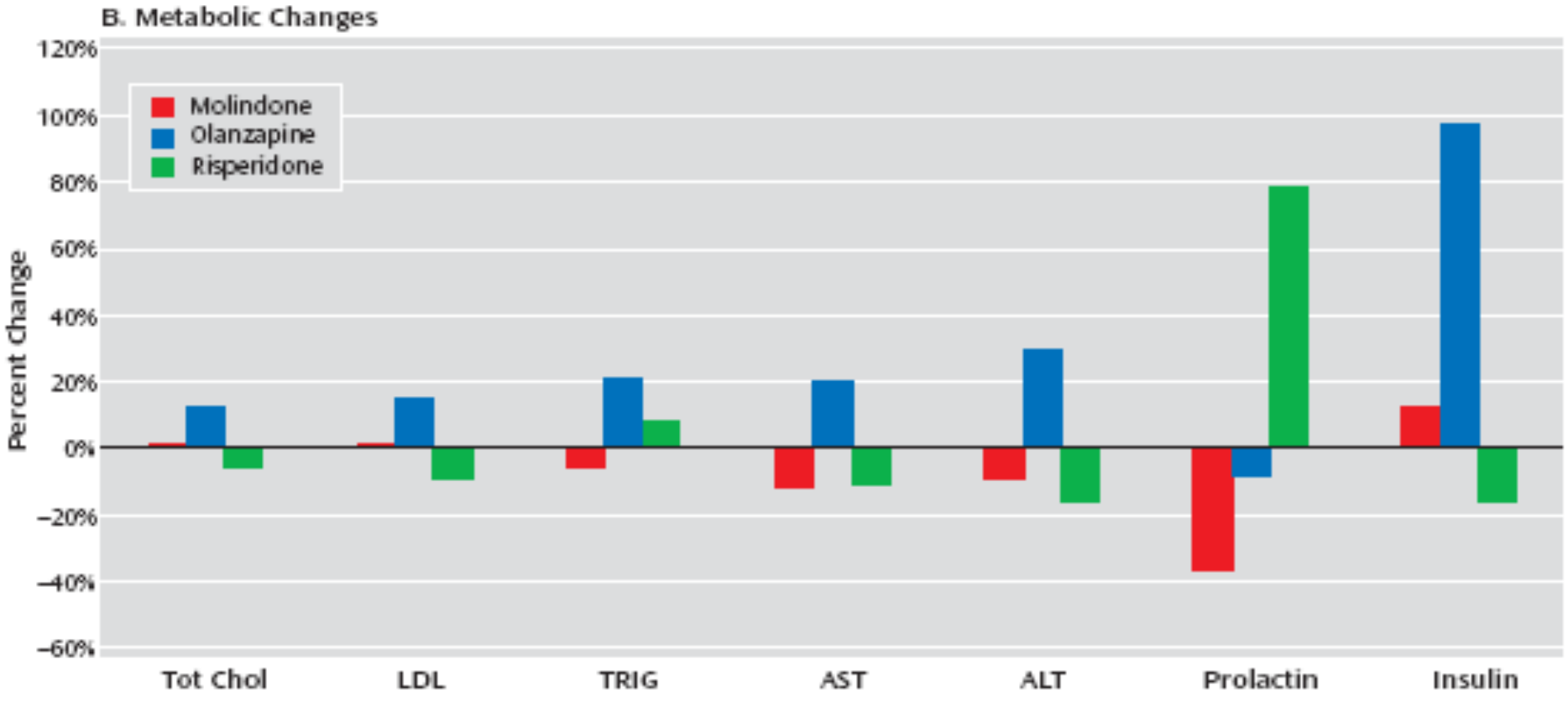
TEOSS PANSS Scores



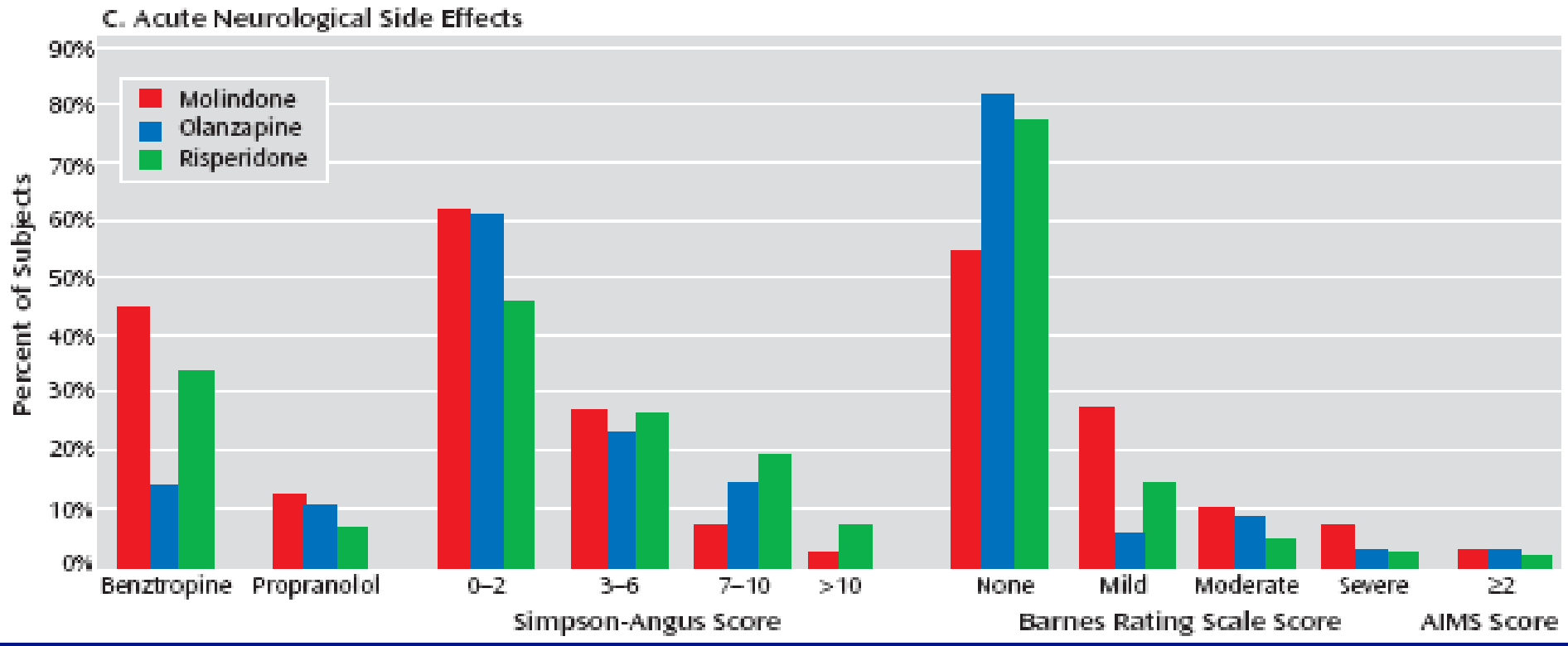
BMI Change in TEOSS



Metabolic Changes in TEOSS



EPS in TEOSS


C. Acute Neurological Side Effects
Molindone
Olanzapine
Risperidone
Percent of Subjects
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Benztropine
Propranolol
0–2
3–6
7–10
>10
None
Mild
Moderate
Severe
≥2
Simpson-Angus Score
Barnes Rating Scale Score
AIMS Score

New Recommendations from Schizophrenia PORT (Kreyenbuhl 2010)

Treatment of Acute Positive Symptoms in People With First-Episode Schizophrenia: Antipsychotic Medication Choice

Recommendation. Antipsychotic medications, other than clozapine and olanzapine, are recommended as first-line treatment for persons with schizophrenia experiencing their first acute positive symptom episode.

NAVIGATE Psychopharmacological Treatment Manual

- Available at https://raiseetp.org/StudyManuals/Psychopharmacology%20Manual.pdfat
- Principles:
  - High goals for treatment
  - Doses that are 50-60% of doses for chronic patients
  - Monitor high sensitivity to side effects
  - Prepare for non-adherence

Navigate Psychopharm Manual

- **Utilizes shared decision making**
- **First choice drugs include: aripiprazole, quetiapine, risperidone, risperidone microspheres, or ziprasidone**
- **Second antipsychotic based on side effects and adherence**

Approaches to Weight Gain and Insulin Resistance

- Cochrane review supports changing antipsychotics
- Early elevations of triglycerides and weight predict later elevations
- Life style interventions work!
- Consider metformin

*ADA Consensus on Antipsychotic Drugs: Monitoring Protocol for Patients on Second-Generation Antipsychotics**

		Short-Term			Long-Term		
	Baseline	4 wk	8 wk	12 wk	Quarterly	Annually	Every 5 y
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

*More frequent assessments may be warranted based on clinical status.

BMI = body mass index.

American Diabetes Association et al. *Diabetes Care*. 2004;27:596.

Schizophrenia Bulletin vol. 41 no. 6 pp. 1227–1236, 2015
doi:10.1093/schbul/sbv125
Advance Access publication September 3, 2015

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

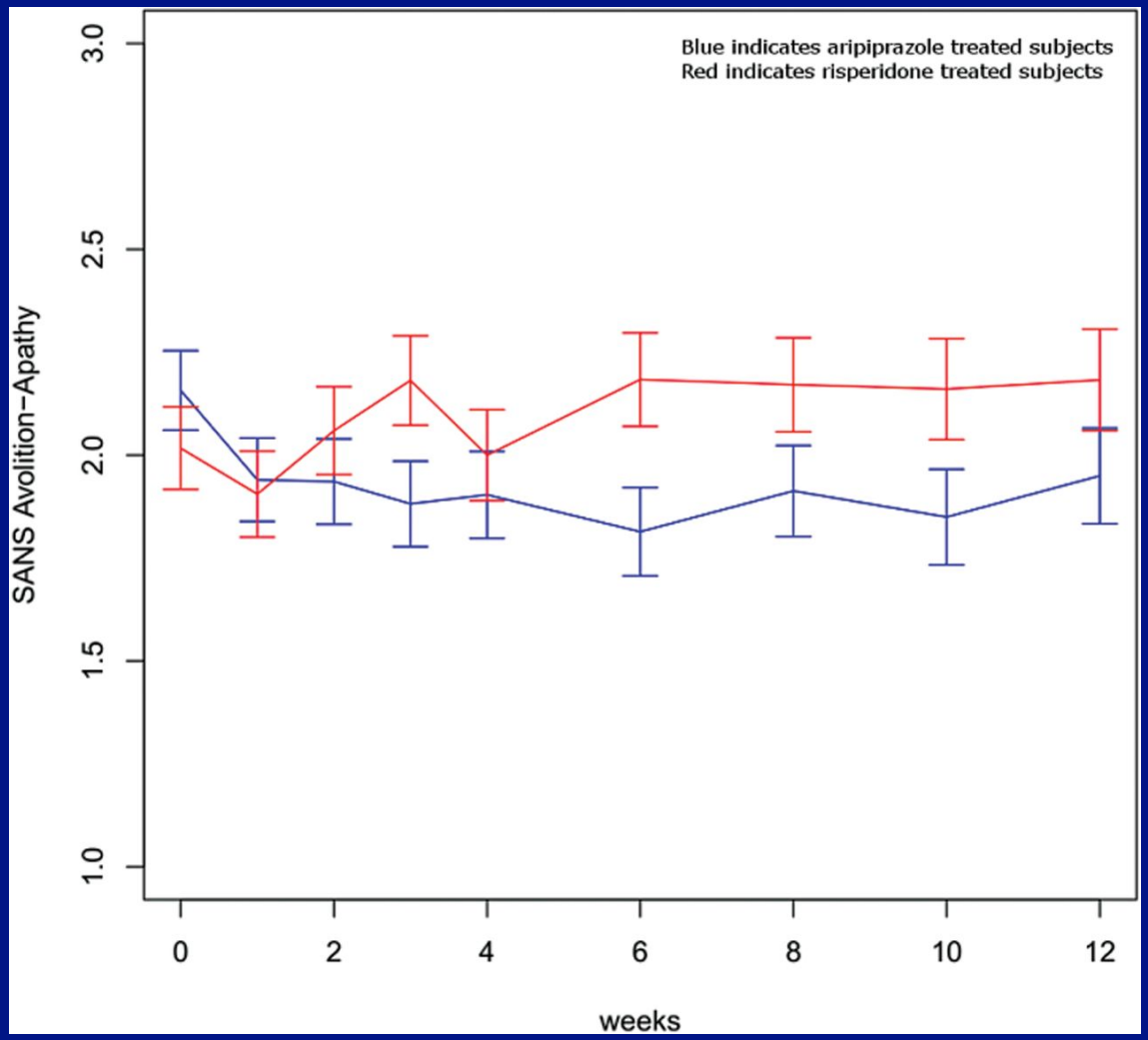
Delbert G. Robinson[*,1–4], Juan A. Gallego[1–3], Majnu John[1,2,5], Georgios Petrides[1–4], Youssef Hassoun[2,3], Jian-Ping Zhang[1–3], Leonardo Lopez[2,3], Raphael J. Braga[2,3], Serge M. Sevy[6], Jean Addington[7], Charles H. Kellner[8], Mauricio Tohen[9], Melissa Naraine[2], Natasha Bennett[2], Jessica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

198 patients treated with risperidone (1-6 mg) or aripiprazole (5-30 mg)

No differences in psychosis response but advantages for aripiprazole in negative symptoms

Aripiprazole caused more akathisia, but had fewer metabolic effects

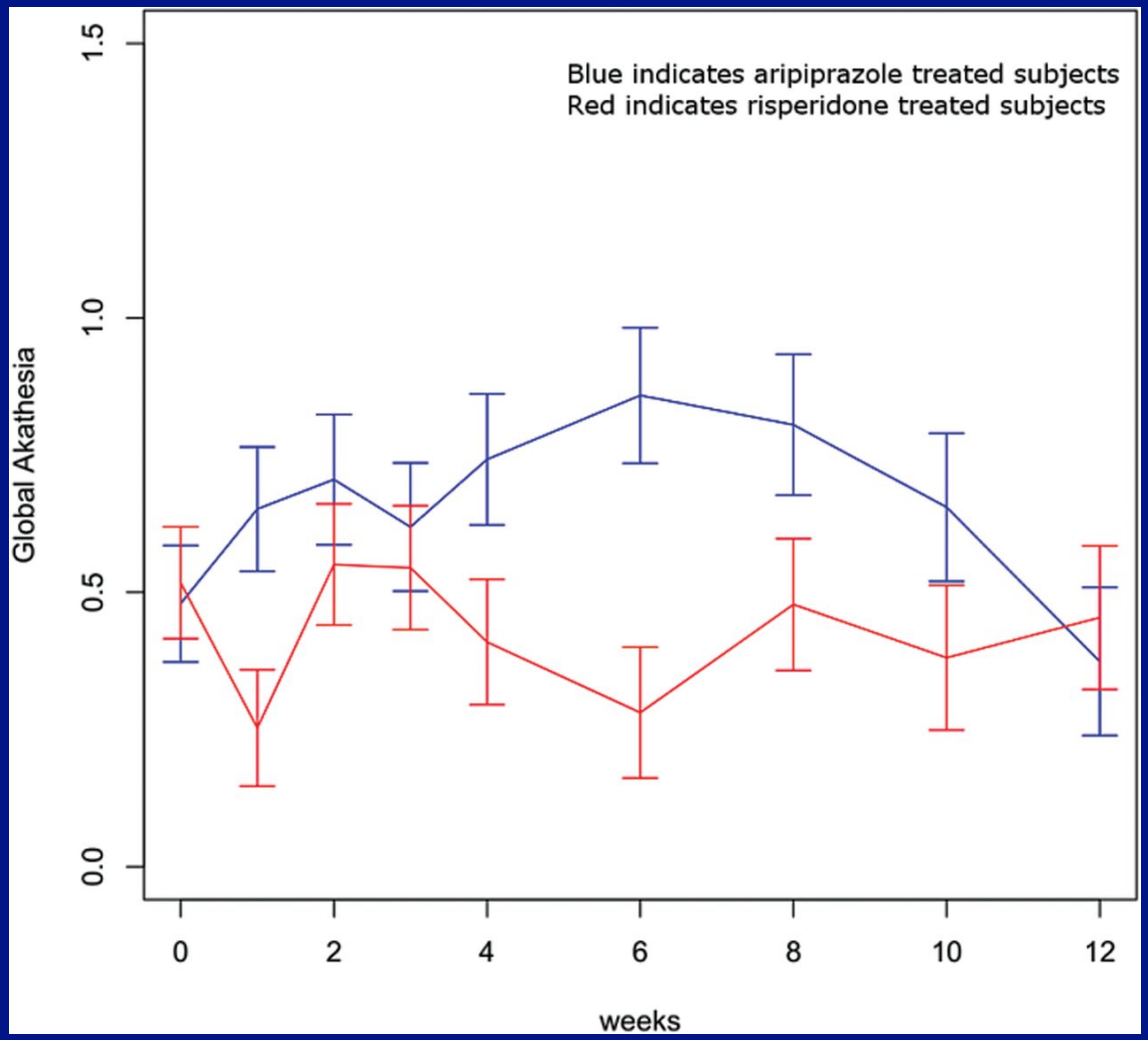
SANS Avolition-Apathy Global Score.



Delbert G. Robinson et al. Schizophr Bull 2015;41:1227-1236

Schizophrenia Bulletin

Global Barnes Akathisia Scores.



Delbert G. Robinson et al. Schizophr Bull 2015;41:1227-1236

Schizophrenia Bulletin

Long-term Antipsychotic Treatment and Brain Volumes

A Longitudinal Study of First-Episode Schizophrenia

Beng-Choon Ho, MRCPsych; Nancy C. Andreasen, MD, PhD; Steven Ziebell, BS; Ronald Pierson, MS; Vincent Magnotta, PhD

Context: Progressive brain volume changes in schizophrenia are thought to be due principally to the disease. However, recent animal studies indicate that antipsychotics, the mainstay of treatment for schizophrenia patients, may also contribute to brain tissue volume decrement. Because antipsychotics are prescribed for long periods for schizophrenia patients and have increasingly widespread use in other psychiatric disorders, it is imperative to determine their long-term effects on the human brain.

Objective: To evaluate relative contributions of 4 potential predictors (illness duration, antipsychotic treatment, illness severity, and substance abuse) of brain volume change.

Design: Predictors of brain volume changes were assessed prospectively based on multiple informants.

Setting: Data from the Iowa Longitudinal Study.

Patients: Two hundred eleven patients with schizophrenia who underwent repeated neuroimaging beginning soon after illness onset, yielding a total of 674 high-resolution magnetic resonance scans. On average, each patient had 3 scans (≥2 and as many as 5) over 7.2 years (up to 14 years).

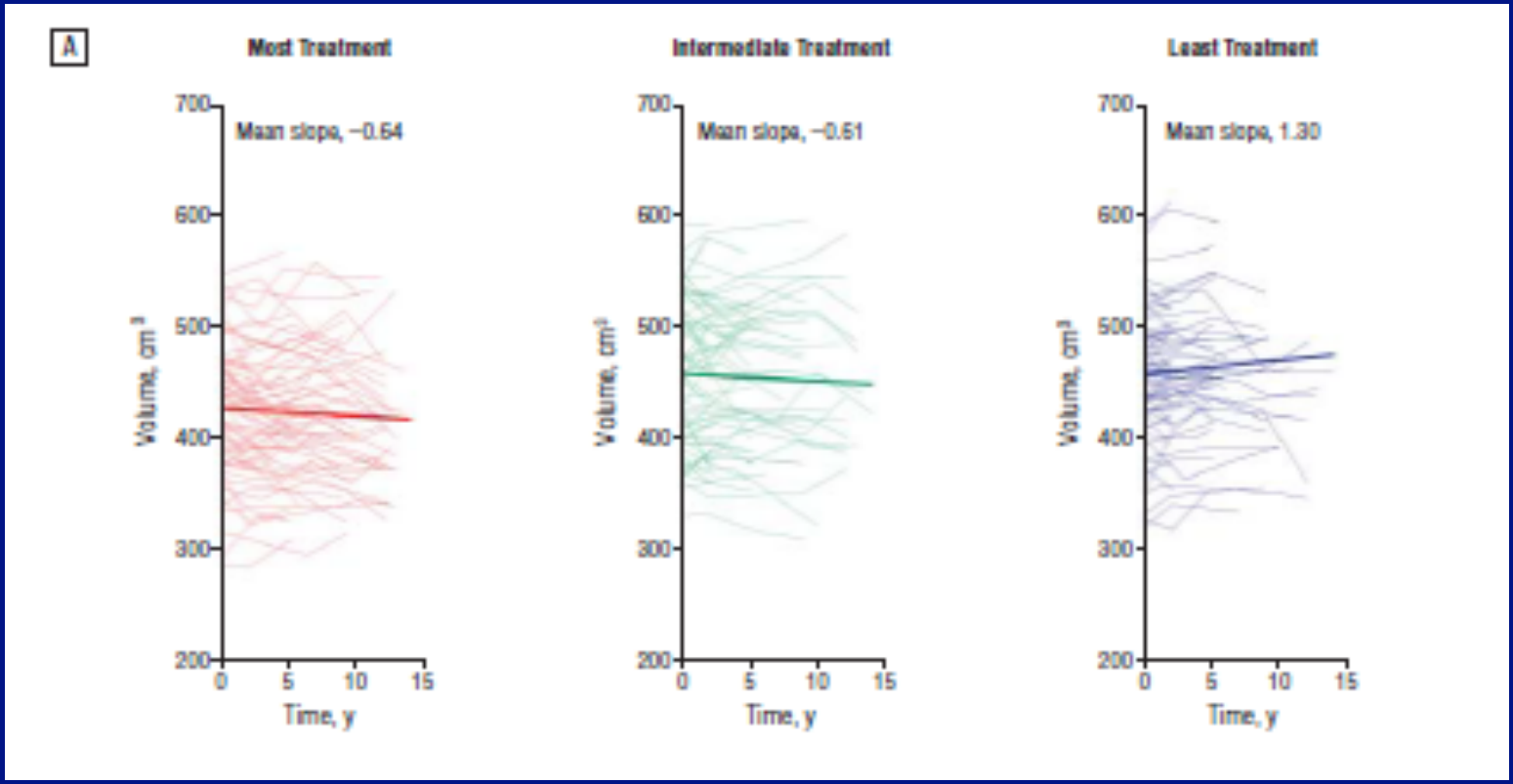
Main Outcome Measure: Brain volumes.

Results: During longitudinal follow-up, antipsychotic treatment reflected national prescribing practices in 1991 through 2009. Longer follow-up correlated with smaller brain tissue volumes and larger cerebrospinal fluid volumes. Greater intensity of antipsychotic treatment was associated with indicators of generalized and specific brain tissue reduction after controlling for effects of the other 3 predictors. More antipsychotic treatment was associated with smaller gray matter volumes. Progressive decrement in white matter volume was most evident among patients who received more antipsychotic treatment. Illness severity had relatively modest correlations with tissue volume reduction, and alcohol/illicit drug misuse had no significant associations when effects of the other variables were adjusted.

Conclusions: Viewed together with data from animal studies, our study suggests that antipsychotics have a subtle but measurable influence on brain tissue loss over time, suggesting the importance of careful risk-benefit review of dosage and duration of treatment as well as their off-label use.

Arch Gen Psychiatry. 2011;68(2):128-137

Ho et al. Total White Matter



Original Investigation

Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy

Long-term Follow-up of a 2-Year Randomized Clinical Trial

Lex Wunderink, MD, PhD; Roeline M. Nieboer, MA; Durk Wiersma, PhD; Sjoerd Sytema, PhD; Fokko J. Nienhuis, MA

- 7 year follow-up of a 2 year randomized trial in first episodes
- Those randomized to dose reduction had higher recovery rates and higher functioning.
- 17 out of 103 patients discontinued antipsychotics. These individuals showeed better functioning at 7 years

Minimizing the burden of antipsychotic medication

- **Dose reduction (with supplementation when patients show prodromal or other symptoms)**
- **Intermittent treatment**
- **Shared decision-making**

ORIGINAL ARTICLE

Long-Chain ω-3 Fatty Acids for Indicated Prevention of Psychotic Disorders

A Randomized, Placebo-Controlled Trial

G. Paul Amminger, MD; Miriam R. Schäfer, MD; Konstantinos Papageorgiou, MD; Claudia M. Klier, MD; Sue M. Cotton, PhD; Susan M. Harrigan, MSc; Andrew Mackinnon, PhD; Patrick D. McGorry, MD, PhD; Gregor E. Berger, MD

Replication Attempts:

NAPLS
Neuropro

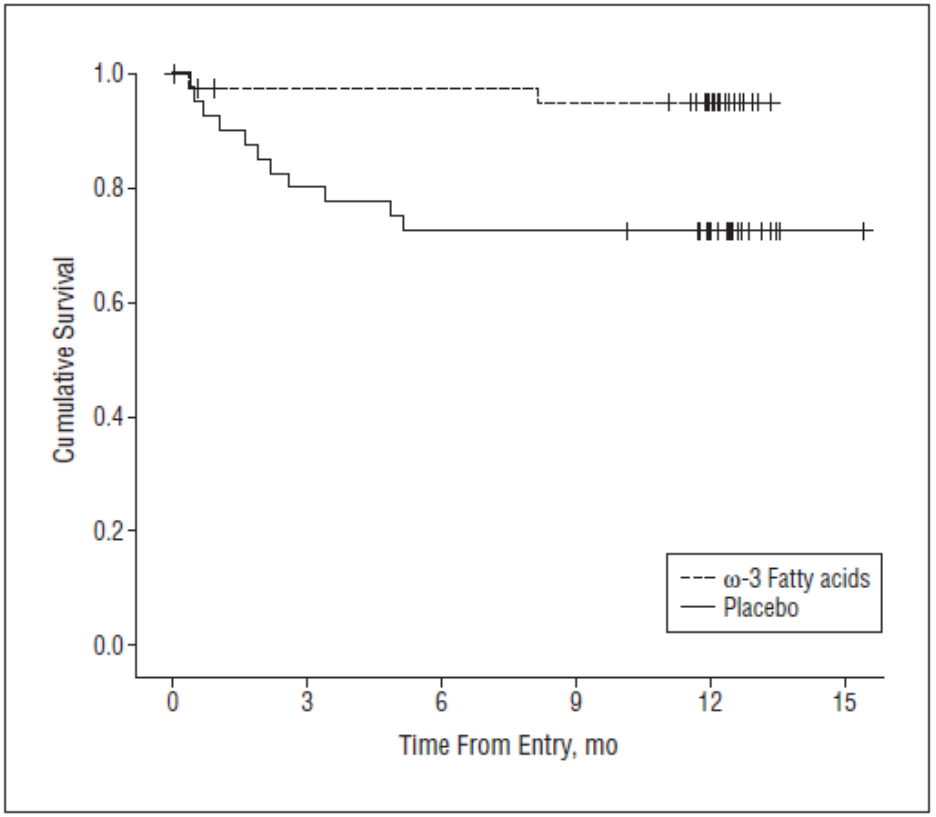


Figure 2. Kaplan-Meier estimates of the risk of transition from the at-risk state to psychotic disorder in patients assigned to ω-3 fatty acids or placebo (P=.007 by log-rank test).

Arch Gen Psychiatry. 2010;67(2):146-154

Omega-3 fatty acids for first episodes

- Since polyunsaturated fatty acids (PUFA) are essential for normal neurodevelopment, disturbances of PUFA metabolism may be involved in the etiology of neurodevelopmental disorders like schizophrenia
- One study of 80 first-episode patients over 12 weeks found n – 3 PUFA eicosapentaenoic acid (EPA) decreased time to response in patients with non-affective psychosis (Berger et al 2007)

Omega 3's (continued)

- A meta-analysis of RCTs revealed no beneficial effect symptom severity in schizophrenia. However, no conclusion could be drawn regarding the medium- to long-term effects of EPA in schizophrenia.
- A 12-week RCT conducted in individuals at high clinical risk of schizophrenia provides preliminary evidence that intervention composed of 1.2 g of PUFA (i.e. EPA + DHA) could prevent transition to first-episode psychosis.

Medication Non-Adherence (from Peter Weiden)

- **50% of patients have significant non-adherence within one year of beginning treatment.**
- **75% within two years.**
- **50% of the direct medical costs of psychiatric hospitalization attributed to non-adherence.**

UCLA Study Design

- **12-month randomized controlled trial with first-episode schizophrenia patients at the UCLA Aftercare Research Program**

- **Patients received Individual Placement and Support, a form of supported education and supported employment, to provide a context of active work rehabilitation**

- **After stabilization, patients were randomly assigned to the medication condition and the psychosocial treatment condition (2 X 2 design)**

From: Long-Acting Injectable Risperidone for Relapse Prevention and Control of Breakthrough Symptoms After a Recent First Episode of Schizophrenia : A Randomized Clinical Trial

JAMA Psychiatry. Published online June 24, 2015. doi:10.1001/jamapsychiatry.2015.0270

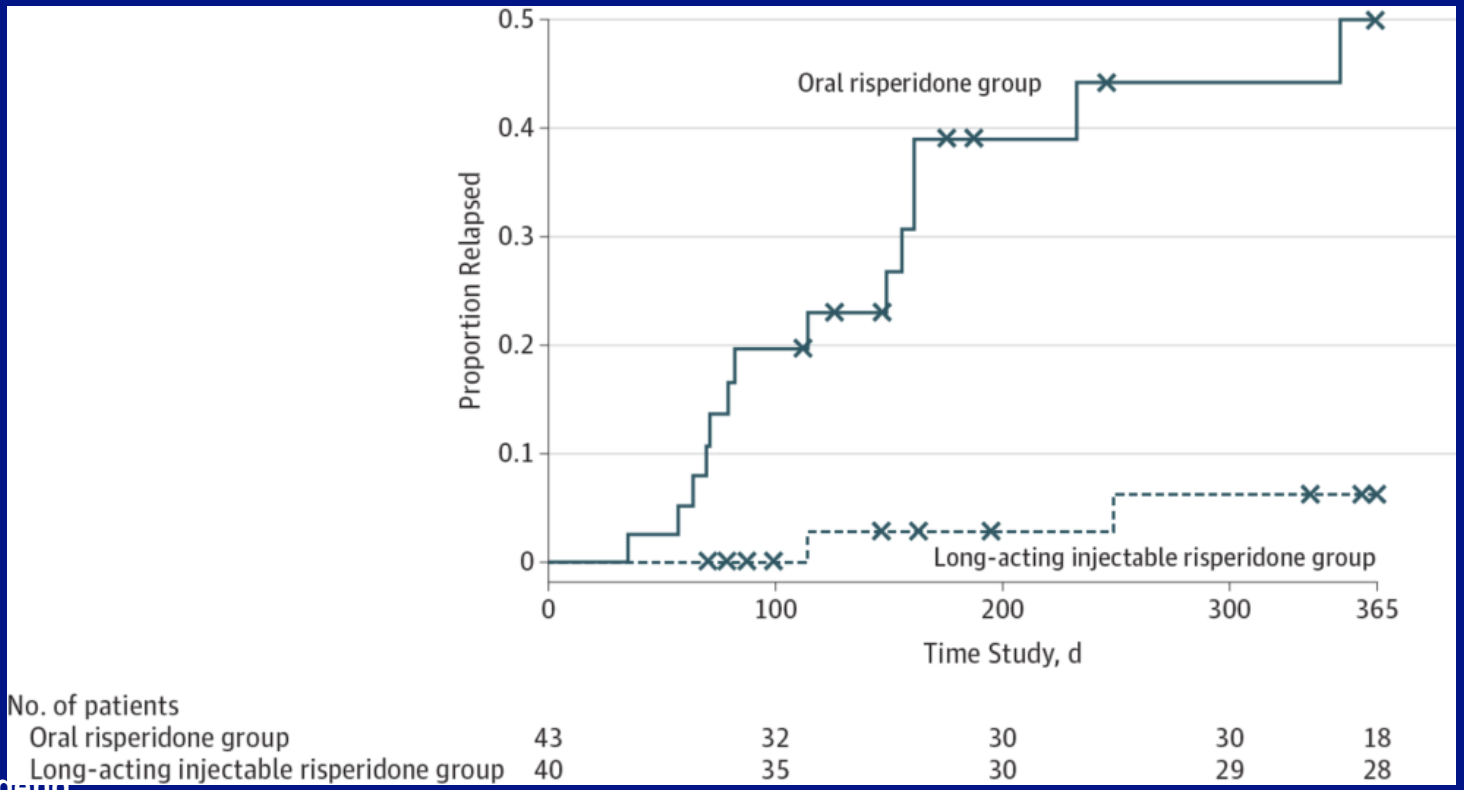
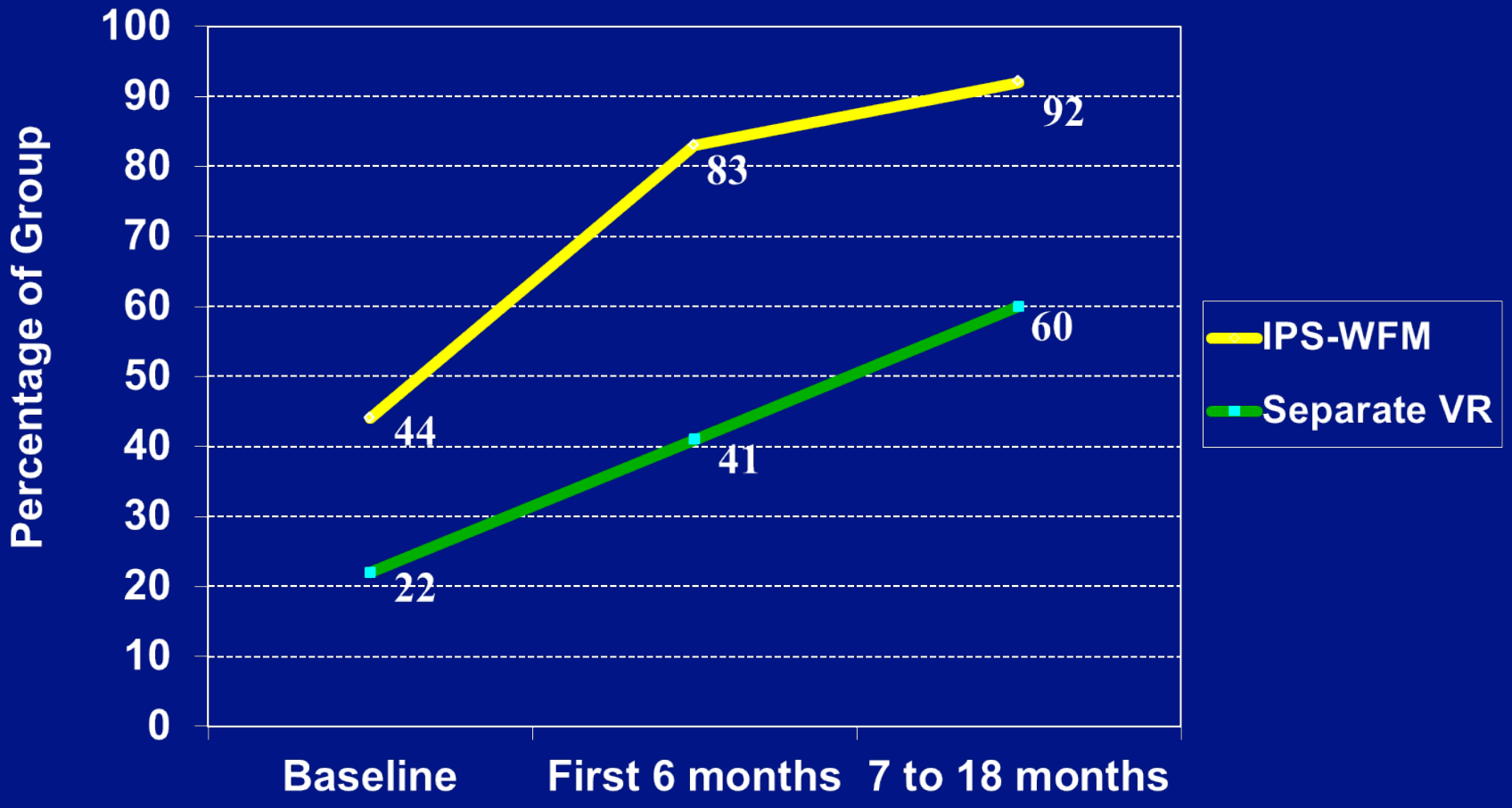


Figure Legend:

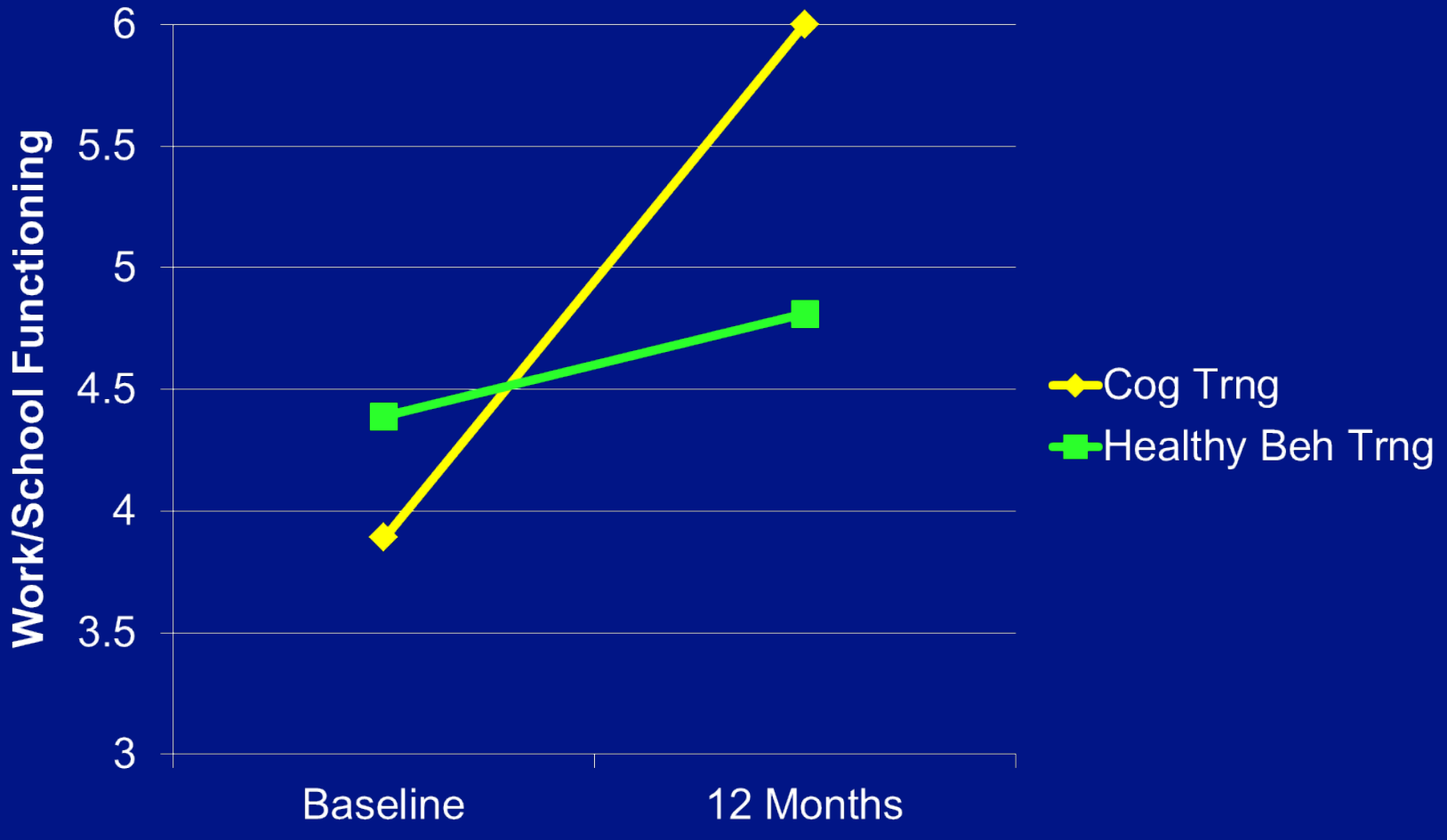
Time to First Psychotic Exacerbation and/or Relapse as a Function of Form of Medication Administration in 83 PatientsThe risk of exacerbation and/or relapse over time was significantly lower for the long-acting injectable risperidone group than for the oral risperidone group. x Indicates censored data.

Percentage Returning to Competitive Work or Regular School (N = 69)



Adjusting for non-significant baseline differences, Wald $x^2 = 7.73$, $p < .0054$ for 1st 6 mos.; Wald $x^2 = 4.73$, $p < .03$ for next year

Global Functioning Scale: Role Effect in 12 Months (n = 53)



Group X Time interaction, p = .03, Cohen's d = .62

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.

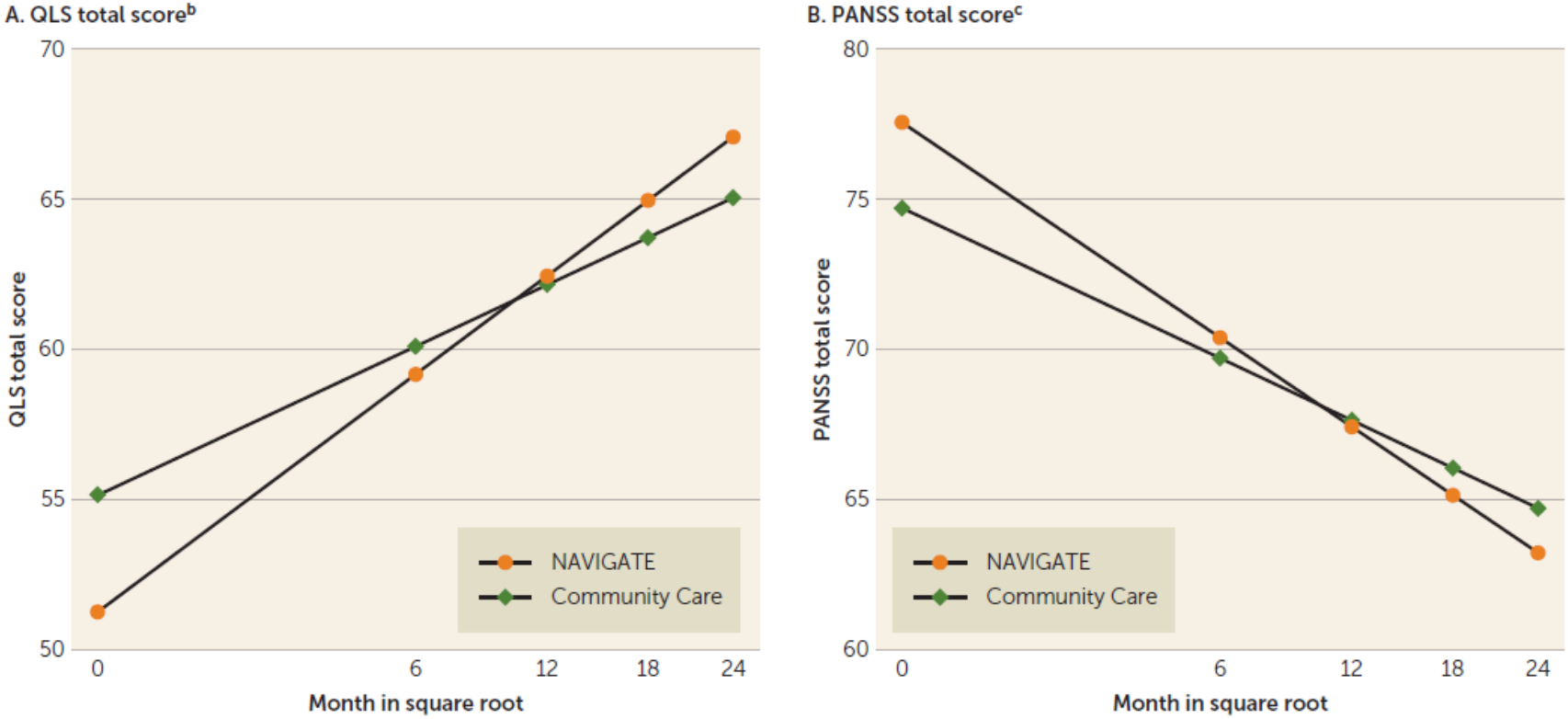
AJP in Advance (doi: 10.1176/appi.ajp.2015.15050632)

Components of RAISE Intervention

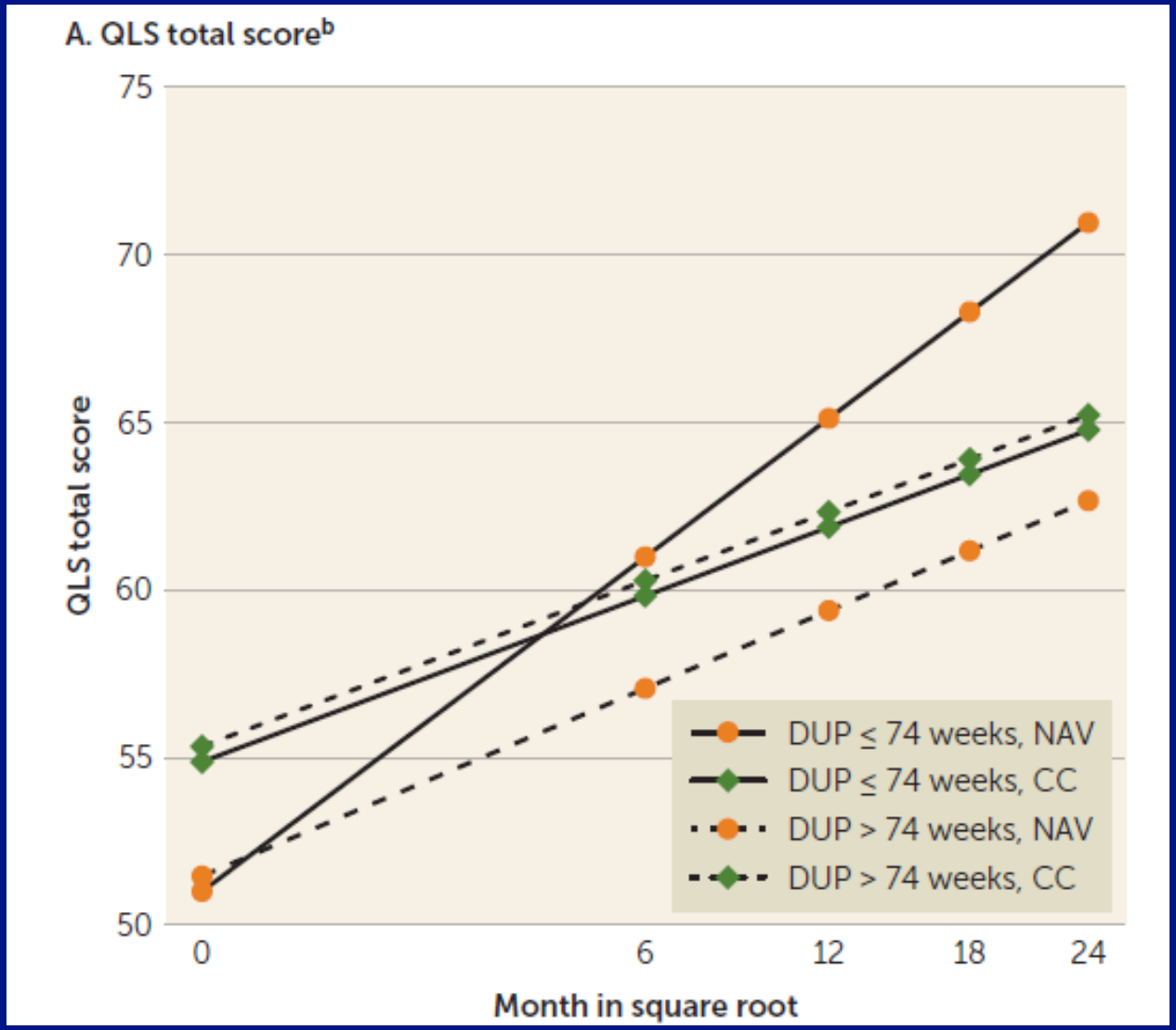
- **Web-based decision support for medication management**
- **family psychoeducation**
- **resilience-focused individual therapy**
- **supported employment and education (SEE)**

KANE ET AL.

FIGURE 2. Model-Based Estimates of Heinrichs-Carpenter Quality of Life (QLS) Total Score and PANSS Total Score[a]

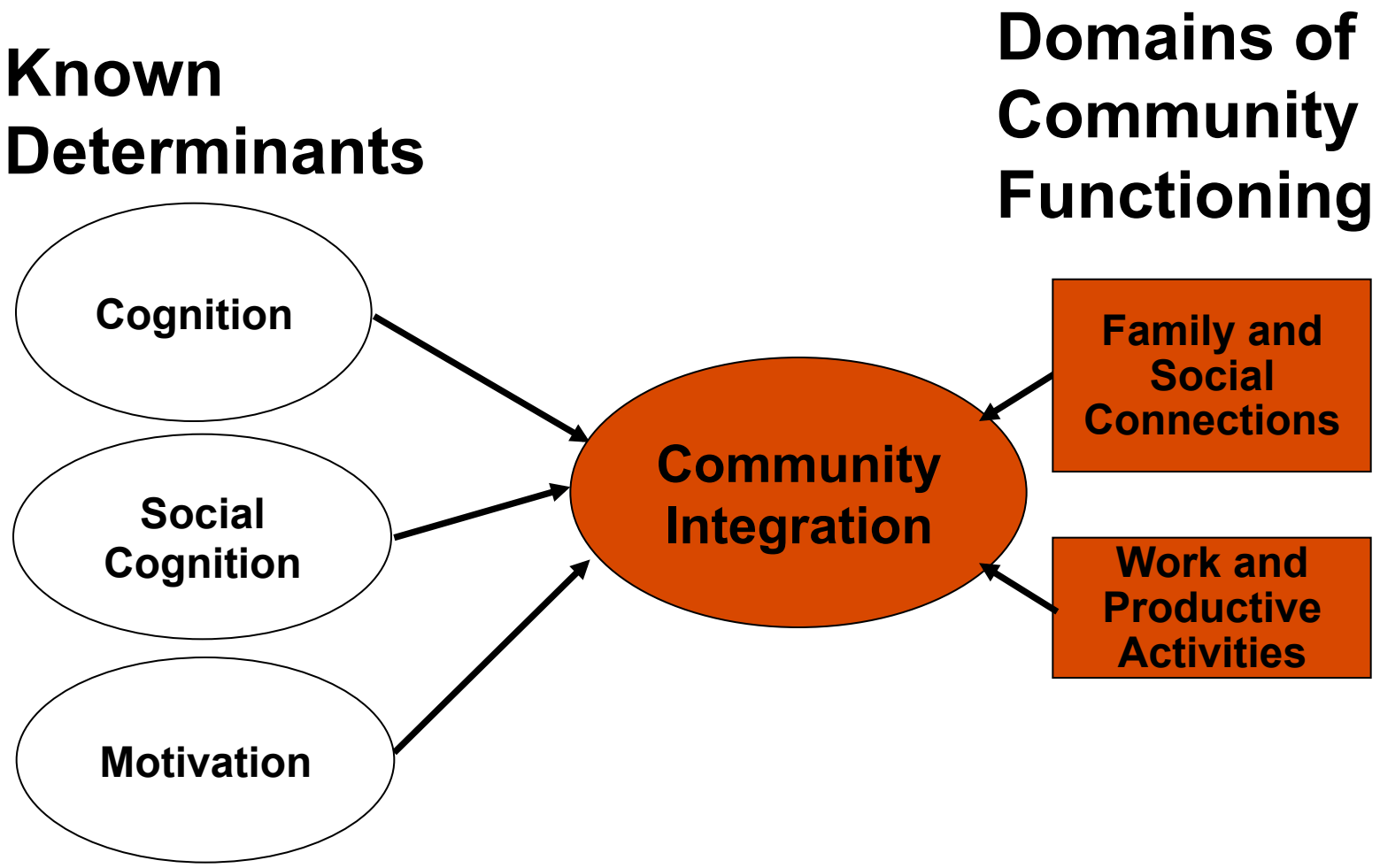


[a] PANSS=Positive and Negative Syndrome Scale.
[b] Treatment by square root of time interaction, p=0.015.
[c] Treatment by square root of time interaction, p=0.016.



[b]DUP by treatment by square root of time interaction, p=0.003.

What does it take for someone with schizophrenia to function in the community?



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NICE Guidelines for attenuated or transient psychosis 2013

- Consider individual cognitive behavioural therapy (CBT) with or without family intervention and offer treatments recommended in NICE guidance for children and young people with any of the anxiety disorders, depression, emerging personality disorder or substance misuse.
- Do not offer antipsychotic medication for psychotic symptoms or mental state changes that are not suffi cient for a diagnosis of psychosis or schizophrenia, or with the aim of decreasing the risk of psychosis.

NICE Guidelines 2013

For children and young people with first episode psychosis offer:

- **oral antipsychotic medication in conjunction with**
- **psychological interventions (family intervention with individual CBT**

NICE Guidelines 2013

- Family intervention should:
- ● include the child or young person with psychosis or schizophrenia if practical
- ● be carried out for between 3 months and 1 year
- ● include at least 10 planned sessions
- ● take account of the whole family's preference for either single-family intervention or multi-family group intervention
- ● have a specific supportive, educational or treatment function and include negotiated problem solving or crisis management work.

NICE Guidelines 2013

Offer clozapine to children and young people with schizophrenia whose illness has not responded adequately to pharmacological treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs each used for 6–8 weeks.