UNC School of Social Work and Wake AHEC
Clinical Lecture Series

Early Identification and Treatment of Psychosis: Potential Promise and Pitfalls

October 14, 2013

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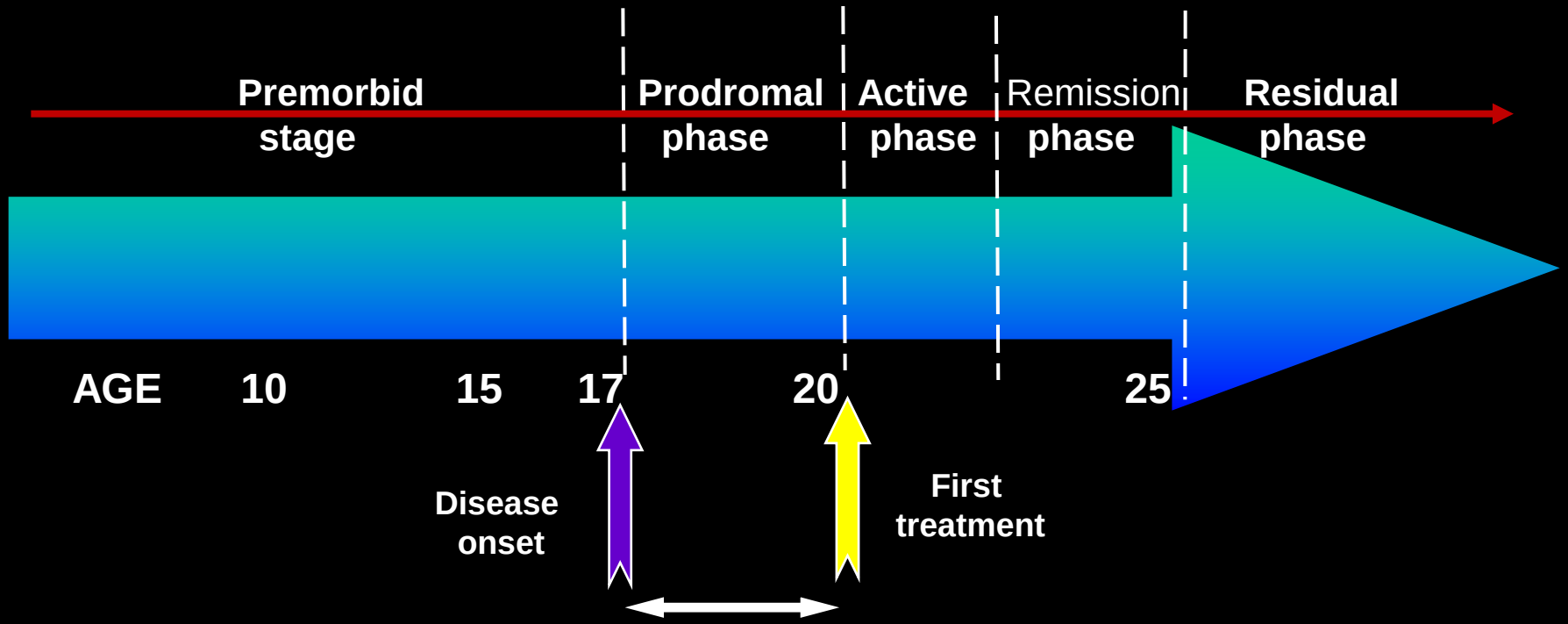
Natural Course of Schizophrenia



Hales RE, et al, eds. *Textbook of Psychiatry.* 5th ed. Arlington, VA: American Psychiatric Publishing; 2008.

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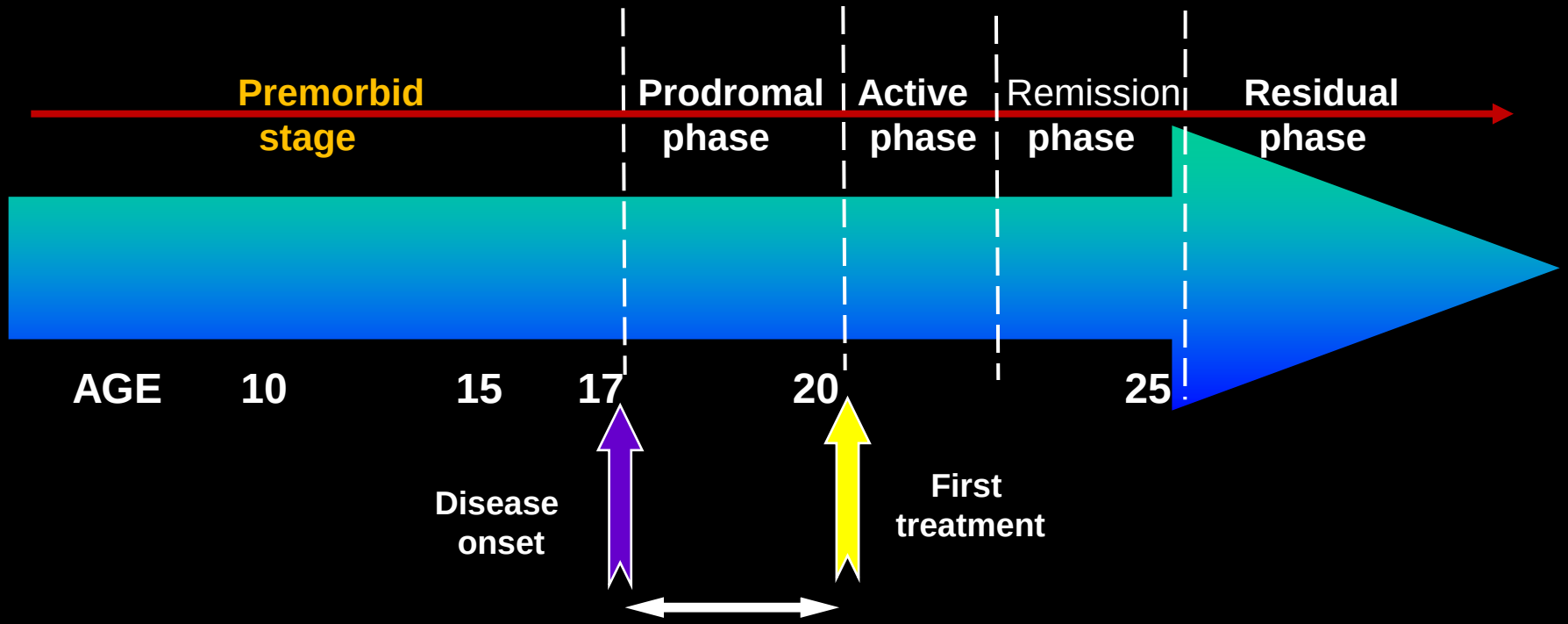


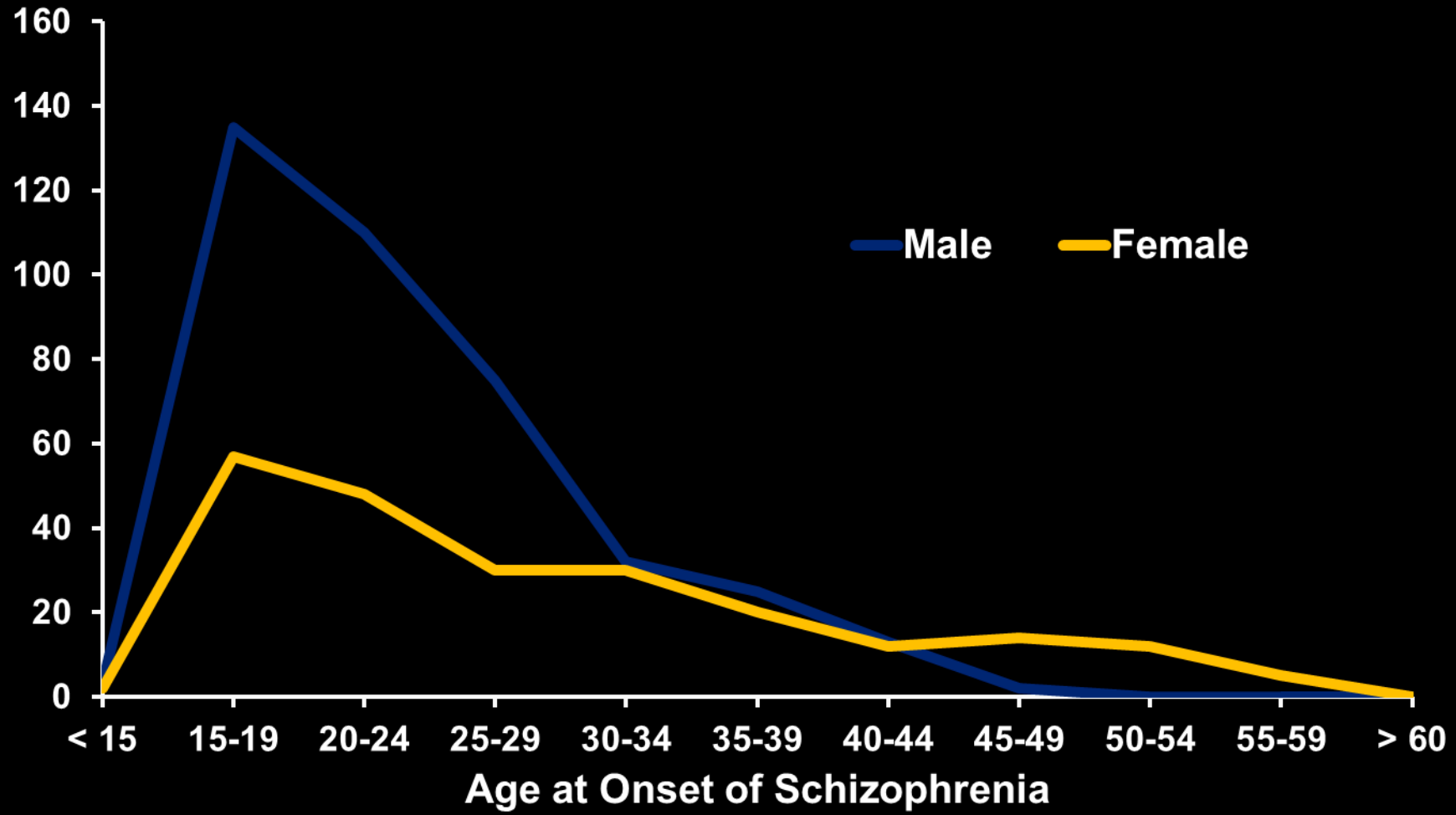
Hales RE, et al, eds. *Textbook of Psychiatry.* 5th ed. Arlington, VA: American Psychiatric Publishing; 2008.

Vulnerability and Course

- Ratio of men to women with schizophrenia: 1.4
- Sex differences in:
  - Age of onset
  - Premorbid function
  - Severity of negative symptoms
  - Structural brain abnormalities
  - Substance use

Aleman A, et al. *Arch Gen Psychiatry*. 2003;60(6):565-571.

Age of Schizophrenia Onset in Males and Females



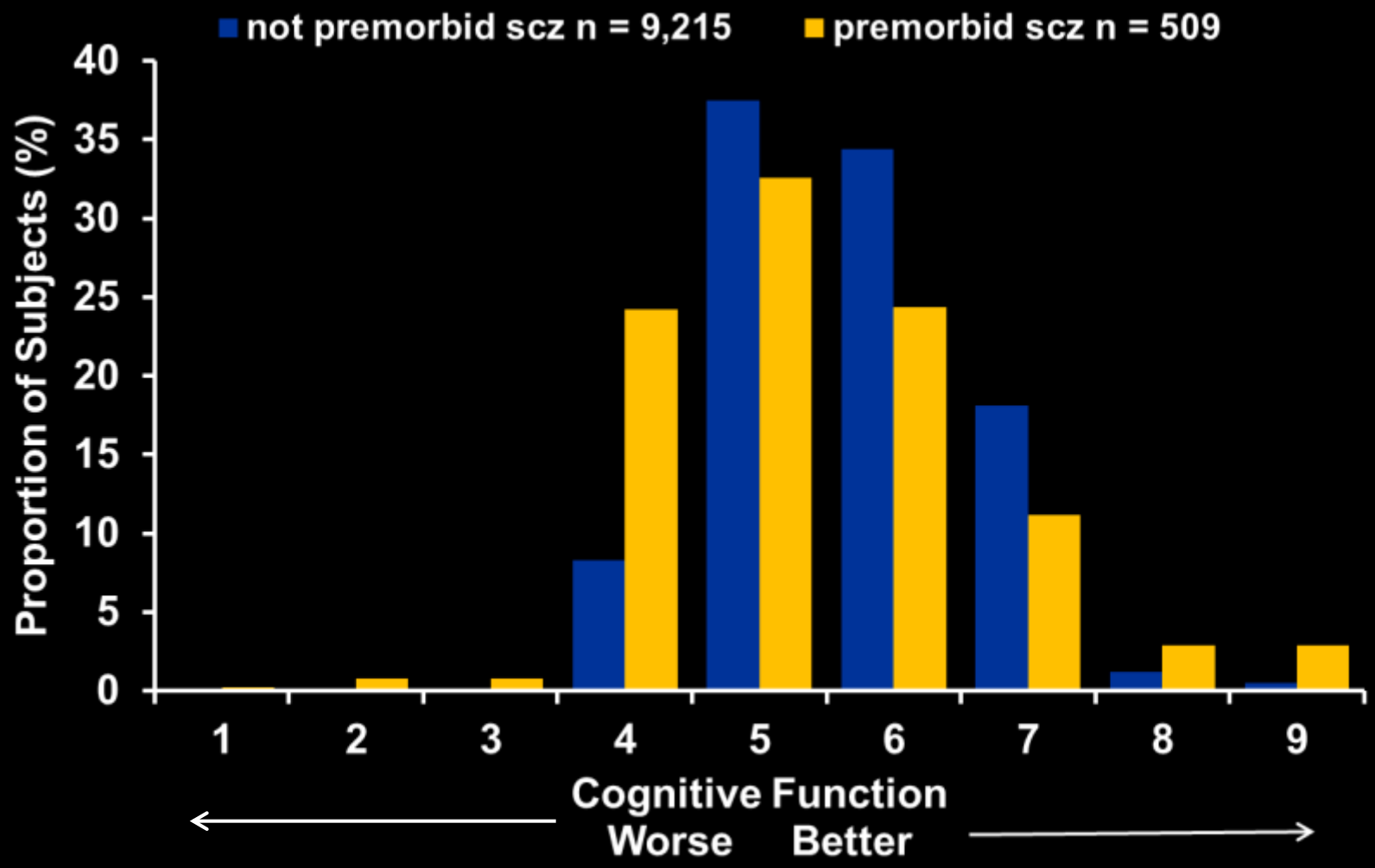
Abel KM, et al. *Int Rev Psychiatry*. 2010;22(5):417-428.

Premorbid Characteristics: Predicting Risk of Schizophrenia

- Intellectual abnormalities
- Impairments in cognitive function
- Socially awkward
- Impulsive
- Minor physical anomalies

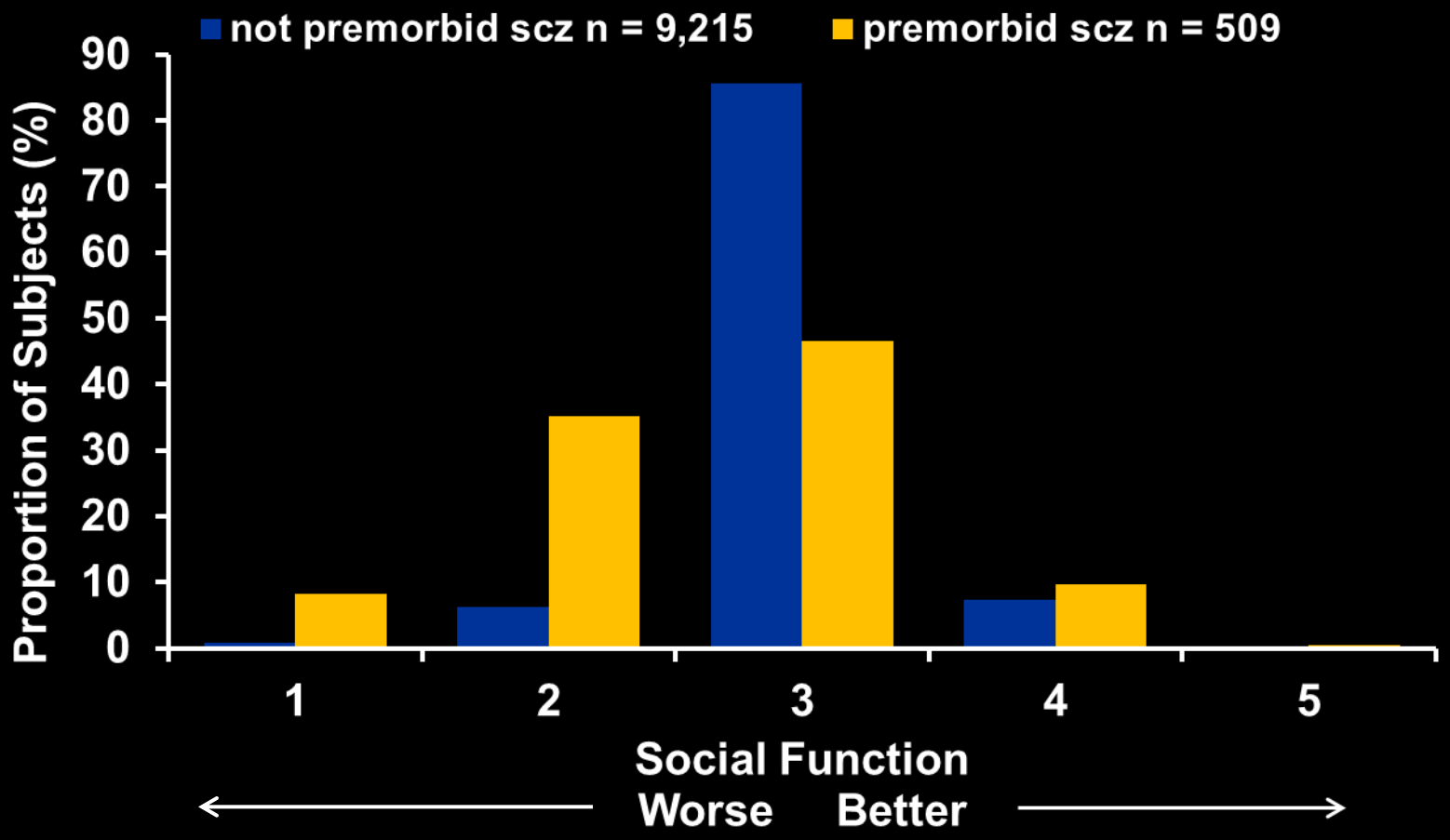
Walker EF, et al. *Am J Psychiatry*. 1993;150(11):1654-1660; Davidson M, et al. *Am J Psychiatry*. 1999;156(9):1328-1335.

Premorbid Intellectual Functioning



Davidson M, et al. *Am J Psychiatry*. 1999;156(9):1328-1335.

Premorbid Social Functioning



Davidson M, et al. *Am J Psychiatry*. 1999;156(9):1328-1335.

Factors Associated with Outcomes: Premorbid Stage

- Sex (male)
- Poor premorbid function
  - Delayed developmental milestones
  - Poor academic performance
  - Few friends
  - “Odd”

Isohanni M, et al. *Br J Psychiatry Suppl.* 2005;48:S4-S7.

Pre-morbid functioning in Schizophrenia

- Patients often have a history of:
  - Poor scholastic achievements
  - Few friends
  - Psychiatric symptoms

- BUT:
  - More patients have a history of average pre-morbid functioning, hence can we predict/delay/prevent schizophrenia based on pre-morbid functioning ?

Meet Michael and Ryan

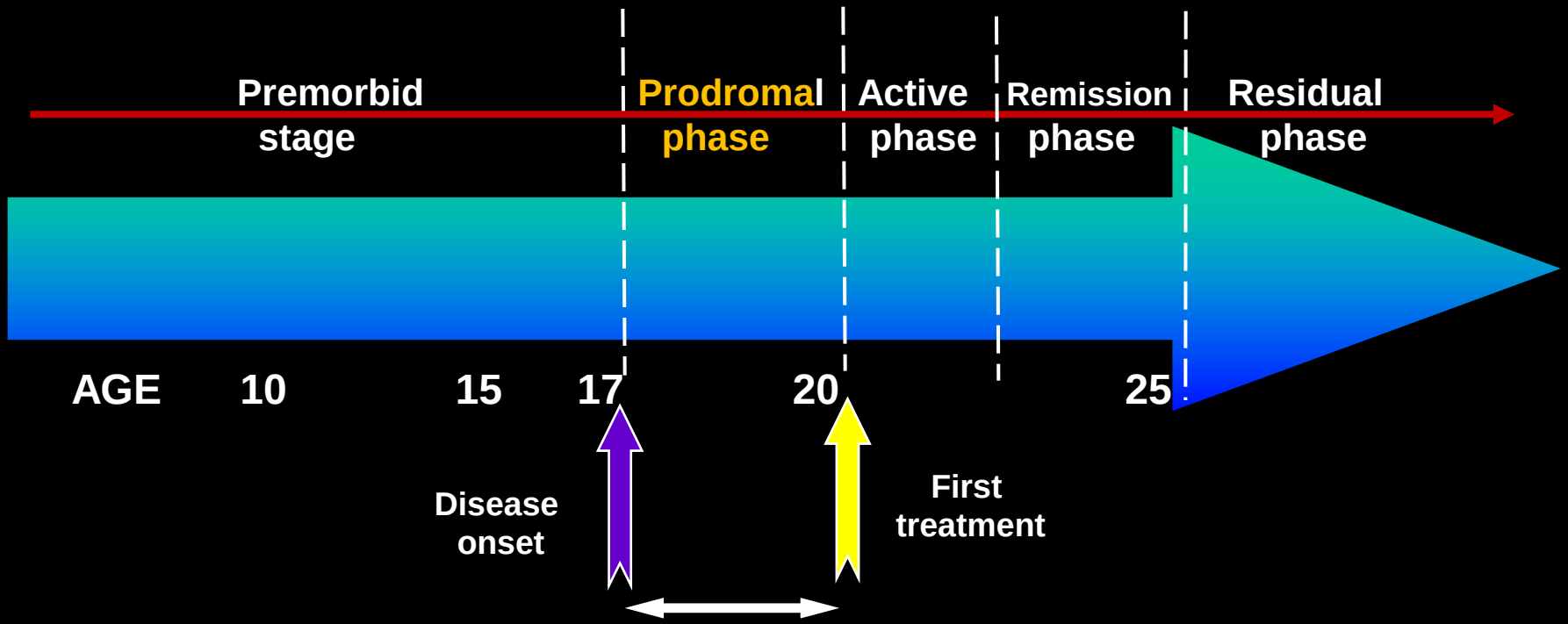
Michael

- “Normal” childhood development
- Good student until second semester junior year in high school, where he struggles academically
- Shy, with few friends
- Talented musically

Ryan

- Normal childhood development
- Elite high school athlete, “A” student
- Popular, social
- Heads off to college, a highly recruited division 1 athlete

Natural Course of Schizophrenia



Hales RE, et al, eds. *Textbook of Psychiatry.* 5th ed. Arlington, VA: American Psychiatric Publishing; 2008.

“Prodromal” Characteristics

- Attenuated Psychosis
  - Ideas of reference / suspiciousness /unusual thought content
  - Perceptual abnormalities
  - Disorganized speech
  - Derealization
- Brief, Intermittent Psychosis
- Negative Symptoms
  - Emotional / affective blunting
  - Diminished drive / motivation
  - Social withdrawal
- Affective
  - Depression/anxiety/hostility
  - Mood lability
  - Sub-threshold obsessive compulsive symptoms

Lieberman JA, et al, eds. *Essentials of Schizophrenia.* Arlington, VA: American Psychiatric Association; 2012.

Initial “Prodromal” Symptoms

- Cognitive
  - Poor attention/distractibility
  - Impairment initiation or train of thought; intrusive thoughts
  - Difficulty in understanding written or spoken language
- Behavioral Disturbances
  - Decline in school function
  - Social withdrawal
  - Impaired hygiene
  - Sleep disturbance
  - Suicidal ideation / attempts
  - Aggressive behaviors

Lieberman JA, et al, eds. *Essentials of Schizophrenia.* Arlington, VA: American Psychiatric Association; 2012.

Attenuated Psychosis Syndrome

- Characteristic symptoms: at least one of the following in attenuated form with intact reality testing, but of sufficient severity and/or frequency so as to be beyond normal variation:
- (i) delusions (unusual thought content)
- (ii) hallucinations (perceptual abnormalities)
- (iii) disorganization (disorganized communication)
  - Present in past month
  - Occur at least 1 per week
  - Begun or worsened in past year
  - Distressing or significantly impact function
  - Not caused by another disorder (eg, PTSD)
  - Never met criteria for a psychotic disorder

American Psychiatric Association: *DSM-5.* Arlington, VA: American Psychiatric Association; 2013.

Unusual Thought Content

- Examples
  - Ideas of reference
  - Sense “something odd is going on”
  - Overvalued beliefs
  - Magical thinking
  - Connections between unrelated event
  - Déjà vu
  - Coincidences
  - Suspiciousness/paranoia
  - Distorted illogical ideas
- “prodromal”=sense of doubt , may be dismissed
- psychotic = sure is true, cannot be dismissed

Thought Content

Attenuated Delusion

A 15-year-old high school student sits in the back of the class because if she sits in the front, she has an uncomfortable feeling that other students are watching her. She knows this is “silly”, but feels better in the back.

Delusion

A 15-year-old high school student believes that other people are talking about her and making fun of her where ever she goes. She is sure this is happening, and she is isolating herself at home because she is uncomfortable in public.

Lieberman JA, et al, eds. *Essentials of Schizophrenia.* Arlington, VA: American Psychiatric Association; 2012.

Perceptual Disturbances

- Examples
  - Illusions
  - Heightened or dulled perceptions
  - Distortions
  - Transient hallucinations
- “prodromal”= understood as “mind playing tricks”
- psychotic = certain is a real experience

Perceptual Disturbances

Attenuated Hallucination

About 2 or 3 times a week a 22-year-old cashier sees shadows, movements, and sometimes formed figures (like an animal) out of the corner of his eye, but when he turns to look nothing is there. He hears beeping sounds that can last for minutes, and once he heard a momentary (a second or two), faint, unintelligible voice. He is not sure, but thinks it is his mind playing tricks on him.

Hallucination

On a daily basis a 22-year-old cashier sees fully formed figures that he calls “shadows”. The shadows remain for minutes to hours. He hears the “shadows” speak to each other about him, and sometimes criticize him or tell him to do something silly. He believes these shadows are real and he is frightened of them.

Lieberman JA, et al, eds. *Essentials of Schizophrenia.* Arlington, VA: American Psychiatric Association; 2012.

Disorganized thoughts/speech

- Examples
  - Odd speech, vague, metaphorical, overelaborate
  - Circumstantial, tangential, not goal directed
  - Redirected through structured questioning
- “prodromal”= can be redirected
- psychotic = not responsive to structuring, disorganized when minimal pressure

Disorganzation

Attenuated Disorganized Speech

A formerly high achieving high school junior reports his friends have great difficulty following him when he explains things to them. This is very frustrating to him. During the interview he had difficulty getting to the point and at times his statements did not answer the question asked. Through direct and structured questioning he was able to answer the questions correctly. He did not have this problem a year ago, and it is getting worse these last few months.

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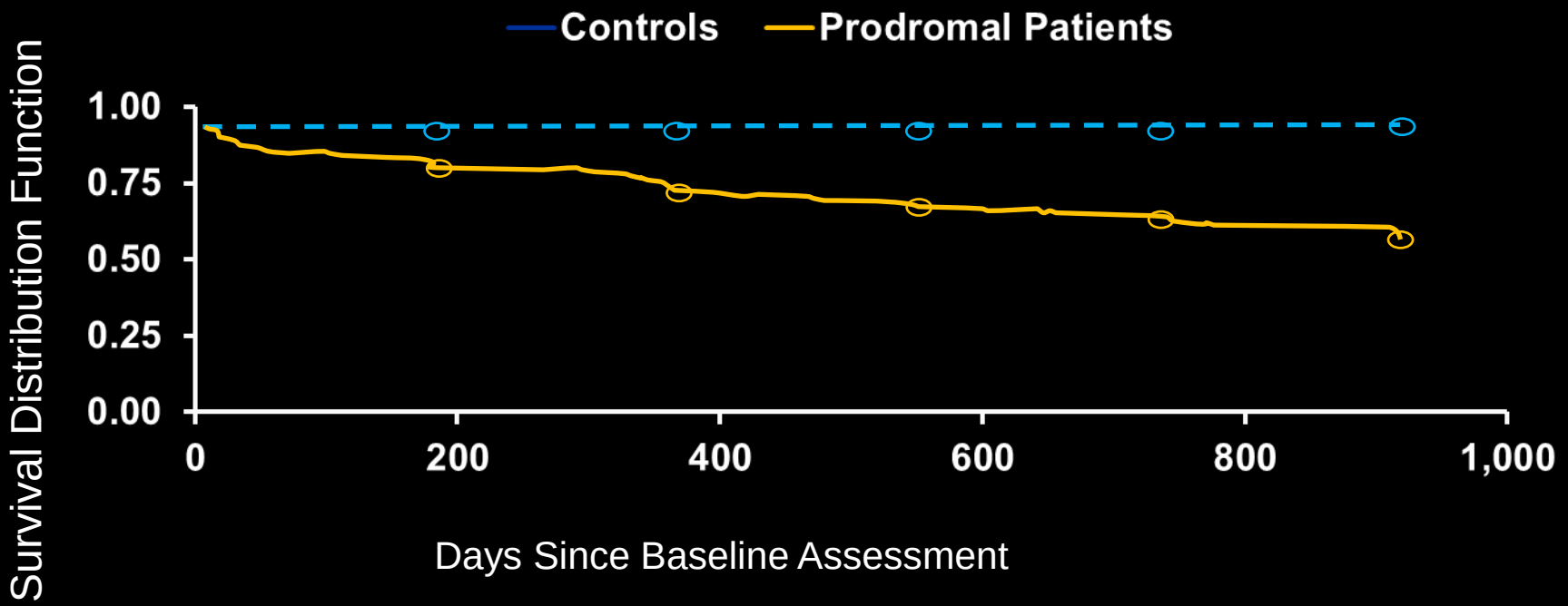
Psychotic Intensity Disorganized Speech

A formerly high achieving high school junior is unable to attend school due to disorganization. He can engage in goal directed speech only when the conversation is highly structured. His speech often doesn't make sense due to loose associations.

Lieberman JA, et al, eds. *Essentials of Schizophrenia.* Arlington, VA: American Psychiatric Association; 2012.

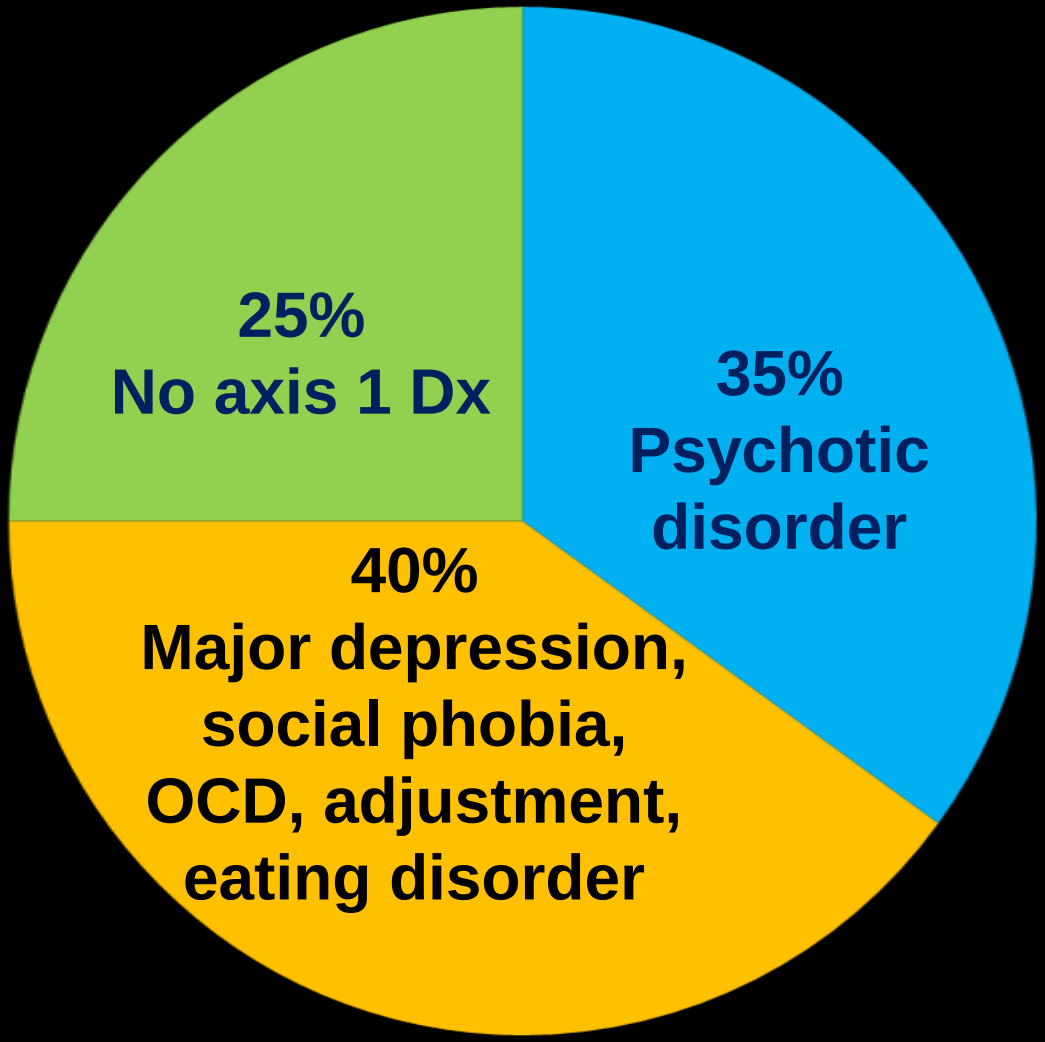
Validity of the Attenuated Psychosis Syndrome Criteria



Risk Estimates in Persons Meeting APS Criteria:
20–25% in 1 year
30–35% in 2 years

Woods SW, et al. *Schizophr Bull*. 2009;35(5):894-908; Cannon TD, et al. *Arch Gen Psychiatry*. 2008;65(1):28-37; Liu CC, et al. *Schizophr Res*. 2011;126(1-3):65-70; Fusar-Poli P, et al. *Arch Gen Psychiatry*. 2012;69(3):220-229.

Diagnosis at 1 Year Follow-Up for Patients with Attenuated Psychosis Syndrome



Woods SW, et al. *Schizophr Bull*. 2009;35(5):894-908.

Symptoms Most Predictive of Psychosis

- Unusual thought content/ suspiciousness/ distorted ideas
- Reduced ideational richness
- Trouble with focus and attention

Reduced Ideational Richness

- Examples
  - Unable to make sense of familiar phrases
  - Difficulty getting “gist of conversation”
  - Decreased fluidity, spontaneity, flexibility of thinking
  - Difficulty with abstract thinking
  - Poverty content

Trouble with Focus/Attention

- Examples
  - Failure in focused alertness/poor concentration
  - Distractible
  - Difficulty shifting focus
  - Loses tract of conversations

Case 1

Max is a 21 y.o. art student at a local college, living in an apartment with a friend from HS. He is close to his parents, who live about ½ hour away. His girlfriend attends the same college, and they spend a lot of time together. Both enjoy smoking marijuana several times a week, but do not think they have a problem with it. Max is a gifted artist and has a 3.0 GPA.

At 16, Max saw his best friend die in a skiing accident, which was extremely traumatic. Periodically during the past five years he has had nightmares. Max never went to therapy afterwards, but through the years has talked about the accident with family and friends.

Lately, Max has been feeling anxious and overwhelmed by his course load. Last night he told his girlfriend that he has been hearing his name called periodically for the past several months, but when he checks, no one has been calling him. He's also finding it uncomfortable to be in crowds and worries that people are looking at him when out in public. He wonders if this is due to fatigue or smoking pot. Max is bothered by these experiences, and his girlfriend is encouraging him to see someone at the school counseling service. He agrees to see a counselor, who then wonders…

Is Max developing a psychotic disorder?

Case 1 - Max

- What symptoms are you concerned about?
- What diagnoses are you considering?
- What recommendations do you have?

Case 1

Max is a 21 y.o. art student at a local college, living in an apartment with a friend from HS. He is close to his parents, who live about ½ hour away. His girlfriend attends the same college, and they tend to spend a lot of time together. Both enjoy smoking marijuana several times a week, but do not think they have a problem with it. Max is a gifted artist and has a 3.2 GPA.

When 16, Max saw his best friend die in a skiing accident, which was traumatic. Periodically during the past five years he has had nightmares. Max never went to therapy, but has talked about the accident with family and friends.

Lately, Max is feeling anxious and overwhelmed by his course load. Last night he told his girlfriend that **he has been hearing his name called periodically for the past several months, but when he checks, no one has been calling him**. **He's also finding it uncomfortable to be in crowds and worries that people are looking at him when out in public**. He wonders if this is due to fatigue or smoking pot. Max is **beginning to feel bothered by these experiences**.

MAX <u>SHOULD</u> BE considered at increased risk for development of psychosis.

Case 2

Jon is a 17 year-old high school student who lives with his parents and younger brother. He has always been a good student, getting good grades, completing his work, and involved in the chess club 2 afternoons a week.

Jon's chess club teacher, who also happens to be his English teacher, has noticed several changes in him recently. He has stopped going to chess club, and his English grades have been dropping, mostly because of incomplete homework. His teacher also said that Jon has had trouble focusing-- his mind seems to be 'off in space'. Then, Jon passed in a writing assignment that was dark and morose, and contained overly detailed images of death, which worried the teacher significantly.

The teacher took his concerns to the school social worker, who agreed to follow up with Jon & his family. She spoke with his mom who shared that Jon's father had just been diagnosed with cancer. The family has been experiencing a lot of stress due to the uncertainty of Dad's prognosis. This situation has been very difficult for Jon. After speaking with the mom, the SW determined that Jon's problems started about the same time his father was diagnosed. Of note, there is a family history of Bipolar I Disorder, but not in the immediate family.

is Jon developing a psychotic disorder?

Case 2 - Jon

- What do you think is going on?
- Does family hx of Bipolar disorder place him at increased risk of psychotic disorder?
- What treatment would you recommend?

Case 2

Jon is a 17 year-old high school student who lives with his parents and younger brother. He has always been a good student, completes his work at school, and is involved in the chess club 2 afternoons a week.

Jon's chess club teacher, who also happens to be his English teacher, has noticed changes in him recently. He has stopped going to chess club, and his English grades have been dropping, mostly because of incomplete homework. His teacher also said that Jon has had trouble focusing-- his mind seems to be 'off in space'-- he's just not the kid he used to be. Then, Jon passed in a writing assignment that was dark and morose, and contained overly detailed images of death, which worried the teacher significantly.

The teacher took his concerns to the school social worker, who agreed to follow up with Jon & his family. She spoke with his mom who said that Jon's father had just been diagnosed with cancer. The family has been under a lot of stress mainly due to the uncertainty of his prognosis. The situation has been very difficult for Jon, who is close to his father. After speaking with the mom **the social worker determined that Jon's problems started about the same time his father was diagnosed.** There is a family history of Bipolar I Disorder, but not in the immediate family.

Jon's symptoms are most likely related to family stressors.

Case 3

Katie is a 20 y.o. college junior who lives with friends off campus. Since freshman year, she has maintained a 3.4 GPA and has been active in community theater. Lately however, she's been forgetting assignments and missing practices. For the past three years, she has consistently volunteered weekly at the food bank with 2 of her close friends. Recently, she has been finding excuses not to go.

When she was 7, Katie was diagnosed with ADHD—she's taken Ritalin periodically since then with good results. In the past couple of months, Katie has seemed preoccupied, distractible, and more withdrawn. She shared some "dark thoughts" (e.g., fleeting suicidal thoughts and unfounded fears of being watched) with her mother, who is now seeking advice from a therapist. She is aware of "connections" between what she is reading about in history class and her life, for example she learned that during prohibition the US government put toxins in industrial alcohol, and that she worries that because she is underage maybe the alcohol she drinks could be adulterated, although she readily admits that this is highly unlikely. These "coincidences" happen several times a week. In the past few months she had had several episodes of seeing shadows moving in her dorm room in the evening, then turning and realizing there was no one there.

IS KATIE AT RISK FOR PSYCHOSIS?

Case 3: Katie

- Is Katie psychotic?
- What is her risk for psychosis?
- What symptoms are most concerning?
- What interventions would you recommend?

Case 3

Katie is a 20 y.o. college junior who lives with friends off campus. Since freshman year, she has maintained a 3.4 GPA and has been active in community theater. Lately however, she's been forgetting assignments and missing practices. For the past three years, she has consistently volunteered weekly at the food bank with 2 of her close friends. Recently, she has been finding excuses not to go.

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KATIE IS AT HIGH RISK FOR PSYCHOSIS

Prodromal Stage: Michael and Ryan

Michael

- Struggled junior and senior year of high school
- Begins smoking pot senior year
- Starting senior year of high school and worsening freshman year at university:
  - Withdrew from friends
  - Thought other students were “making fun” of him
  - Couldn’t pay attention in class, every little thing a distraction
  - Frequently noticed connections between unrelated events
  - Began to think he had “some sort of special mission”
  - Depressed, suicidal thoughts

Ryan

- Hard adjustment freshman year
- During first semester freshman year:
  - Thought team mates were “saying bad things” about him
  - Thought team mates might be conspiring against him, attributed to “Jealousy”

RECOGNITION AND TREATMENT OF PSYCHOSIS RISK:

DOES THE HARM OUTWEIGH THE GOOD?

Potential Risks/Risk Mitigation

- Stigma
  - Is a “risk syndrome” stigmatizing?
    - Imply disease rather than a potential for disease ?
    - Imply possibility of prevention of disease?
    - Does “help-seeking” impact stigma risk?


There you go. After a few weeks you'll hardly notice them.
BARMY
MENTAL
MAD

Potential Risks/Risk Mitigation

- Stigma
  - Does a “risk syndrome” decrease stigma?
    - Imply disease rather than a potential for disease ?
    - Imply possibility of prevention of disease?
    - Does “help-seeking” impact stigma risk?
- Treatment:
  - Inappropriate antipsychotic use may increase
  - Evidenced based interventions of a defined syndrome—could this impact on inappropriate antipsychotic use?

Evidence Base: Treatment of Psychosis Risk Syndrome

Treatment Implications

- Attenuated psychotic symptoms indicate a vulnerability to mental illness
- Eventual diagnosis varied
  - ~ 35% develop a psychotic disorders
  - ~ 40% develop a non-psychotic mood disorder
  - ~ 25% recover
- Conservative treatment indicated

Cannon TD, et al. *Arch Gen Psychiatry.* 2008;65(1):28-37; Corell CU, et al. *J Child Adolesc Psychopharmacol.* 2005;15(3):418-433.

Cannabinoids in Humans

- Endocannabinoid system regulates:
  - Release of multiple neurotransmitters, including dopamine, glutamate, GABA, and serotonin
  - synaptic plasticity
  - neurodevelopment (*in utero* through adolescence)
- Anandamide (AEA): the bodies main (endogenous) cannabinoid receptor agonist

Cannabinoids in Humans

- Marijuana contains
  - **Delta(9)Tetrahydrocannabinol (THC)**:
    - CB1 agonist, stimulates cannabinoid system
    - Evidence suggests worsens psychosis
  - **Delta (8) Tetrahydrocannabinol (cannabidiol)**:
    - blocks anandamide, down-regulates cannabinoid system
    - May have antipsychotic effects

Cannabis Use and Schizophrenia Risk

- In the US, by age 18:
  - Up to half of adolescence have tried marijuana
  - 15% report daily use for at least a month
- IV THC produces transient positive and negative symptoms in healthy persons
- Persons who experience cannabis-induced psychosis have a 50% risk of schizophrenia
- Maybe a gene-environment interaction?
  - One study finds11-fold increase in schizophrenia risk in cannabis users with a low activity metabolic enzyme (COMT) for dopamine

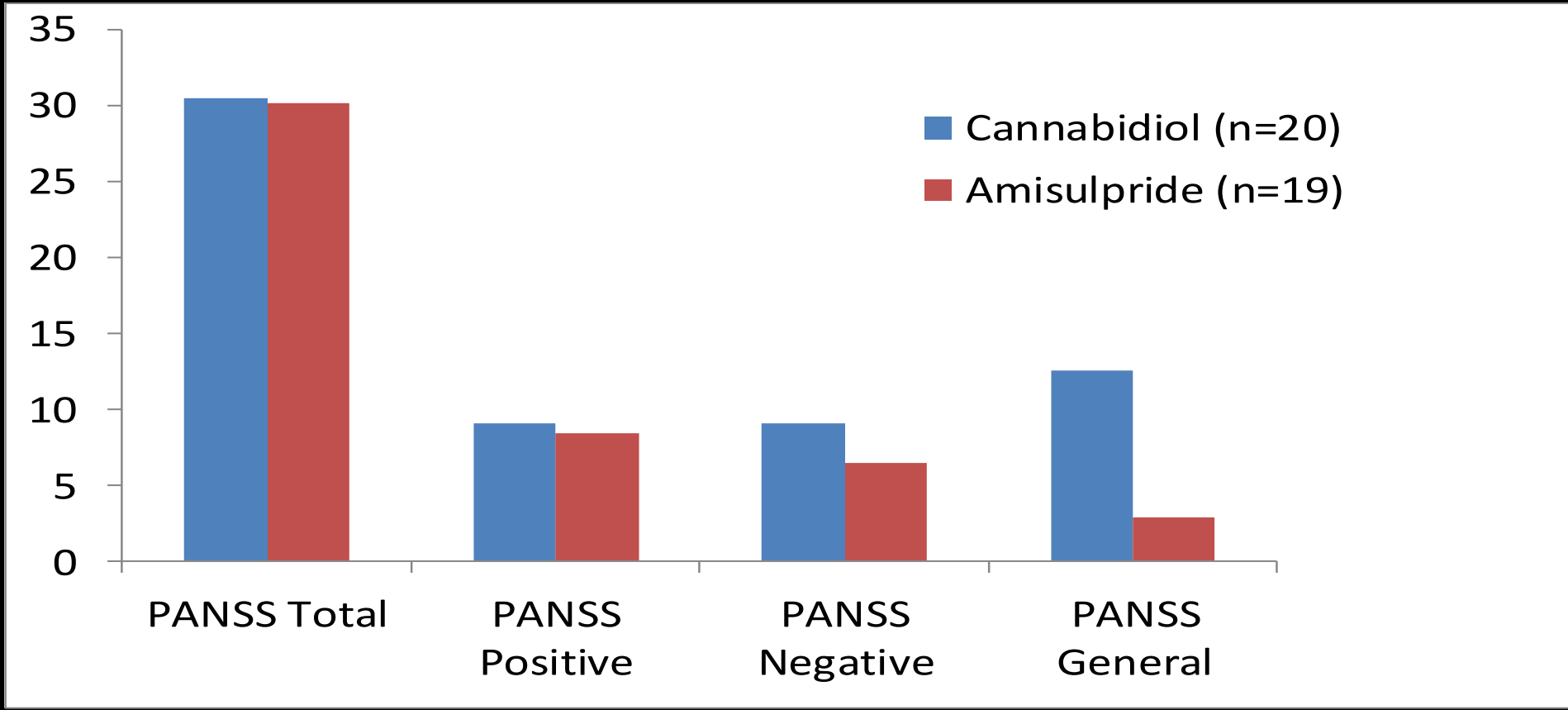
Malone et al. British Journal of Psychopharmacology 2010;160:511-520
Fernandez-Espejo et al. Psychopharmacology 2009;206:531-549
Nierni-Pynttari J Clin Psychiatry 2013

Cannabis Use and Schizophrenia Risk

- Unclear if increase in cannabis use in adolescents is associated with an increase incidence of schizophrenia
- In a small study 4/6 schizophrenia patients who reported cannabis improved symptoms actually experienced improvement with administration of dronabinol (synthetic THC)
- First episode patients who use cannabis have less severe negative symptoms and better functional outcomes

Malone et al. British Journal of Psychopharmacology 2010;160:511-520
Fernandez-Espejo et al. Psychopharmacology 2009;206:531-549

Phase II Clinical Trial: Cannabidiol vs Amisulpiride



Leweke 2012 Translational Psychiatry doi:10.1038/tp.2012.15

Summary

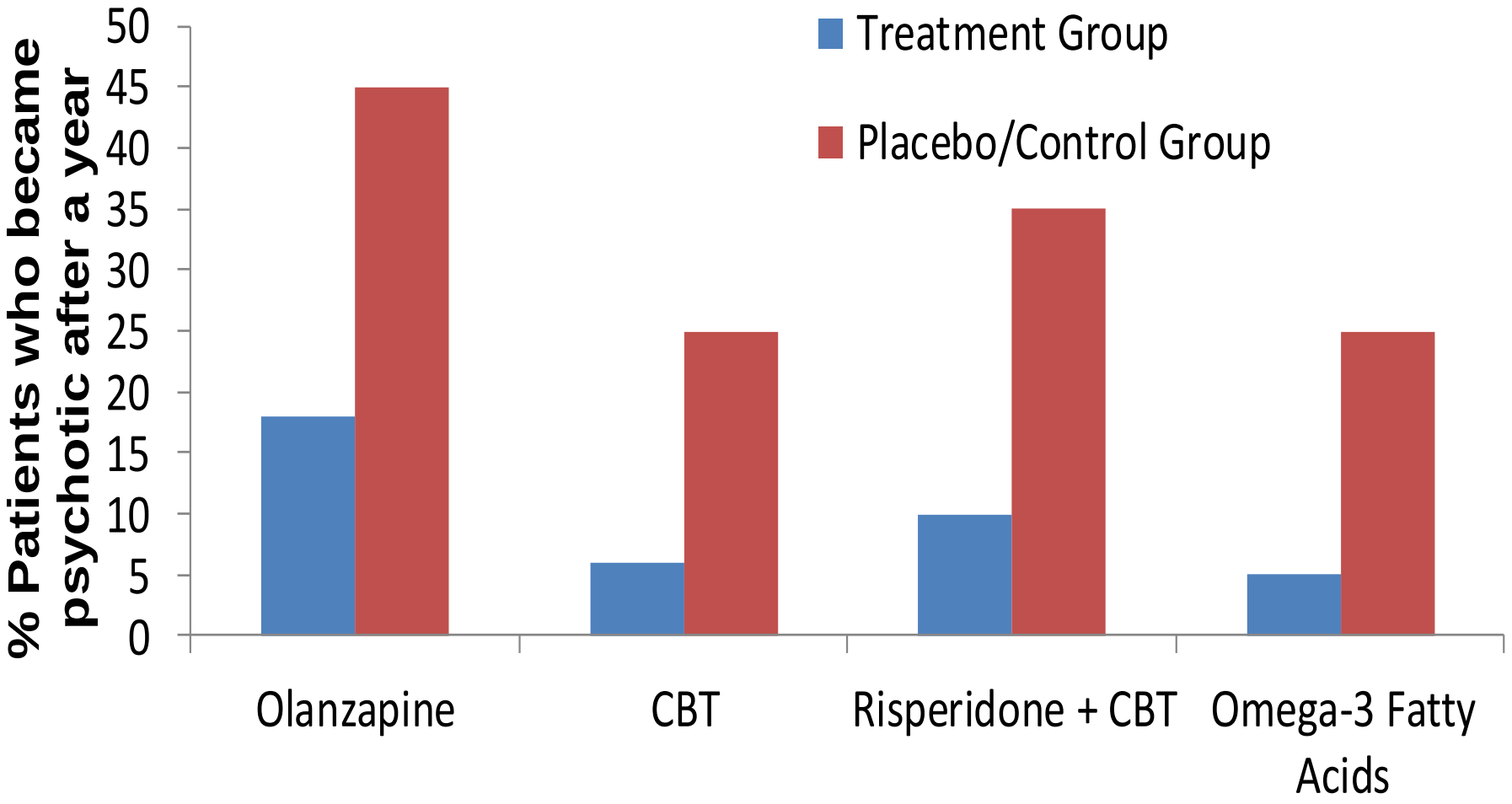
- Marijuana contains THC and cannabidiol with opposite effects on the CB1 receptor activity
  - Cannabidiol promising as antipsychotic
- Cannabis in an environmental risk factor for the development of schizophrenia
  - Very heavy marijuana use in adolescence increases risk of schizophrenia by 6-fold
  - The “type” of schizophrenia related to cannabis may have less severe negative symptoms and better functional outcome

“Prodromal” Stage Interventions Studies with Randomized Clinical Trials

- Antipsychotic medication
- Cognitive behavioral therapy
- Omega-3 fatty acids

McGlashan et a. 2006 AJP 163:790-799; McGorry et al. Arch Gen Psychiatry 59:921-928; Aminger et al. 2010 Arch Gen Psychiatry 6:146-154;Morrison et al. 2007 Schizophr Bull 33:682-687

Similar Benefits



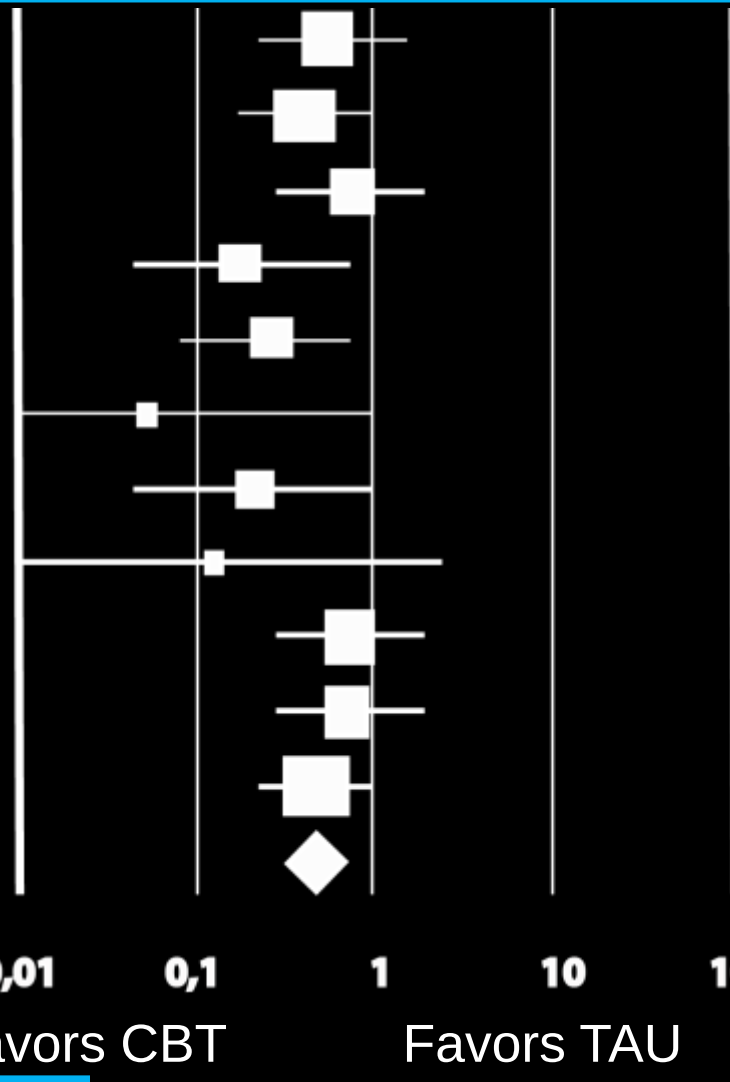
Meta-analysis Prevention Interventions

Comparison	Time point (months of treatment)	No (%) of trials in analysis	No (%) of participants in analysis	Risk ratio (95% CI), random effects	Heterogeneity (I^2 (%), χ^2 (P))	Quality of evidence (GRADE)
CBT *v* supportive counseling[23-25, 28, 29]	0-6	4 (80)	591 (88)	0.62 (0.29 to 1.31)	17, 3.6 (P=0.31)	Low*‡
	6-12	5 (100)	645 (71)	0.54 (0.34 to 0.86)	0, 2.51 (P=0.64) =0.P2)	Moderate*
	12+	4 (80)	570 (85)	0.63 (0.40 to 0.99)	0, 2.50(P=0.48)	Low*‡
CBT and risperidone *v* supportive counselling[24, 30]	0-6	2 (100)	130 (100)	0.35 (0.13 to 0.95)	0, 0.59 (P=0.44)	Very low*‡§
	6-12	2 (100)	130 (100)	0.63 (0.33 to 1.21)	0, 0.25 (P=0.61)	Very low*‡§
	12+	1 (50)	41 (32)	0.59 (0.34 to 1.04)	NA	Very low*‡§
Integrated psychotherapy *v* supportive counselling[37]	6-12	1 (100)	125 (100)	0.19 (0.04 to 0.81)	NA	Very low*‡¶
	12+	1 (100)	125 (100)	0.32 (0.11 to 0.92)	NA	Very low*‡¶
Integrated psychotherapy *v* standard care[35]	6-12	1 (100)	67 (85)	0.24 (0.07 to 0.81)	NA	Low*‡
	12+	1 (100)	65 (82)	0.52 (0.26 to 1.02)	NA	Low*‡
CBT and risperidone *v* CBT and placebo[24]	0-6	1 (100)	87 (100)	1.02 (0.15 to 6.94)	NA	Very low*‡§
	6-12	1 (100)	87 (100)	1.02 (0.39 to 2.67)	NA	Very low*‡§
Olanzapine *v* placebo[27]	6-12	1 (100)	60 (100)	0.43 (0.17 to 1.08)	NA	Very low*‡§
Omega 3 fatty acids *v* placebo[26]	0-6	1 (100)	76 (94)	0.13 (0.02 to 0.95)	NA	Low*§
	6-12	1 (100)	81 (100)	0.18 (0.04 to 0.75)	NA	Low*§

*Reason for downgrading: imprecision. NA = not applicable; NBI = needs-based intervention. Stafford MR, et al. *BMJ.* 2013;346:f185.

Meta-analysis CBT vs TAU

Study	Risk Ratio	*P* Value
McGorry, 2002	0,542	0,169
McGlashan, 2006	0,425	0,071
McGorry, 2013a	0,760	0,583
Amminger, 2008	0,177	0,019
Nordentoft, 2006	0,264	0,031
Bechdolf, 2012	0,054	0,043
Morrison, 2004	0,207	0,041
Addington, 2011	0,128	0,166
McGorry, 2013b	0,742	0,552
Morrison, 2012	0,700	0,456
Van der Gaag 2012	0,473	0,046
	0,463	0,000



CBT = cognitive behavioral therapy; TAU = treatment as usual.

van der Gaag M, et al. *Schizophr Res*. 2013;149(1-3):56-62.

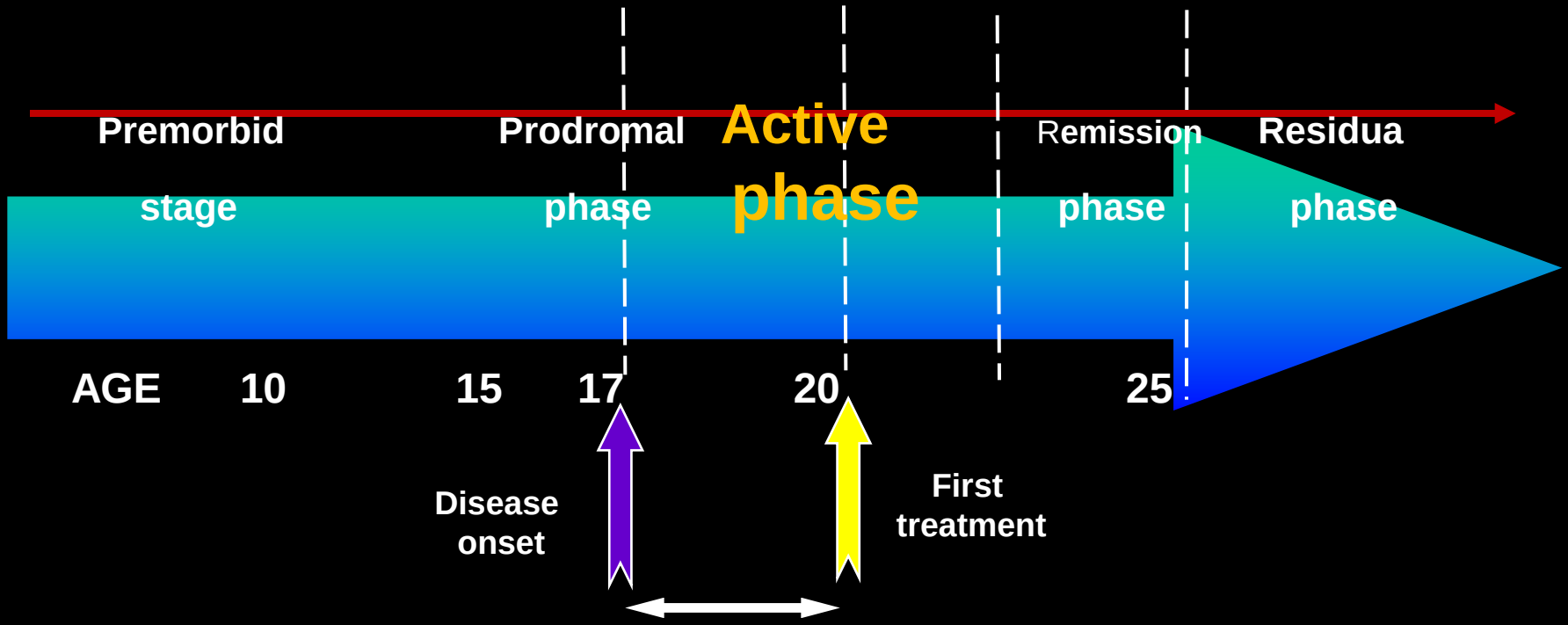
Different Risks

- Antipsychotics
  - Weight gain/metabolic effects
  - Sedation
  - Unknown risks for 65% of patients who were not really prodromal for psychosis
- CBT
  - Time intensive
- Omega 3 fatty acids
  - Fishy burp

Interventions in the “at risk” patient: A stepped-care approach

- Mild symptoms/impairments
  - Identify and address vulnerability factors
    - Cannabis use
    - Co-morbid disorders (e.g. major depression)
    - Identify and address functional impairments
    - Discuss option of fish oil supplementation
  - Provide psychoeducation: range of outcome, warning signs of psychosis
  - Monitor symptoms over time
- Moderate/severe
  - Individual and Family Psychotherapy, address stress, stress resiliency

Natural Course of Schizophrenia



Hales RE, et al, eds. *Textbook of Psychiatry.* 5th ed. Arlington, VA: American Psychiatric Publishing; 2008.

The First Episode of Psychosis

- Defined by psychotic intensity of positive symptoms
  - Delusions
  - Hallucinations

Hales RE, et al, eds. *Textbook of Psychiatry.* 5th ed. Arlington, VA: American Psychiatric Publishing; 2008; Perkins DO, et al. *Am J Psychiatry*. 2005;162(10):1785-1804.

Emergence of Psychosis: Michael and Ryan

Michael

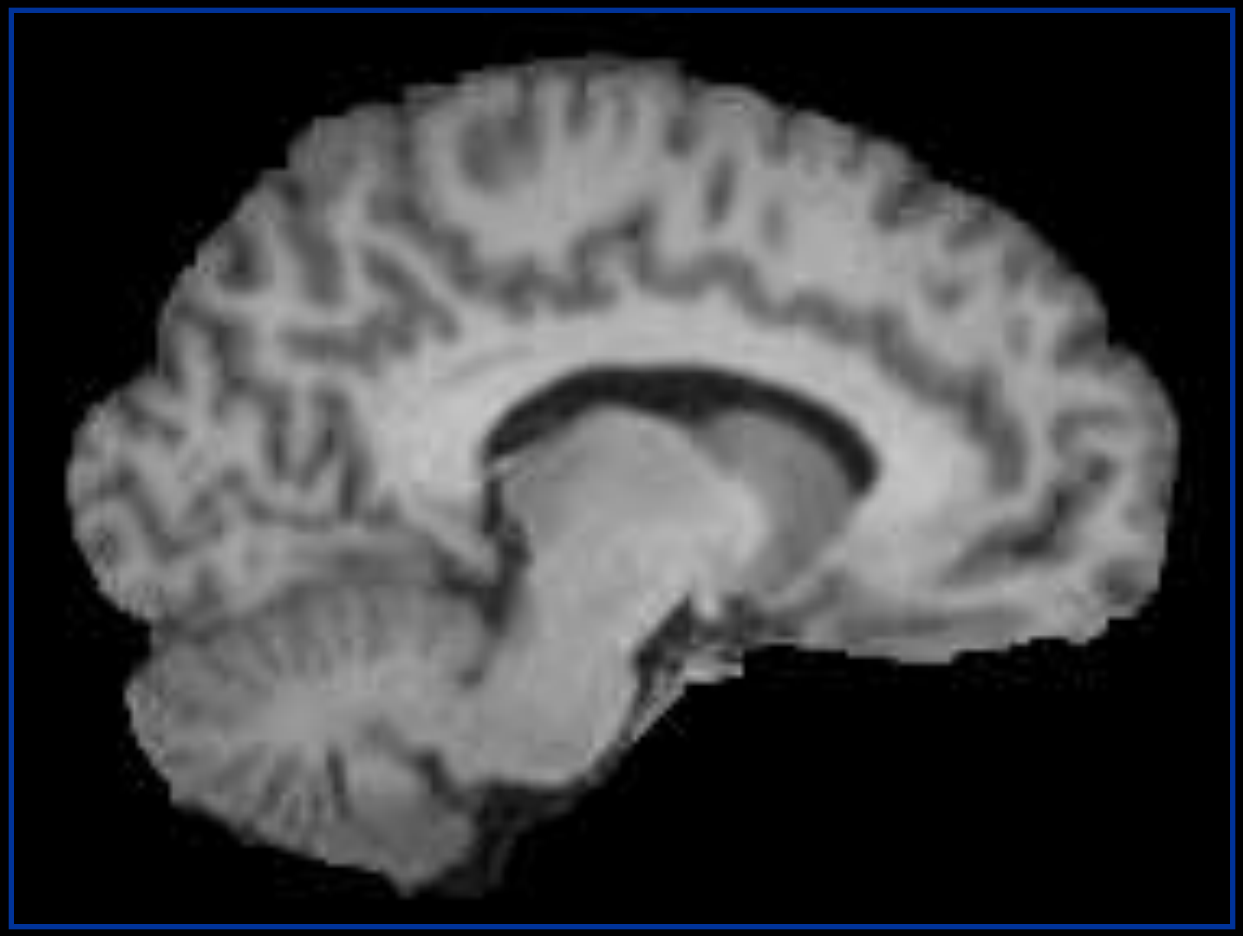
- Delusion that he could cure cancer
- Heard messages from God and spirits guiding him on his mission
- Professors were “praising” him and “encouraging” his “work” to cure cancer
- Very anxious, still with suicidal thoughts
- Roommate concerned, took him to student health, started on antidepressant
- Went home for Thanksgiving Break, isolating self from family
- After went back to school went to library, took off all his clothes, was video taped by other student and put on Facebook
- Campus police took to ER, diagnosed as psychotic and admitted to hospital, began antipsychotic

Ryan

- Second semester freshman year concerns about team mates worsened, isolated from them
- Thought were poisoning his food, stopped eating on campus
- Heard whispering outside room, opened door no one there, thought they were playing “jokes”
- At home for break avoided talking about school, continued with delusions and hallucinations
- Symptoms waxed and waned over 4 years; he kept to himself
- School performance marginal but passed classes
- By junior year delusions and hallucinations had religious themes, “spiritual warfare”
- Became highly involved in fundamentalist religious group, dropped off team to devote time to religion
- Graduated, returned home, seclusive
- Parents became more confrontational, took to a therapist, who recognized psychosis but diagnosed as depression
- Became delusional about cat, tried to strangle cat, ended up in altercation with father, police called, taken to ER, hospitalized, where psychosis diagnosed

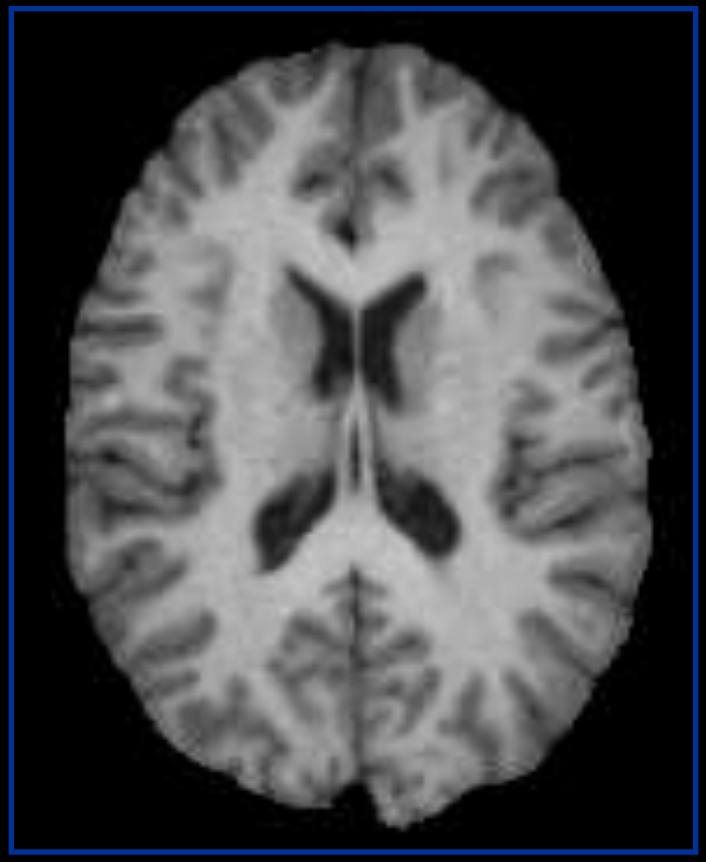
First Episode Schizophrenia: Change in Brain Volume Over 6 Months

Midsagittal

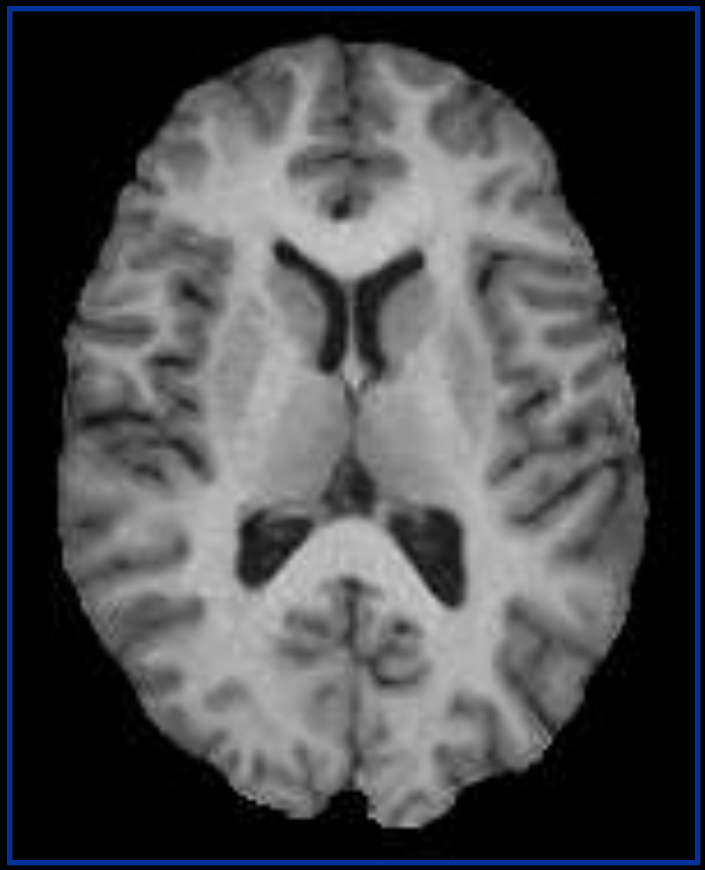


Joshi S, et al. *Neuroimage*. 2004;23(Suppl 1):S151-S160.

FE Schizophrenia: Change in Brain Volume Over 6 Months



axial slice 1



axial slice 2

Joshi S, et al. *Neuroimage*. 2004;23(Suppl 1):S151-S160.

Time from Onset of Psychosis to Onset of Treatment

- Treatment delays are common
  - On average a year or more elapses from onset of psychosis to onset of treatment
  - Why the delay?
    - Early stage of psychosis clinically different
      - Patient's look more "more normal"
      - Less severe negative symptoms
      - Substance use, school failure, behavioral problems may obscure underlying psychosis
    - Symptoms recognized but misinterpreted
    - Stigma

Hales RE, et al, eds. *Textbook of Psychiatry.* 5th ed. Arlington, VA: American Psychiatric Publishing; 2008;
Franz L. *Early Interv Psychiatry*. 2010;4(1):47-56.

Duration of Untreated Psychosis and Outcomes

- Duration of untreated psychosis (DUP)
  - May impact:
    - Treatment response
    - Risk of relapse
    - Long-term outcomes (clinical and functional)
    - Symptom severity at first treatment
  - May represent a modifiable prognostic factor

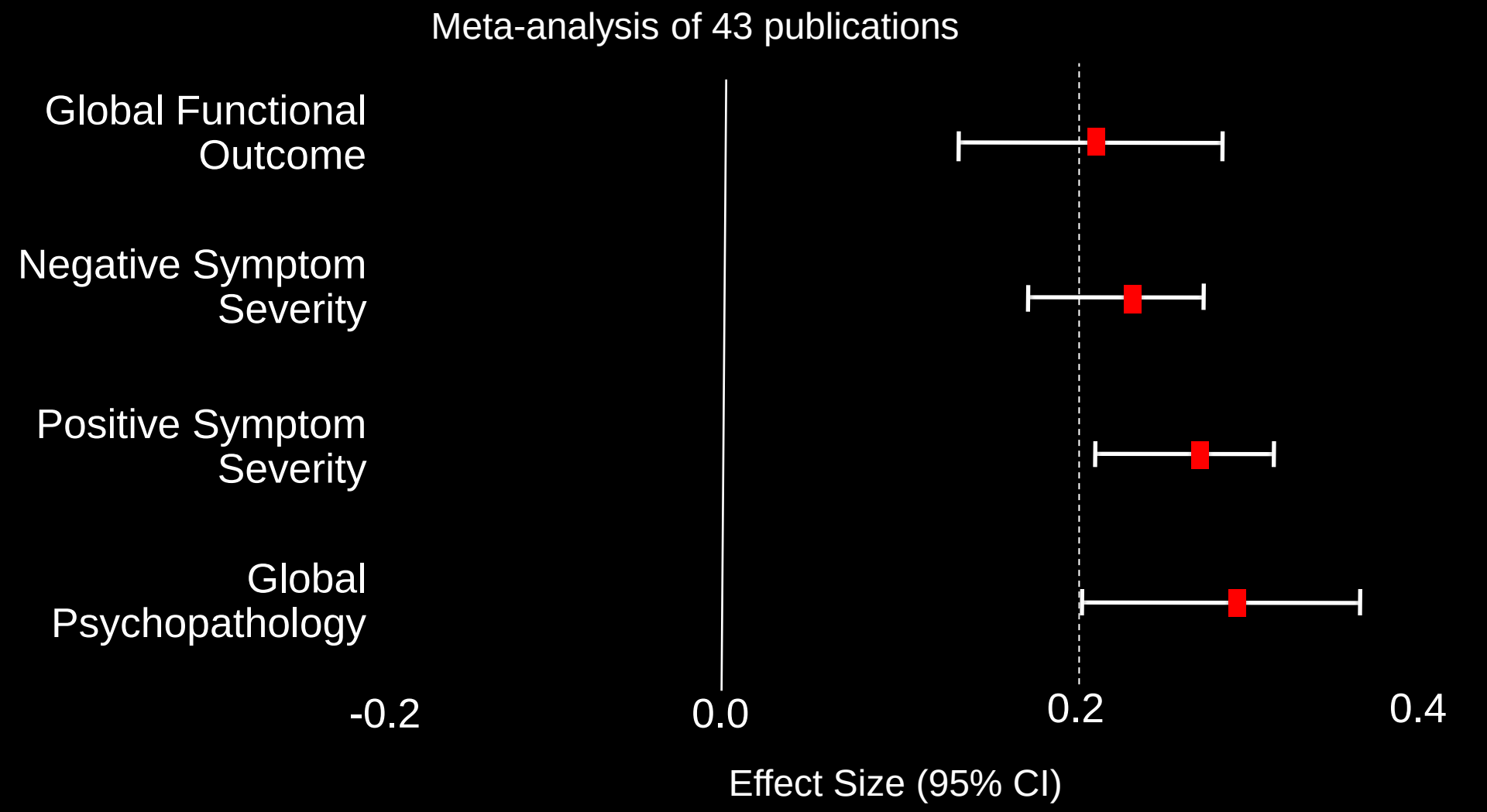
Perkins DO, et al. *Am J Psychiatry.* 2005;162(10):1785-1804.

The Longer the Treatment Delay, the Worse the Prognosis

- Greater the chance of aggression and violence prior to first treatment contact
- Social and role function derailment
- Longer time to recovery
- Less likely to recover from first episode
- Chronic symptoms more severe and worse social and role function
- Greater risk of brain tissue loss

Hales RE, et al, eds. *Textbook of Psychiatry.* 5th ed. Arlington, VA: American Psychiatric Publishing; 2008;
Franz L. *Early Interv Psychiatry*. 2010;4(1):47-56.

The Relationship Between Duration and Severity of Untreated Psychosis and Treatment Response



Perkins DO, et al. *Am J Psychiatry.* 2005;162(10):1785-1804.

Public Education Programs Are Effective in Reducing DUP

- Clinician's need to recognize the early stages of schizophrenia
  - In Norway an intense education campaign about the signs and symptoms of psychosis reduced DUP to less than a month. Patients presented with less severe symptoms and recovery rates improved.

Treatment and Intervention in Psychosis. www.tips-info.com. Accessed 9/30/13; Miller T, et al, eds. *Early Intervention in Psychotic Disorders*. The Netherlands: Kluwer Academic Publishers; 2001.

Duration of Untreated Psychosis and Treatment Response: Michael and Ryan

Michael

- DUP: 2 months
- Remission of psychosis after 4 weeks of treatment with an antipsychotic
- Residual symptoms included
  - Subjective sense that emotions were dull,
  - Mentally “not as sharp”
  - Easily stressed by small events
  - Depression, discouragement, thoughts life not worth living

Ryan

- DUP: 45 months
- Marginal response to antipsychotics
  - Hallucinations and delusions improved
  - Residual symptoms included:
    - When “out and about” thinks other talking about him
    - Spirits talk to him infrequently, when stressed
    - Significant negative symptoms
    - Significant cognitive impairments

Variable Outcomes in Schizophrenia

- Most patients experience positive symptom remission after a first episode
- Without maintenance antipsychotic medication, most relapse
- Relapse is associated with symptomatic, functional, and brain progression

McGorry P, et al. *JAMA Psychiatry*. 2013; Epub ahead of print; Gitlin M, et al. *Am J Psychiatry*. 2001;158(11):1835-1842; Wunderink L, et al. *J Clin Psychiatry*. 2007;68(5):654-661.

Early Psychosis Treatment Principles

- Low dose antipsychotics (minimize secondary negative symptoms)
- Address stress reactivity:
  - Psychotherapy
  - Complementary treatments (exercise, mindfulness, yoga, L-theanine, NAC, anti-inflammatory medications)
- Relapse management
- Relapse prevention
- Include family, address family concerns

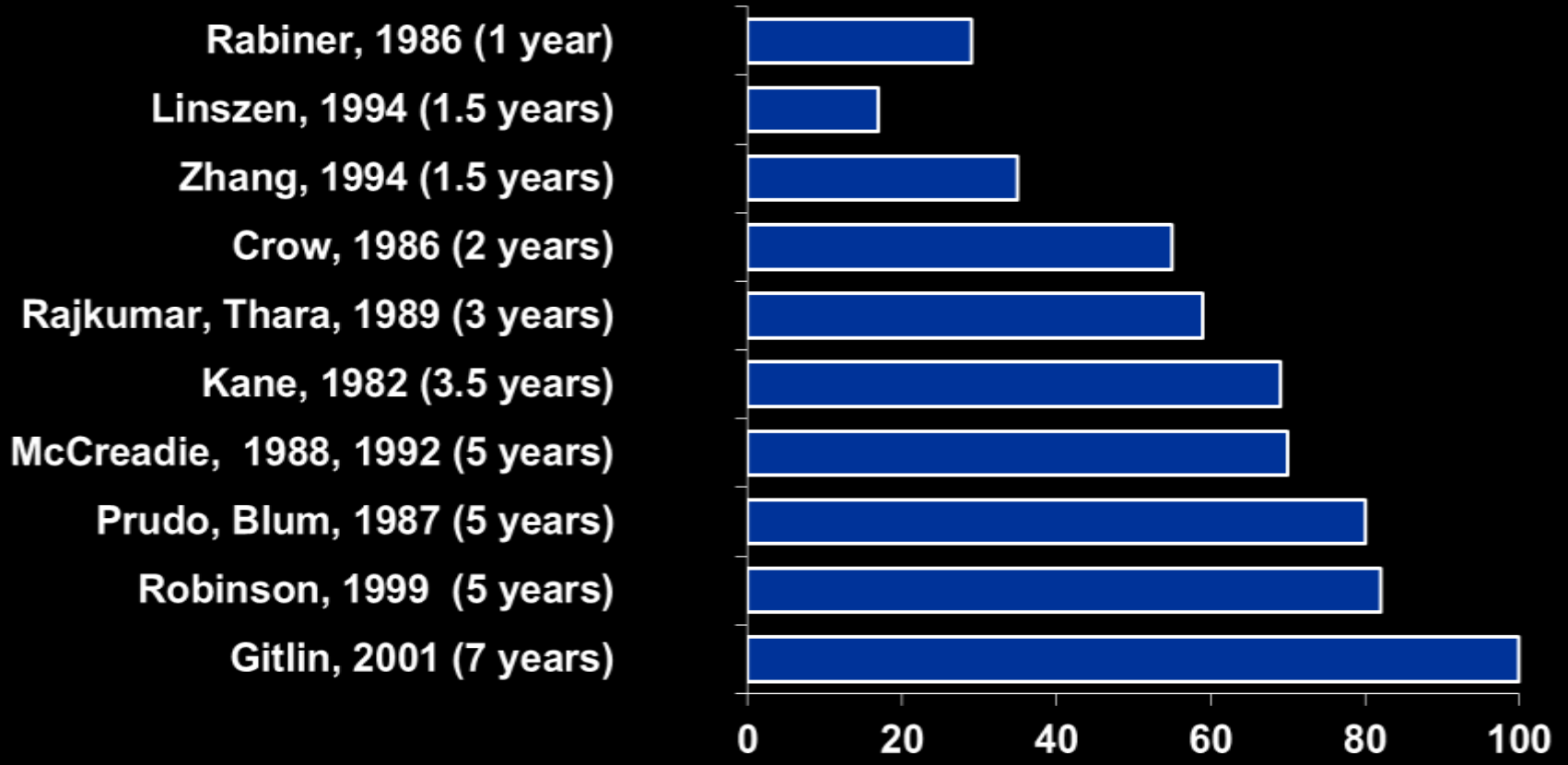
Lehman AF, et al. *Am J Psychiatry*. 2004;161(2 Suppl):1-56; Buchanan RW, et al. *Schizophr Bull*. 2010;36(1);71-93; National Institute of Mental Health (NIMH). www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml. Accessed 9/30/13; Ritsner MS, et al. *J Clin Psychiatry*. 2011;72(1):34-42; Bangalore NG, Varambally S. *Int J Yoga*. 2012;5(2):85-91.

Relapse: Systematic Review and Meta-Analysis

- Clinical definitions of relapse vary widely
  - Worsening of symptoms or rehospitalization within year after discharge
- Among first episode patients:
  - ~ 96% will attain remission within 12 months of treatment
  - ~ 80% will relapse within 5 years
- Relapse associated with:
  - ↑ risk of chronicity psychotic symptoms
  - ↑ cost of treatment (4× that of stable patient)
  - Possible ↓ in medication efficacy
- Incidence ~ 5× greater with nonadherence

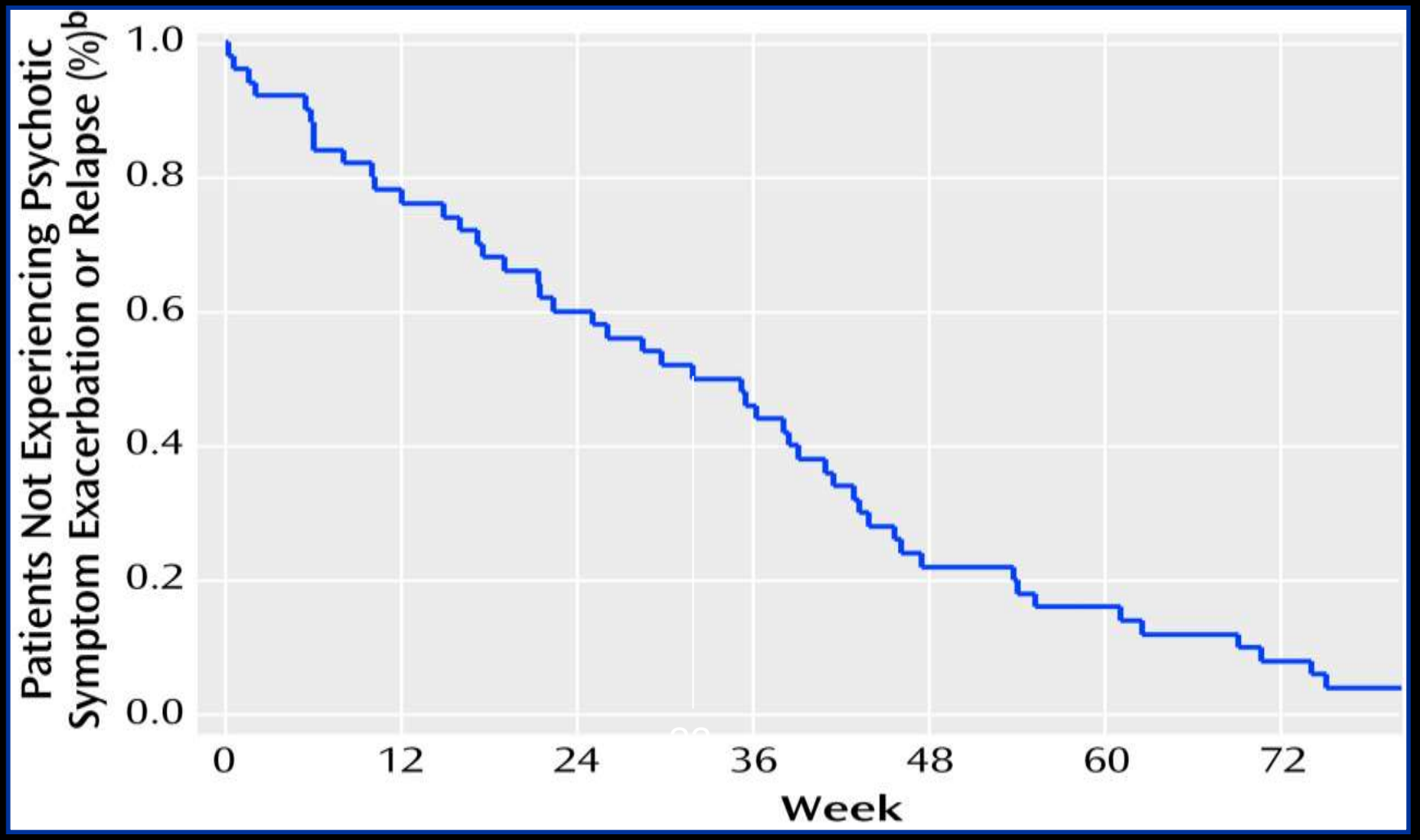
Álvarez-Jiménez M, et al. *Schizo Bull.* 2011;37(3):619-630.

Relapse After Treatment of a First Episode: Naturalistic Studies



Rabiner CJ, et al. *Am J Psychiatry*.1986;143(9):1155-1158; Linszen DH, et al. *Psychiatry Res*. 1994;54(3):273-281; Zhang M, et al. *Br J Psychiatry Suppl*. 1994;24:96-102; Crow TJ, et al. *Br J Psychiatry*. 1986;148:120-127; Rajkumar S, Thara R. *Schizophr Res*. 1989;2(4-5):403-409; Kane JM, et al. *Arch Gen Psychiatry*. 1982;39(1):70-73; McCreadie RG. *Soc Psychiatry Psychiatr Epidemiol*. 1992;27(1):40-45; McCreadie RG, Phillips K. *Br J Psychiatry*. 1988;152:477-481; Prudo R, Blum HM. *Br J Psychiatry*. 1987;150:345-354; Robinson D, et al. *Arch Gen Psychiatry*. 1999;56(3):241-247; Gitlin M, et al. *Am J Psychiatry.* 2001;158(11):1835-1842.

Time to Relapse in 50 Stable Patients With Recent-Onset Schizophrenia Who Voluntarily Entered an Antipsychotic Withdrawal Protocol



Gitlin M, et al. *Am J Psychiatry*. 2001;158(11):1835-1842.

Predictors of Relapse Following Hospital Discharge

- Study to examine relapse in the year after hospital discharge (N = 200)
- At 1 year 57% had experience ≥ 1 relapse
- Relapse more common among patients who were:
  - Non-responsive to treatment at discharge
  - Not in remission at discharge
  - Not receiving atypical antipsychotics
- Predictors of relapse: lack of insight, ↑ Rx side effects, poor attitude about treatment, ↑ HAM-D score, poor discharge planning

Schennach R, et al. *Psychiatric Serv.* 2012;63(1):87-90.

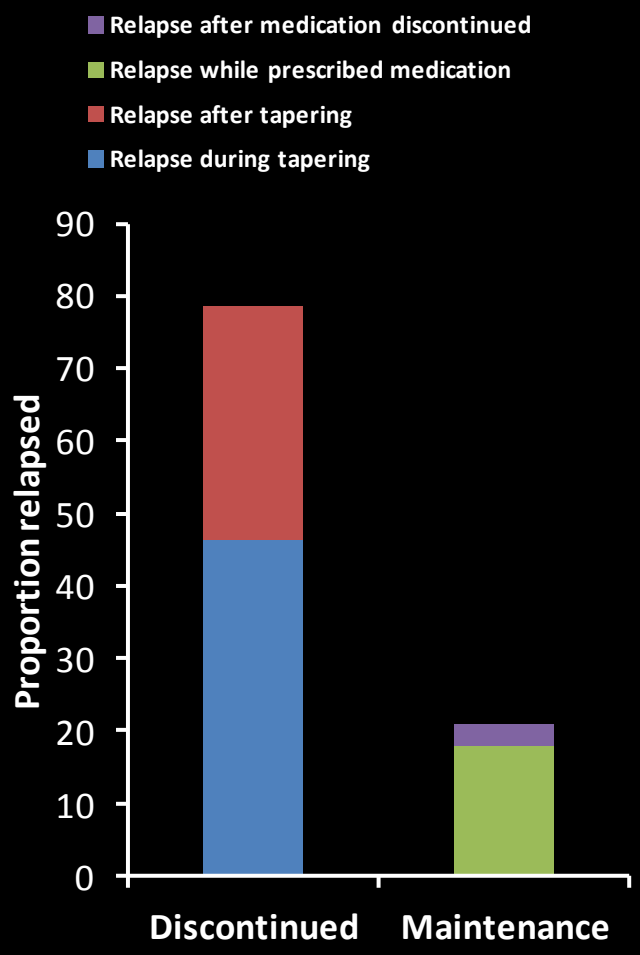
Importance of Relapse Prevention

- Each relapse associated with (short-term)
  - Increased distress and dysfunction
  - Vocational and social disruption
  - Increased risk of suicide and violence
  - Increased costs of care
- With each relapse (**long-term**)
  - Subsequent recovery is less complete
  - Remission takes longer to achieve
  - Illness becomes more resistant to treatment
  - Regaining prior function level more difficult

Glick ID, et al. www.acnp.org/g4/GN401000084/CH083.html. Accessed 9/30/13.

Guided Discontinuation vs Maintenance Treatment in Remitted First-Episode Psychosis: Relapse Rates and Functional Outcome

- DESIGN
  - 131 remitted first episode patients age 18–45 with < 3 months of antipsychotic (schizophrenia or related psychotic disorders)
  - Randomized to maintenance treatment (n = 63) or guided discontinuation (n = 68)
  - Followed for 18 months
- PRIMARY OBJECTIVES
  - Relapse: clinical deterioration for at least 1 week having consequences (med change, admission, more frequent visits) and PANSS positive item > 5



Wundering L, et al. *J Clin Psychiatry*. 2007;68(5):654-661.

Relapse: Michael and Ryan

Michael

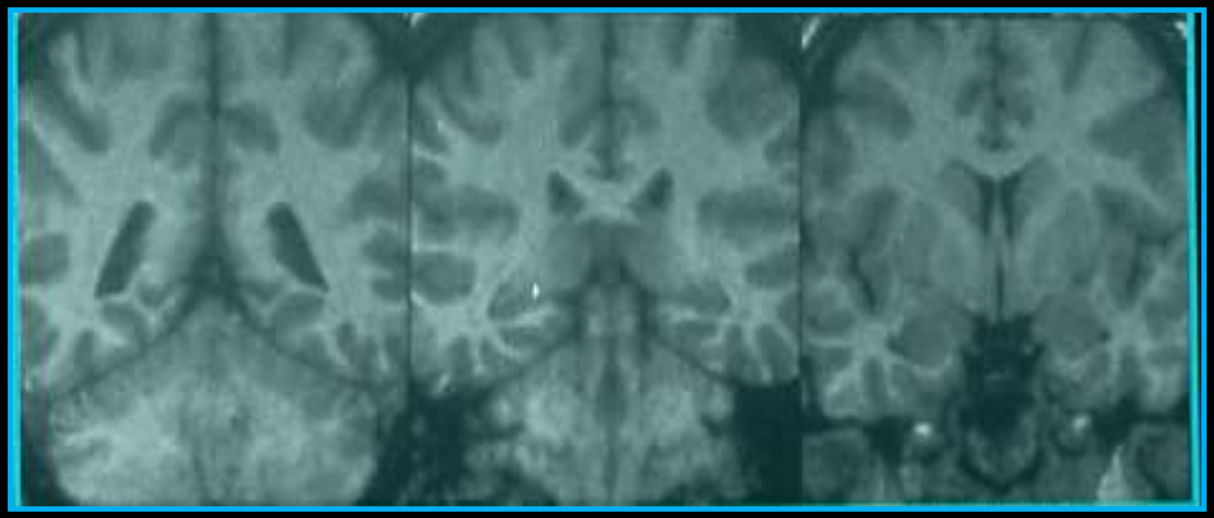
- Good insight into illness
- Returned to university
  - Intermittently adherent
  - 2 brief relapses
  - On long-acting injectable antipsychotic
- Residual symptoms addressed
  - Negative symptoms and stress reactivity responded to L-Theanine
  - Cognition gradually improved

Ryan

- Poor insight
- Refused any antipsychotic
- Re-hospitalized after relapse
- Re-started on clozapine
- Began clozapine
  - Hallucinations and delusions much less severe
  - Residual symptoms included:
    - When “out and about” thinks other talking about him
    - Spirits talk to him infrequently, when stressed
    - Significant negative symptoms
    - Significant cognitive impairments

Progressive Loss of Gray and White Matter Occurs in Most Patients with Recurrent Episodes

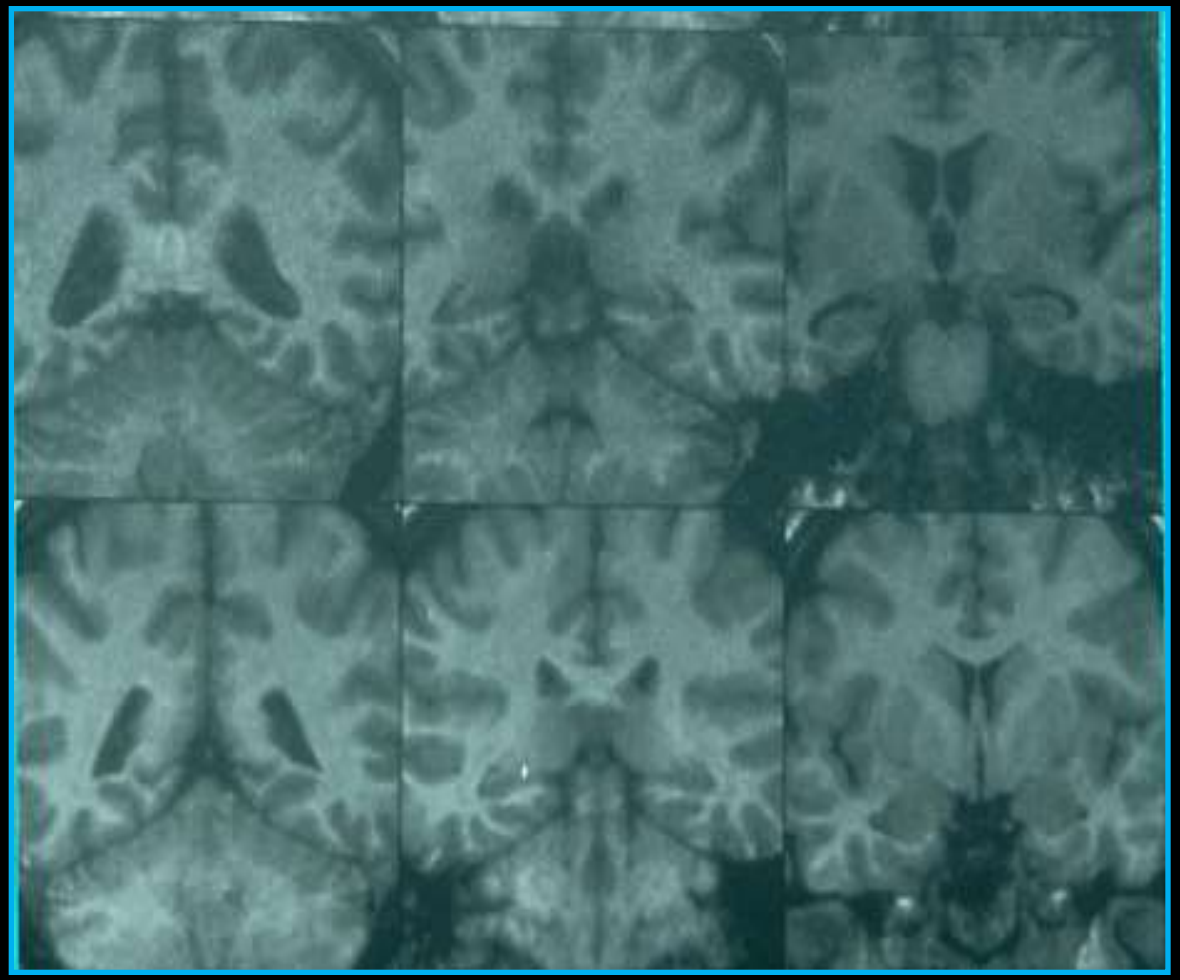
First Treatment



Progressive Loss of Gray and White Matter Occurs in Most Patients with Recurrent Episodes (cont'd)

~ 1 Year Later

First Treatment

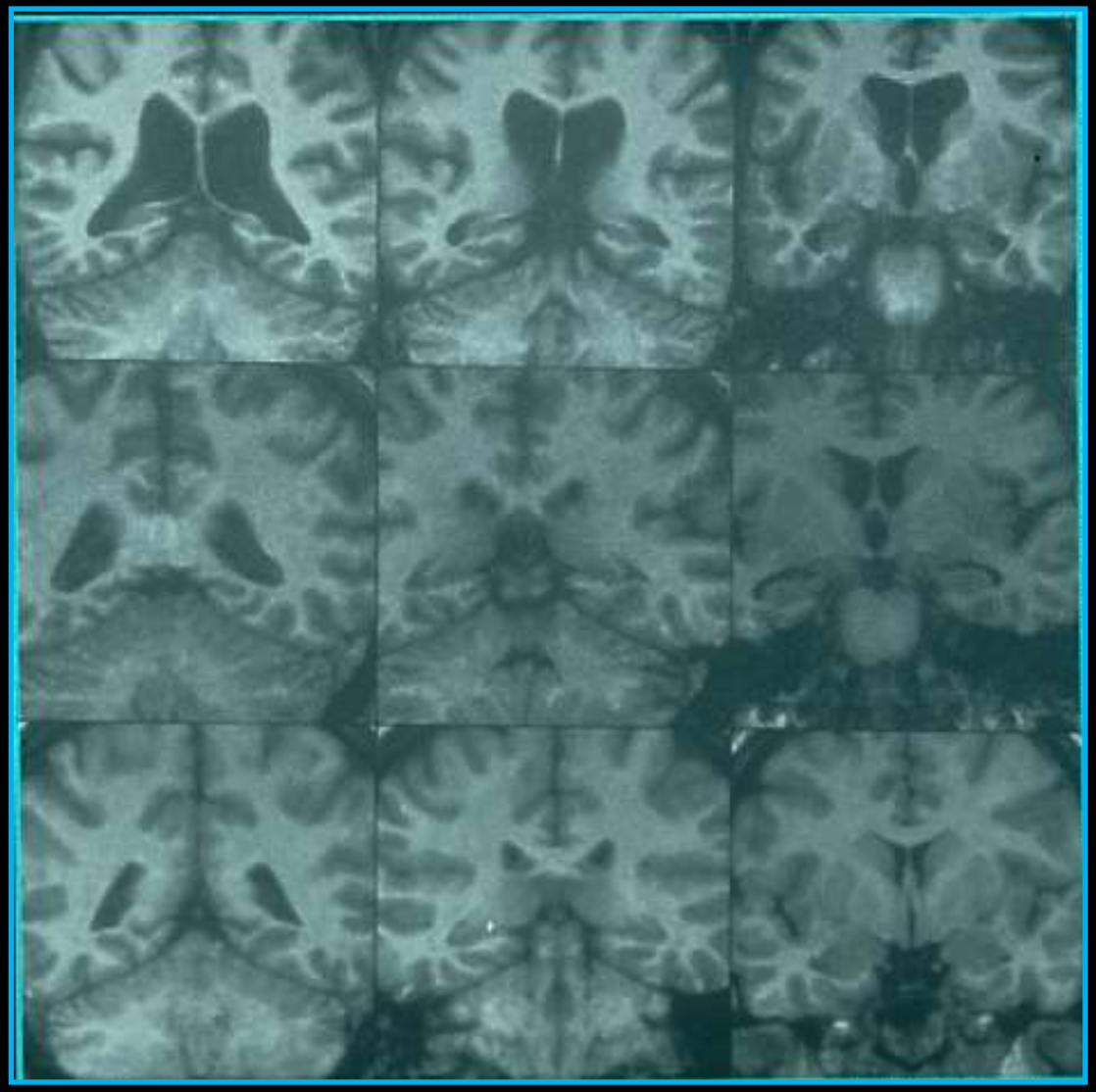


Progressive Loss of Gray and White Matter Occurs in Most Patients with Recurrent Episodes (cont'd)

~ 3 Years Later

~ 1 Year Later

First Treatment

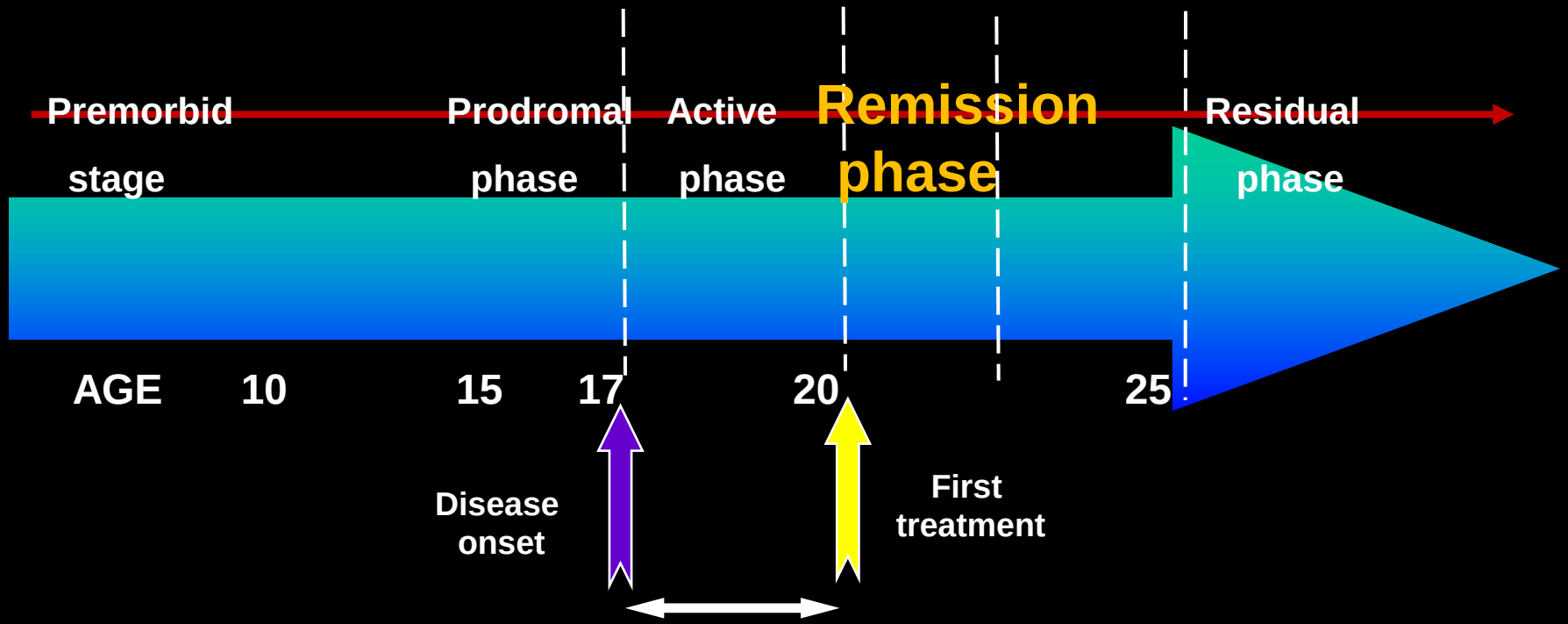


Why Does the Brain Shrink?

- We don’t find:
  - Loss of large neurons
- What we find are:
  - Regional loss of connections between neurons
  - Damage to insulation (myelin) of connections between neurons
  - Regional loss of small neurons (interneurons) and supporting cells (glia)
- Hypothesize these are potentially reversible
  - Connections between neurons remodeled all the time
  - Myelin regrowth
  - New small neurons and supporting cells are regenerated

Whitford TJ. *Schizophr Bull*. 2012;38(3):486-494.

Natural Course of Schizophrenia



Hales RE, et al, eds. *Textbook of Psychiatry.* 5th ed. Arlington, VA: American Psychiatric Publishing; 2008.

Recovery Factors

- Biology
- Timing
  - Intervene as early as possible
  - Manage then prevent relapses
- Treatment
  - Address residual symptoms
  - Engage families in recovery process

Perkins DO, et al. *Am J Psychiatry*. 2005;162(10):1785-1804; Lehman AF, et al. *Am J Psychiatry*. 2004;161(2 Suppl):1-56.

Factors Associated with Outcomes: Recovery/Residual

- Environment
  - Rural better than urban
  - Family and friends make a big difference

Jablensky A, et al. *Psychol Med Monogr Suppl*. 1992;20:1-97; Kreyenbuhl J, et al. *Schizophr Bull*. 2010;36(1):94-103; Eack SM. *Soc Work*. 2012;57(3):235-246.

Factors Associated with Outcomes: Recovery/Residual

- Quality of treatment
  - Remediation interventions
    - Social consequences of psychosis
      - Stigma
      - Family relationships
      - Friendships
    - Psychological consequence psychosis
      - Self-stigma
      - Demoralization
    - Biological consequences of psychosis/treatment
      - Higher dose antipsychotic may impair functional recovery
      - Prevent relapse
      - Control psychosis
      - Address residual symptoms

Jablensky A, et al. *Psychol Med Monogr Suppl*. 1992;20:1-97; Kreyenbuhl J, et al. *Schizophr Bull*. 2010;36(1):94-103; Eack SM. *Soc Work*. 2012;57(3):235-246.

Recovery/Residual Stage: Michael and Ryan

Michael

- Good insight into illness
  - Fully adherent to treatment
  - Well-developed illness management strategy
- Complete recovery
  - No symptoms
  - Full functional recovery
  - Lives independently

Ryan

- Partial insight
  - Family helps with adherence
- Partial recovery
  - No psychosis
  - Residual negative and cognitive symptoms
  - Attends community college part time
  - Lives with parents, active productive family member

Staged Intervention: Key Principles

- Attenuated Psychosis Syndrome
  - Accurate identification of syndrome
  - Evidence base supports psychotherapeutic treatment
  - Antipsychotics NOT indicated
- Early Active Phase: Psychosis
  - Intervene early (minimize duration of untreated psychosis)
  - Adherence and relapse management key
- Recovery/Residual
  - Engage patient in recovery process
  - Patient needs to develop good illness management strategies
  - Identify and address residual symptoms
  - Low-dose antipsychotic minimizes iatrogenic symptoms

Tsuang MT, et al. *Schizophr Res*. 2013; Epub ahead of print; Perkins DO, et al. *Am J Psychiatry*. 2005;162(10):1785-1804; Lehman AF, et al. *Am J Psychiatry*. 2004;161(2 Suppl):1-56.