Safety and Tolerability of Atypical Antipsychotics

	Antichol-inergic	Elevated prolactin	EPS	Ortho-stasis	QTc Increase	Sedation	Weight Gain
Clozapine	++++	0/+	0/+	+++	+	++++	++++
Risperidone	+	++++	++	++	+	+	+++
Olanzapine	++	++	+	++	+	+++	++++
Quetiapine	+	0/+	0/+	++	+	++	++
Ziprasidone	+	+	+	+	++	+	0/+
Aripiprazole	0/+	0/+	+	+	0	+	0/+

Adapted from: Pappadopulos EA, Jensen PS, Schur SB, et al (2002). *Schizophr Bull* 28:111-121.

TRAAY: Pocket Reference Guide for Clinicians in Child and Adolescent Psychiatry (2004). NYS-OMH & CACMH

AE Monitoring During Treatment With Antipsychotic Agents

- Vital signs, weight & height
- Thorough review of systems
- Targeted physical exam, including assessing
  - EPS
  - Cardiac function
  - Prolactin-associated phenomena (gynecomastia, galactorrhea, amenorrhea)
- Ongoing monitoring of liver function and glucose metabolism &, if warranted, lipids

Marder SR, Essock SM, Miller AL, et al (2004). *Am J Psychiatry* 161(8): 1334-1349.

AP SIDE-EFFECTS CHECKLIST

Patient _____

Rater _____ Date _____

INSTRUCTIONS

Rate the severity of the following side effects from 0 (not present) to 3 (severe). Side effects marked with a † should be scored using only 0 (not present) or 1 (present). Refer to the pocket guide for BMI scores and age percentiles.

ANCHORS

0 = None *2 = Moderate* *N/A = Not Assessed*
1 = Mild *3 = Severe*

Life-Threatening
NMS † _____
Decreased ANC _____
Agranulocytosis † _____
Marked increase in LFTs _____

EPS
Akathisia _____
Akinesia _____
Tremor _____
Muscle Rigidity _____
Dystonia † _____
Tardive Dyskinesia _____

Cognitive Effects
Confusion _____
Memory Problems _____
Sedation _____
Hypersomnia _____
Irritability _____
Headache _____

Cardiac
QTc Prolongation _____
Tachycardia _____
Hypotension _____

Weight and Diabetes
Height _____ inches
Baseline Weight _____ lbs.
Current Weight _____ lbs.
Weight Gain _____ lbs.
BMI _____
BMI Percentile _____
Elevated Glucose _____
Elevated Cholesterol _____
Elevated Triglycerides _____

Endocrine
Amenorrhea † _____
Galactorrhea † _____
Gynecomastia † _____

Anticholinergic
Dry Mouth _____
Blurred Vision _____
Constipation _____

Other
Insomnia _____
Nausea/Vomiting _____
Sexual Dysfunction _____
Decreased Libido _____
Dermatological _____
Hypersalivation _____
Enuresis _____

Current Issues in Adverse Events

- EPS
- Weight gain (especially on atypicals but also on mood stabilizers)
  - Increased chance of emergent diabetes
  - Polycystic Ovaries-like condition (insulin resistance, androgen effects)
- Prolactin elevation (>60–100 ng/mL)
  - Increased risk of menstrual disturbances in women
  - Impotence, oligospermia, galactorrhea and gynecomastia in males
- Metabolic abnormalities
  - Diabetes
  - Hyperlipidemia

Marder SF, Essock SM, Miller AL, et al (2004). *Am J Psychiatry* 161(8): 1334-1349.

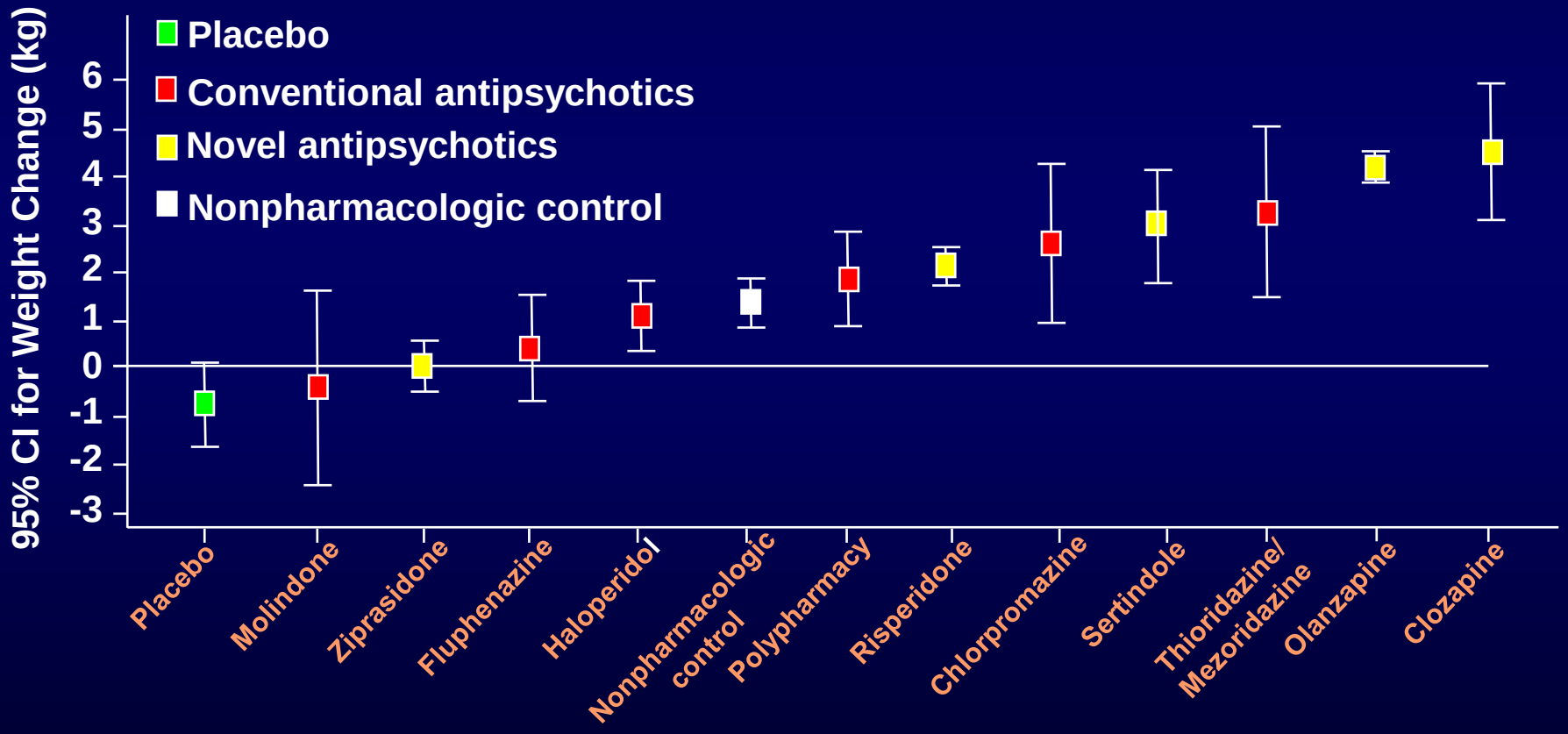
ADA Monitoring Protocol for Managing Weight Gain in Patients on Antipsychotics

	Baseline	4 wk	8 wk	12 wk	Quarterly	Yearly	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

BMI = Body mass index

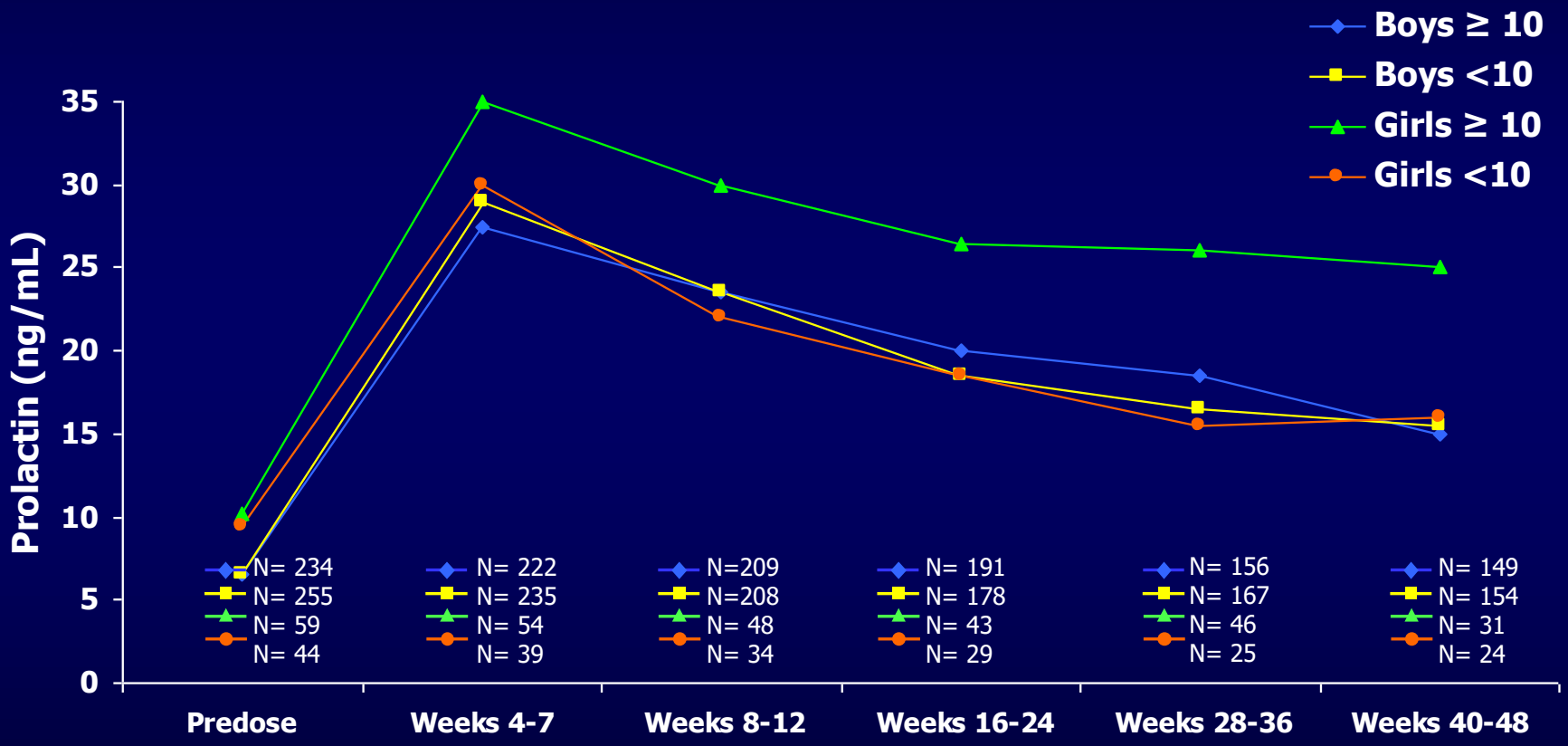
American Diabetes Association (2004). *Diabetes Care* 27(2):596-601.

Weight Gain and Type 2 Diabetes Risk Are Concerns for Some Atypical Antipsychotics



Allison DB, Casey DE (2001). *J Clin Psychiatry* 62(suppl 7):22-31.

Mean Prolactin Observations of Youth on Risperidone (n=592)



Mean daily dose: 1.3 ± 0.7 mg/day

* Upper limit of normal (18 ng/mL for boys; 30 ng/mL for girls).

Findling RL, Kusumaker V, Daneman D, et al. Normalization of prolactin levels in children after long-term treatment with risperidone. CINP, 2002.

Potentially Life Threatening or Highly Medically Concerning *(AP=Antipsychotic)*

Side Effect	*First Line Options*	*Additional Considerations*
NMS	Discontinue AP; emergency internal medicine/pediatrics consult	Start different AP once NMS resolves
Decreased ANC	Repeat lab; hematology consult; discontinue AP	Start different AP once ANC returns to normal
Agranulo-cytosis	Emergency hematology consult; immediately discontinue AP; repeat lab	Start different AP once agranulocytosis resolves
Increased LFT	Repeat lab; internal medicine/pediatrics consult; consider discontinuing AP	Decrease dose; if condition continues, discontinue AP, allow to resolve and start different AP

TRAAY: Pocket Reference Guide for Clinicians in Child and Adolescent Psychiatry (2004). NYS-OMH & CACMH

Extrapyramidal Symptoms

Side Effect	*First Line Options*	*Additional Considerations*
Akathisia	Decrease dose	Add beta adrenergic Antagonist; switch AP
Akinesia	Decrease dose	Add anticholinergic; switch AP
Tremor	Decrease dose	Add anticholinergic; switch AP
Muscle Rigidity	Add anticholinergic;decrease dose	Add dopamine agonist; switch AP
Dystonia	Add anticholinergic; add lorazepam	Decrease dose
Tardive Dyskinesia	Neurology consult; discontinue AP	Switch AP

Weight & Diabetes

Side Effect	*First Line Options*	*Additional Considerations*
Weight Gain (≥ 5-10 % of baseline weight/2-5 BMI)	Nutrition consult, implement diet/exercise plan; monitor fasting glucose, cholesterol, triglycerides	Switch AP
Diabetes	Obtain fasting glucose at baseline for high risk patients; endocrine consult, implement diet/exercise plan; symptom management education	Switch AP

Endocrine

Side Effect	First Line Options	Additional Considerations
Hyper-prolactinemia	No action needed: Prolactin levels, in absence of symptoms, need not be drawn	
Galactorrhea	Decrease dose; obtain prolactin level; endocrine consult	Switch AP
Amenorrhea	Rule out pregnancy; obtain prolactin levels; gynecology consult	Wait to see if amenorrhea resolves; decrease dose; switch AP
Gynecomastia	Obtain prolactin level; endocrine consult	Switch AP
Decreased Libido/ Erectile Dysfunction	Decrease dose	Switch AP

Cardiac

Side Effect	*First Line Options*	*Additional Considerations*
Slightly prolonged QTc Interval (>450 & < 500 Msecs)	Repeat EKG; decrease dose	Cardiology consult; discontinue AP, start different AP once QTc interval returns to normal
Very prolonged QTc Interval (> 500 Msecs)	Repeat EKG; cardiology consult; discontinue AP	Start different AP once QTc interval returns to normal
Tachycardia	Cardiology consult; decrease dose	Switch AP
Orthostatic Hypotension	Teach patient to change posture slowly; increase hydration; decrease dose	Cardiology consult; switch AP

Avoiding Polypharmacy

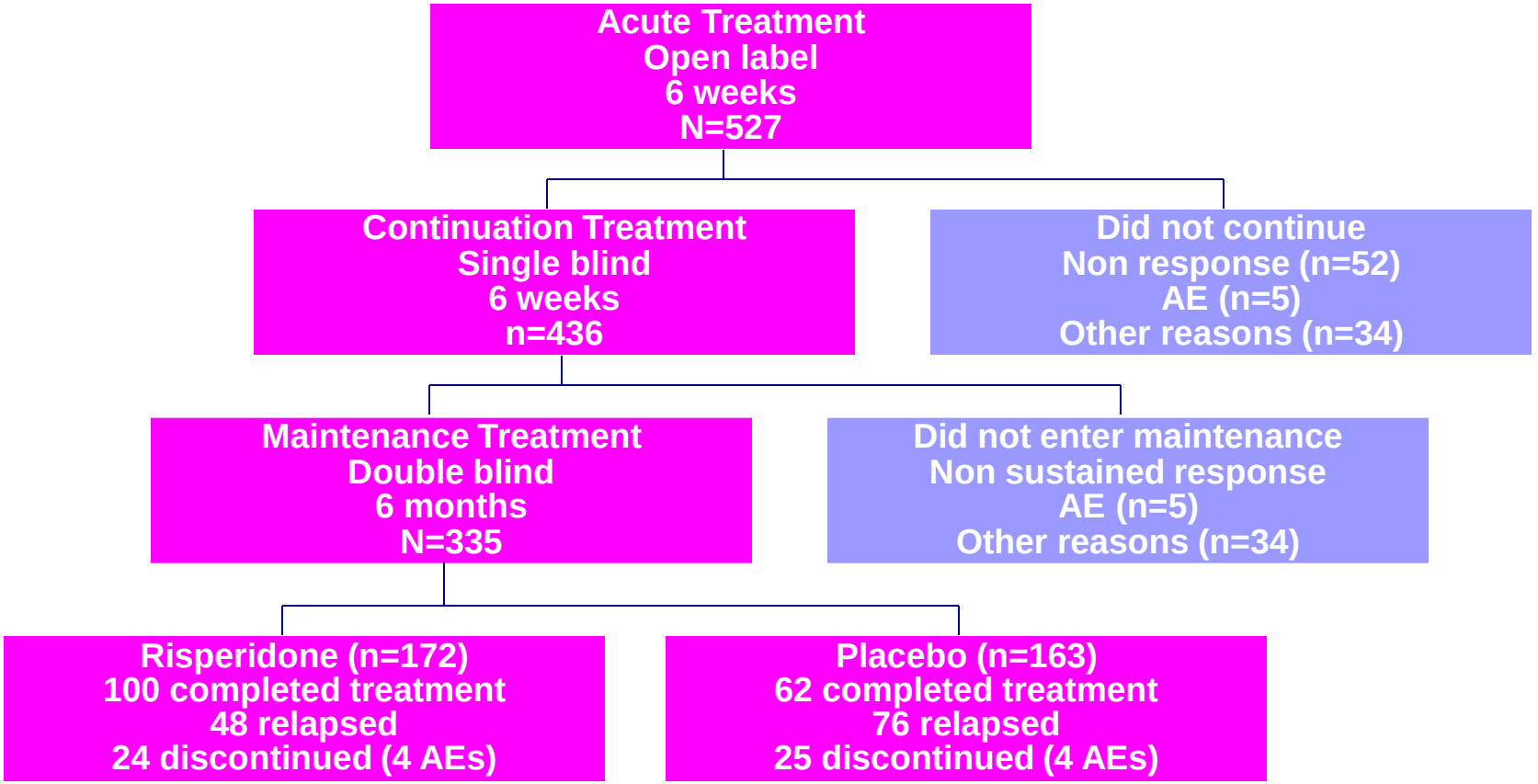
- Avoid using multiple medications simultaneously whenever possible
- Re-evaluate regimen of patient who does not experience decreased aggression while receiving multiple medications
- Consider tapering/discontinuing one or more medications if patient is on 4 medications without clear benefit

Tapering/Discontinuing Medications

- Consider tapering atypical antipsychotic medications in patients showing remission of aggressive symptoms for 6 months or longer
- If tapering of dose is well tolerated, discontinue the medication

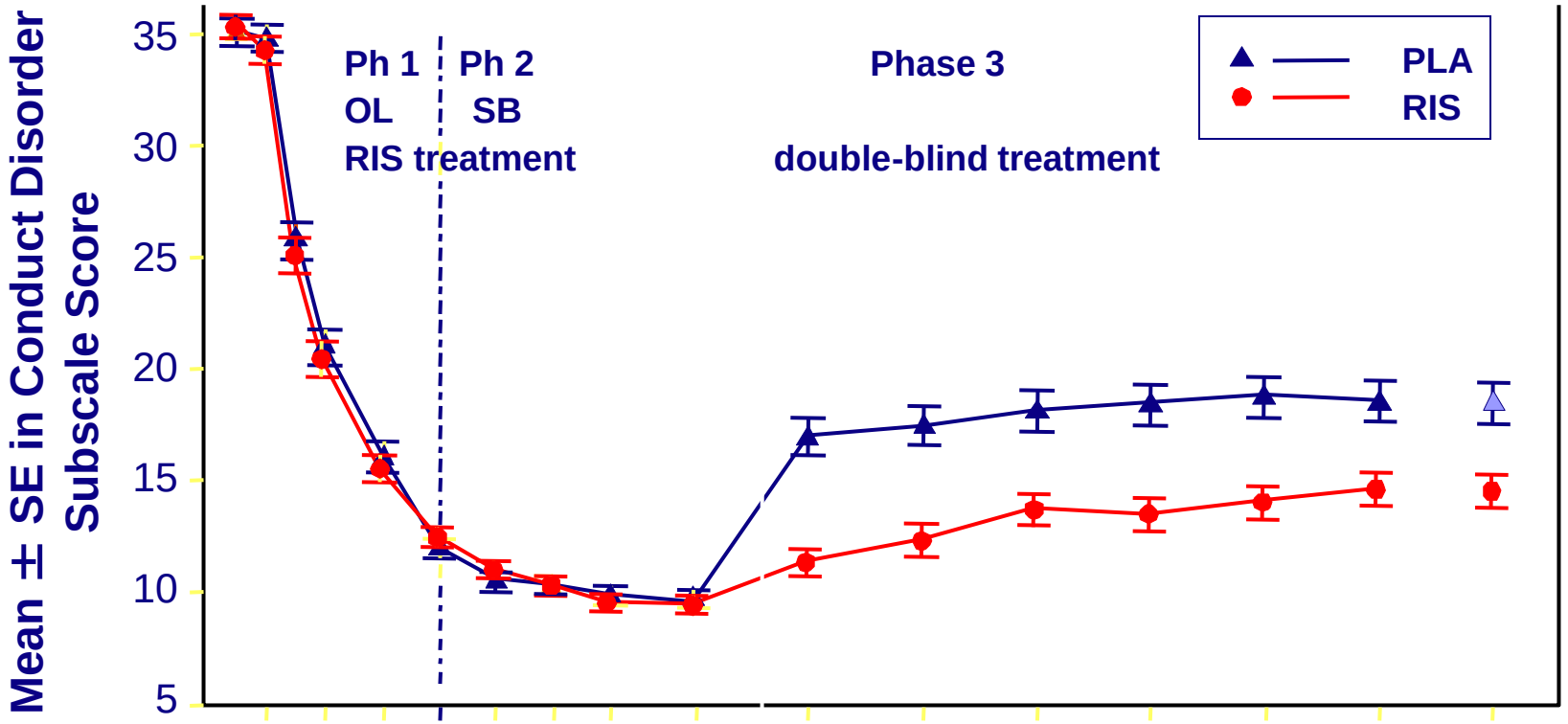
Relapse Prevention of Disruptive Behavior Disorders in Children and Adolescents

Disposition of patients throughout study



Reyes M et al. Poster presented at the IACAPAP. August 2004, Berlin, Germany.

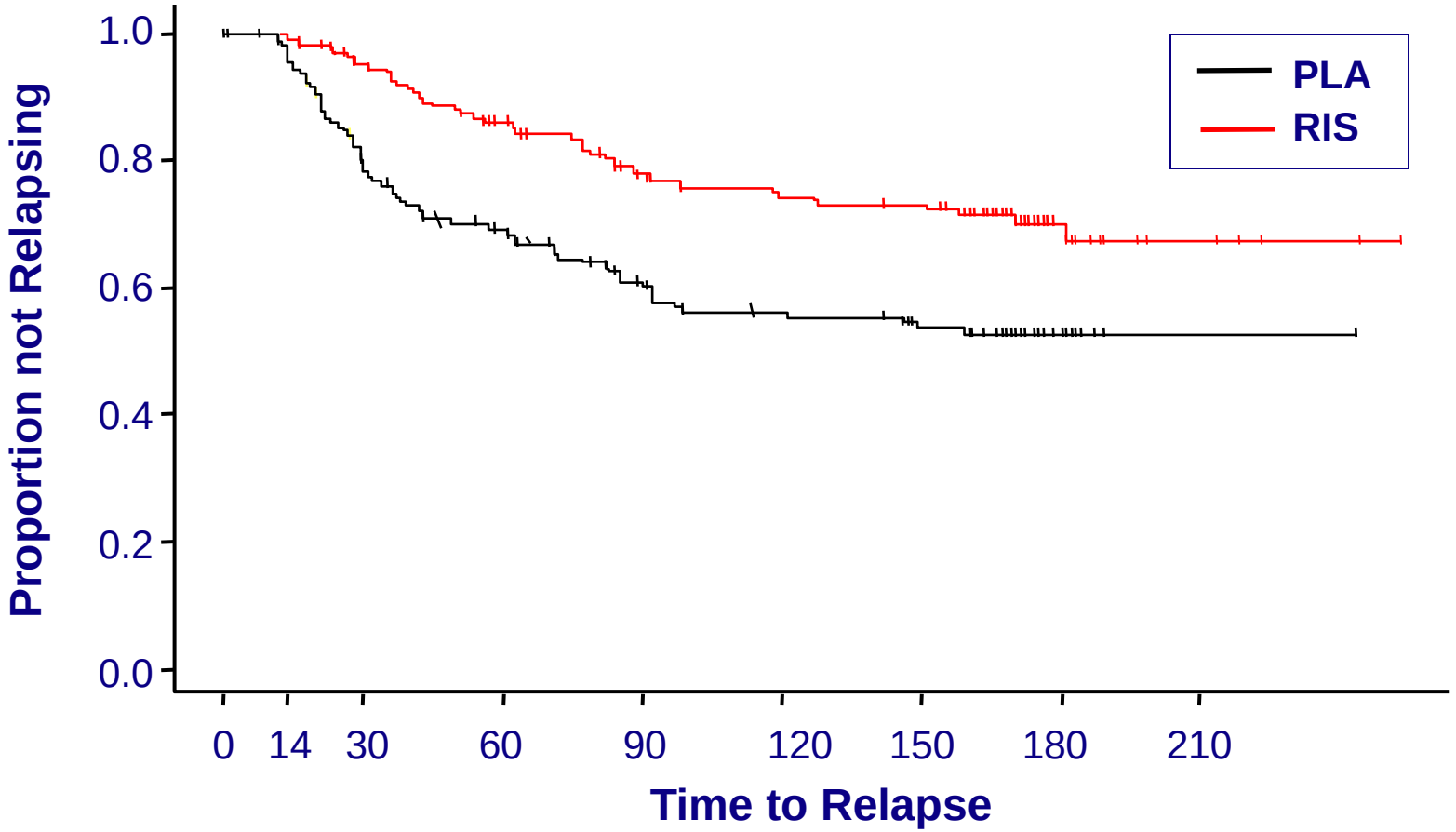
Mean Scores in N-CBRF Conduct Problem Subscale Score During Treatment (LOCF)



PLA	156	163	163	163	163	163	163	163	159	161	161	161	161	161	161
RIS	171	172	172	172	172	172	172	172	167	170	170	170	170	170	170

Reyes M et al. Poster presented at the IACAPAP. August 2004, Berlin, Germany.

Kaplan-Meier Estimates of Time (days) From Initiation of Maintenance Treatment to Relapse



p<0.001

PLA	162	152	120	101	77	69	62	11	1
RIS	171	170	158	138	118	110	107	24	6

Reyes M et al. Poster presented at the IACAPAP. August 2004, Berlin, Germany.

Center for Education and Research Therapeutics in Behavioral Health

Treatment Recommendations for the Outpatient Management of Behavior Problems in Youth

Assessment and Diagnosis
- Engage patient and parents during initial evaluation.
- Conduct a thorough initial evaluation and diagnostic work-up before pharmacological treatment.
- Assess treatment effects and outcomes with standardized measures.

Initial Management and Treatment Planning
- Provide psychoeducation for patients and families and set realistic expectations about treatment.
- Partner with patient and family in developing an acceptable treatment plan.
- Help the family establish community supports.

If Acute Agitation/Aggression

- Conduct risk assessment and if necessary, consider referral to psychiatrist or ER evaluation.
- Help parents/family prepare a safety plan and connect with community resources and supports
- Consider prescribing medication at the first visit depending on:
  - Potential harm to self or others
  - History of severe impulsive or aggressive behavior
  - Previous positive response to medication treatments.

If Chronic Aggression

Psychosocial Interventions
- Provide or assist the family in obtaining evidence-based parent and child skills training.

Medication Treatment
- Initial medication treatment should target the underlying disorder(s).
- Where available, follow evidence-based guidelines for primary disorder.
- **Use recommended titration schedule and deliver an adequate medication trial before changing or adding medication.**
- **If needed, consider a first-line atypical antipsychotic for aggression**
- Avoid using more than 2 medications from the same class or greater than 3 medication simultaneously.

Side Effects Assessment and Management

Routinely assess for side effects & medication interactions.
- **Use structure rating scales to monitor side effects**

TR11. If no response, try a different first-line atypical

TR12. If partial response, consider augmentation with a mood stabilizer

If good response, continue treatment for 6 months

Taper or discontinue atypical antipsychotic medications in patients who show a remission in aggressive symptoms for 6 months or longer

Question 1

Clinicians may consider tapering atypical antipsychotic medications in patients showing remission of aggressive symptoms for this duration or longer:

a) 2 weeks
b) 1 month
c) 2 months
d) 3 months
e) 6 months

Question 2

The TRAAY guidelines suggested that for individuals with slightly prolonged QTc Interval (>450 & < 500 msecs), the first line options include:

a) Repeat EKG and decrease dose of antipsychotic

b) Increase dose of antipsychotic

c) Abrupt discontinuation of antipsychotic

d) Cardiology consult

e) Add antiarrhythmic agent

Answers

1: e

2: a