Attention Deficit Hyperactivity Disorder FCAP

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DSM-IV Criteria for ADHD Are Child Oriented

Attention-Deficit/Hyperactivity Disorder

A. Either (1) or (2):

(1) six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities

(b) often has difficulty sustaining attention in tasks or play activities

(c) often does not seem to listen when spoken to directly

Inattention (continued)

(d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)

(e) often has difficulty organizing tasks and activities

(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort such as schoolwork or homework

(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)

(h) is often easily distracted by extraneous stimuli

(I) is often forgetful in daily activities

(2) six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

- ***Hyperactivity***

(a) often fidgets with hands or feet or squirms in seat

(b) often leaves seat in classroom or in other situations in which remaining seated is expected

(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescent or adults, may be limited to subjective feelings of restlessness)

Hyperactivity *(continued)*

(d) often has difficulty playing or engaging in leisure activities quietly

(e) is often “on the go” or often acts as if “driven by a motor”

(f) often talks excessively

- ***Impulsivity***

(a) often blurts out answers before questions have been completed

(b) often has difficulty awaiting turn

(c) often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school (or work) and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupations functioning.

E. The symptoms do not occur exclusively during the course of Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Code based on type:

314.01 **Attention-Deficit/Hyperactivity Disorder**, Combined Type: if both Criteria A1 and A2 are met for the past 6 months

314.00 **Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type**: if Criterion A1 is met by Criterion A2 is not met for the past 6 months

314.01 **Attention-Deficit/Hyperactivity Disorder, predominantly Hyperactive-Impulsive Type**: if Criterion A2 is met but Criterion A1 is not met for the past 6 months.

Coding note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, "In Partial Remission" should be specified.

314.9 **Attention-Deficit/Hyperactivity Disorder Not Otherwise Specified**

This category is for disorders with prominent symptoms of inattention or hyperactivity-impulsivity that do not meet criteria for Attention-Deficit/Hyperactivity Disorder.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

Epidemiology

1) Prevalence of 3-5% school-age children; 2-4% adolescents
2) Recent studies suggest as high as 6-8% of school-age children
3) 80-90% male in youth, but closer to 50% female in clinics treating adults

Adult ADHD epidemiology studies

Murphy and Barkley,	1996	4.7%
DuPaul, Weyandt et al,	1997	4.5%
Heiligenstein et al,	1997	4.0%

ADHD

Etiology

- No single cause to explain the vast majority of ADHD cases
- Data support a biologic basis for ADHD
- Future research may more fully elucidate the roles of neurophysiology, genetics, and environment in producing this disorder
- Rising research on the Dopamine Transporter gene

ADHD ETIOLOGY

Imaging Studies Summary

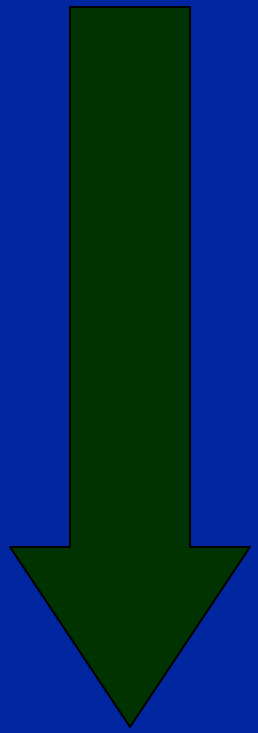
- **Results support prominent role of**
  - **frontal lobe dysfunction in ADHD**
  - **cortical-subcortical circuits**
- **Neuroimaging techniques have not been validated as tools for ADHD diagnosis or to inform treatment and are very expensive**

Course of Disorder

1) Earliest presentation is in toddlers
2) 2/3 of adolescents diagnosed as children with ADHD have symptoms
3) 1/3 of adults diagnosed as children with ADHD have symptoms
4) Symptom course tends to be from motoric in younger children to cognitive in adolescents and adults

ADHD Developmental Trends: Symptoms of ADHD May Change from Childhood to Adulthood

Children



Adults

- Motoric hyperactivity
- Aggressiveness
- Low frustration tolerance
- Impulsiveness
- Easily distracted
- Inattentiveness
- Shifts activities
- Easily bored
- Impatient
- Restlessness

Adapted from: Wilens, et al., Annual Review of Psychiatry, 1999;19:1-34, Millstein RB, et al. J Attn Disord 1997;2(3):159-166

ADHD

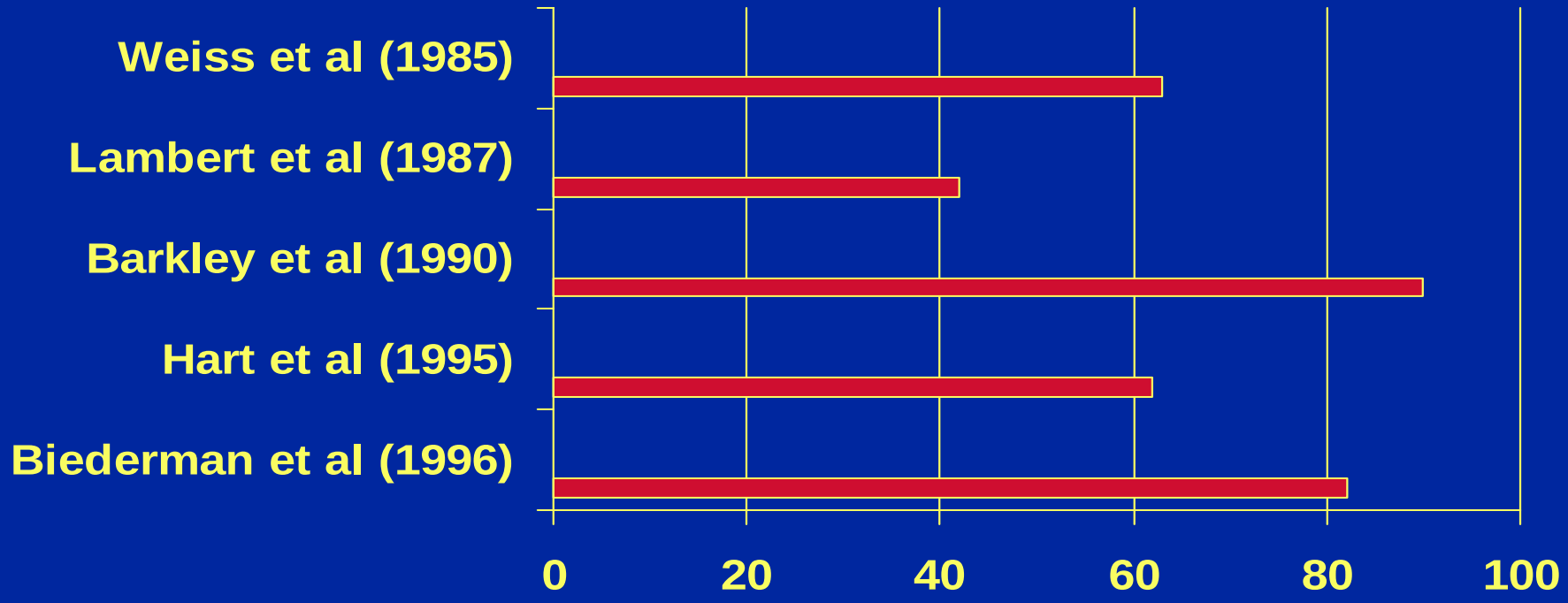
Clinical Presentation

Adolescent (Ages 13-18)

- May have a sense of inner restlessness (rather than hyperactivity)
- School work disorganized and shows poor follow-through; fails to work independently
- Engaging in “risky” behaviors (speeding and driving mishaps)
- Poor self-esteem
- Poor peer relationships
- Difficulty with authority figures

Greenhill J Clin Psychiatry 1998-59(suppl 7):31.
Conners and Jett. ADHD in adults and Children. Compact Clinicals; 1999

ADHD: Persistence Into Adolescence and Adulthood



Comorbidity

1) 40% of ADHD children have another disruptive behavior disorder
2) 30% of ADHD children also have an anxiety disorder or mood disorder
3) A similar pattern of comorbidity is present for adolescents and adults. It is also especially important to screen for alcohol and drug abuse
4) 50% have Axis I condition of one or more specific developmental disorders

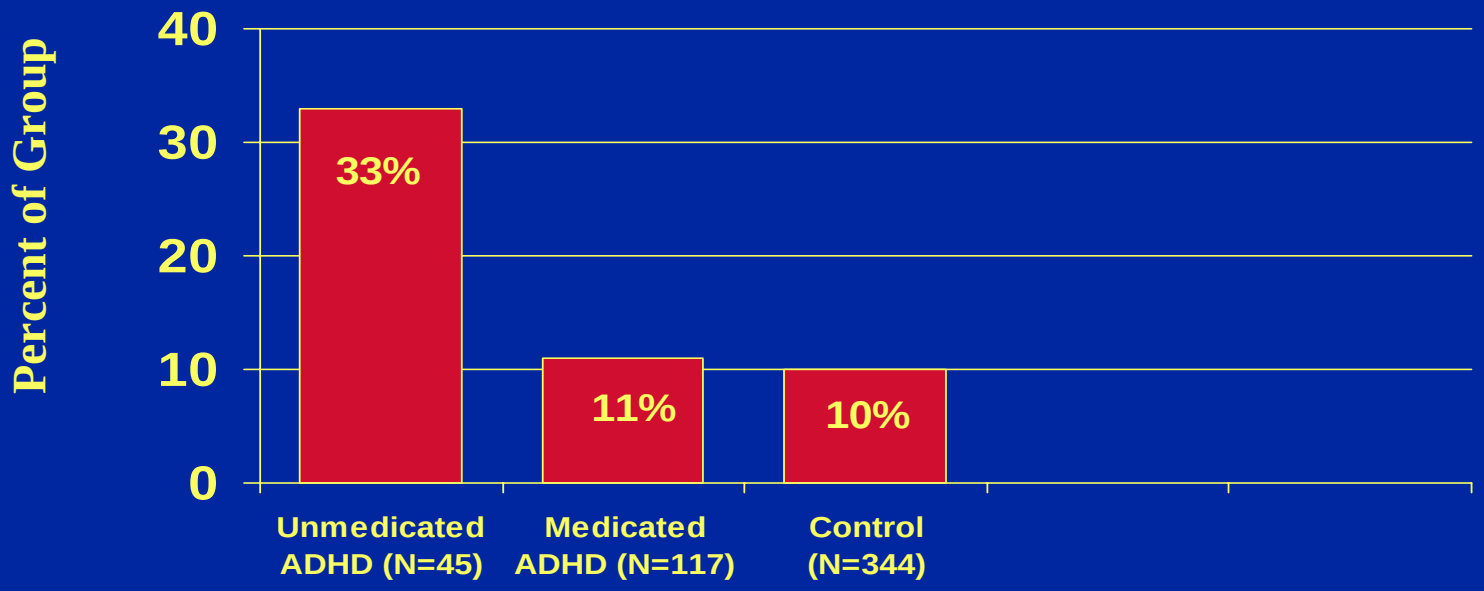
ADHD and Psychoactive Substance Use Disorders (PSUD)

- 4-year follow-up of a clinically referred sample of boys 6 to 17 years old at baseline (ADHD N=140; control N-120)
  - no difference in the rate of alcohol or drug abuse between groups (15% vs 15%), mean age-early adolescence
  - Risk for PSUD mediated by conduct disorder and bipolar disorder with or without ADHD
- Adults with ADHD (N-139) vs controls (N-268)
  - significantly greater lifetime rate of PSUD than controls (55% vs 27%)
  - Age of onset of PSUD in subjects with ADHD averaged 3 years earlier than controls (late adolescence/early adulthood)
  - ADHD was a significant risk factor independent of comorbid diagnoses

Biederman et al., JAACAP 1997-36:21
Biederman et al., BioPsychiatry 1998:44:269

ADHD
Pharmacotherapy and Substance Abuse

Overall Rate of PSUD



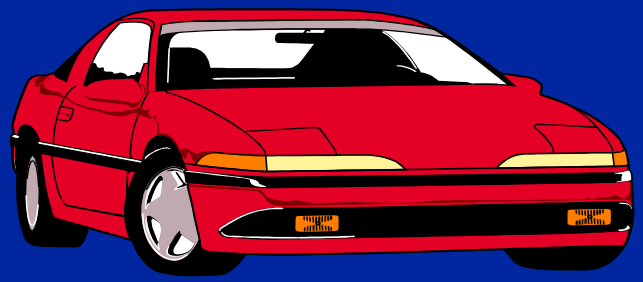
Wilens, 2003

Controversy regarding this report. Other studies do not support this – e.g.,

1) ***Pelham***
2) ***Manuzza, Klein***

ADHD
Motor Vehicle Driving

Study of 16 to 22 year olds
-35 with ADHD (*not on medication*)
-36 controls



Significantly more drivers with ADHD
- **drove without a license**
- **had licenses revoked or suspended**
- **had multiple crashes (2+)**
- **had multiple traffic citations (3+), especially for speeding**

Subgroups of ADHD with comorbid oppositional defiant or conduct disorder were at highest risk

Barkley et al. Pediatrics 1993;92-212

Adult ADHD: Heavy Toll in the Workplace

Work Performance

- Employers rate ADHD adults as
  - Less adequate in fulfilling work demands
  - Less likely to work independently
  - Less likely to get along well with supervisor
- More likely to be fired or laid-off than normal controls
- Ability to fulfill potential
- ADHD adults in general have lower job status
- More likely to quit a job or change jobs

Weiss G, Hechtman LT. Hyperactive children grown up:ADHD in children and adults, 1993.

Assessment

1) This is a clinical diagnosis based on establishing a persistent pattern across settings in inattention, distractibility, hyperactivity and impulsivity
2) Screening for general good health, adequate nutrition, adequate hearing and vision is essential; lead level problems are regionally based (>20 is significant)
3) Laboratory tests do not establish a diagnosis
4) Helpful instruments are the Conners rating forms and the Child Behavioral Checklist for parents and teachers by Achenbach for Children and Adolescents, and for adults the ADHD rating scale by Barkley

Diagnosis of ADHD

Summary

Diagnosis relies strongly on DSM-IV criteria in domains of

- inattention
- impulsivity
- hyperactivity

- Comorbidity is common
- Diagnostic assessment includes a thorough gathering of information from multiple sources
- Treatment should be targeted to and assessed by changes in specific areas of impairment

The Disorder is Vulnerable to Fads in Assessment and Treatment

1) Examples; fluorescent lights, diet, quantitative EEG, SPECT scan, biofeedback, association with thyroid function, new medications
2) Be careful before incorporating them into your practice

Differential Diagnosis Controversies

1) Is there overdiagnosis? *(and over-treatment?)*
   no - Jensen - J Amer Acad Child Adoles Psych (1999)38:797-804
   yes - *Angold - J Amer Acad Child Adoles Psych (2000)39:975-984*
2) Diagnosis in high functioning individuals, with onset after age 7
3) Bipolar disorder controversy

Bipolar Disorder

1. Current controversy
2. Relationship of adult to childhood disorder
3. Prevalence in childhood and adolescence
4. Relation of Bipolar disorder to ADHD

Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

1. Inflated self-esteem or grandiosity
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
3. More talkative than usual or pressure to keep talking
4. Flight of ideas, or subjective experience that thoughts are racing
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

There is a paucity of literature describing the treatment of children and adolescents with bipolar disorder.

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Great Smokey Mountain Study of Youth

No cases of mania and 0.1% rate of hypomania in 9-13 year olds

VS

Beiderman finding of 20% of ADHD patients with Bipolar

Diagnosis of Juvenile Bipolar Disorder

Not a clear precursor of bipolar disorder in adults

Difficult to fit children and adolescents into adult criteria

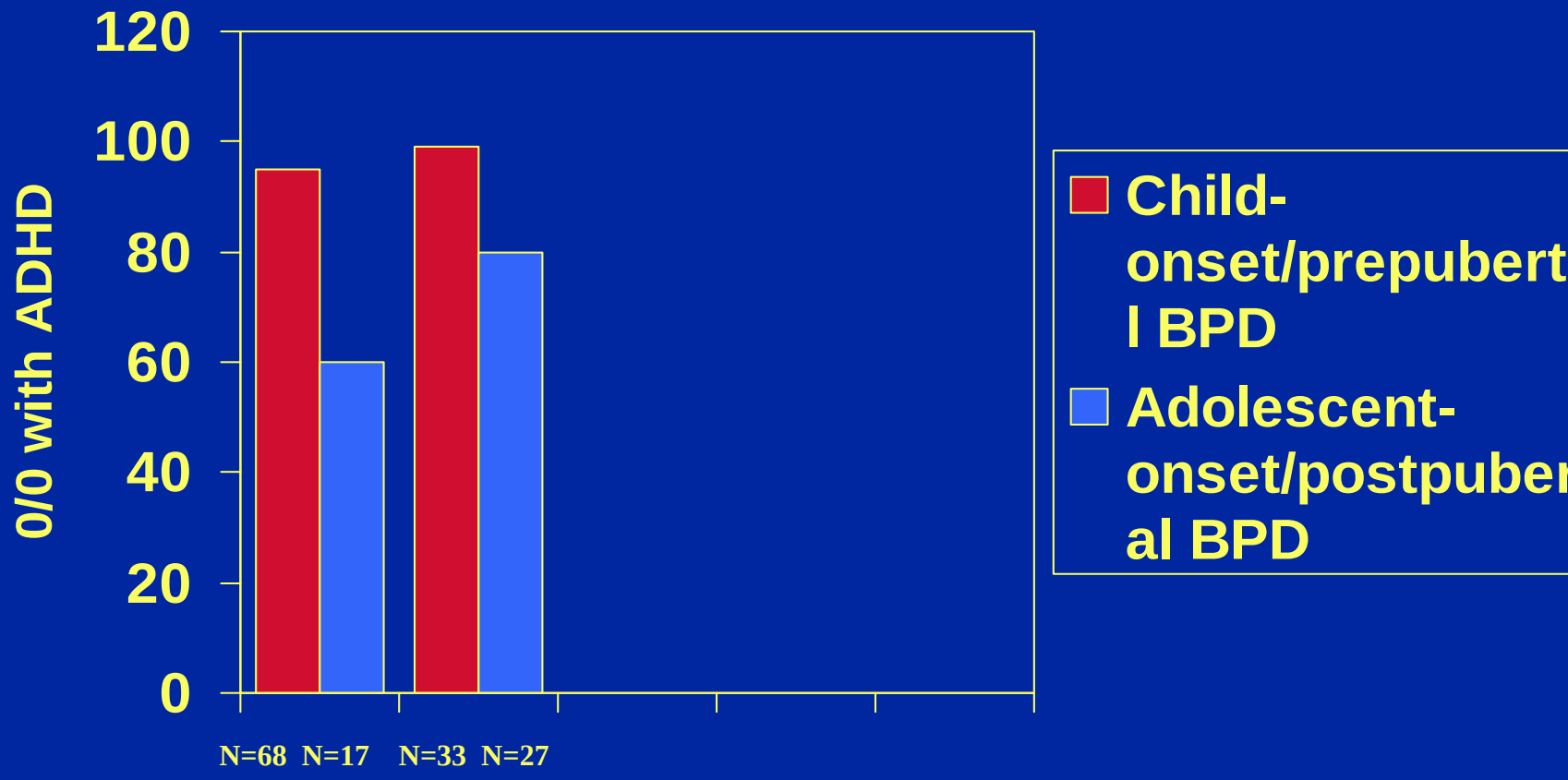
Children and adolescents with bipolar disorder often present with mixed features

Comorbidity in children and adolescents with bipolar disorder complicates the diagnosis and may contribute to a poorer prognosis

ADHD and Bipolar Disorder

Patients with bipolar disorder commonly also have ADHD

Comorbidity of ADHD in Early-Onset BPD



Faraone et al., 1997 Geller et al., 1988

Bipolar Disorders vs. ADHD

ADHD

- Constant problems with distractibility, attention, organization regardless of mood state
- Irritable, accelerated speech, increased energy
- Younger age of onset
- Improved concentration and reduced impulsiveness on Ritalin

Bipolar:

- Elated mood, grandiosity, suicidal gestures, racing thoughts, decreased need for sleep, hypersexuality, poor judgment, daredevil acts, excessive silliness, uninhibited people seeking
- Cycling mood episodes, psychosis
- Family history BD
- Cycle acceleration on Ritalin

Three Types of Problems

- ADHD is present: BP/mania starts sometime later
  - Clearest with childhood ADHD and adolescent-onset BP
    - Up to 60% of teen BP has comorbid ADHD: 20% of adult onsets do
    - Remember if ADHD is a comorbidity with bipolar, all of the language disorders, ODD/CD, anxiety disorders) become additionally relevant.
- Onset of mania that **looks** like ADHD
- ADHD and "rages" that get mistaken for BP

Bottom line: one condition can be easily mistaken for the other; but both can simultaneously occur

Adults with Bipolar Disorder Retrospective Report:

31% onset before 15

25% onset 15-19

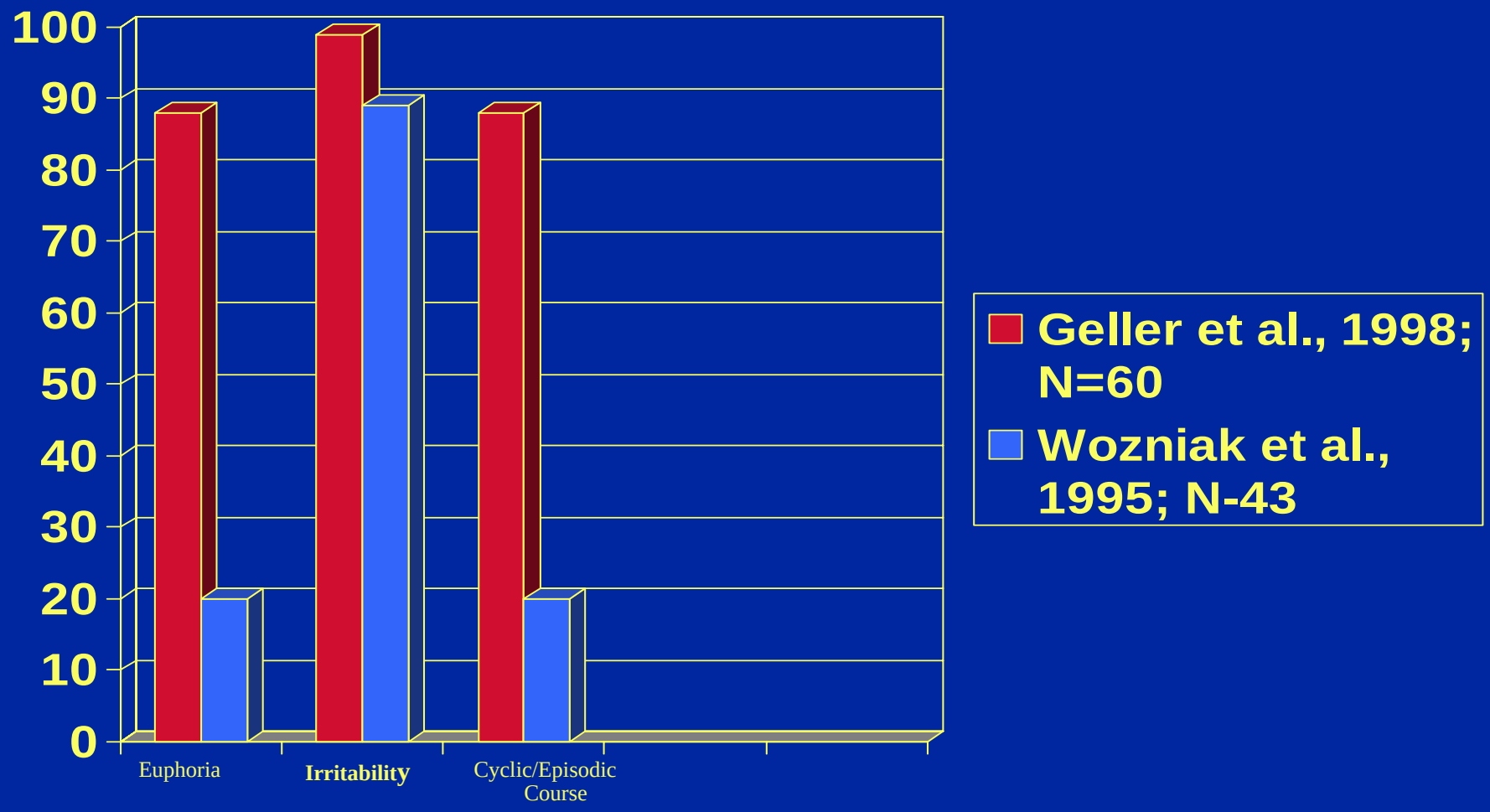
Longitudinal Data

- 208 boys 9-13
- 124 with ADHD
- 25/124 with mania as well
- 1/25 with mania or hypomania 6 years later

Severe Mood Dysregulation:

How does it differ from bipolar disorder?

Early-Onset Bipolar Disorder



Children in the Community Study with Severe Irritability (Cohen et al., 1993)

Longitudinal epidemiological study (N=776, T1-Te= 8 years)

	Age (y)
Time 1	13.8 ± 2.5
2	16.2 ± 2.7
3	22.1 ± 2.7

Do episodic and chronic irritability differ in their associations with psychopathology?

Episodic Irritability (Time 1) associated with:
Time 2: BPD, GAD, and phobia
Time 3: BPD

Chronic Irritability (time 1) associated with:
Time 2: ADHD, ODD
Time 3: MDD

Episodes and Hallmark Symptoms

- EPI more likely than CHR to endorse each manic sx except irritability and agitation ($p<0.001$)
- Hallmark sxs: elation, grandiosity
- Significant association between EPI and # hallmark sxs ($U=89.5$, $p=.0001$)

Conclusions

- The presence of episodes and cardinal symptoms are important in the diagnosis of pediatric BPD.

- Be cautious about making the diagnosis of pediatric BPD on the basis of chronic irritability

Clinical Phenotypes of Juvenile Mania

- Narrow: full-duration episodes and hallmark sx's (elevated mood or grandiosity)
- Intermediate:
  - -(Hypo)mania-NOS: short episodes
  - -Irritable (hypo)mania: no hallmark sx's
- Broad: Chronic, no hallmark sx's

PREVALENCE OF PSYCHOTROPIC MEDICATION PRESCRIPTION IN YOUTH

1) Stimulants
   a) 10 fold increase from 1980 to 2000
   b) 3 fold increase in 2 to 4 year olds from 1991 to 1995
2) Alpha 2-Agonist
   25 fold increase in youth under 5 from 1991 to 1995
3) SSRI's
   a) 792,000 prescriptions 1996 to 1997 for youth
   b) 500% increase in children under 5 in period 1991-1995
4) Upward trends continuing to present

ADHD Medication for Patients New to Medication – August, 2003

19% Strattera
19% Concerta
22% Adderall XR

MTA
Multiple Center Study
14 months

Much better outcome with intensive expert treatment vs community clinical results

Study	vs	Community Comparison
Mean Dose of methylphenidate:		
35mg/day		20mg/day
Given 3 x day		Given 2 x day
1 visit per month		1 visit per year
30 minute session		18 minute session
Regular School Contact		Rare school contact

Combined behavioral and medication vs medication alone

1) No differences in degree of improvement of ADHD symptoms in combined vs medication
2) Lower doses of medication in combined vs medication alone
3) Better outcome in combined Rx on social skills, aggression, arguing, anxiety, academics
4) Specificity of response outcome related to child (e.g., anxiety) and parental variables (e.g., depression or substance abuse)

MTA - 2-Year Follow-up

1) Effects of active treatment not as robust
2) Patients with less morbidity have better outcomes
3) Concerns regarding growth on stimulants

Treatment

1) Medication alone is not enough
2) Multimodal
    a) Medication used judiciously
    b) Parent and patient education
    c) School consultation
    d) Support for family
    e) Social skill training, behavior management treatment and psychotherapy if indicated
    f) Vocational counseling
3) Duration of treatment is dependent on duration of symptoms, persistent evidence of response and relative freedom from side effects
4) Attention to treatment of comorbid symptoms is essential

Medication for ADHD

I. Primary - Stimulants

a) Methylphenidate (Ritalin**, Metadate ER**, CD Concerta**, Methylin**)

b) Dextroamphetamine (Dexedrine***, Dextrostat***)

c) Amphetamine/Dextroamphetamine (Adderall***)

d) Dexmethylphenidate (Focalin)**

** non FDA approved to Rx ADHD*
*** FDA approval to Rx ADHD for children 6 and over*
**** FDA approval to Rx ADHD for children 3 and over*

Medication for ADHD

II. Secondary

a) Atomoxetine (Strattera)

b) Alpha - 2 Agonists

1) Clonidine (Catapres*)
2) Guanfacine (Tenex*)

c) Other Antidepressants

1) Bupropion (Wellbutrin*)
2) Venlafaxine (Effexor*)

d) Tricyclic Antidepressants

1) Imipramine (Tofranil*)
2) Nortriptyline (Pamelor*)
3) Desipramine (Norpramin*)

e) Stimulant

1) Pemoline (Cylert)**

f) Other

1) Modafinil (Provigil*)

** non FDA approved to Rx ADHD*
*** FDA approval to Rx ADHD for children 6 and over*
**** FDA approval to Rx ADHD for children 3 and over*

Longer Acting Stimulants

1) Offer hope of once-a-day dosing
2) Better acceptance
3) More costly

METHYLPHENIDATE

1) Dose: Generally, 5-80mg/day
   not more than 2 mg/kg/day
2) q.d. to q.i.d. dosing, depending on
   patient and form of medication
3) Optimize dosing
4) Side effects
   a) Decrease in appetite
   b) Sleep problems
   c) Tics
   d) Irritability/Depression
5) Tolerance (can occur with all stimulants), with need for
   dose advance or switch to alternative medication

Methylphenidate (continued)

5) Available in multiple preparations:
   a) Ritalin 5, 10 and 20mg regular acting; 20mg sustained release; Ritalin LA 20, 30, 40mg with 50/50 immediate/extended release beads ratio
   b) Metadate ER and CD
   c) Concerta
   d) Methylin: available in 5, 10, 20mg regular acting methylphenidate and in 10 and 20mg extended release (ER) tablets
   e) Transdermal patch

Recently Developed Long-acting MPH Medications

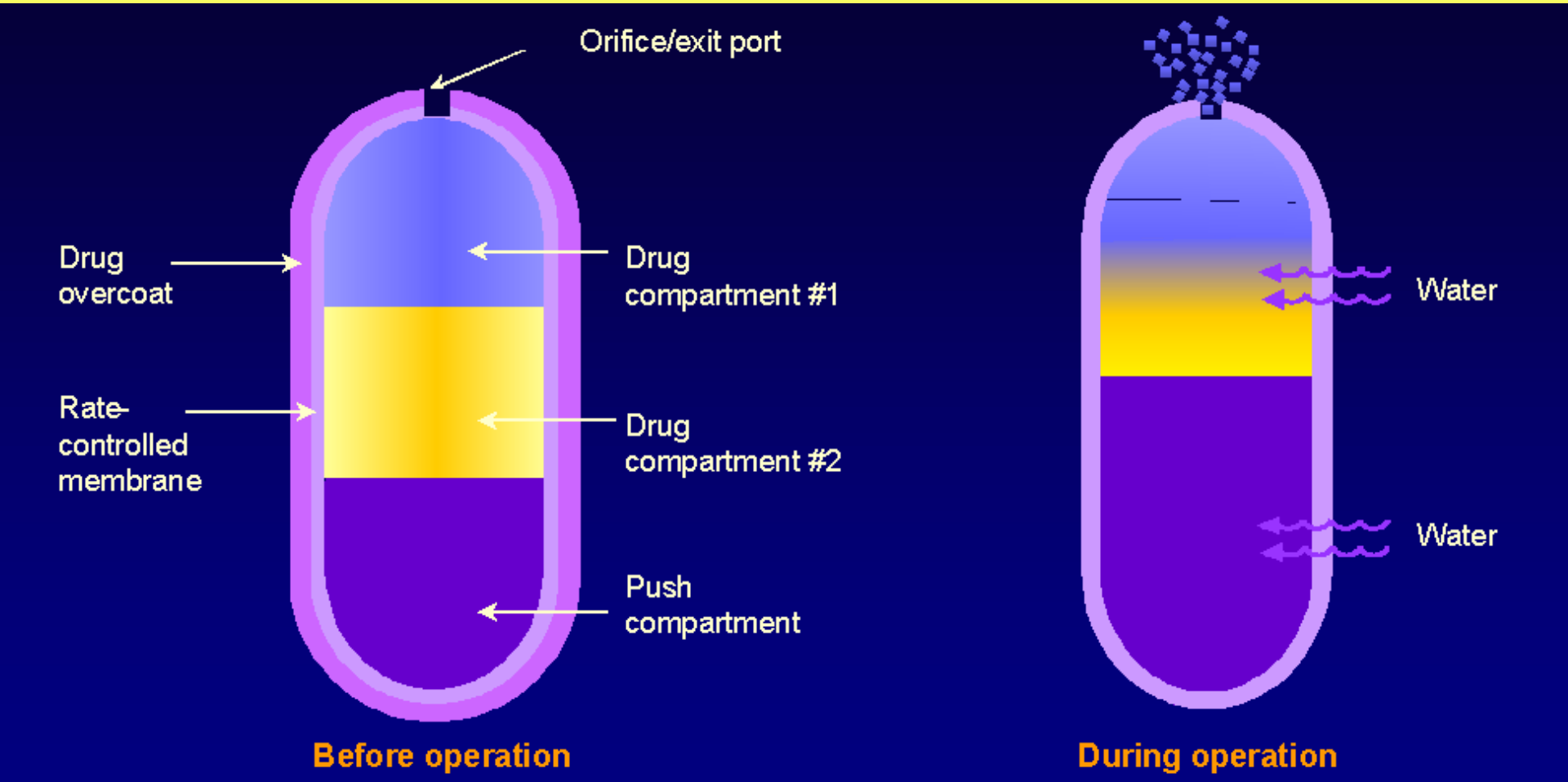
Products	Concerta®	Metadate® CD	Ritalin® LA
Formulation Technology	OROS ®	Diffucaps ®	SODAS™
Dose mg	18mg/27 mg/36 mg/54 mg	10,20,30 mg	20mg/30 mg/40
Immediate Release	**22%** 4 mg/6 mg/8 mg/12 mg	**30%** 6 mg	**50%** 10 mg/15 mg/20 mg
Sustained/ 2nd release	**78%** 14 mg/21 mg/28 mg/42 mg	**70%** 14 mg	**50%** 10 mg/15 mg/20 mg

Concerta® [package insert]. Mountain View, CA: Alza Corporation; 2001. OROS® is a registered trademark of ALZA Corporation.
Metadate® CD [package insert]. Rochester, NY: Celltech Pharmaceuticals, Inc; 2002. Diffucaps® is a registered trademark of Eurand.
Ritalin® LA [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2002. SODAS™ is a trademark of Elan Corporation, Plc

Concerta (Methylphenidate)

1) 18,27,36 and 54mg tablets
2) OROS system
3) Duration of Action 10 -16 hours
4) Somewhat less potent than regular acting methlyphenidate

Concerta® Tablets: OROS® Delivery System



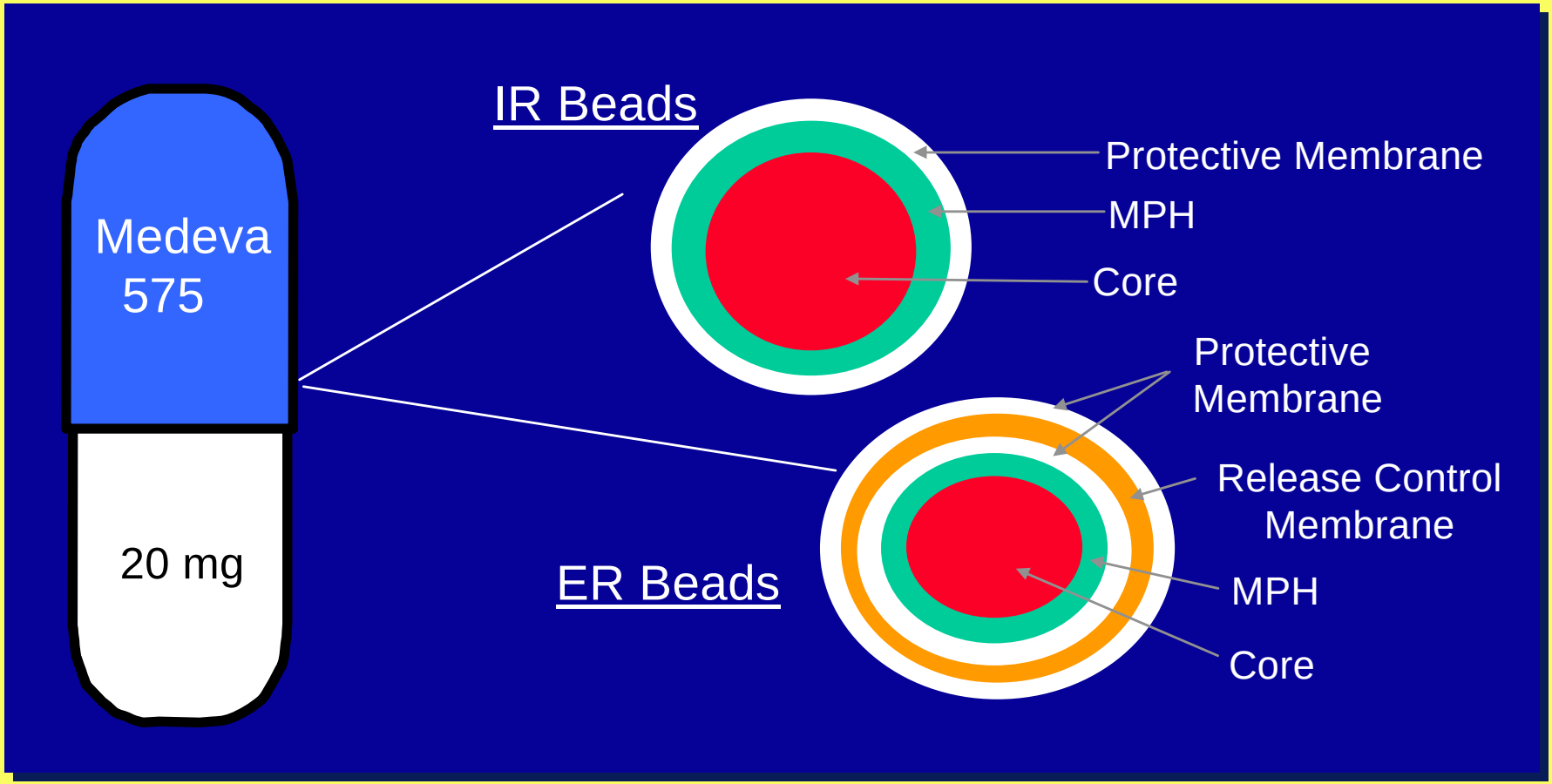
Swanson JM et al. Comparison of efficacy and safety of Concerta™ (methylphenidate HCl) with Ritalin® and placebo in children with ADHD. Presented at Region IX and X Annual Meeting of the Ambulatory Pediatric Association; February 12-13, 2000; Carmel, CA.

Metadate CD (Methylphenidate)

1. ER: 10 + 20mg
2. CD: 10mg, 20mg, 30mg Extended Release Capsules
    a) Duration of action 6 – 10 hours
    b) Capsule with immediate release (IR) + extended release (ER) beads
    c) Biphasic release
    d) 30/70 IR/ER ratio

Metadate® CD Capsules: Diffucaps® Delivery System

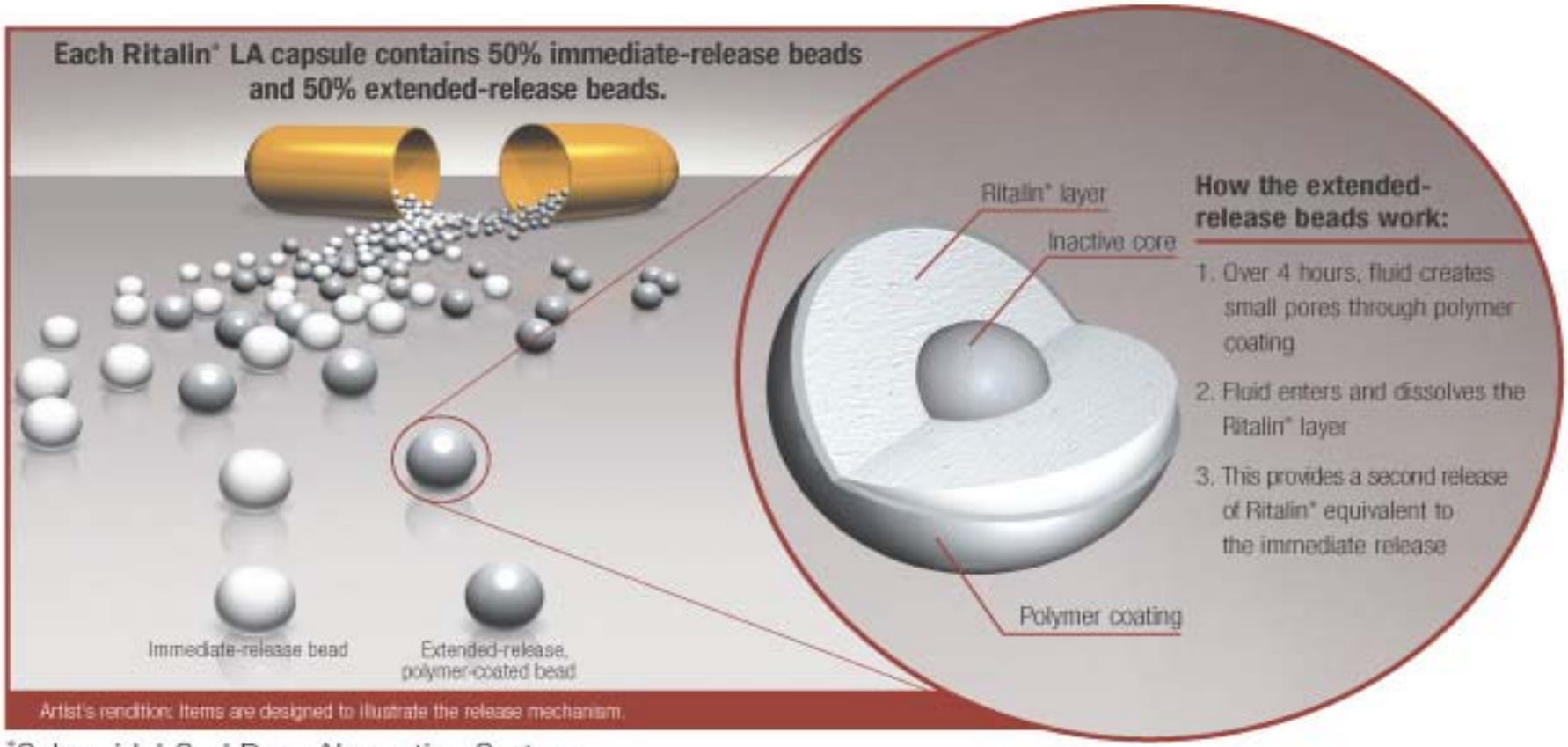
30% Immediate / 70% Extended Release



Ritalin LA (Methylphenidate)

- Extended Release Capsules of 20, 30, 40mg
- Duration of action 6 – 10 hours
- Capsule with immediate release (IR) + extended release (ER) beads
- Biphasic release – immediate and at 4 hours
- 50/50 IR/ER ratio

Ritalin® LA Capsules: SODAS™ Delivery System



®Spheroidal Oral Drug Absorption System.

Dexmethylphenidate (Focalin)

1. Active isomer of methylphenidate
2. Twice as potent
3. Uncertain if it offers an advantage over methylphenidate

DEXTROAMPHETAMINE

1) Dose: 5-50mg
2) Generally similar to Methylphenidate; twice as potent with equal efficacy
3) Available in 5mg (Dexedrine and Dextrostat) and 10mg tablets (Dextrostat) and longer acting 5,10 and 15mg spansules (Dexedrine)

Dextroamphetamine/Amphetamine

1) Combination of amphetamine 25% and dextroamphetamine 75%
2) Generally similar to methylphenidate, twice as potent with equal efficacy
3) Duration of action longer than methylphenidate
4) Available in 5,10,20, and 30mg regular acting generic and Adderall tablets, and in Adderall XR-longer acting capsule form

Adderall XR

1) 5, 10, 15, 20, 25, and 30mg capsules
2) Biphasic Release: IR + ER beads
3) Once a day dose
4) Ambrosini 2002 report suggesting clinician and family preference for Adderall XR is not a comparison study

Efficacy of Stimulants

1) About ¾ of patients with ADHD respond to a single stimulant
2) Of the ¼ who don't respond to one class of stimulant, about ½ will respond to a stimulant of a different class (e.g., amphetamine after methylphenidate or methylphenidate after amphetamine)
3) Response rate to one class of stimulant probably about the same as to another class. Metanalysis by Faraone suggests small advantage of Adderall versus methylphenidate.

Atomoxetine (Strattera)

1. NA reuptake inhibitor
2. Multiple trials with ADHD benefit in children, adolescents and adults
3. Released January 2003
4. 1,000,000 prescriptions written by September 2003

Atomoxetine

1) Dose for children 1.4mg/kg/day; adult mean dose 93/mg/day; may need to go higher
2) qd or bid
3) Metabolized by Cytochrome p450 2D6-interaction with fluoxetine

Atomoxetine

- What role will it play?
- Primary versus Secondary
- Too early yet, but probably at least first choice if stimulants don’t work

Atomoxetine

- Available in 10,18,25,40 and 60mg capsules
- Side effects:
  - Nausea, vomiting
  - Dyspepsia
  - Fatigue
  - Decreased appetite
  - Mood swings

ALPHA-2 AGONISTS

Alpha-2 agonists

1. Clonidine
   a) Dose: .05-.4mg/day; bid to qid; patch (hypersensitivity)
   b) Primary symptom relief with hyperactivity and aggression
   c) May reduce stimulant dose requirement
   d) Side effects:
      1) Sedation
      2) Hypotension
      3) Depression
   e) Tolerance is common
   f) Rebound hypertension is common during withdrawal: tapering is necessary
   g) Some capacity to reduce tics
   h) Reports of sudden death in combination with stimulants- not a clear relationship

Alpha-2 Agonists

2. Guanfacine
    a) Dose: 0.5 to 4.0 mg/day in divided doses
    b) Similar effect but with longer half-life (18 vs 2 1/2 hours)
    c) Possibly fewer side effects, especially less sedation vs clonidine

Bupropion (Wellbutrin)

"Activating "antidepressant

Dosage: 50-300 mg/day

4 of 5 studies with positive effect

Side effects

1) seizures: 4/1000, less with long acting preparation
2) agitation
3) anorexia
4) tics

Now with XL qd preparation

Venlafaxine (Effexor)

1. Dosage: Starting dose 37.5; typical dose = 75mg/day; range 37.5 to 300)
2. Available in 25, 37.5, 50, 75 and 100mg tablets and in XR form
3. Side effects: Nausea, (reportedly less with XR form) somnolence, dizziness, increased blood pressure, sexual dysfunction
4. Combined effects on 5HT (+)NA at greater than 150mg/day
5. Only open trials for ADHD

Tricyclic Antidepressants

1) To consider in children after stimulant failure
2) Dose Imipramine 1-5mg/kg/day
   Nortriptyline .5-3mg/kg/day
   Desipramine 1-5mg/kg/day
3) Sudden death controversy on desipramine
4) Overdose lethality

Tricyclic Protocol

1) Baseline EKG
2) Begin at 1mg/kg/day
   (.5 mg/kg/day for nortriptyline)
3) Dose advance every 5 days
4) Repeat EKG, at 3.0mg/kg/day and at any subsequent dose increase
   a) PR 0.18 in children >10
   b) QRS<0.12
   c) QTc <.450
5) Vital signs
   a) increased BP
   b) increased pulse
   c) orthostatic BP and pulse changes accompanied by symptoms

PEMOLINE

1) Dose: 37.5-112.5 milligrams/day
2) Generally similar to methylphenidate, but not as effective
3) A special issue is liver toxicity – **BLACK BOX WARNING** - IMPORTANT. Secondary agent
4) Longer onset of effect and longer duration of action - usually given once a day
5) Mythology of needing several days to a few weeks before achieving efficacy

Modafinil (Provigil)

Only FDA approved indication is for narcolepsy

Study of effect on ADHD now underway

Recent reports of misuse to stay awake *(e.g., truck drivers)*

Combinations of Medications

1) To manage partial response to ADHD
   e.g., 1) Can't sustain effect
2) Side effect management
   e.g., 1) sleep disturbance
   2) rebound
   3) moodiness or irritability
3) Comorbid disorders

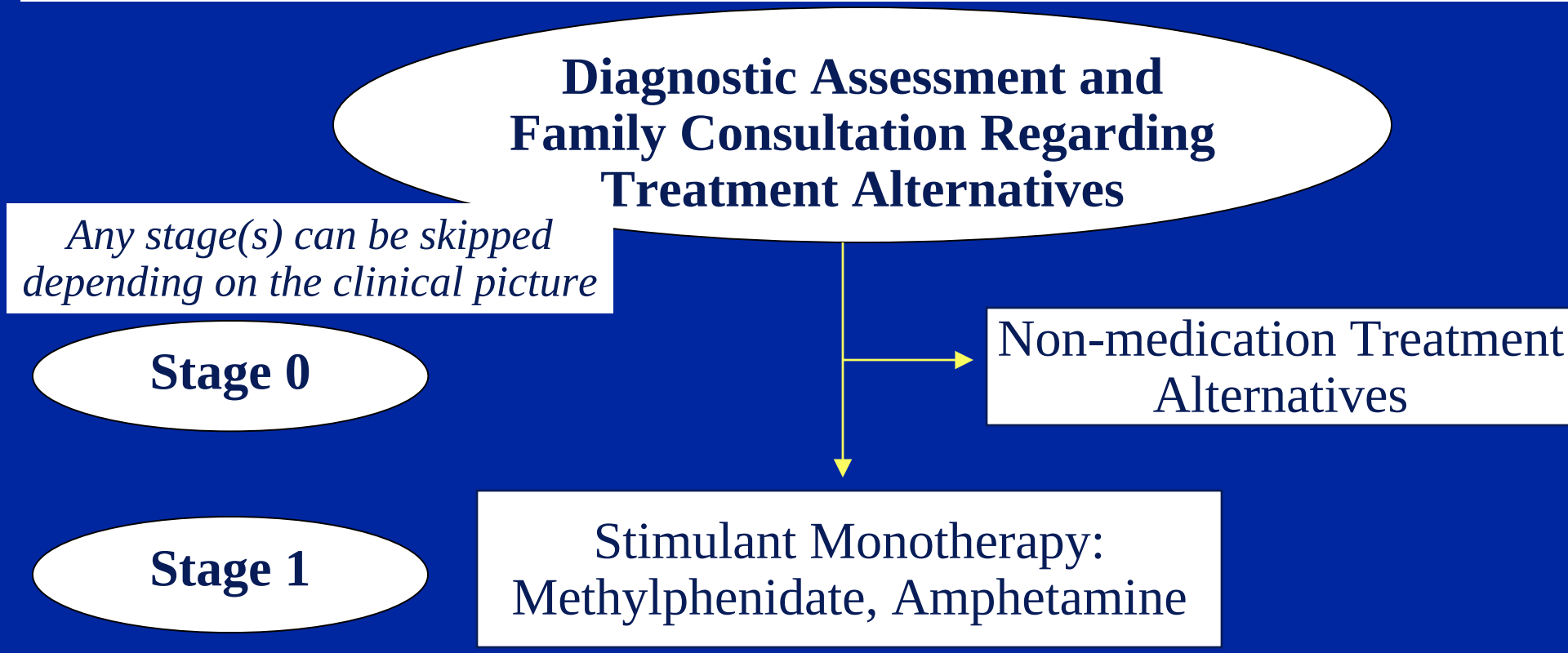
Combined Pharmacotherapy

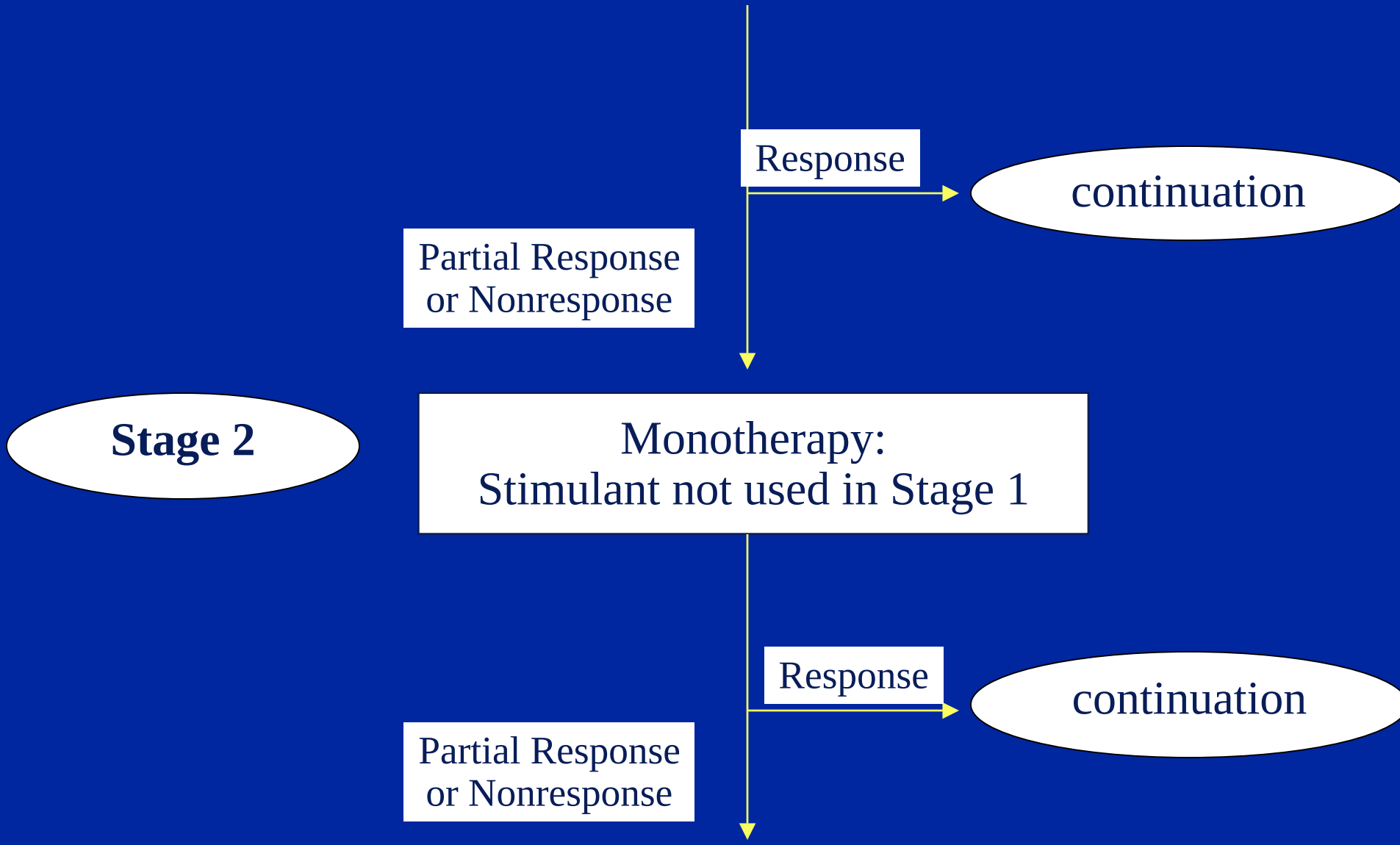
Common practice

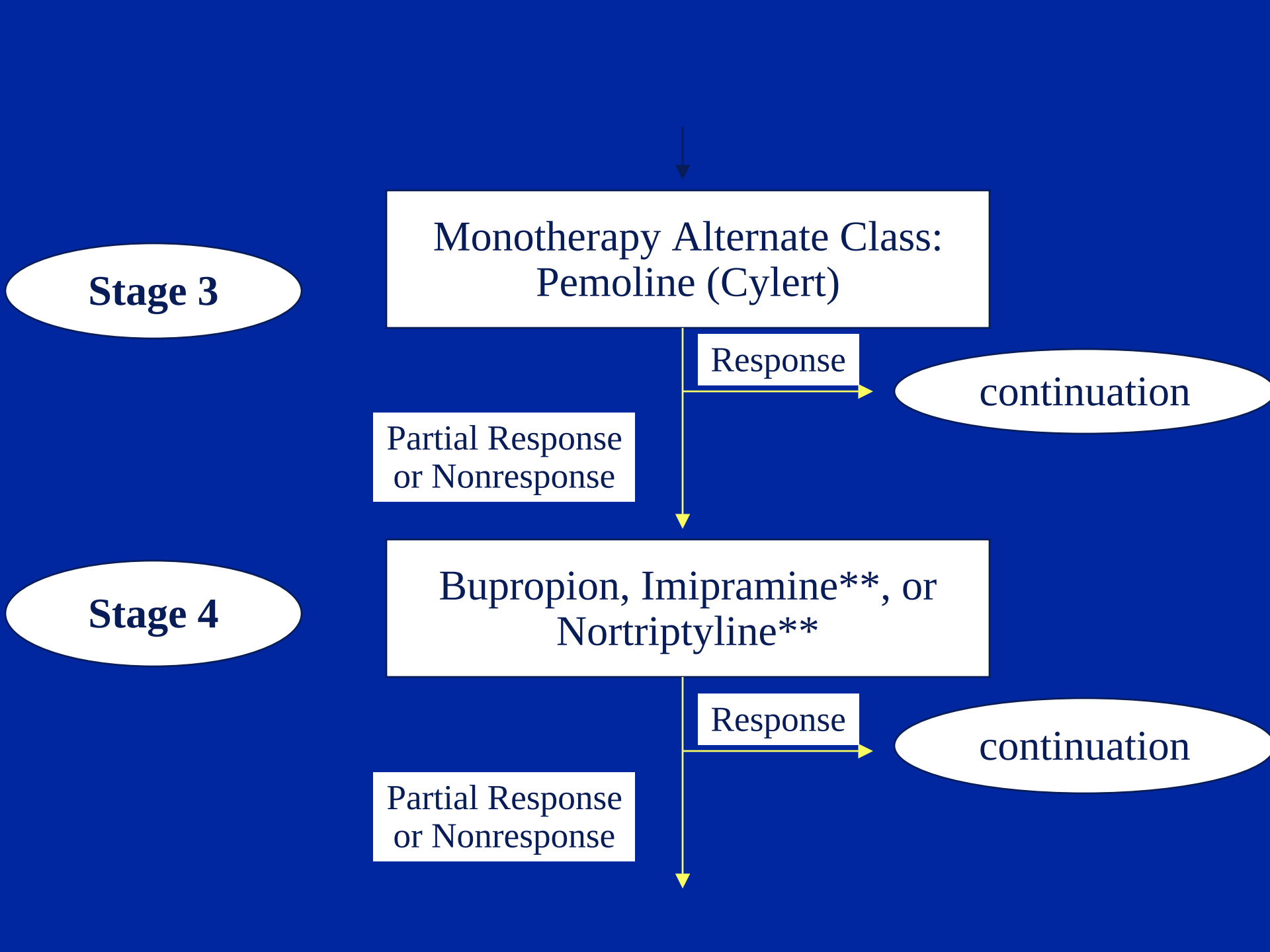
Practice far exceeds data base, controlled or open trials

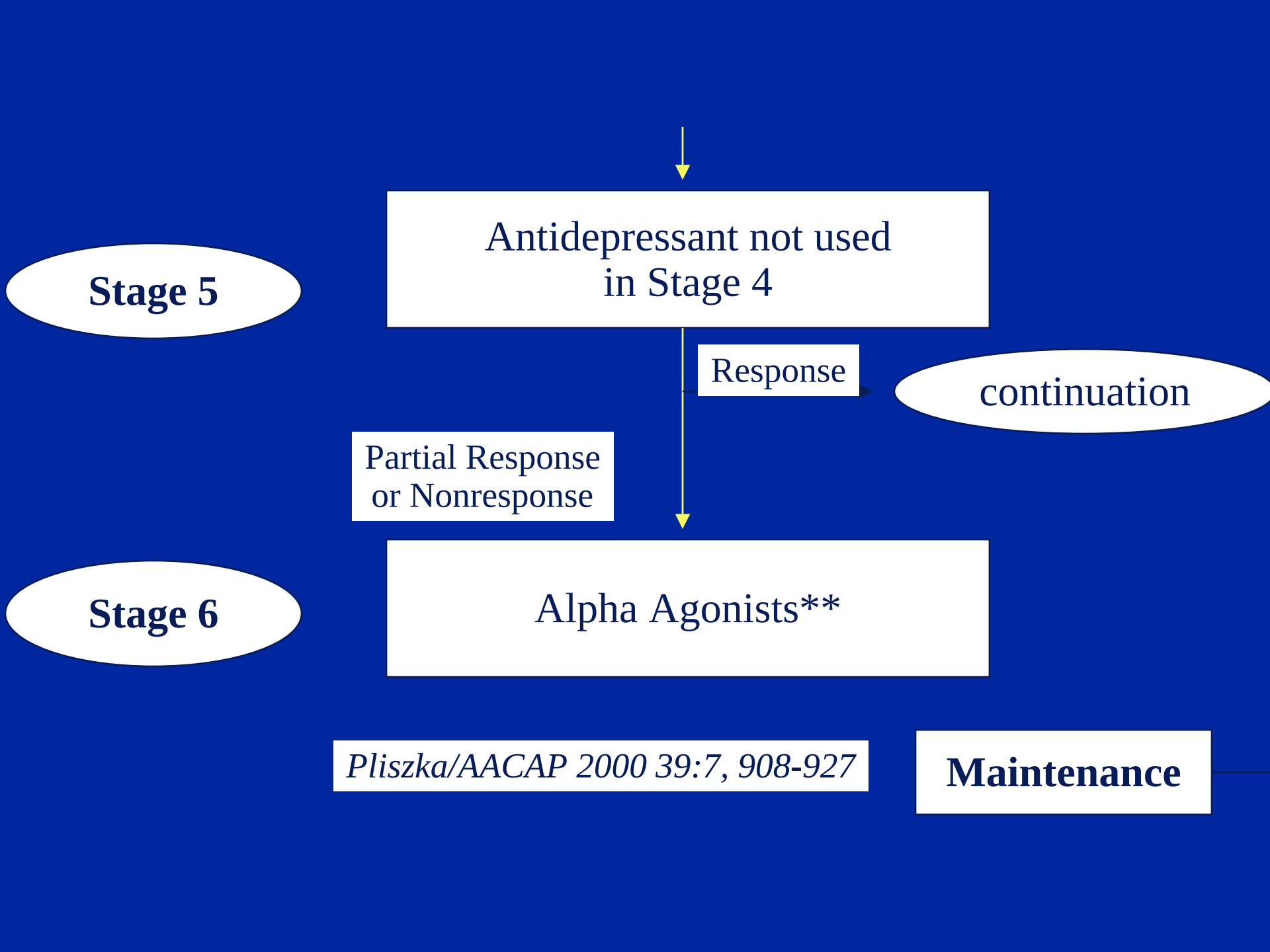

Algorithm for the medication treatment of attention-deficit/hyperactivity disorder without comorbid psychiatric disorder. *Plus liver function monitoring, securing substance abuse history and new guidelines. **Cardiovascular side effects.
Diagnostic Assessment and Family Consultation Regarding Treatment Alternatives
Stage 0
Non-medication Treatment Alternatives
Any stage(s) can be skipped depending on the clinical picture.
Stage 1
Stimulant Monotherapy: Methylphenidate, Amphetamine
Partial Response or Nonresponse
Response
continuation
Stage 2
Monotherapy: Stimulant not used in Stage 1
Partial Response or Nonresponse
Response
continuation
Stage 3
Monotherapy Alternate Class: Pemoline (Cylert)I*
Partial Response or Nonresponse
Response
continuation
Stage 4
Bupropion, Imipramine**, or Nortriptyline**
Partial Response or Nonresponse
Response
continuation
Stage 5
Antidepressant not used in Stage 4
Partial Response or Nonresponse
Response
continuation
Stage 6
Alpha Agonists**
Maintenance
Pliszka/AACAP 2000, 39:7, 908-927

Algorithm for the medication treatment of attention-deficit/hyperactivity disorder without comorbid psychiatric disorder. *Plus liver function monitoring, securing substance abuse history and new guidelines. **Cardiovascular side effects.

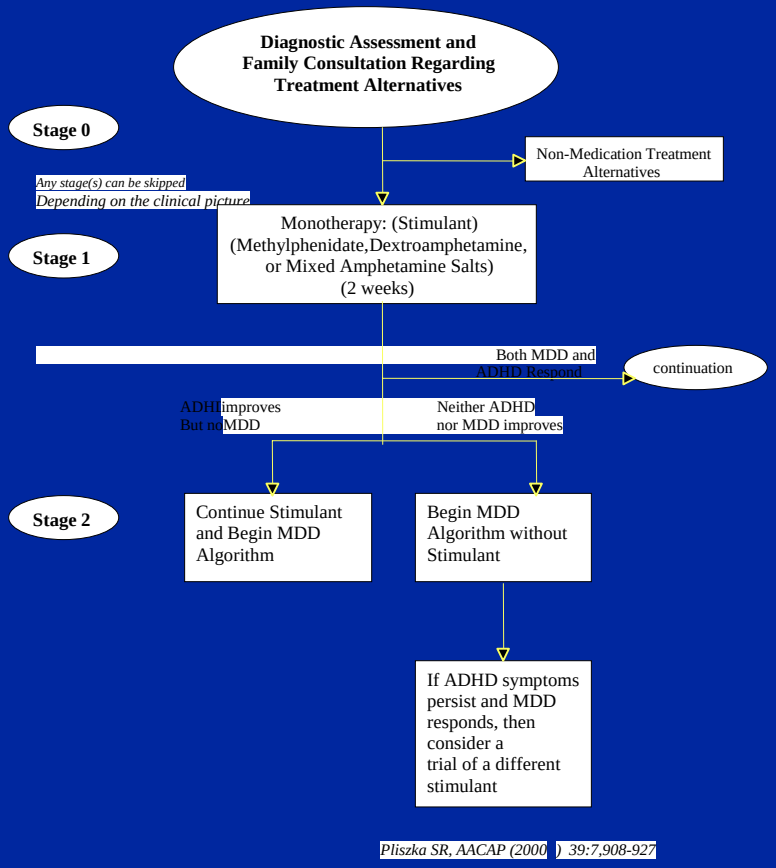



Response
continuation
Partial Response
or Nonresponse
Stage 2
Monotherapy:
Stimulant not used in Stage 1
Response
continuation
Partial Response
or Nonresponse


Stage 3
Monotherapy Alternate Class: Pemoline (Cylert)
Response
continuation
Partial Response or Nonresponse
Stage 4
Bupropion, Imipramine**, or Nortriptyline**
Response
continuation
Partial Response or Nonresponse

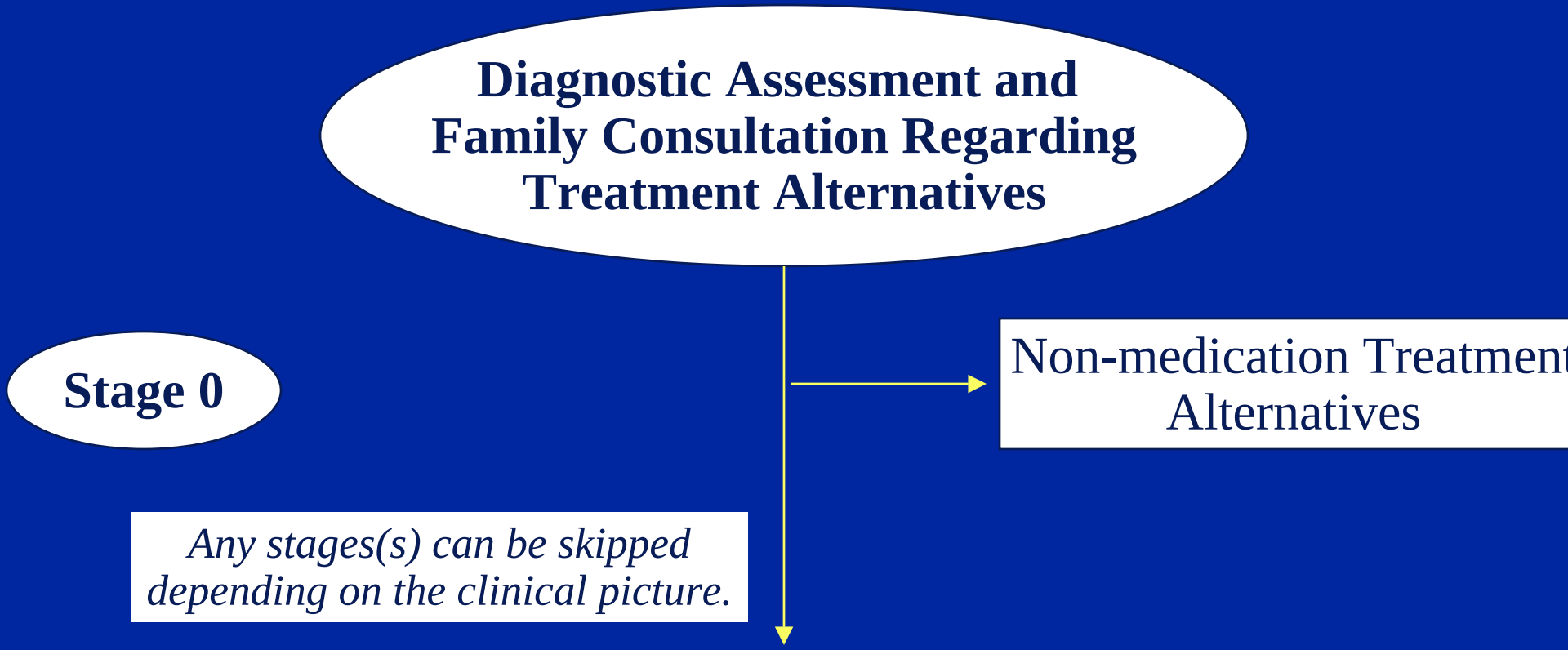

Stage 5
Antidepressant not used
in Stage 4
Response
continuation
Partial Response
or Nonresponse
Stage 6
Alpha Agonists**
Pliszka/AACAP 2000 39:7, 908-927
Maintenance

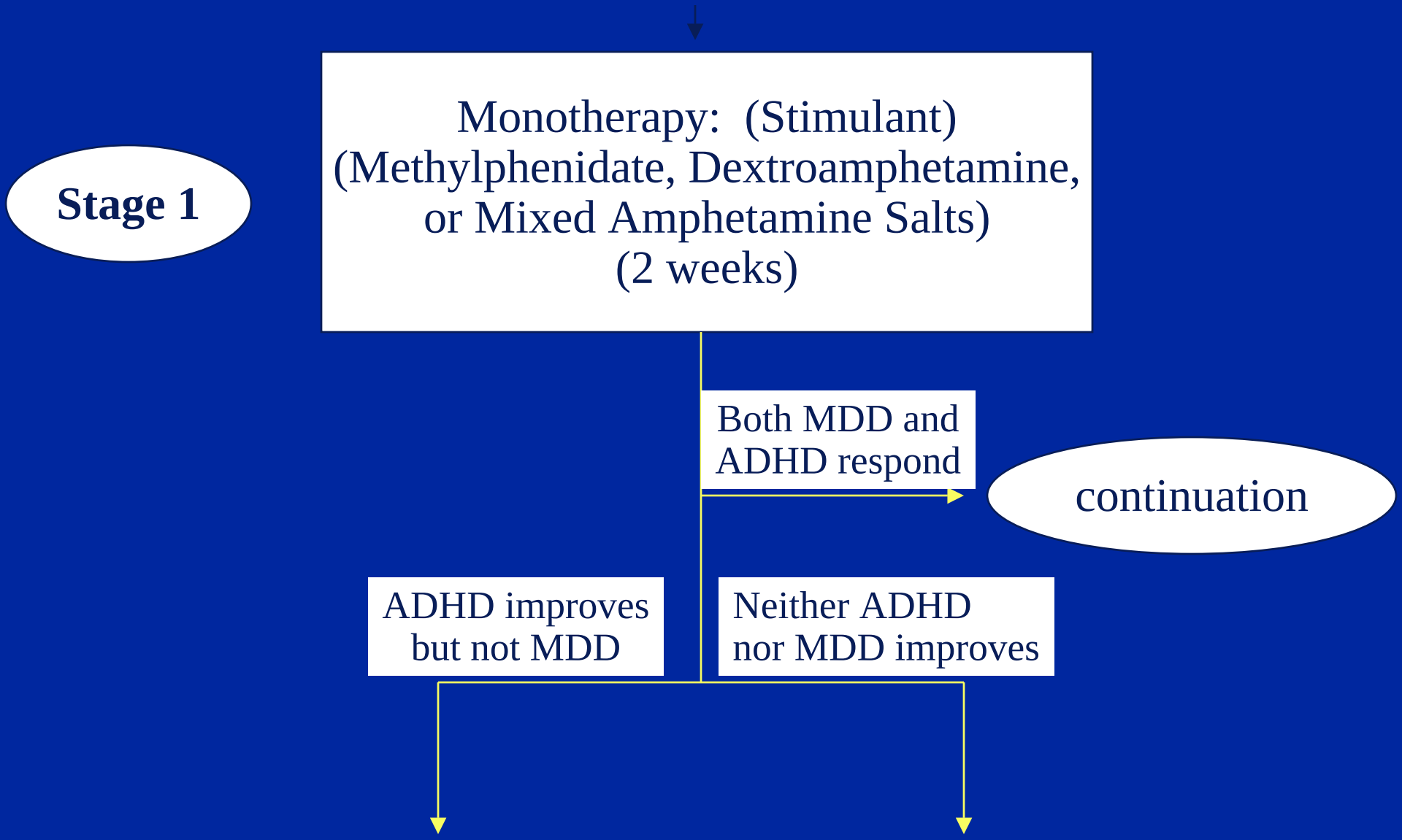
Algorithm for the medication treatment of attention-deficit/hyperactivity disorder (ADHD) with comorbid depressive or anxiety disorder. MDD -- major depressive disorder.



Pliszka SR, AACAP (2000) 39:7,908-927

Algorithm for the medication treatment of attention-deficit/ hyperactivity disorder (ADHD) with comorbid depressive or anxiety disorder. MDD --major depressive disorder.




Stage 1
Monotherapy: (Stimulant)
(Methylphenidate, Dextroamphetamine,
or Mixed Amphetamine Salts)
(2 weeks)
Both MDD and
ADHD respond
continuation
ADHD improves
but not MDD
Neither ADHD
nor MDD improves

Stage 2

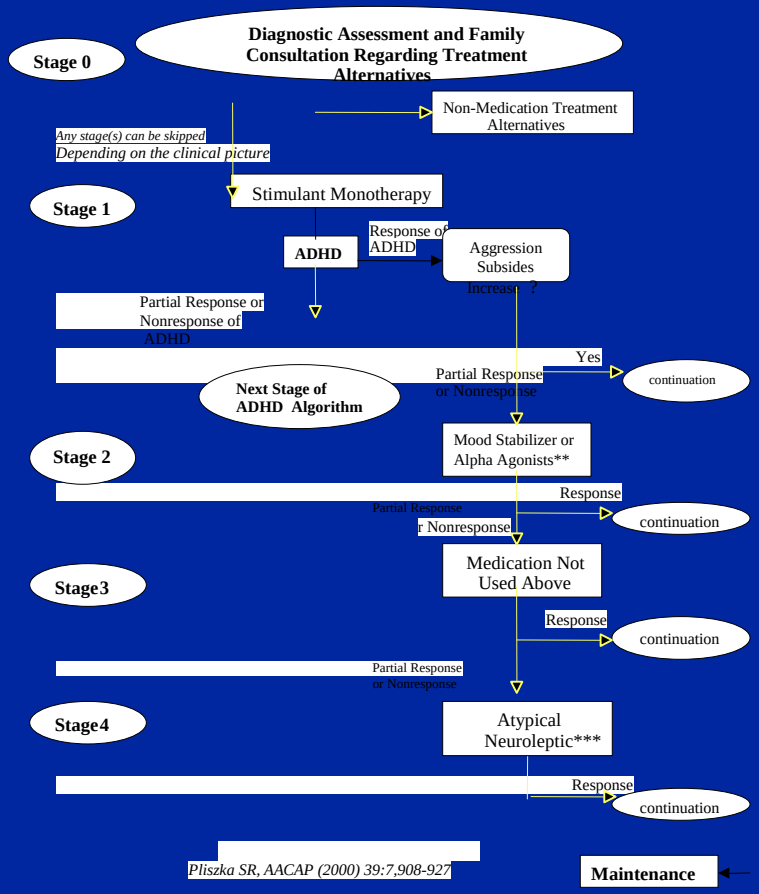
Continue stimulant and begin MDD algorithm

Begin MDD algorithm without stimulant

If ADHD symptoms persist and MDD responds, then consider a trial of a different stimulant

Pliszka SR, AACAP (2000) 39:7, 908-927

Algorithm for the medication treatment of attention-deficit/hyperactivity disorder (ADHD) with comorbid intermittent explosive disorder. **Caution: Cardiovascular side effects. ***Caution: risk of extrapyramidal symptoms of tardive dyskinesia.



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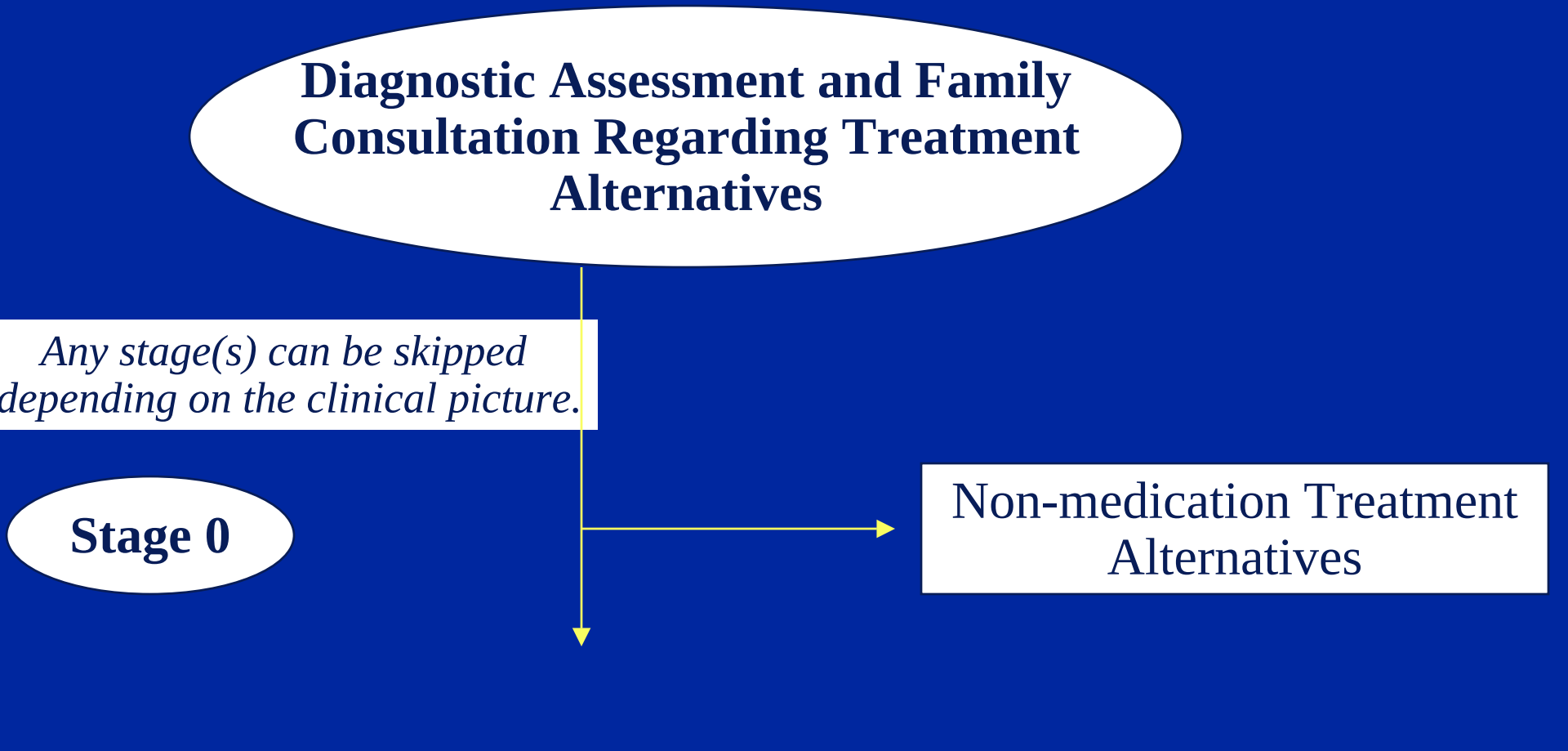
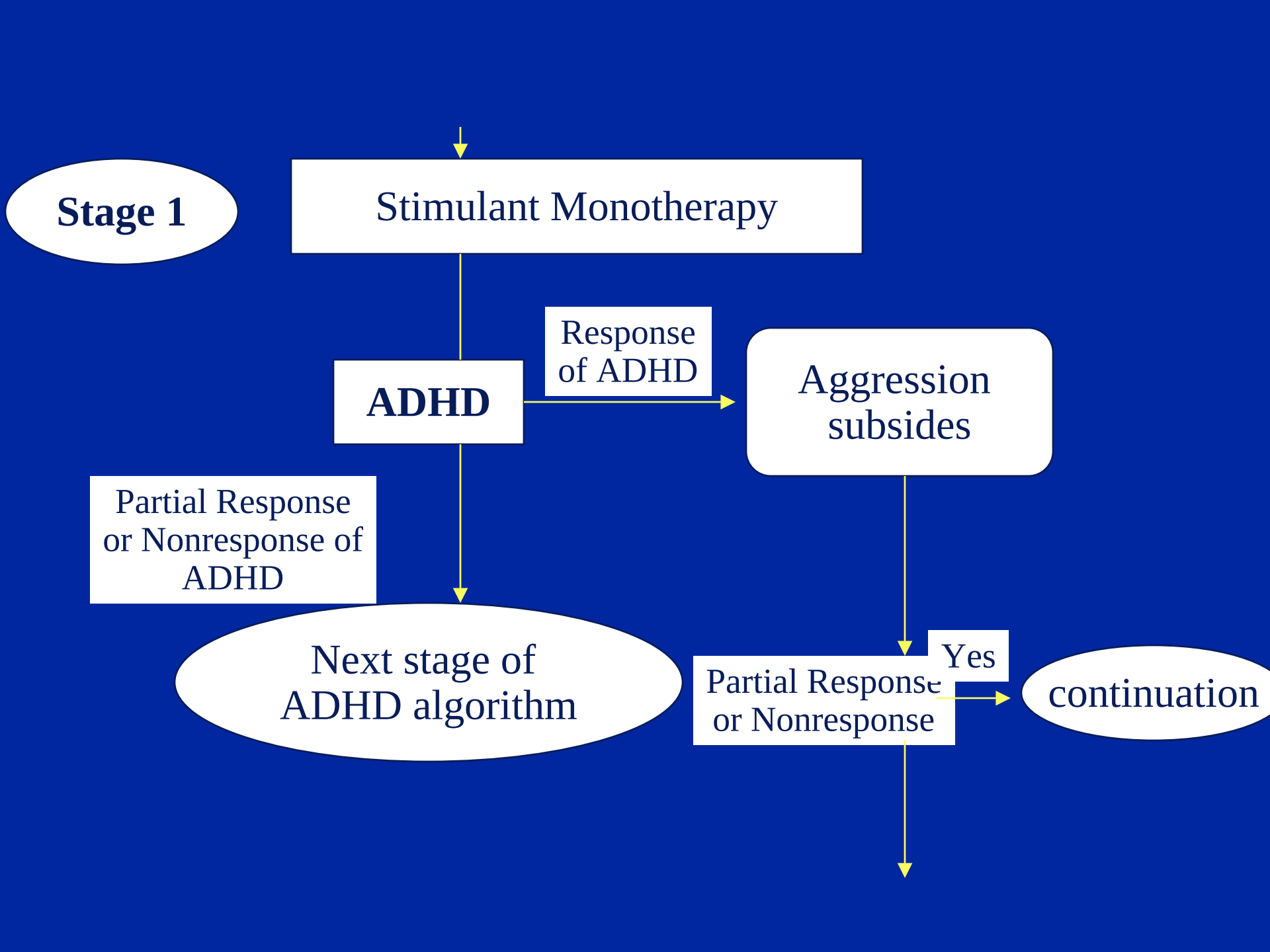
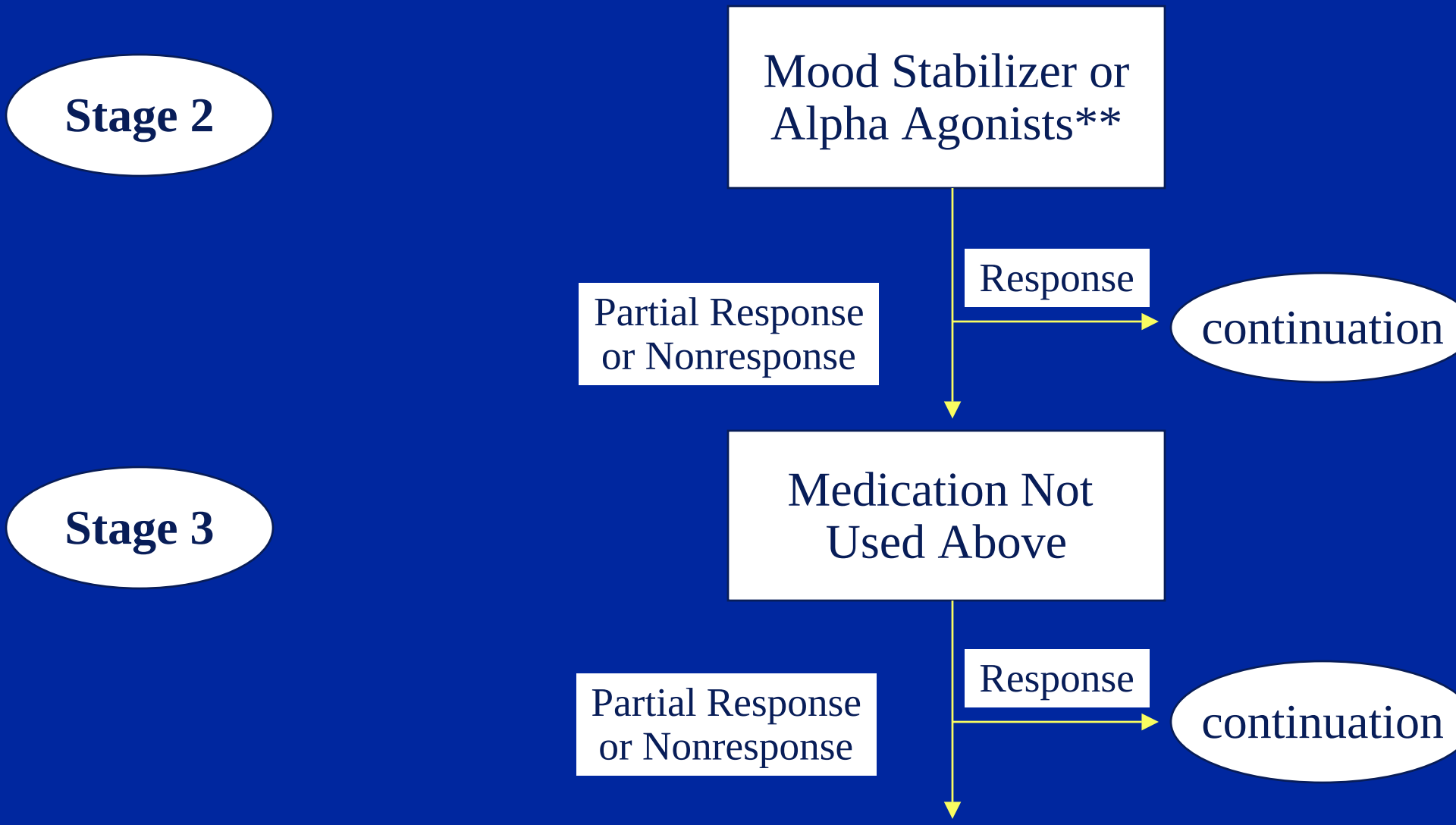



Stage 1
Stimulant Monotherapy
ADHD
Response of ADHD
Aggression subsides
Partial Response or Nonresponse of ADHD
Next stage of ADHD algorithm
Partial Response or Nonresponse
Yes
continuation


Stage 2
Mood Stabilizer or Alpha Agonists**
Response
continuation
Partial Response or Nonresponse
Stage 3
Medication Not Used Above
Response
continuation
Partial Response or Nonresponse

Stage 4

Atypical Neuroleptic***

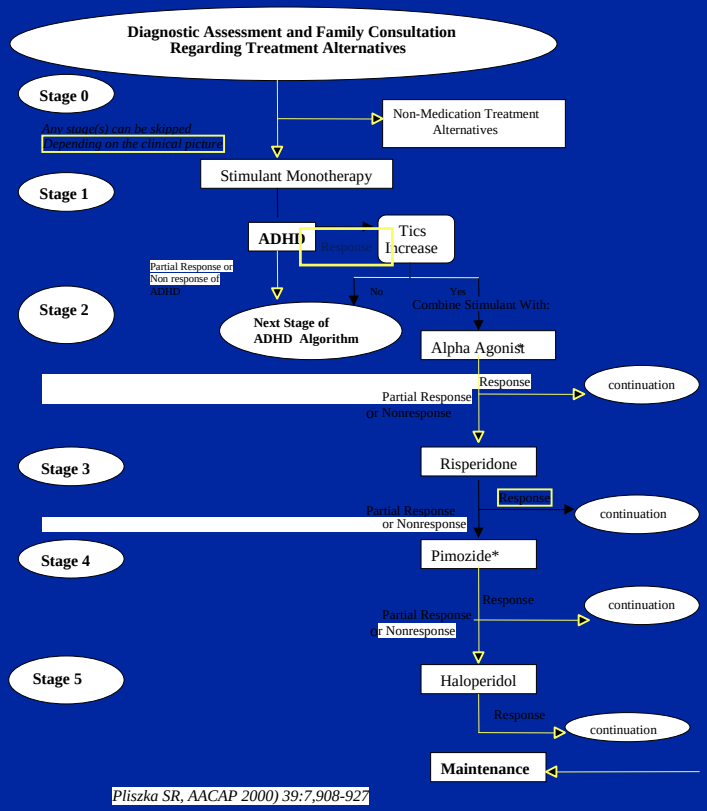
Response

continuation

Pliszka SR, AACAP (2000) 39:7, 908-927

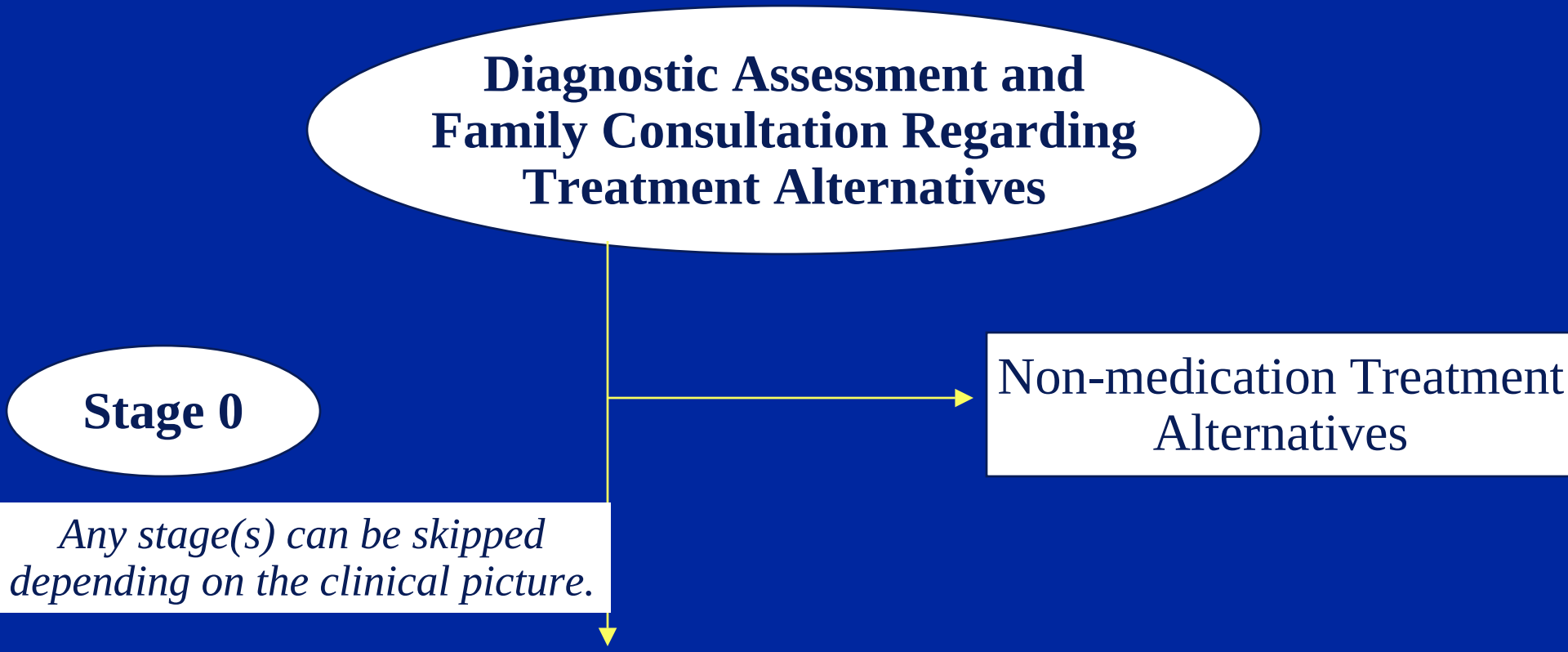
Maintenance

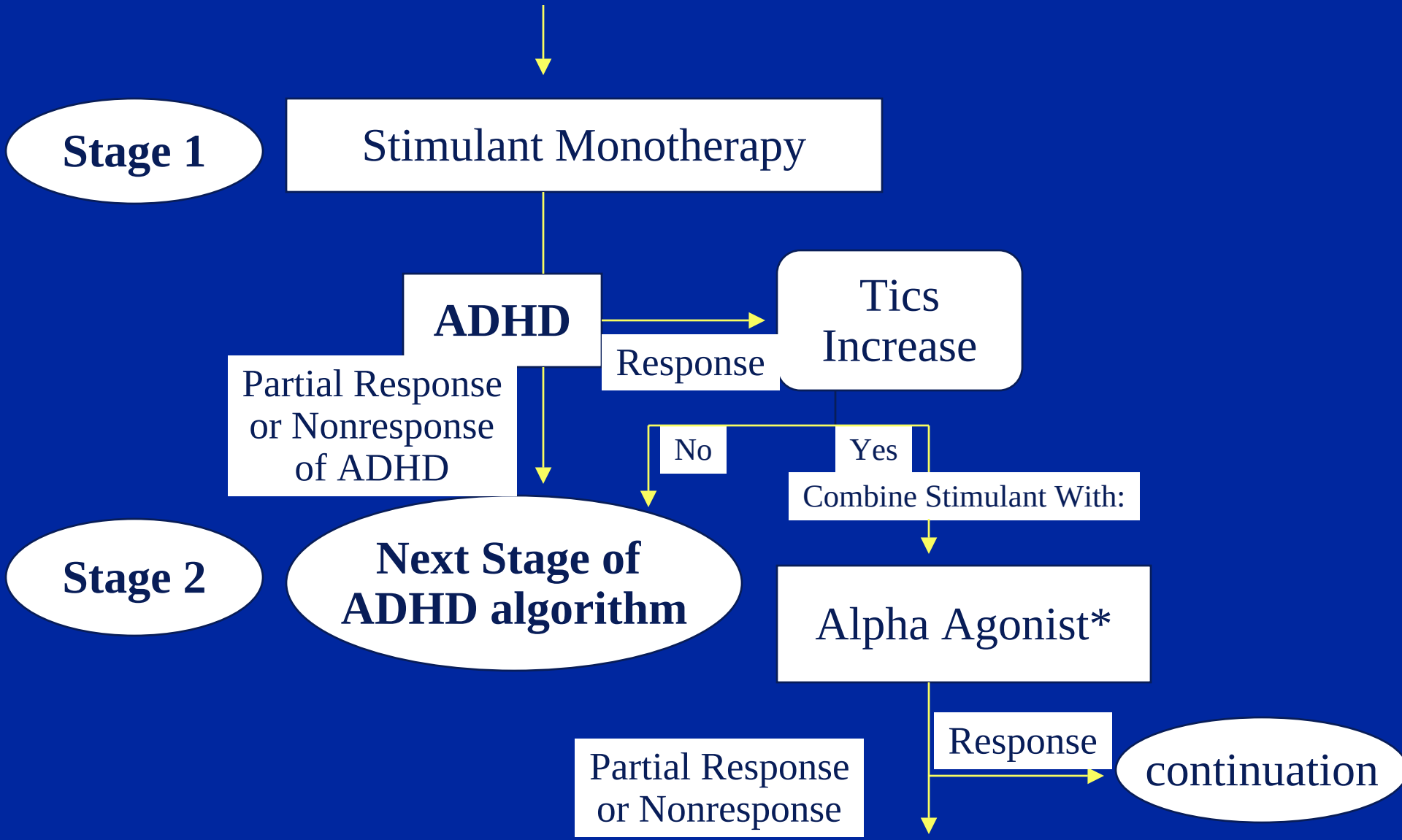
Algorithm for the medication treatment of attention-deficit/hyperactivity disorder (ADHD) with comorbid tic disorder. *Caution: cardiovascular side effects.

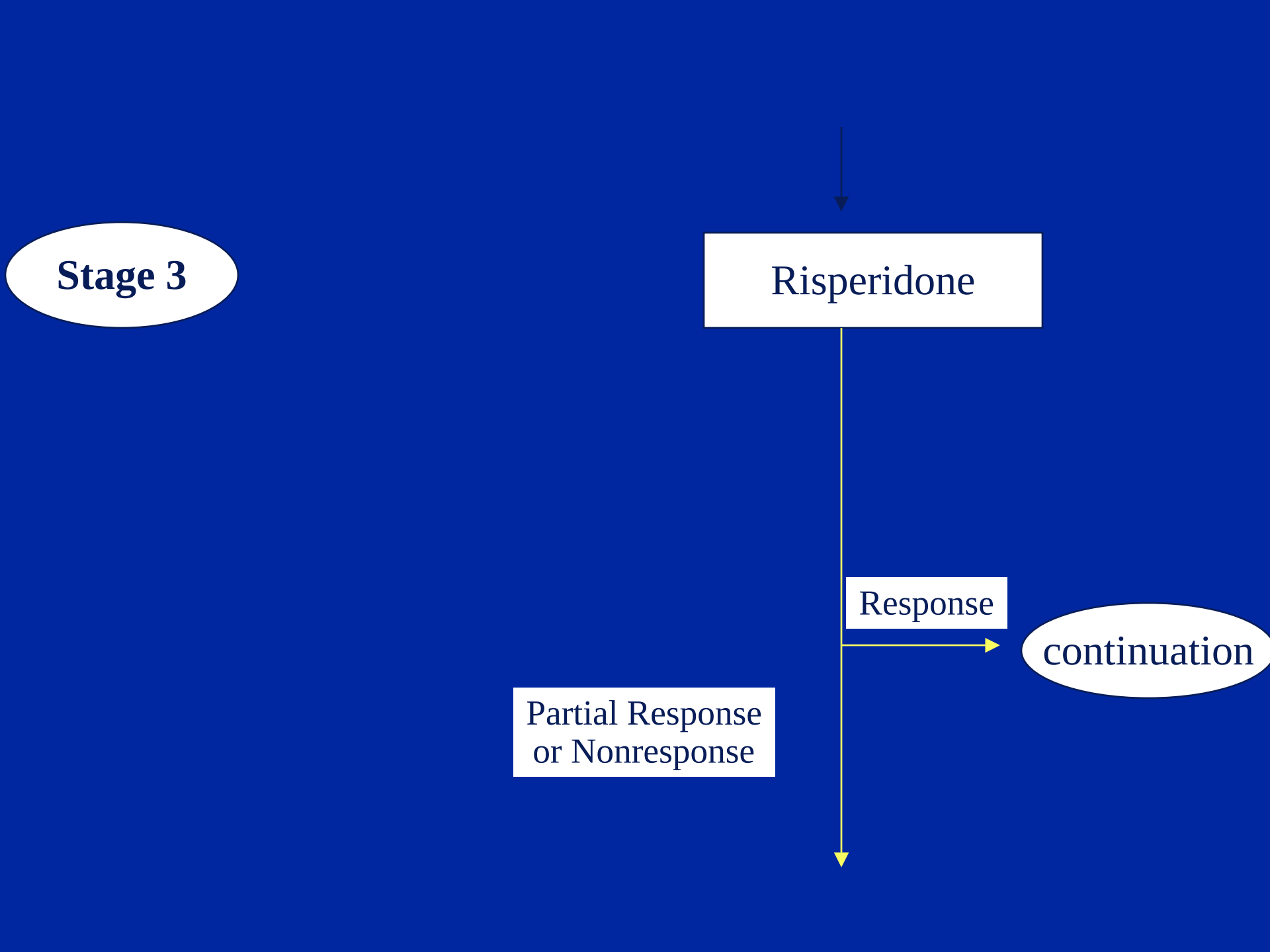


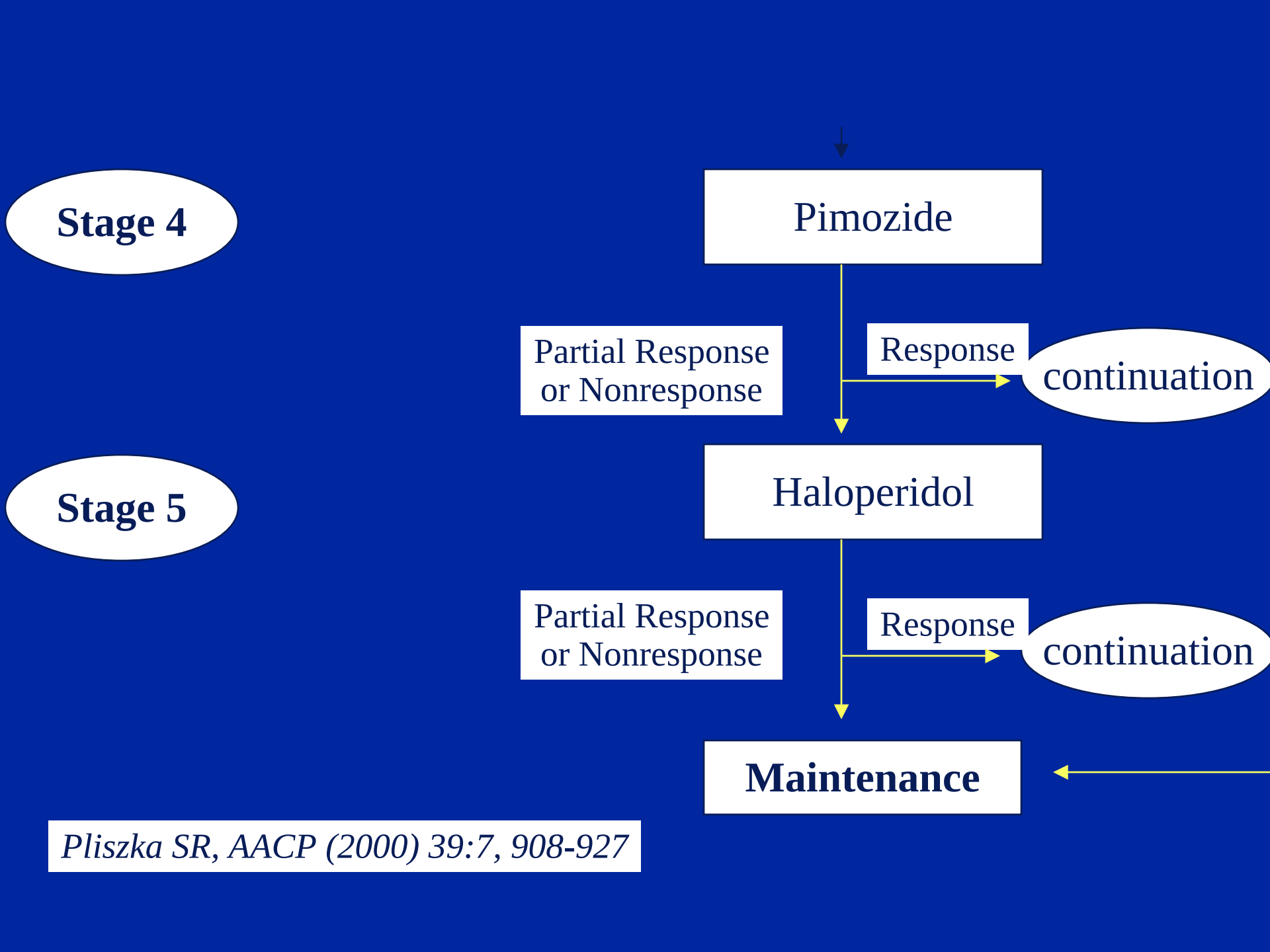
Pliszka SR, AACAP 2000) 39:7,908-927

Algorithm for the medication treatment of attention-deficit/ hyperactivity disorder (ADHD) with comorbid tic disorder.
*Caution: cardiovascular side effects.




Stage 1
Stimulant Monotherapy
ADHD
Partial Response or Nonresponse of ADHD
Response
Tics Increase
No
Yes
Combine Stimulant With:
Stage 2
Next Stage of ADHD algorithm
Alpha Agonist*
Response
continuation
Partial Response or Nonresponse


Stage 3
Risperidone
Response
continuation
Partial Response
or Nonresponse



Pliszka SR, AACP (2000) 39:7, 908-927

REFERENCES

American Academy of Child and Adolescent Psychiatry. Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. J Am Acad child Adolesc Psychiatry. 1997;36:1-15.

American Academy of Pediatrics. Clinical practice guidelines: diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. Pediatrics. 2000;105(5):1158-1170.

American Academy of Pediatrics. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108(4):1033-1044.

Angold A, Erkanli A, Egger HL, et al. Stimulant treatment for children: A community perspective. J Amer Acad Child Adoles Psych 2000;39:975-984

Beiderman J, Klein RG, Pine DF, Klein DF. Mania is mistaken for ADHD in prepubertal children. Affirmative: J Am Acad child Adolesc Psychiatry. 1998;37(10):1091-1093.

Jensen PS, Kettle L, Roper MT., et al. Are stimulants over prescribed? Treatment of ADHD in four U.S. communities. J Amer Acad Child Adoles Psych 1999;38:797-804.

MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 1999;56:1073-1086.

ADHD A Complete and Authoritative Guide. Michael I. Reife, M.D., FAAP, Editor with Sherill Tippins. Amer Acad Pediatrics 2003.