

An Update on AD/HD in Childhood and Adulthood

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PNNS - January 12, 2008

Converging on Consensus

- *AD/HD as a (heterogenous) Neurobehavioral Disorder*
 - Deriving from brain systems, affecting behavior
- *AD/HD as a Neurodevelopmental Disorder*
 - Unfolding with development, affecting development
- *Centrality of Comorbidity*
- *Efficacy of Medical Treatment*
- *Importance of a Multimodal Approach*
- *Chronic Illness Model*
 - Focus on Management and Coping Skills

Presumed Genetic Basis

- Concordance in immediate families
 - 15-20% in Mothers; 25-30% in Fathers; 32% in siblings
- MZ vs. DZ twin studies
 - Concordance of 50%-80% for MZ; 0%-33% for DZ
 - Genetic factors account for 30%-40% of variance in symptom presentation
 - Heritability of .75 to .91 (Levy, et. al. 1997: Australian sample of 1938 families with twins and siblings age 4-12)
- Adoption studies
 - Genetic factors: 47% of the variance in CBCL Attention Problems Index (biol. parents and adopted-out children)
 - Moderate relationship between F's criminality and AD/HD in their offspring

Candidate Genes

- But: “Although overall findings lend some confidence to a tentative conclusion that (dopamine) DAT1 and DRD4 genes are among the family of genes that are involved in ADHD, much more research is needed to confirm the possible involvement of (catechol-) COMT and (noradrenergic) polymorphisms. More challenging will be the task of unraveling how any of the proposed genes operate together over the course of development and in interaction with environmental forces to produce the final common pathway known as ADHD. In and of themselves, each specific gene only conveys a very modest risk for the disorder, and most likely under its own set of specific environmental circumstances and developmental time frames” (Jensen, C&A Psy Clin NA, July 2000, 9:3)

Acquired AD/HD (“Phenocopies”)

- Behavioral syndromes that closely resemble AD/HD but have different etiologies.
 - Ischemic pre- and peri-natal events:
 - Maternal smoking:
 - 22% of AD/HD (vs. 8% of normals) had mothers who smoked a pack/day for at least 3 months (Milberger et. al. 1996)
 - Accounted for 29% of variance in AD/HD symptomatology [and 47% of mothers of “at risk” kids smoked (vs. 24% normals)] Milberger et. al. 1998)
 - Low birth weight babies (who have hypoxia and ischemia)
 - AD/HD in 22-34% of low birth weight children (<1500 grams)

Acquired AD/HD (“Phenocopies”)

- Ischemic pre- and peri-natal events:
 - Fetal Alcohol Syndrome and Fetal Alcohol Effects
 - Dose-related effects on growth, cognition and behavior
 - High Levels of Family Problems and Emotional Stress during Pregnancy (23% vs 11%)
- Toxins:
 - Cumulative Lead Exposure
 - dose related effects on learning and attentional problems, as well as depression and aggression
- Traumatic Brain Injury
- All these are preventable!

Acquired AD/HD (“Phenocopies”)

- Other neurologically-based disorders
 - Epilepsy, prior CNS infection, progressive neurometabolic diseases, Tourette’s Syndrome, etc.
 - In children, early manifestations of developing Schizophrenia or Bipolar Disorder may meet criteria for AD/HD
- Although phenocopies often respond to standard AD/HD treatment, they need to be distinguished in both treatment and research

AD/HD as a Frontal-Subcortical Disorder

- At least 5 major Frontal-Subcortical circuits, three of which are behaviorally-relevant:
 - Dorsolateral Prefrontal – mediates “executive” functioning
 - Anterior Cingulate – motivational mechanisms
 - Orbitofrontal – personality and emotion
 - Lateral – integration of emotional information into appropriate behavioral responses
 - Medial – integration of visceral-amygdalar functions
 - Motor
 - Oculomotor

Neuropsychological
Manifestations of Frontal Lobe
Lesions II

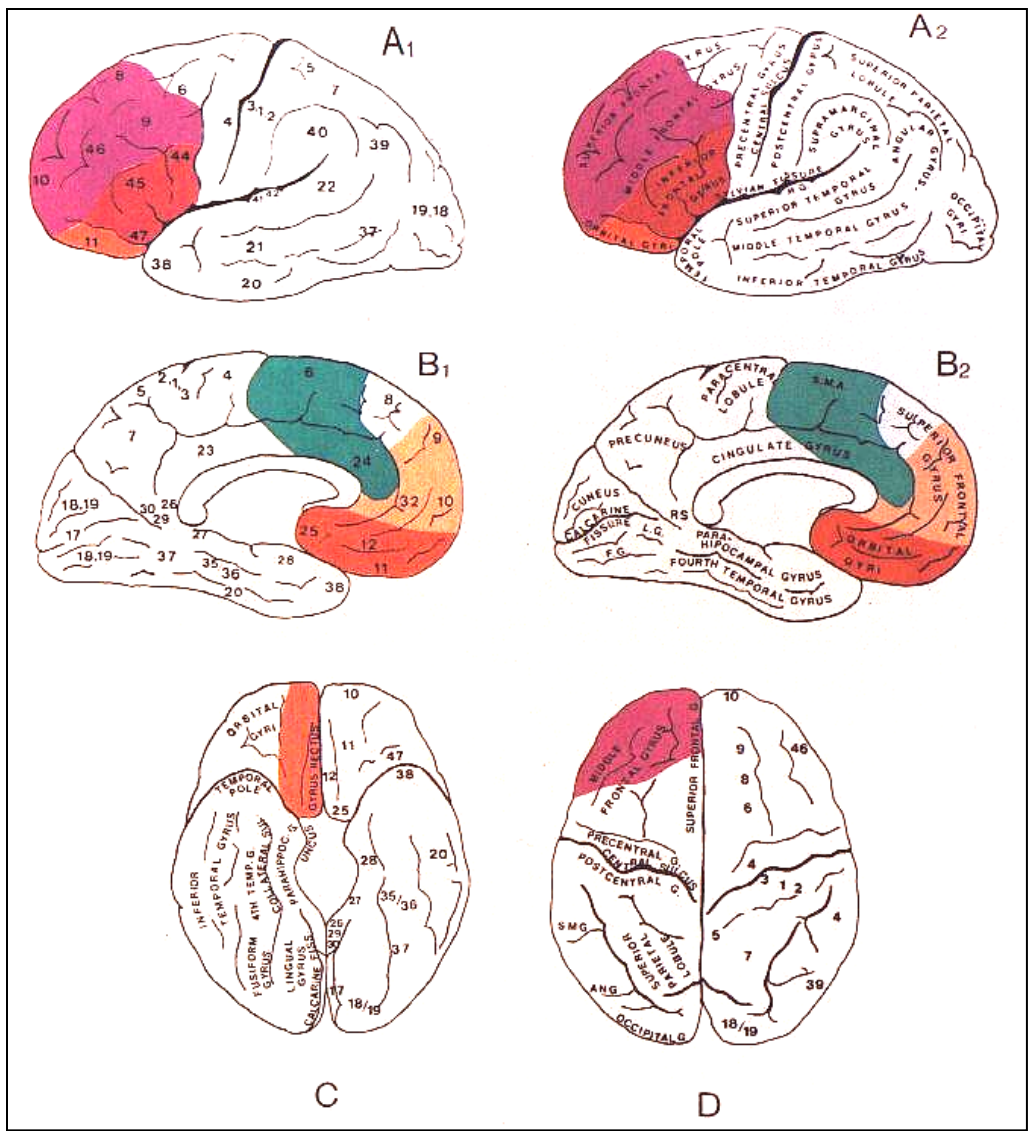
Inferior Mesial Region

A) Orbital Region (10, 11)

Lesions in this region produce disinhibition, altered social conduct, “acquired sociopathy”, and other disturbances due to impairment in fronto-limbic relationships

B) Basal Forebrain (posterior extension of inferior mesial region, including diagonal band of Broca, nucleus accumbens, septal nuclei, substantia innominata)

Lesions here produce prominent anterograde amnesia with confabulation (material specificity present, but relatively weak)



Tranel, 1992

Neuropsychological Manifestations of Frontal Lobe Lesions III

Lateral Prefrontal Region (8,9,46)

Lesions in this region produce impairment in a variety of “executive” skills that cut across domains. Some degree of material-specificity is present, but relatively weak.

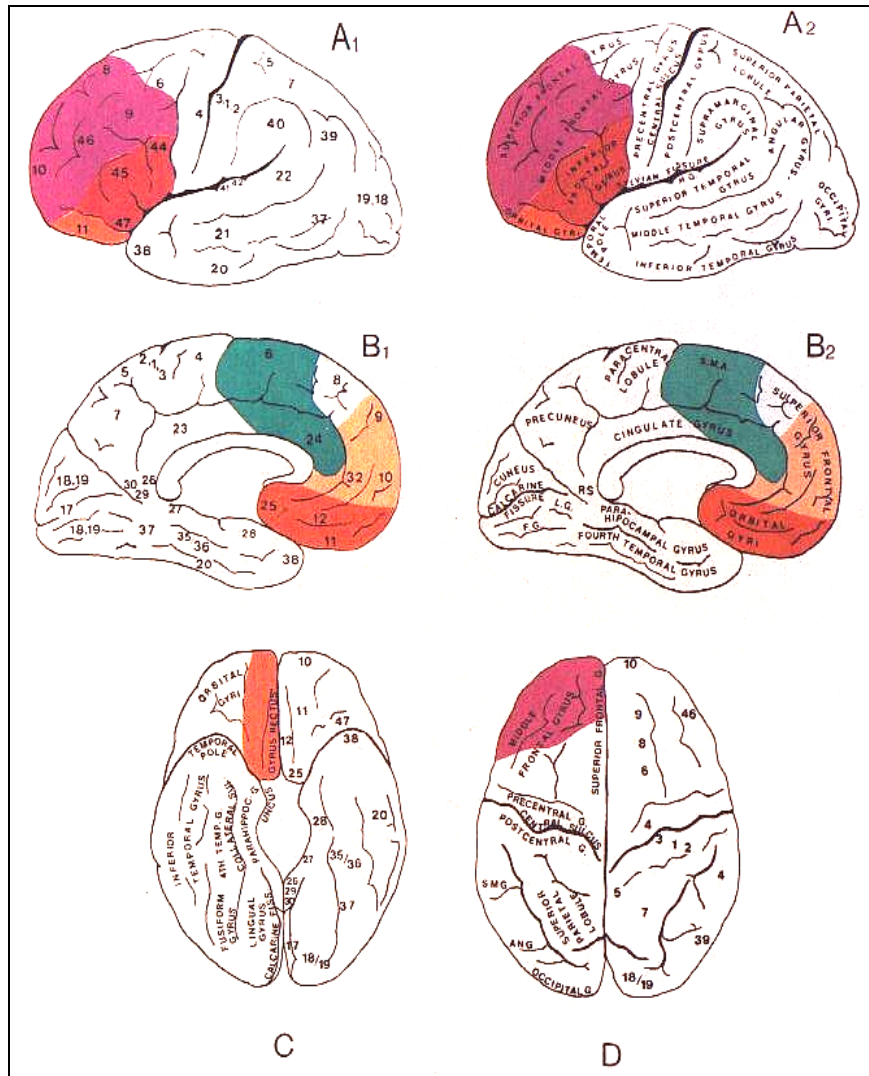
A) Fluency: impaired verbal fluency (left) or design fluency (right)

B) Memory impairments: defective recency judgment, metamemory defects, difficulties in memory monitoring

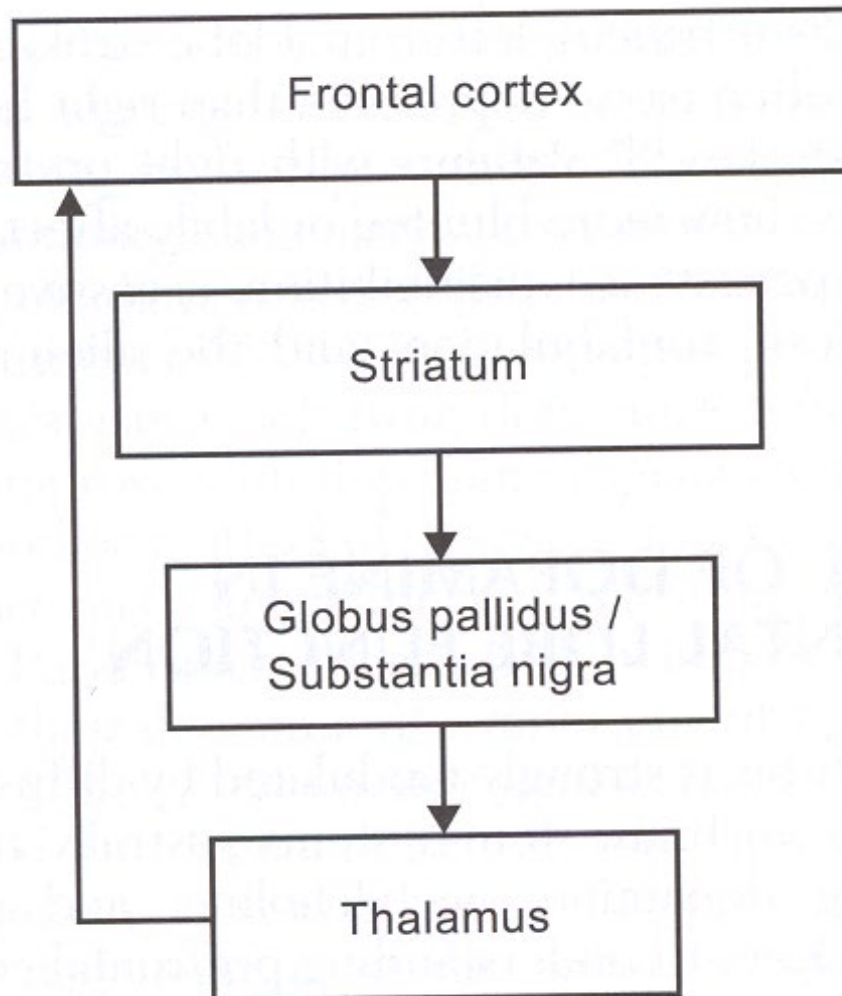
C) Impaired abstract concept formation and hypothesis testing

D) Defective planning, motor sequencing

E) Defective cognitive judgement and estimation



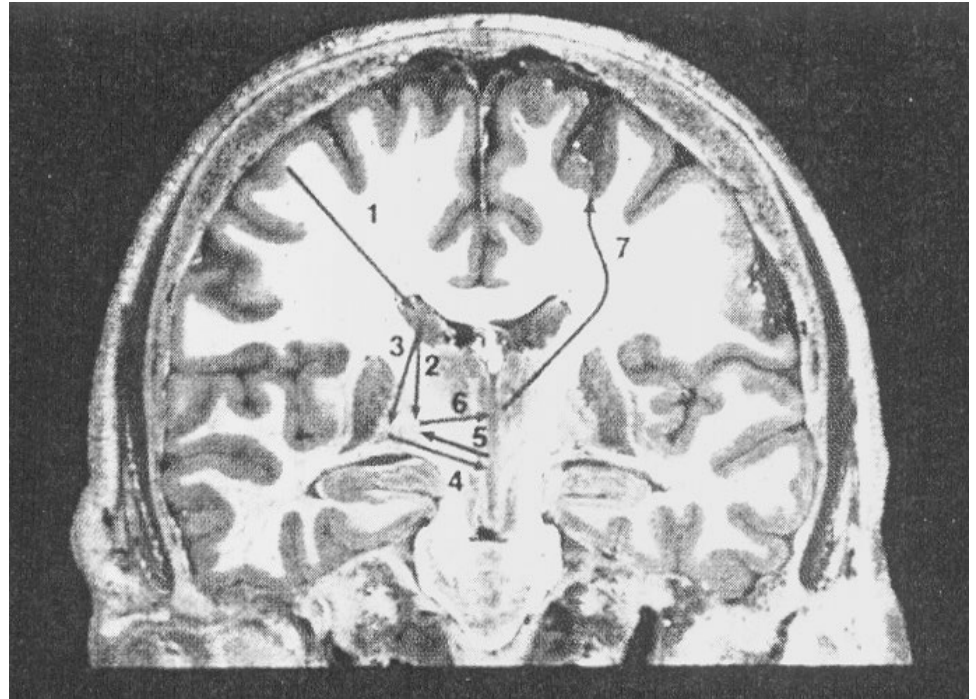
General Organization of Frontal cortical-striatal-pallidal-thalamic-cortical loops

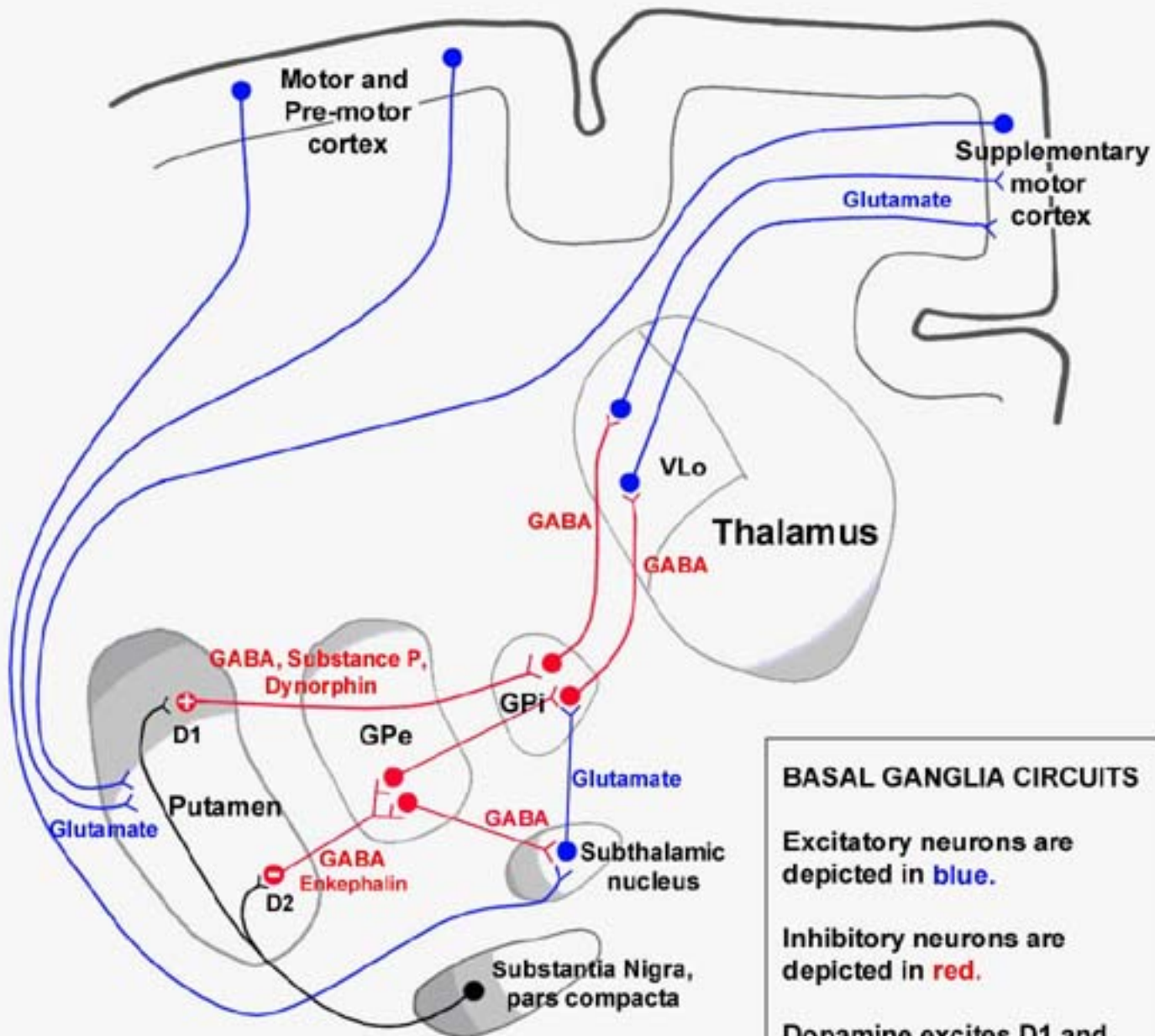


Frontal-Subcortical Circuitry

1. Excitatory glutamatergic
2. Direct Inhibitory
GABA/enkephalin (D1)
3. Indirect inhibitory
GABA/enkephalin (D2)
4. Indirect inhibitory GABA
5. Indirect excitatory
glutamatergic
6. Inhibitory outflow GABA
7. Excitatory

(Litvan et. al. 1998)





BASAL GANGLIA CIRCUITS

Excitatory neurons are depicted in blue.

Inhibitory neurons are depicted in red.

Dopamine excites D1 and inhibits D2 receptors.

TABLE 16.2 Four Parallel Channels through the Basal Ganglia

SOURCES OF CORTICAL INPUT	BASAL GANGLIA INPUT NUCLEI	BASAL GANGLIA OUTPUT NUCLEI ^a	THALAMIC RELAY NUCLEI ^b	CORTICAL TARGETS OF OUTPUT
MOTOR CHANNEL				
Somatosensory cortex; primary motor cortex; premotor cortex	Putamen	GPi, SNr	VL, VA	Supplementary motor area; premotor cortex; primary motor cortex
OCULOMOTOR CHANNEL				
Posterior parietal cortex; prefrontal cortex	Caudate, body	GPi, SNr	VA, MD	Frontal eye fields; supplementary eye fields
PREFRONTAL CHANNEL				
Posterior parietal cortex; premotor cortex	Caudate, head	GPi, SNr	VA, MD	Prefrontal cortex
LIMBIC CHANNEL				
Temporal cortex; hippocampus; amygdala	Nucleus accumbens; ventral caudate; ventral putamen	Ventral pallidum; GPi; SNr	MD, VA	Anterior cingulate; orbital frontal cortex

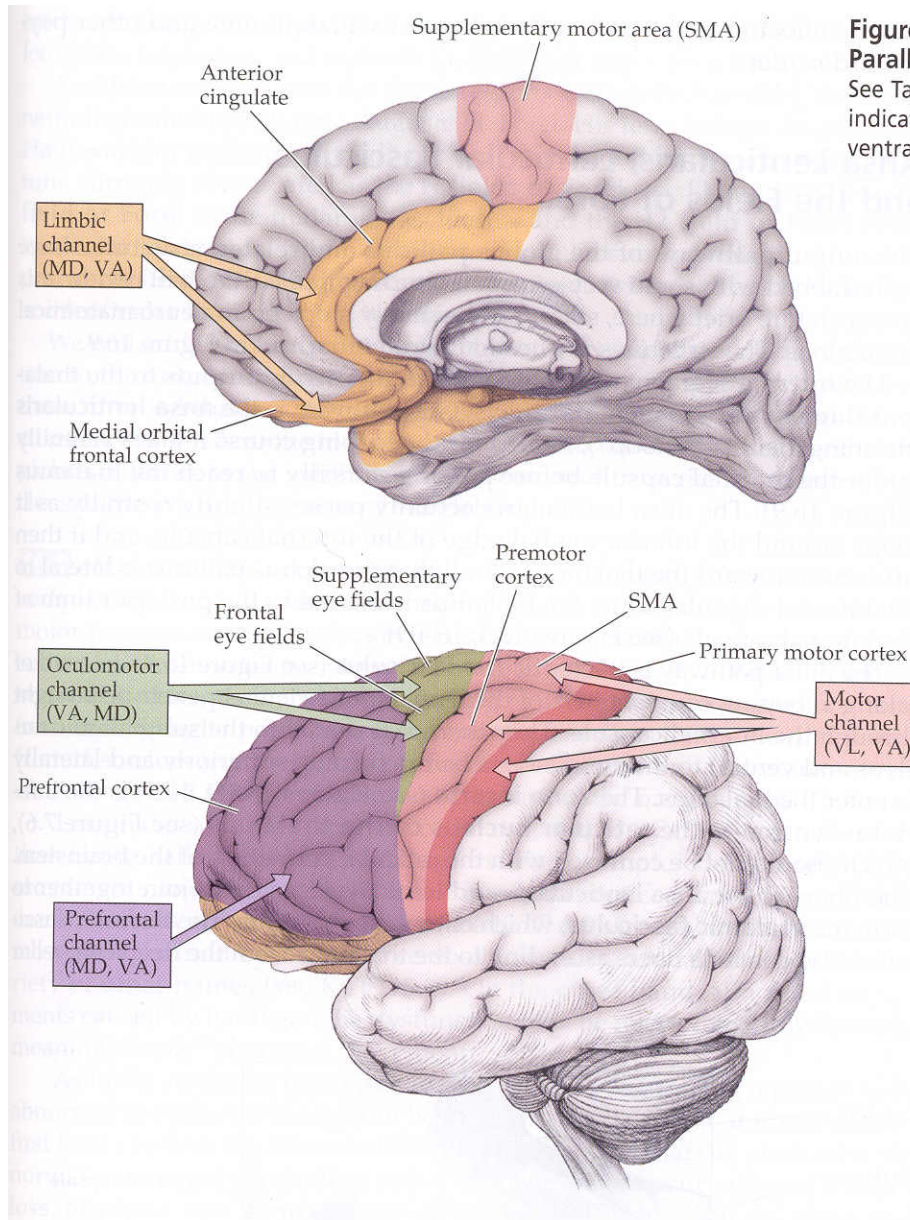
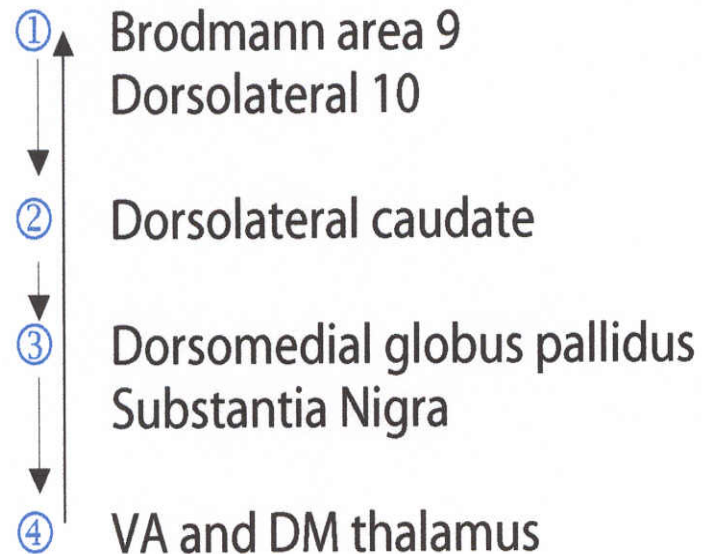


Figure 16.8 Frontal Lobe Outputs of the Four Parallel Channels through the Basal Ganglia
 See Table 16.2. Thalamic origins of the outputs are indicated. Thalamic nuclei: VL, ventral lateral; VA, ventral anterior; MD, mediodorsal.

Dorsolateral Loop

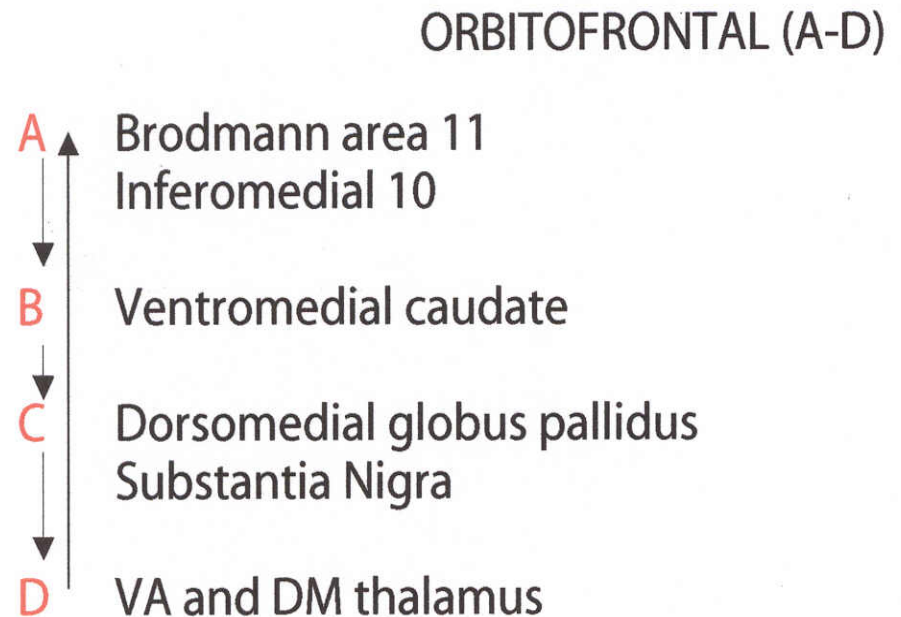
- Critical for executive function
- Damage produces
 - Inflexibility
 - Planning
 - Problem-solving
 - Goal-directed behavior

DORSOLATERAL (1-4)



Orbitofrontal Loop

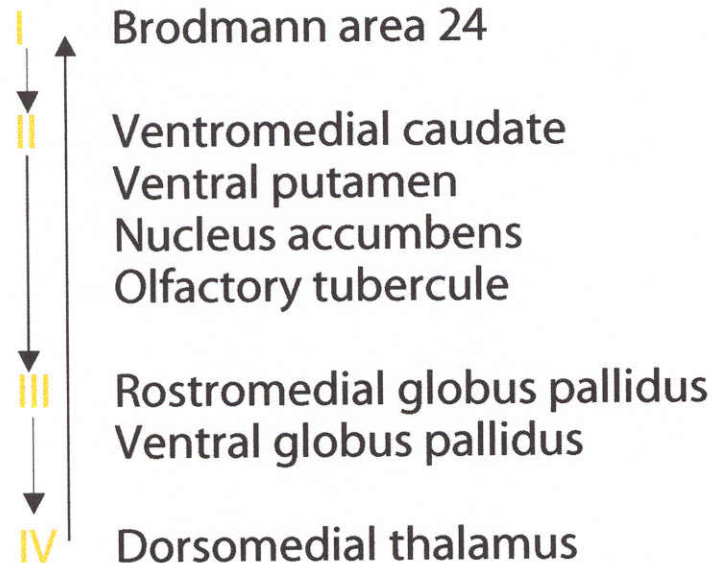
- Involved in social and emotional functioning
- Damage produces:
 - Disinhibition
 - Hyperactivity
 - Emotional lability
 - Aggressiveness
 - Reduce self-awareness



Medial Frontal/Cingulate Loop

- Important in behavioral activation
- Damage results in
 - Akinetic mutism
 - Abulia
 - Impairments in spontaneous initiation of behavior

ANTERIOR CINGULATE (I-IV)



AD/HD as a *Neurodevelopmental Disorder*

- “ADHD is increasingly conceptualized as a ‘chronic disease’ with symptoms, comorbidities, and impairments that multiply, intensify, and persist into adolescence and even adulthood, and the treatment of which may require intensive intervention in multiple areas of functioning in multiple settings over years rather than weeks or months.”
(Wells, et. al, 2000)
- “When ADHD is untreated there is a gradual accumulation of adverse processes and events that increase the risk of serious psychopathology later in life. Whether these can be reverse *by long-term* treatment remains unknown.”
(Goldman, et. al. JAMA, 1998)

AD/HD as a Neurodevelopmental Disorder

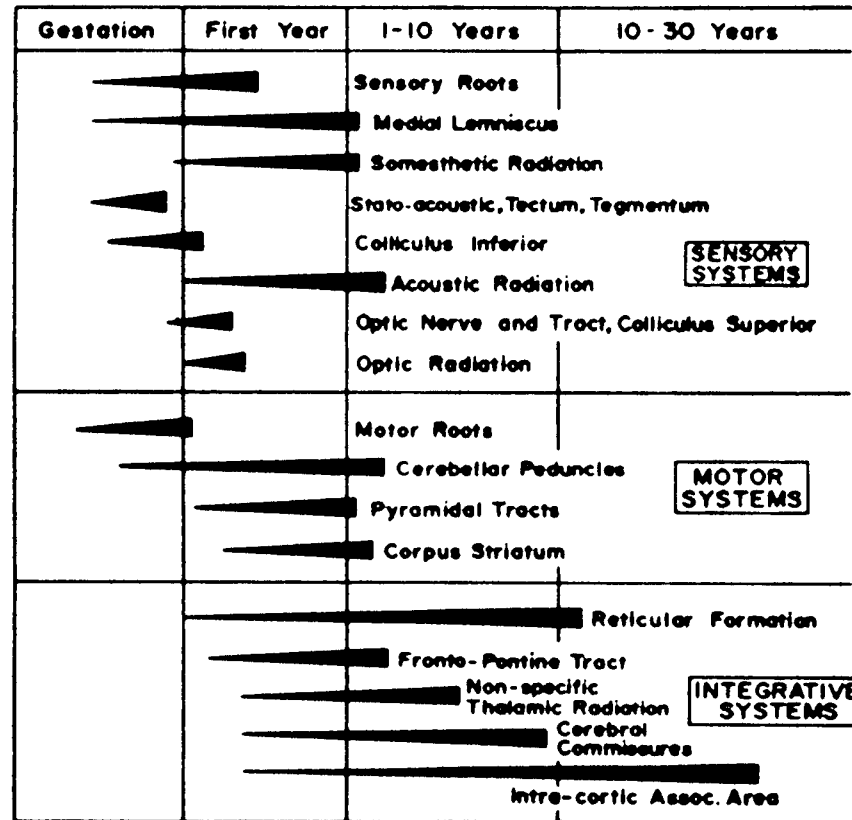
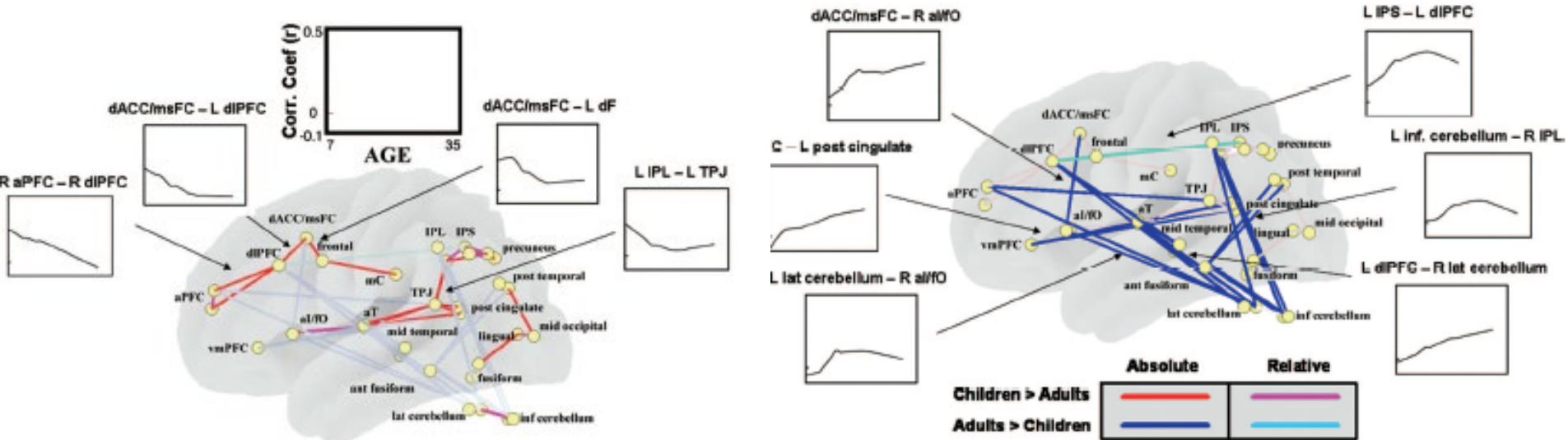


Figure 1-10. The myelogenetic cycles of regional maturation in the human brain (Yakovlev and Lecours 1967).

Neuroscience-neuropsychology-behaviour Development

Increased long-range and decreased short range connectivity with age



Fair et al., 2007

Delay or interruption in these developmental processes might be associated with cognitive deficits in ADHD.

Course of Disorder

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

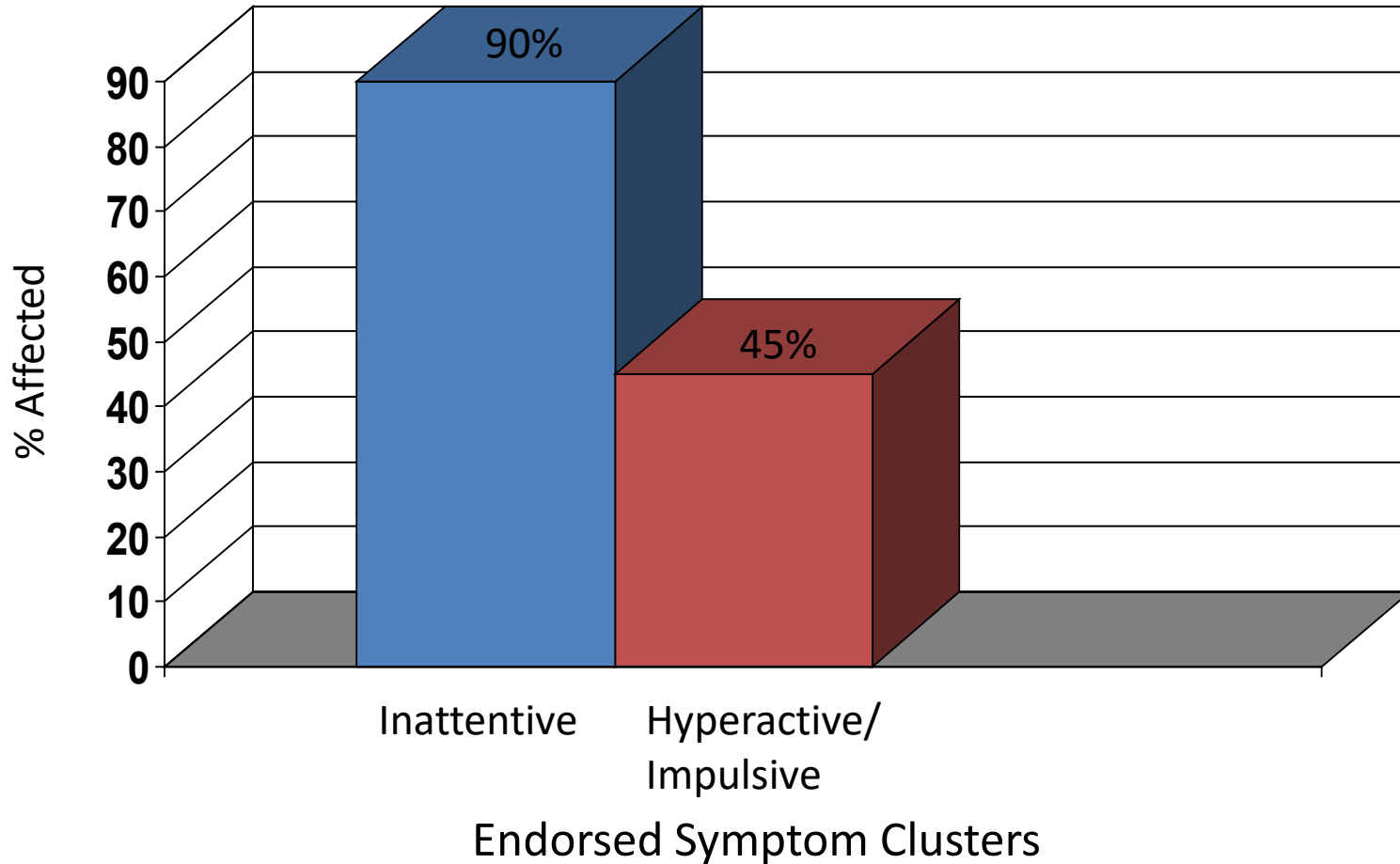
ADHD Clinical Presentation: Adolescence (Ages 13-18)

- 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

Inattention Drives Presentation of ADHD in Adults

N = 149

P=.05



AD/HD as a *Neurodevelopmental Disorder:* *Transactional Effects*

- “Research has established that, (in) ADHD, neurobiological risk factors are accentuated by parenting and school-related variables in shaping symptomatology, and that children and adolescents with this disorder display severe impairments in important functional domains.” (Hinshaw, 2002)

Transactional Effects: Peer/Social

- “Impaired social functioning is one of the most debilitating aspects of (the) disorder, with serious long-term consequences. . . . Peer rejection of the ADHD child forms quickly and remains stable over time, even in light of behavioral improvement.” (Pfiffner, et. al., 2000)
- “The intensity and frequency of negative feedback and failure that these children encounter have major, enduring consequences in terms of adjustment in adolescence and adulthood.” (Hoffman and DuPaul, 2000)

Transactional Effects: Familial

- Elevated incidence of ADHD, Conduct & Antisocial Disorder, Depression, Personality Disorder, Substance Abuse, etc. in parents and family members
- Elevated incidence of marital conflict, separation and divorce; more parenting stress and a decreased sense of parenting self-competence; decreased extended family contacts
- Parents display more negative reactivity, more commanding directive behavior, less positive responsiveness to ADHD children than do parents of normal children (Wells, et. al. 2000)

Transactional Effects: Familial (early)

- Parental intrusiveness and overstimulation in the early caregiver-child relationship are significant early antecedents of later hyperactivity in kindergarten. (Jacobvitz and Sroufe, 1987)
- “Mother-child interactions involving preschoolers are ameliorated by MPH, (which) appears to have a linear dose-response effect on improvements in the mother-child interaction [including maternal warmth], perhaps related to increasing child compliance and decreased symptomatic intensity in the child.” (Greenhill & Ford, 2002)

Transactional Effects: Familial

- “Although disrupted parent-child interaction is probably not etiological in ADHD, it may have a primary, causal role in the development, escalation, and maintenance of the oppositional and aggressive behavior that is characteristic of ODD and CD. . . . (which) have very high comorbidity rates in ADHD, (are) associated with much of the parent-child interactional conflicts in ADHD families, (and which) mediate the increased risk for later substance abuse, criminality, and antisocial spectrum disorders in adulthood.” (Wells, et. al. 2000)

Transactional Effects: Impairment in Adulthood

- “ADHD in adulthood is not a benign condition. It is associated with a higher risk of impairment in one or more major life activities and more numerous such impaired activities.”
- “The symptoms of ADHD, when they occur often or more frequently, are not trivial and produce an adverse impact on the ability of these adults to function satisfactorily in the vast majority of major life activities important to adult adjustment.” (Barkley, et. al., 2008)

Transactional Effects: Familial

- Adults with ADHD (and their spouses) tend to report less marital satisfaction in their current marriage than controls
- They had an earlier start to sexual activity and earlier pregnancies, and were more likely to contract an STD by age 21 (Barkley, et.al. 2008)
- And have trouble sustaining friendships and intimate relationships
- They are seen as self-centered, immature, verbally explosive and quick to anger, with poor awareness of others' needs and poor listening skills (Barkley, 1998)

Transactional Effects: Academic and Occupational

- Effects on: Academic Skill Development
 - Especially as workload increase in later elementary
 - And as organizational demands increase in middle school and high school
- Transactional effects on:
 - Peer Group Identification
 - Connections to prosocial adults (teachers, coaches, etc.)

Transactional Effects: Academic and Occupational

- “Education or the school setting was far and away the domain most likely to be adversely impacted by ADHD (over 90%), followed by daily chores and responsibilities (75%).”
- “Reports of adults about themselves or those provided by others . . . Are likely to be impressively correlated . . . About degree of impairment ($r_s = .70-.80$).”
- “Such severity, especially at clinically elevated levels (four or more symptoms) is highly likely to be associated with risk of impairment in one or more major life activities (100%) are impaired.” (Barkley, et. al., 2008)

Transactional Effects: Academic and Occupational

- Impaired in classwork, homework, class behavior, behavior at recess and in lunchroom, and in time management.
- Lower college graduation rates. More retention in grade, dx'd with LD, placed in special education. Higher percentage of poor (D & F) grades throughout school. Lower HS GPA. More likely to drop classes in college.
- Adults with ADHD had lower scores in arithmetic, spelling and reading than the Clinical and Community controls, and poorer listening comprehension than the Community Controls.
- But SAT's and HS standardized tests were not lower, suggesting *ability* was not lower. (Barkley, et. al., 2008)

Transactional Effects: Occupational

- Adults with ADHD are more likely to:
 - Have been fired (53% vs 31%)
 - Impulsively quit a job (48% vs. 16 %)
 - Changed jobs (6.9 times vs 4.6 times)
 - Had chronic employment difficulties (77% vs 57%)
(Murphy and Barkley 1996)
- Increased risk of further head injury
 - More motor vehicle crashes, speeding citations, license suspensions, fewer safe driving habits (e.g. Barkley, et. al. 2002)

Transactional Effects: Drug Use and Antisocial Behavior

- “Elevated risk for both later substance use and abuse as well as for many forms of antisocial activities and their legal consequences. The presence of CD greatly elevates these risks.”
- No evidence that treatment with stimulants was associated with increased drug use or abuse Some evidence showed that being treated with stimulants as a child reduced the likelihood of using certain drug types (amphetamines, illegally obtained prescription drugs).

Centrality of *Comorbidity*

- Comorbidity is the rule, rather than the exception and must be addressed
 - By research into developmental etiologies, and
 - By treatment paradigms and in each child/adult's treatment
- “Overall, perhaps as many as 65% of children with ADHD will have 1 or more comorbid conditions, although their presence will not be recognized without appropriate questioning and evaluation.” (Goldman, et. al., 1998)

NIMH Multimodal Treatment Study of Children with ADHD (MTA):

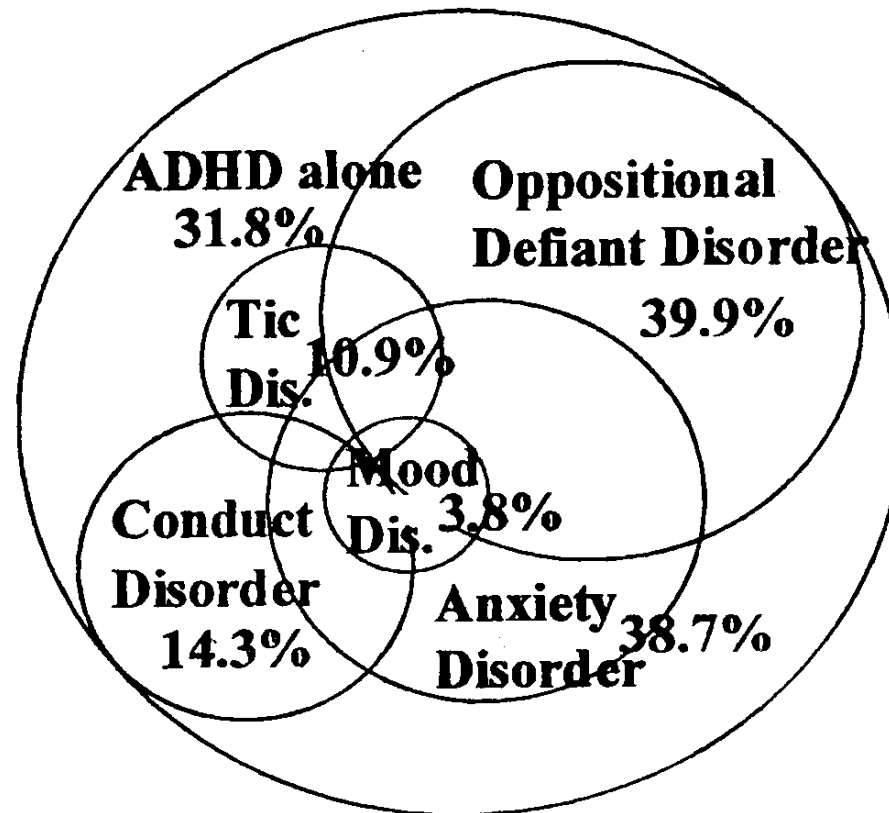


Figure 1. Overlap of co-occurring disorders in Multimodal Treatment of ADHD (MTA) Sample (n = 579) at baseline, prior to randomization to the four treatment groups. All subjects met criteria for attention-deficit hyperactivity disorder (ADHD), Combined-Type.

Centrality of *Comorbidity*

- In a 13 year followup of 147 hyperactive children (Fischer, et. al.,2002), with mean age of 20-21:
 - 59% (vs 36%) had a nondrug psychiatric disorder
 - 26% MDD
 - 21% Antisocial
 - 18% Passive-Aggressive Personality Disorder
 - 14% Borderline PD
 - 12% Histrionic PD
 - Antisocial PD was mediated by Teenage Conduct Disorder
 - Severity of Conduct problems contributed to the risk for PD's

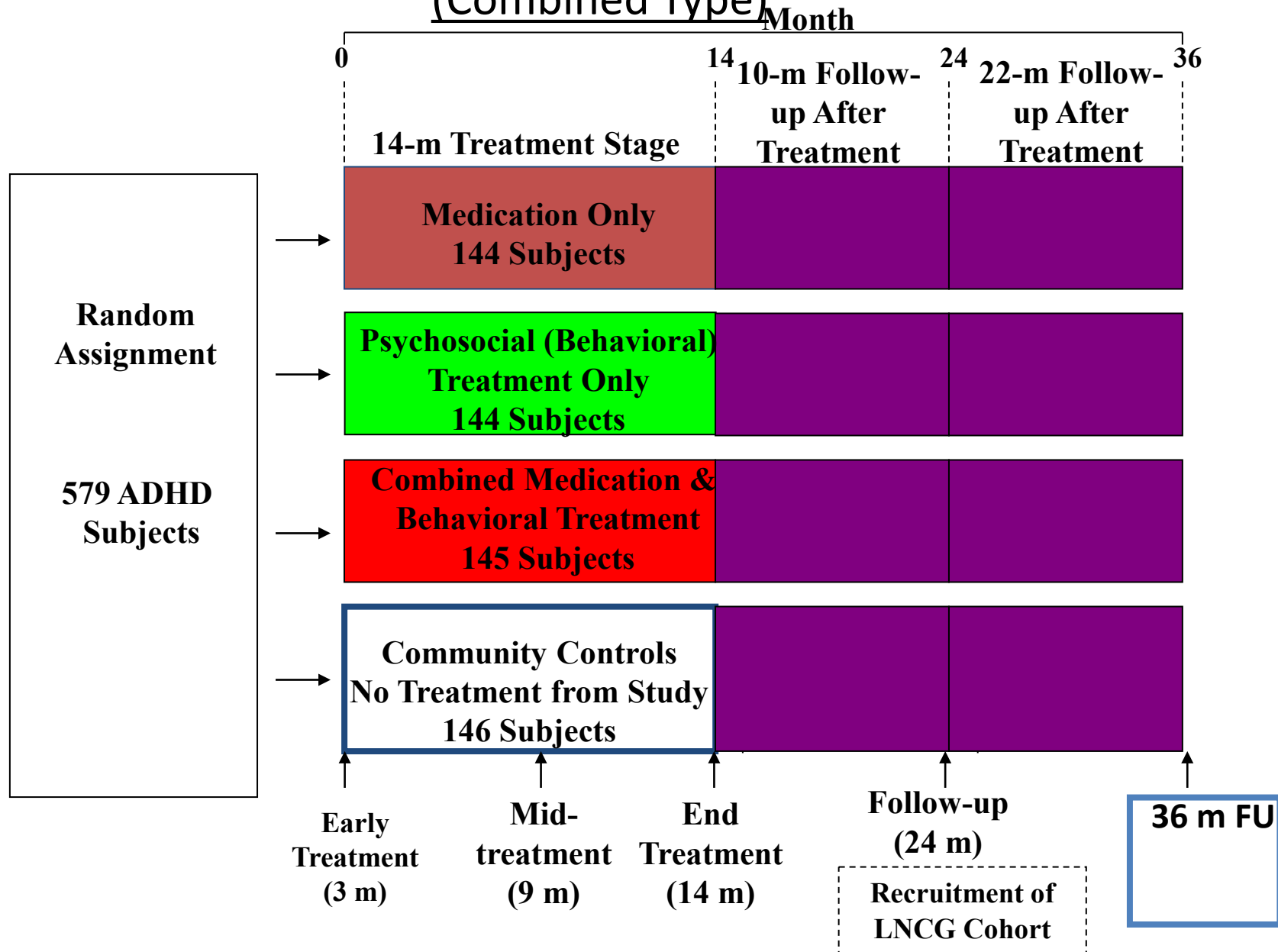
Centrality of *Comorbidity*

- Increased risk of dysthymia, depression, anxiety, ODD, conduct disorder, alcohol use disorders and drug use disorders.
- In adults, suicidal thinking (27-29%) and suicide attempts (8%), largely mediated by the presence of comorbid MDD and dysthymia.
- “ADHD in adults is therefore likely to require polypharmacy . . . And comorbid disorders (will) require separate treatment approaches.”

(Barkley, et. al., 2008)

NIMH Multimodal Treatment Study of Children with ADHD

(Combined Type)



NIMH Multimodal Treatment Study of Children with ADHD (Combined Type)

- 579 children, ages 7.0-9.9 years old; 7 sites
- Randomized to 14 month long:
 - **Community Comparison (CC)** (68% received medication, although less intensively: 2.1 doses/day [vs 2.9], 18.7 mg. total daily dose [vs. 32.8], 2.3 visits/year [vs.8.8])
 - **Medication Management** (titrated dose, tid; monthly ½ hr. FU and contact with teachers)
 - **Behavioral Treatment (only):** 8 week, day-long Summer Treatment Program; 35 sessions, parent management training; behavioral aide in classroom ½ day for 12 weeks; 16-20 therapist consultations to teacher; NB. Tapered over last 4-6 months of treatment
 - **(Integrated) Combined Treatment**

NIMH Multimodal Treatment Study of Children with ADHD (MTA): *Outcomes*

- For *Core ADHD* Symptoms
 - Combination Rx did not differ significantly from Med Mgmt.
 - Proportion of children in these two groups no longer meeting full criteria was 90% and 88% (NS)
 - Beh. Rx and CC did not differ from one another on any core ADHD outcome measure
 - Effect size for Comb. And Med. Mgmt versus Beh. Rx and CC was 0.5 to 0.6 (moderate effect)

MTA: Other Symptom/Functional Outcomes

- All three active MTA treatments rarely differed *from one another* for:
 - Oppositional/aggressive symptoms
 - Internalizing symptoms
 - Social skills
 - Parent-child relations
 - Academic functioning
- Only the Combined Rx fairly consistently showed superiority to CC
- Combined superior to Beh. Rx for
 - 14 month academic Fx: WIAT Reading
 - Parent-reported Internalizing & Oppositional/Aggressive Sx's
- Med. Mgmt. Scored in-between

MTA: *Other Symptom/Functional Outcomes*

- Effect size for Combination's superiority was 0.26 to 0.28 (real, but small)
- Which scored first on the 19 outcome measures?
 - Combination: 12/19
 - Med. Mgmt. 4/19
 - Behavioral Rx 2/19
 - CC 1/19
- Parent treatment satisfaction was highest in the Combination and Behavioral Rx. Groups.

MTA: Outcomes

“Normalization” of ADHD and ODD Sx’s

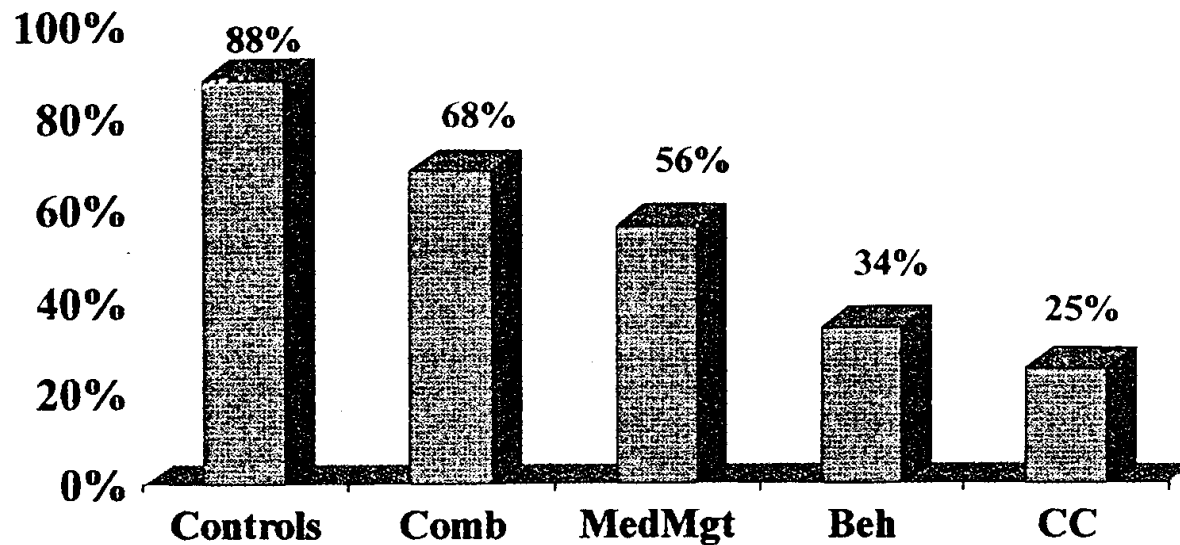


Figure 6. Percent “normalized” at 14-month endpoint across the four MTA groups. The classroom controls were drawn from the s classroom cohorts as MTA children were originally, and were age- and gender-matched to assure comparability with MTA subjects. “normalization” indicator was based on a composite of parent and teacher ratings, with the overall symptom cutoff required to be indicati “little or no” symptoms (Swanson et al, 2001).¹⁵

MTA: Mediators of Successful Outcome

- High quality medication practices and attendance
- Parents (in Comb. Grp.) who showed substantial improvement in negative/ineffective discipline had children rated by teachers as *fully normalized* in terms of ADHD & disruptive sx's in school

Treatment of Toddlers

- Signs and symptoms may be evident before age 3:
 - Pronounced motor activity, excessive climbing, aggressivity, and destructiveness
 - They may be disruptive to family life and make nursery school attendance impossible.
- Hyperactive preschoolers do not “grow out of it.” (Campbell, et. al. 1977)
- 9 controlled studies (N=206 total): 8 showed strong positive effects of MPH
- Higher rates of side effects, such as fearfulness, proneness to crying, crabbiness and irritability, than would be expected in school-aged children (PATS: Preschool ADHD Treatment Study, 2006)
- Preschoolers metabolize MPH more slowly, and require lower doses (0.7 +/- 0.4 mg/kg/day versus 1.0 mg/kg/day in MTA study)
- Mother-child interactions improved by treatment in dose-response fashion.

Treatment of Toddlers

- Evaluate carefully, including cognitive, emotional, environmental and parental-interaction factors.
- Consider using behavior management techniques.
- But if the child is very hyperactive, do give serious consideration to Combination treatment. Important skills are learned (or not learned) at this age.
- Monitor closely for side effects.

The Lost Girls

- Gender ratio in children is 3:1, but in adults it's 1:1. Are we missing the girls because they have less severe or obvious disruptive and aggressive behavior?
- “Girls and boys with ADHD are quite similar in their presenting symptoms, but girls may manifest somewhat lower symptom levels and are considerably less likely to manifest aggression.”
(Barkley, 2006)
- So:
 - Attend to inattention
 - Look for non-physical, interpersonal aggressiveness
 - How do girls manifest hyperactivity? “Chatty Cathy?”
 - ADHD girls are equally at risk (e.g. peer rejection)

Adults with ADHD: Barkley's 4 Questions

- Credible evidence for ADHD-type symptoms in early childhood that by middle school years led to substantial and chronic impairment?
- Credible evidence that ADHD-type symptoms currently cause substantial and consistent impairment across settings?
- Are there explanations other than ADHD that better account for the clinical picture?
- For patients who meet criteria, is there evidence for comorbid conditions?
 - For 1 & 2: **“By credible we mean evidence that is capable of corroboration by some other means than just the patient’s verbal self-report.”**

Adults with ADHD: Highlights of Barkley's Adult ADHD Clinic Procedures

- Patient, Spouse or significant other, and Parent or Sibling each complete rating scales
- “We strongly encourage a spouse, parent, or significant other who knows the patient well to participate in the evaluation.” (Helps with subsequent treatment, too)
- “Patients are emphatically asked to search for and bring any and all kinds of objective records that attest to their prior history and behavior. These records include report cards, past testing evaluations, IEP's, college transcripts, performance evaluations
- They screen for LD and do a CPT (“an opportunity to observe the patient cope with a task that requires sustained attention and impulse control”)

Adults with ADHD: Diagnosis

- A. Six (or more) of the following symptoms have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:
1. Is often easily distracted by extraneous stimuli.
 2. Often makes decisions impulsively.
 3. Often has difficulty stopping activities or behavior when he/she should do so.
 4. Often starts a project or task without reading or listening to directions carefully.
 5. Often shows poor follow-through on promises or commitments made to others.
 6. Often has trouble doing things in their proper order or sequence.
 7. Often more likely to drive a motor vehicle much faster than others (excessive speeding).

Adults with ADHD: Diagnosis (con.)

8. Often has difficulty sustaining attention in tasks or leisure activities
 9. Often has difficulty organizing tasks or activities.
-
- B. Some symptoms that cause impairment were present before age 16 years.
 - C. Some impairment from the symptoms is present in two or more settings (e.g. work, educational activities, home life, social functioning, community activities, etc.).
 - D. There must be clear evidence of clinically significant impairment in social, academic, domestic (cohabitating, financial, driving, child-rearing, etc.) or occupational functioning.
 - E. The symptoms do not occur exclusively during the course of a 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).

Adults with ADHD: Diagnosis (con.)

- The single item “easily distracted” achieved an overall classification accuracy of 97% for both the ADHD and the Community control group (but not from the Clinical control group).
- 6 of 9 identifies
 - 92% of the ADHD group,
 - only 1% of the Community control group,
 - But 47% of the Clinical control group

Proposed by Barkley & Murphy, The ADHD Report, 2006.

Adults with ADHD: Impairment

- Consider using
 - the Current Symptoms Scale and Childhood Symptoms Scale with patient, parents and sig. other
 - The Impairment Rating Scales with patient, parents/sig. other and employer (both: Barkley & Murphy, 2006)
 - The clinician rated global Social and Occupational Functioning Assessment Scale (SOFAS: Patterson & Lee, 1995)
- Consider using effort testing
 - “20% of college students seeking evaluation significantly exaggerated their symptoms or willfully malingered concerning ADHD.”(Harrison, 2006)

TABLE 11.1. Documenting Requests for Accommodations under the Americans with Disabilities Act

1. Show that DSM-IV symptoms occur to a degree that is significantly greater than the normal population (state that DSM-IV was employed; report number of symptoms endorsed for current functioning).
2. Show that DSM-IV symptoms arose in childhood (state that DSM-IV was employed retrospectively; report number of symptoms endorsed for childhood; report approximate age of onset of symptoms [onset before age 12 is acceptable—cite Barkley & Biederman, 1997, to support his adjustment to age of onset if need be]).
3. Present evidence of impairment since childhood. Indicate how disorder has significantly interfered with the individual's social, educational, or occupational functioning.
4. Present evidence of cross-setting symptoms/impairment. Provide history of symptoms producing impairment in home and school settings in childhood.
5. Demonstrate corroboration of symptoms in childhood from someone who knew the patient well (parents, siblings, longtime friend, etc.).
6. Demonstrate corroboration of current symptoms of ADHD from someone who knows the patient well (spouse, dating partner, parent, sibling, or employer, etc.).
7. Show evidence of current impairment in a major life activity (education, occupation, social, etc.). Impairment has been defined in the ADA as being relative to the average person or the majority of the population—*not* relative to a high achieving, highly intelligent, or high-functioning peer group (graduate, professional, or medical students, college students, etc.). State the evidence and how it has reduced the person's functioning well below that of the average person.
8. State a differential diagnosis was conducted and other disorders were ruled out that might have better accounted for this person's performance problems or current symptoms and impairment.
9. Describe the history of prior treatment and its success.
10. Describe any history of prior accommodations for the disorder and their success. If no prior accommodations were ever provided for disorder, explain why not.
11. State accommodations being recommended *and* why; what is the rationale for each and why are they reasonable for this disorder in this person.
12. If the diagnostician does not hold a terminal degree in clinical psychology or psychiatry, indicate what training qualifies the professional to conduct a differential diagnosis of mental illness.

Adults with ADHD: Impairments and ADA

Barkley, 2008: “Impairment should mean serious dysfunction in the performance of the major life activities (family, marital, social, occupational functioning, etc.) required of society in general, More to the point, this view holds that that impairment should be defined as being relative to the norm or the average person, as required by the ADA, and not relative to some narrow, highly specialized and accomplished subset of adults or to an estimate of one’s general cognitive ability, such as IQ. . . . Individuals should not be viewed as disordered and granted special protections, accommodations, disability financial benefits, or other societal privileges when they are not below the average of the population at large. It is inherently unfair to grant advantages to those who are not actually subnormal.”

(See Gordon & Murphy in Gordon & Keiser, 1998 on legal documentation for ADHD)

Adults with ADHD: Treatment

- Basically follows the same format as with children, including working with significant others, monitoring functioning in multiple areas, addressing comorbidity, and using medication from morning 'til bedtime.
- There may be grief and self-concept issues that need to be processed (years lost, "Who am I?").
- But adults may also need specific help in developing and consistently and deliberately using metacognitive skills, building use into their life: use of day timers, attention to time management, organizational strategies at home and at work, etc.
- And comorbidities will need to be addressed.

Medications for ADHD

Information courtesy of
Christopher Varley, MD
Seattle Children's Hospital

Medications

The two most common mistakes with medication are:

1. Not optimizing dose
2. Not switching to alternative medication if first agent not helpful

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)**

** FDA approval to Rx ADHD for children 6 and over

*** FDA approval to Rx ADHD for children 3 and over

Medication for ADHD

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) 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*

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)

6) Available in multiple preparations:

- a) Ritalin 5, 10 and 20mg regular acting; 20mg sustained release; Ritalin LA 10, 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 (Daytrana)

Long-acting Oral MPH Medications

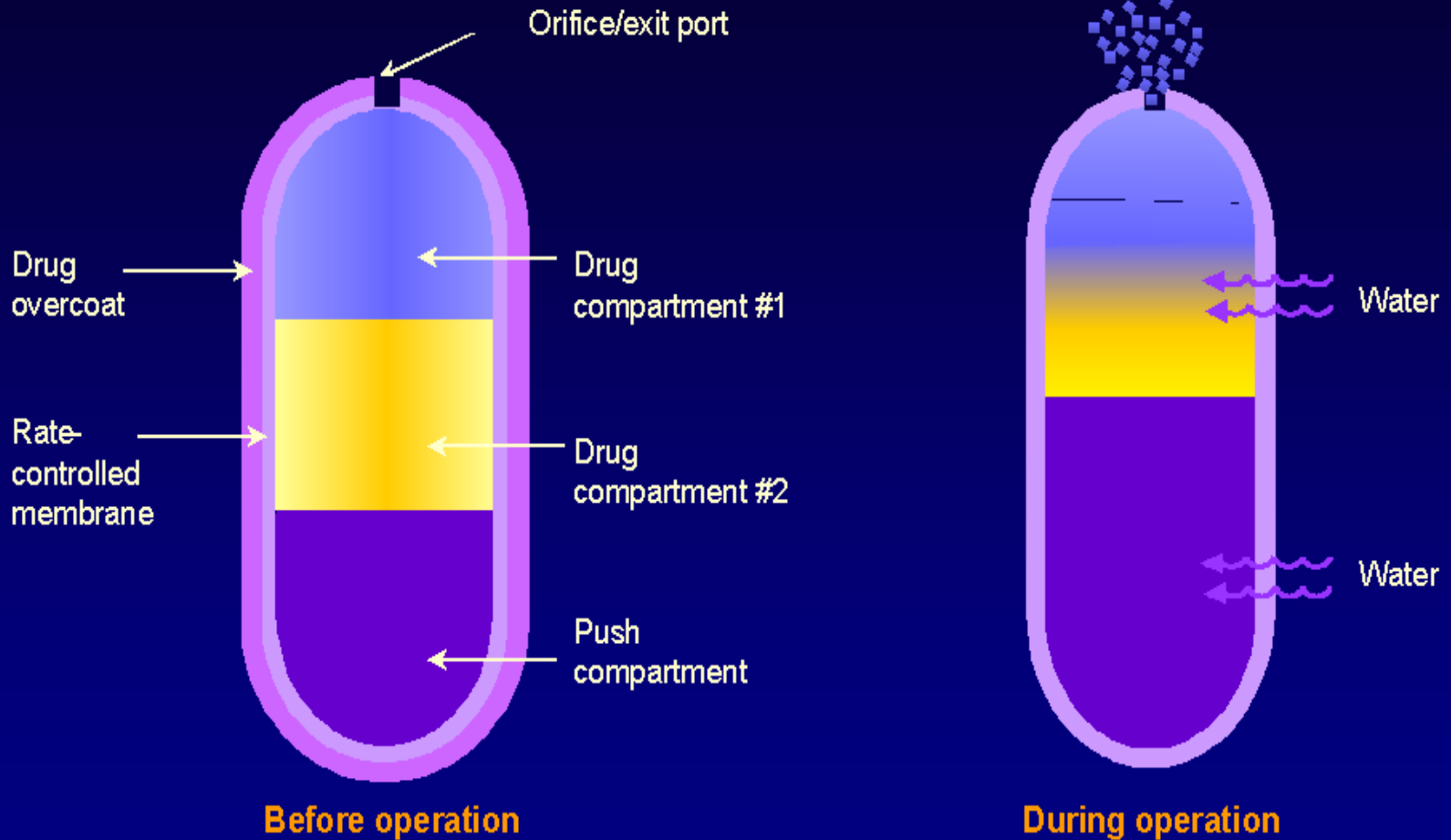
Products	Concerta®	Metadate® CD	Ritalin® LA
Formulation Technology	OROS ®	Diffucaps ®	SODAS™
Dose mg	18mg/27 mg/36 mg/54 mg	10,20,30 mg	20mg/30 mg/40
Immediate Release	22% 4 mg/6 mg/8 mg/12 mg	30% 6 mg	50% 10 mg/15 mg/20 mg
Sustained/ 2nd release	78% 14 mg/21 mg/28 mg/42 mg	70% 14 mg	50% 10 mg/15 mg/20 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 54 mg tablets
2. OROS system
3. Duration of Action 10 -16 hours
4. Somewhat less potent than regular acting methylphenidate
5. May need dose increase over time
6. Approval now up to 72mg for product labeling in adolescents
7. FDA indication for adults 7/1/08

Concerta[®] Tablets: OROS[®] Delivery System



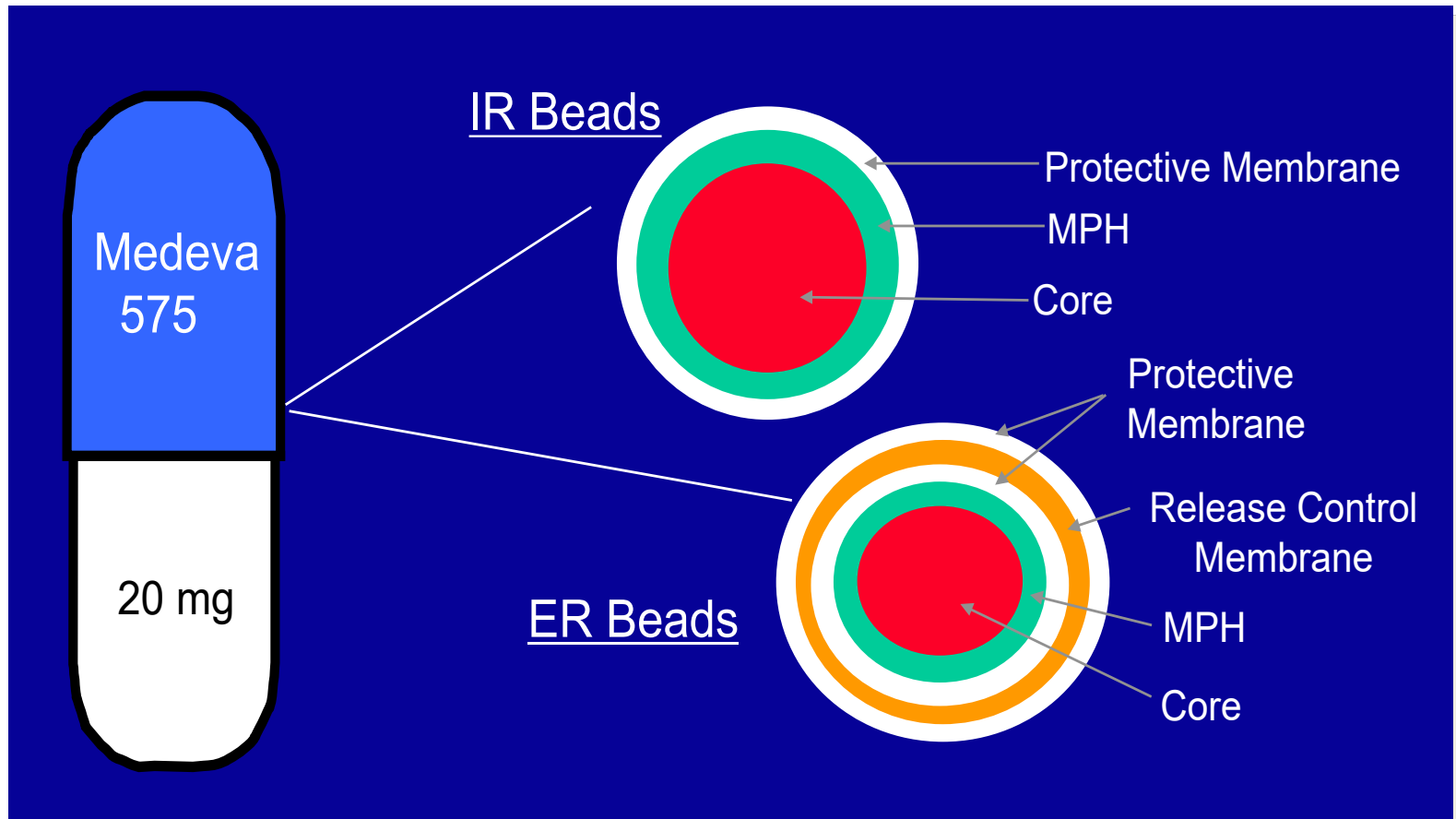
Swanson JM et al. Comparison of efficacy and safety of Concerta[™] (methylphenidate HCl) with Ritalin[®] and placebo in children with ADHD. Presented at Region IX and X Annual Meeting of the Ambulatory Pediatric Association; February 12-13, 2000; Carmel, CA.

Metadate CD (Methylphenidate)

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

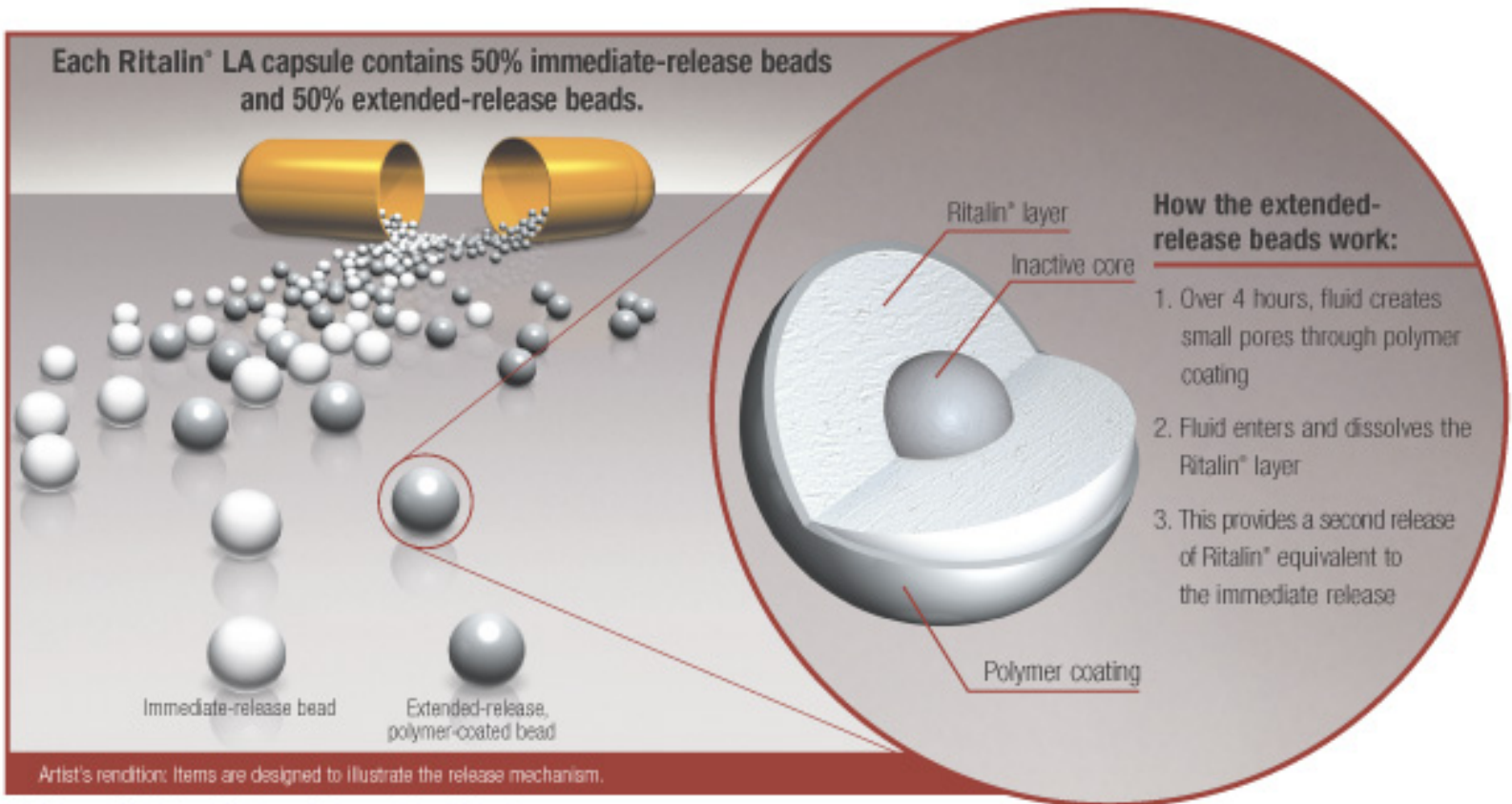
Metadate[®] CD Capsules: Diffucaps[®] Delivery System



Ritalin LA (Methylphenidate)

- Extended Release Capsules of 10, 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.

Methlyphenidate Transdermal Patch (Daytrana)

- FDA approval 4/06; released 6/06
- 9 hour application with 12 hour effect
- Skin reactions common
- Brand name is Daytrana

Dexmethylphenidate (Focalin)

- 1) Active isomer of methylphenidate
- 2) Twice as potent

Focalin XR

- 1) Capsule: immediate release (IR) and extended release (ER) beads in 50/50 ratio
- 2) Duration of action 6-12 hours

Focalin XR

- 1) 5, 10, 20mg
- 2) FDA approved up to 20mg/day
- 3) Adult ADHD indication

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 (Adderall)

- 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 suggesting clinician and family preference for Adderall XR is not a comparison study

FDA Warning (Not BLACKBOX)

August 2006

Followed Advisory Panel 2-9-2006 recommendations

- 8-7 vote for the FDA to display a BLACK BOX warning about possible cardiovascular risks though
 - “We didn’t find the sudden death data very persuasive”
- 15-0 for FDA to create “Medication Guides” explaining possible risk
 - Possible Cardiovascular risks
 - Psychiatric side effects, including psychosis

American Heart Association 5/2008

Now a Class IIa recommendation that children with ADHD get a careful cardiac evaluation, including an EKG before starting stimulant, which means it is reasonable to consider an EKG, but at the physician's judgment. It is not mandatory.

Vyvanse

Amphetamine prodrug, bound to lysine

- Inactive initially, converted in gut
- Presumably lower abuse potential re injection or inhalation
- FDA approval, 2-07, as a Schedule II drug
- Adult indication

Triphasic Amphetamine

- Three bead system (immediate, 4 hour, 8 hour release)
- Clinical trials done
- Duration of effect – 16 hours

Efficacy of Stimulants

- 1) About $\frac{3}{4}$ of patients with ADHD respond to a single stimulant
- 2) Of the $\frac{1}{4}$ who don't respond to one class of stimulant, about $\frac{1}{2}$ 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

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 second 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

Atomoxetine

WARNING

- Adding to labeling after 2 cases of markedly elevated hepatic enzymes during first 2 years of post marketing experience with 2 million patients
- May be underreported as cases require recognition

- Not clear if monitoring will be of benefit
- D/C medication at first sign of jaundice or liver laboratory abnormality

Comparison Studies

Comparison Studies Have All Been Industry Sponsored

- Have to consider results in that context

Atomoxetine vs Concerta
Double Blind Placebo
Controlled

Results

Both superior to placebo

Effect size

Concerta 0.8

Strattera 0.6

In Medication Naive Subjects

No difference in effect
size:

Concerta	1.0
----------	-----

Atomoxetine	0.9
-------------	-----

Metadate CD vs Concerta (COMACS)

- Clinical Effect Correlated with Serum MPH Level
- Both Superior to Placebo

Ritalin LA vs Concerta

- 2 studies
- In both studies active drug significantly better than placebo

Morning superiority of Ritalin LA vs Concerta

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

Guanfacine

Long-acting preparation in
development

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

MODAFINIL

EFFICACY

- Response rate 60-65%
- Effect size = .75, moderate
- Efficacy similar to atomoxetine, but less than stimulants

Modafinil

- Additional safety concerns raised by the FDA
- Sent back to company for further review of the safety concerns by FDA
- Application then withdrawn by Cephalon

Recent Trials Indicate
Benefit of Combining
Stimulant + Atomoxetine

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; Adults
- 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

Combinations of Medications

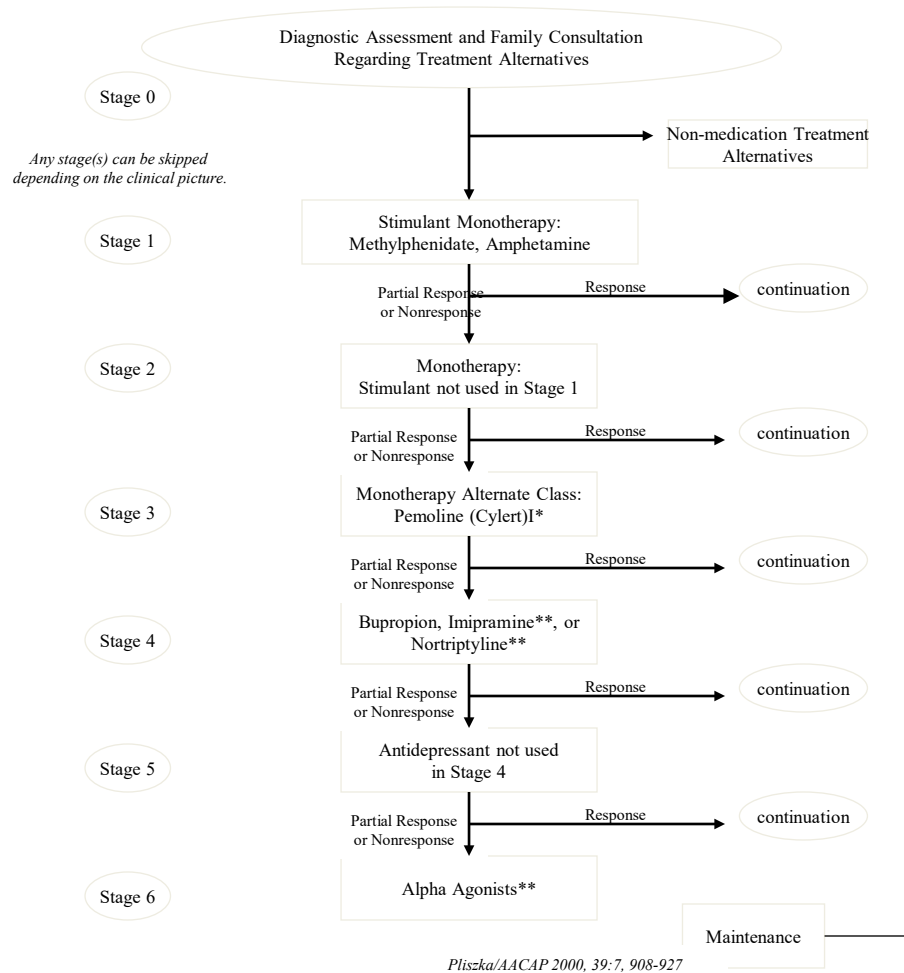
- 1) To manage partial response to ADHD
e.g., Can't sustain effect
- 2) Side effect management
e.g., 1) sleep disturbance
2) rebound
3) moodiness or irritability
- 3) Comorbid disorders

Combined Pharmacotherapy

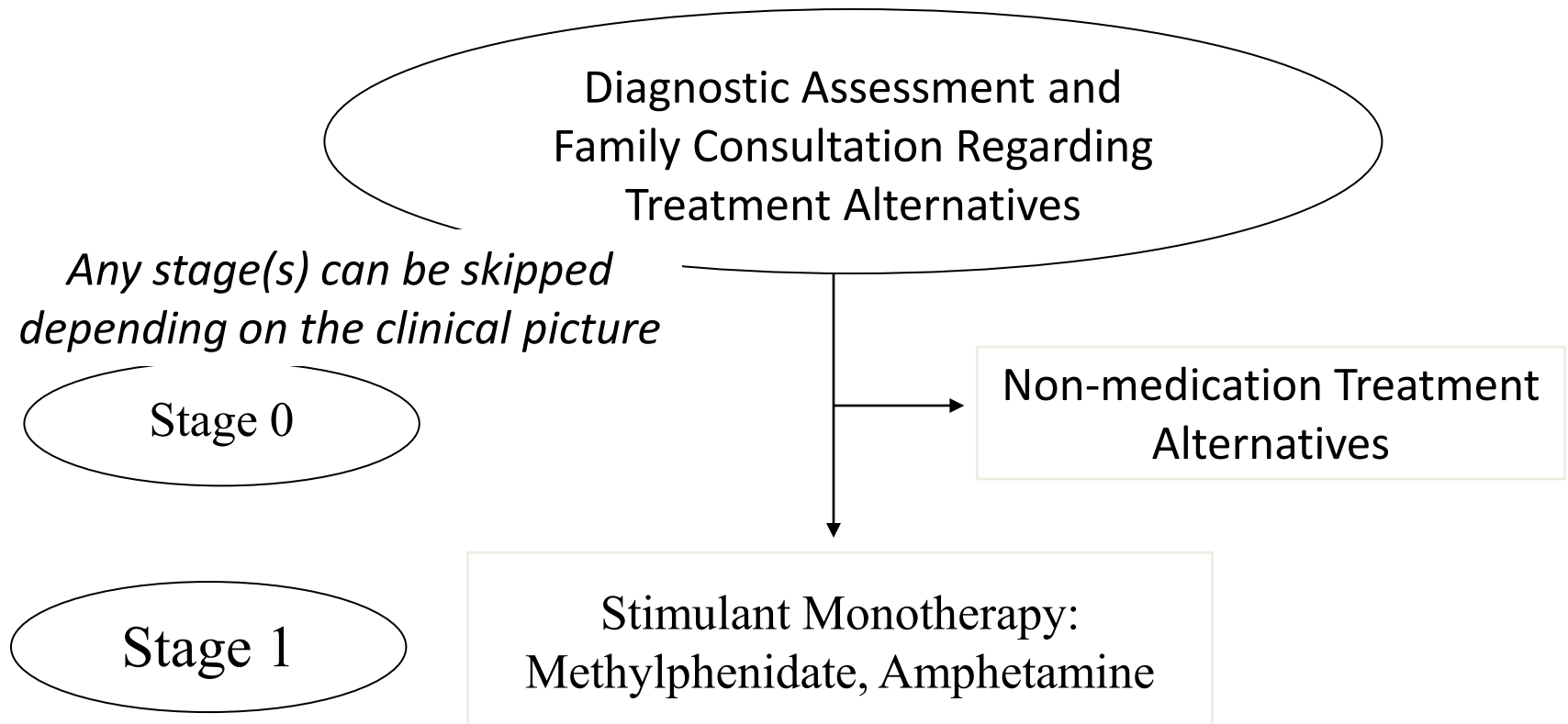
Common practice

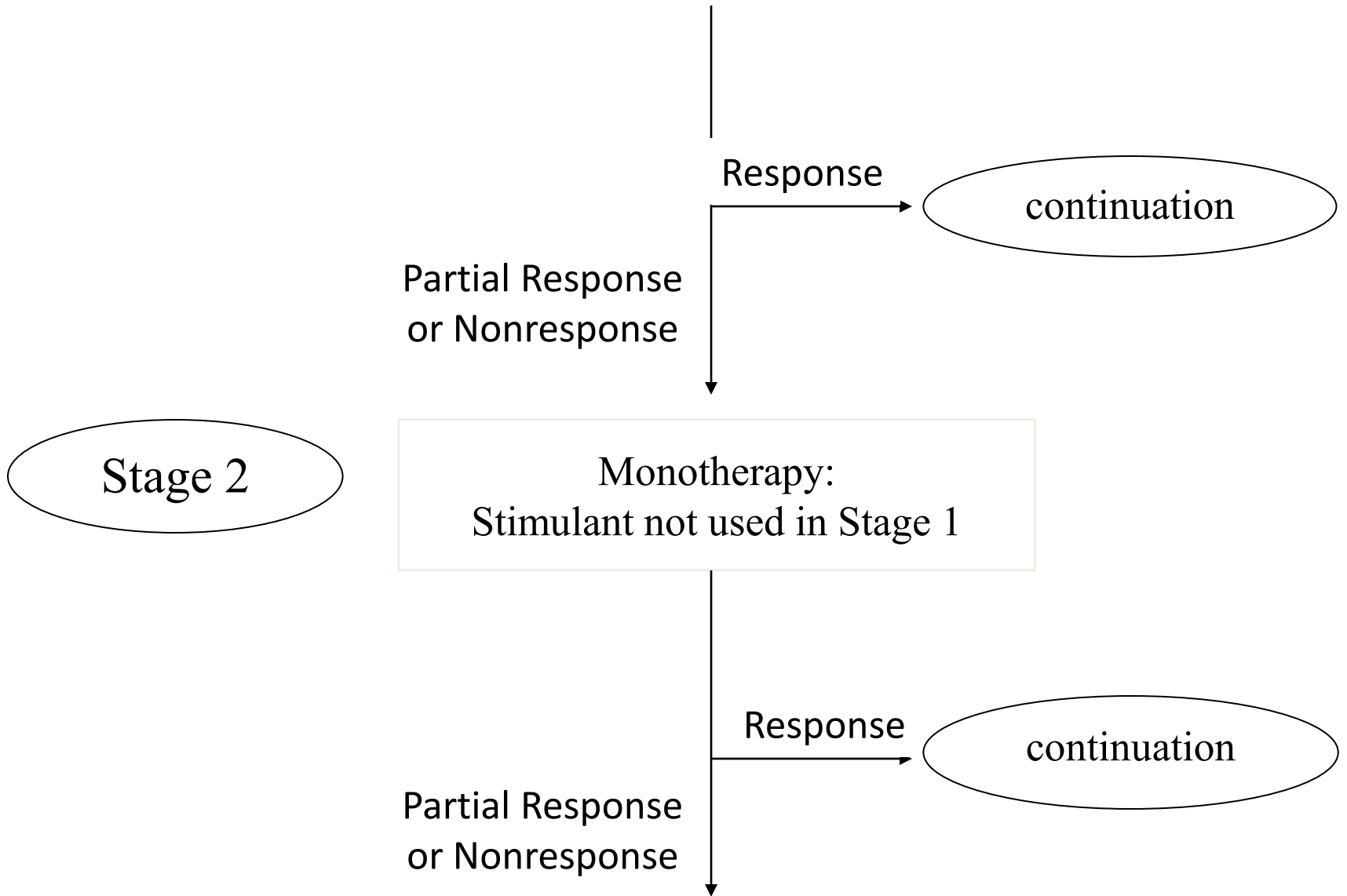
Practice far exceeds data base, controlled or open trials

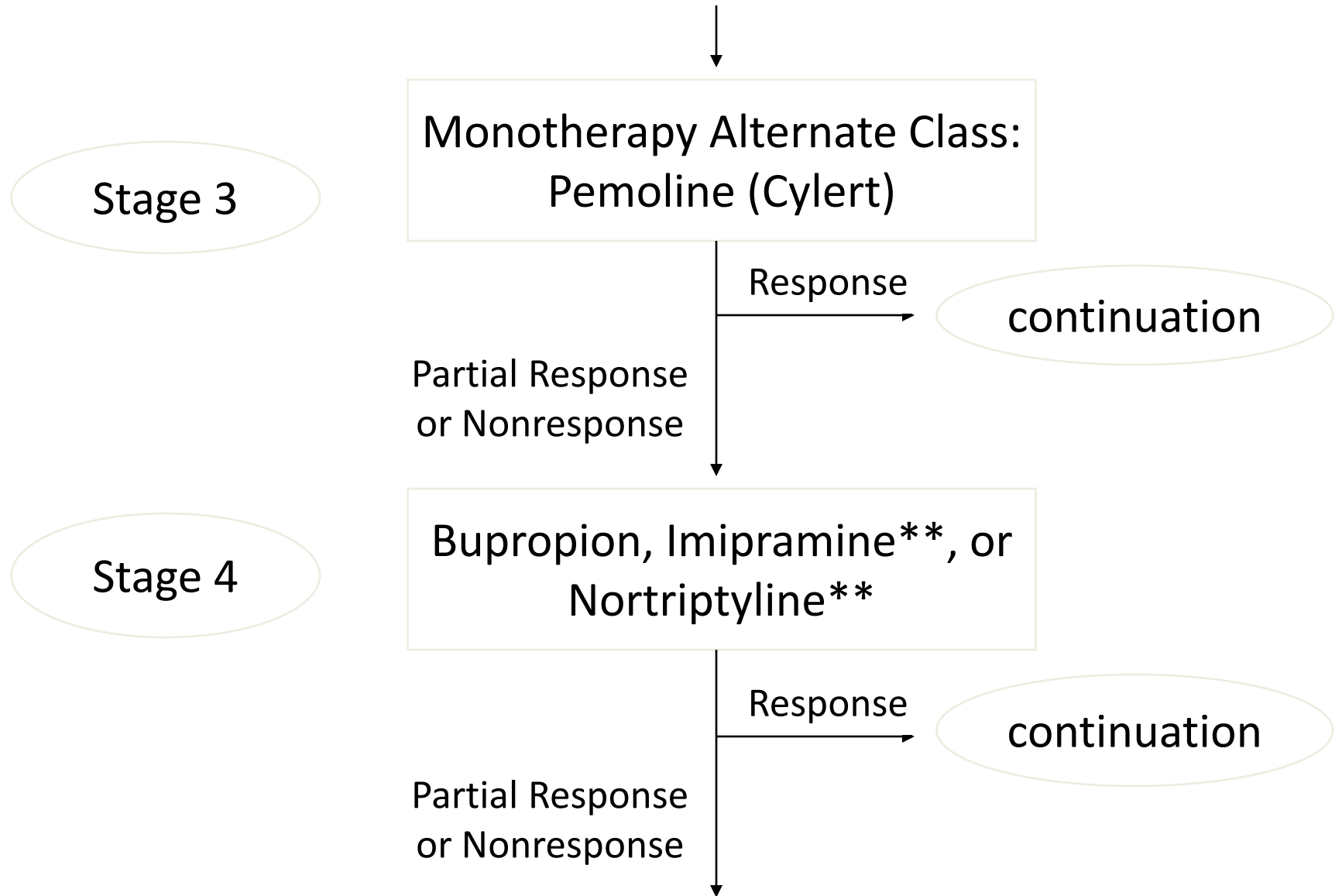
Algorithm for the medication treatment of attention-deficit/hyperactivity disorder without comorbid psychiatric disorder. *Plus liver function monitoring, securing substance abuse history and new guidelines. **Cardiovascular side effects.

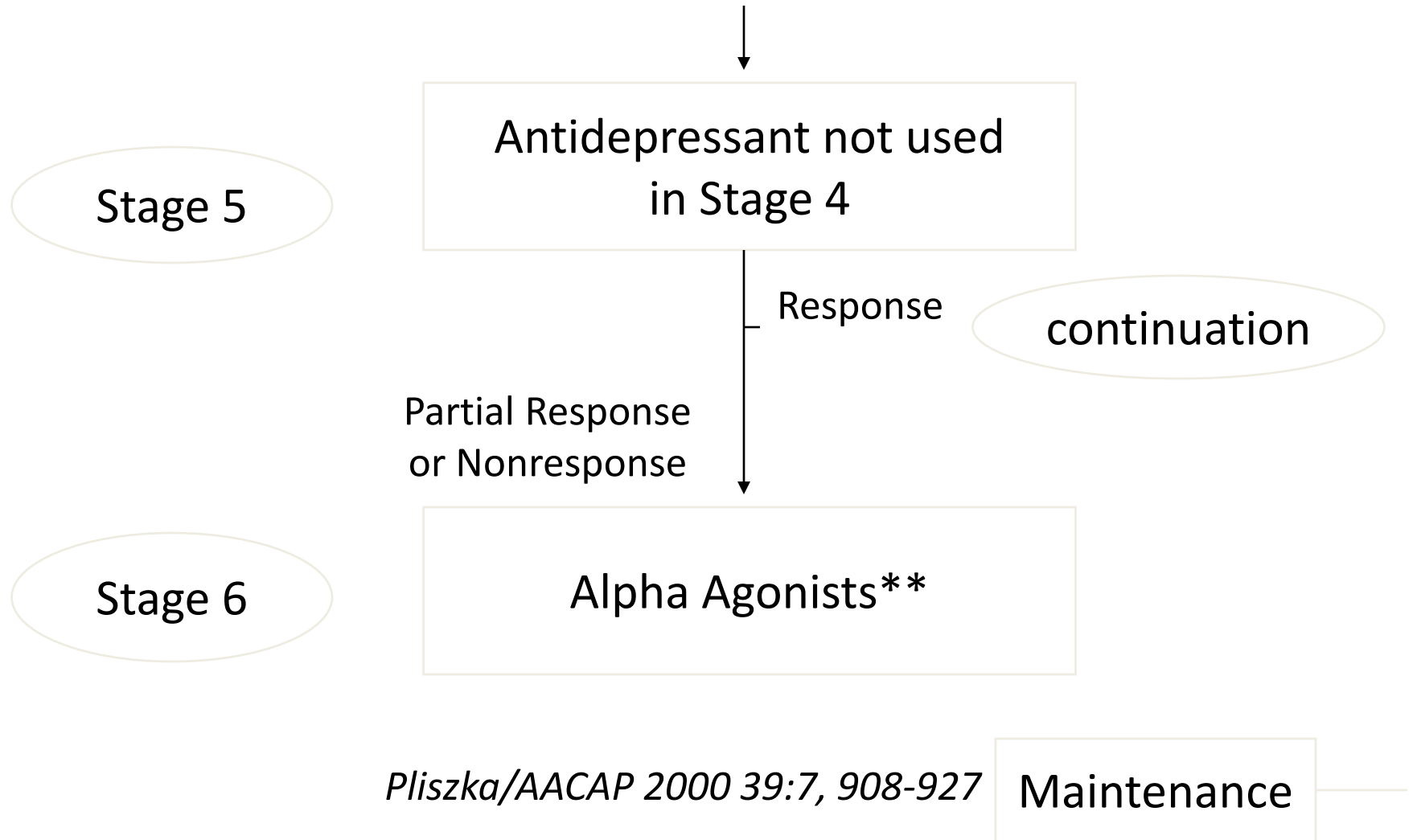


Algorithm for the medication treatment of attention-deficit/hyperactivity disorder without comorbid psychiatric disorder. *Plus liver function monitoring, securing substance abuse history and new guidelines.
**Cardiovascular side effects.





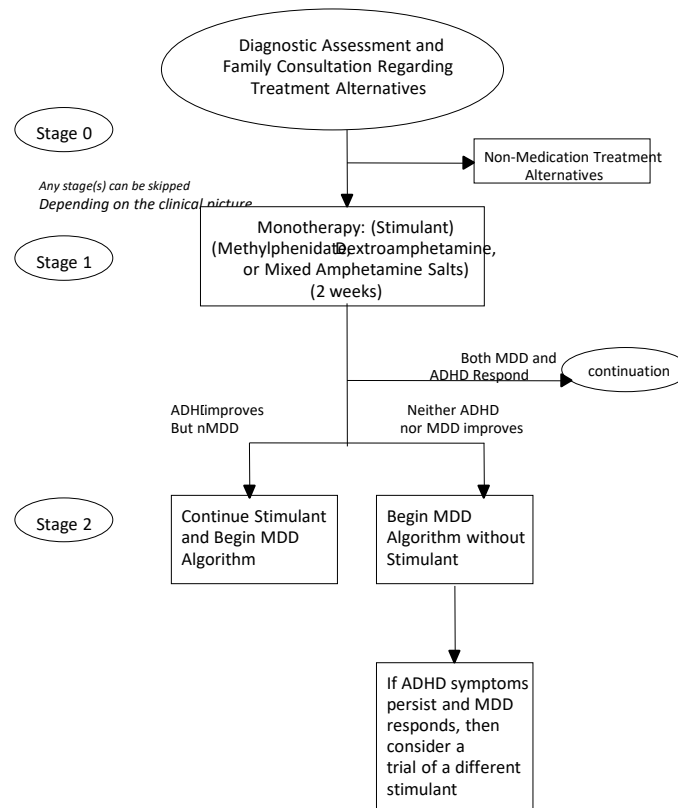




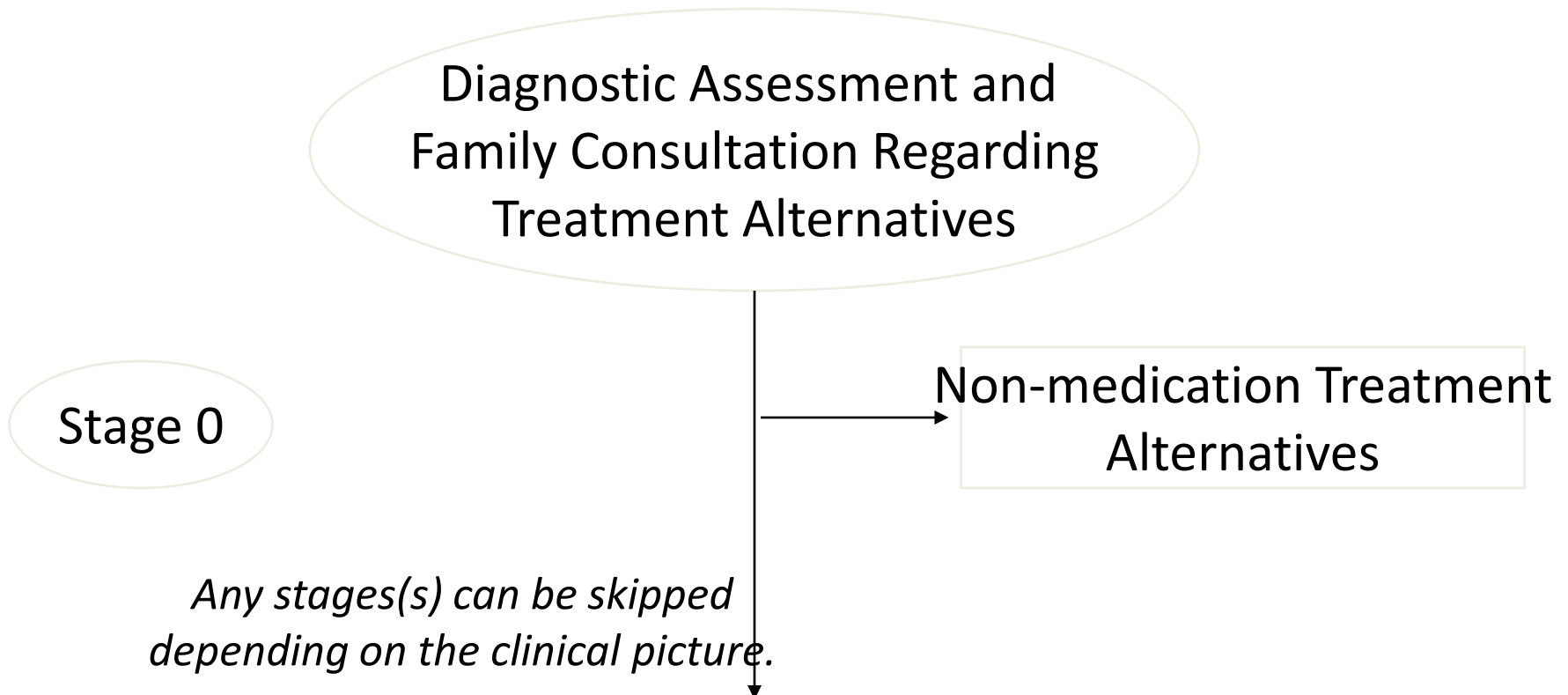
Treatment

Optimize ADHD, then
address comorbidity

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



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)

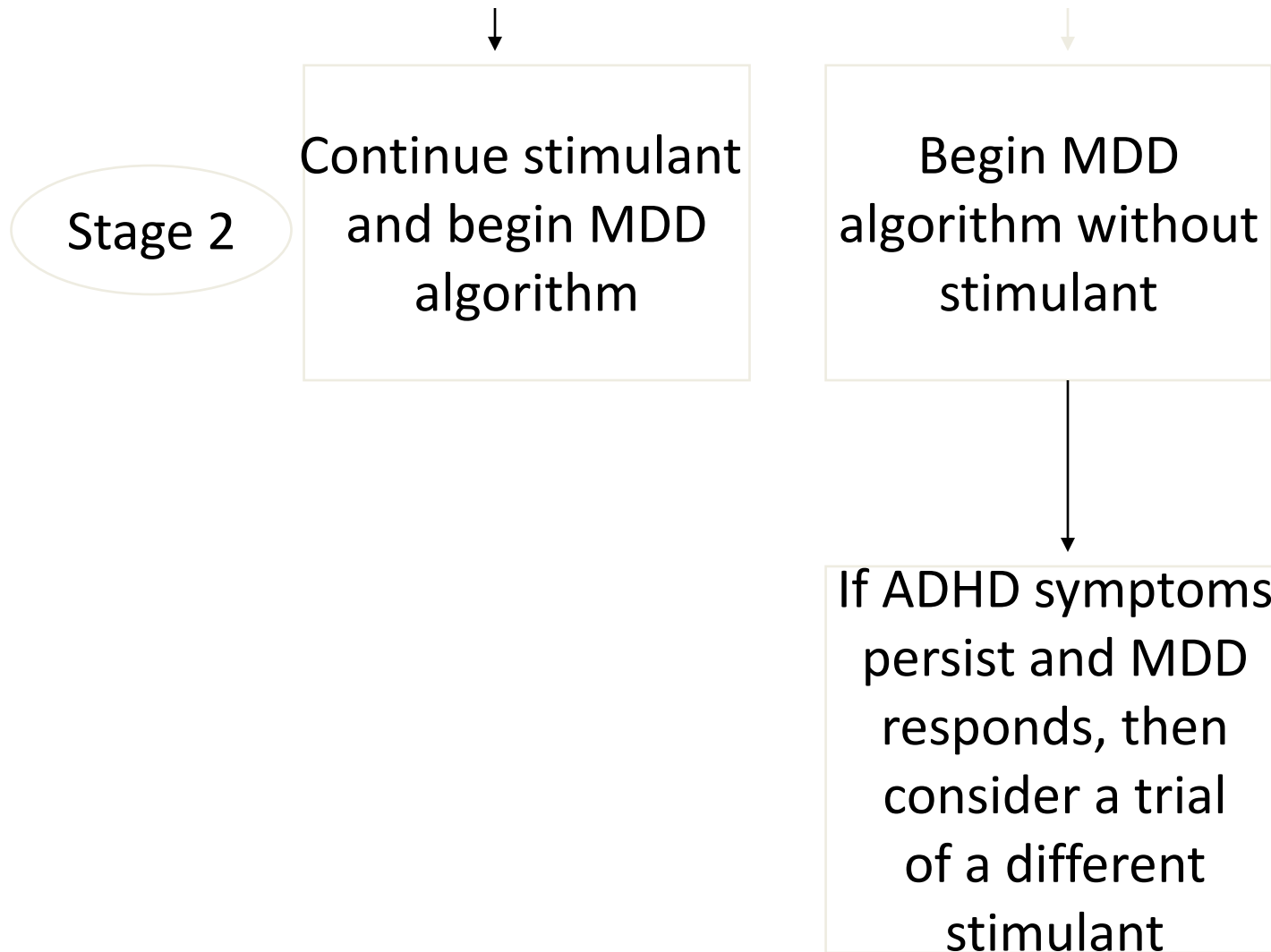
Both MDD and
ADHD respond

continuation

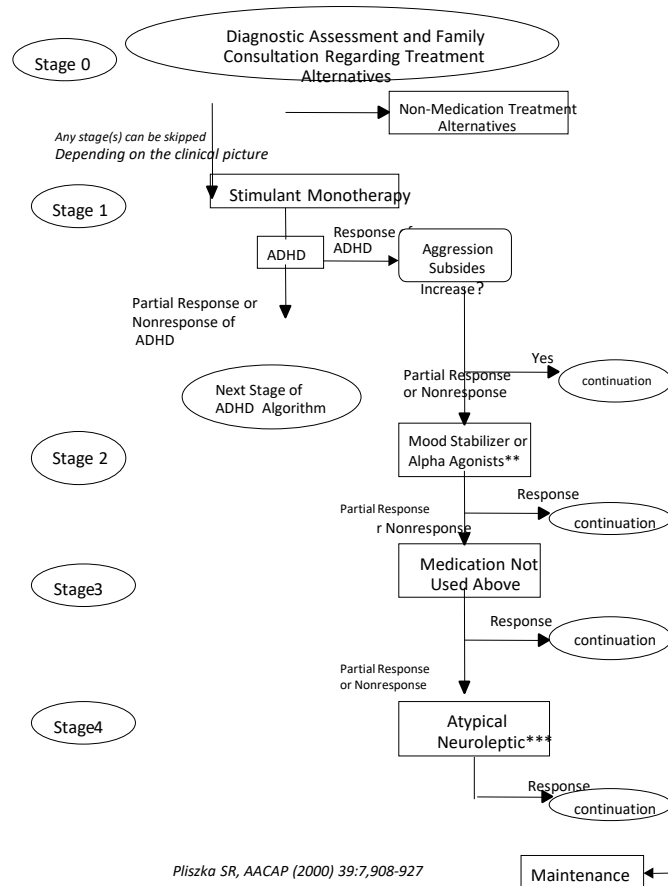
ADHD improves
but not MDD

Neither ADHD
nor MDD improves

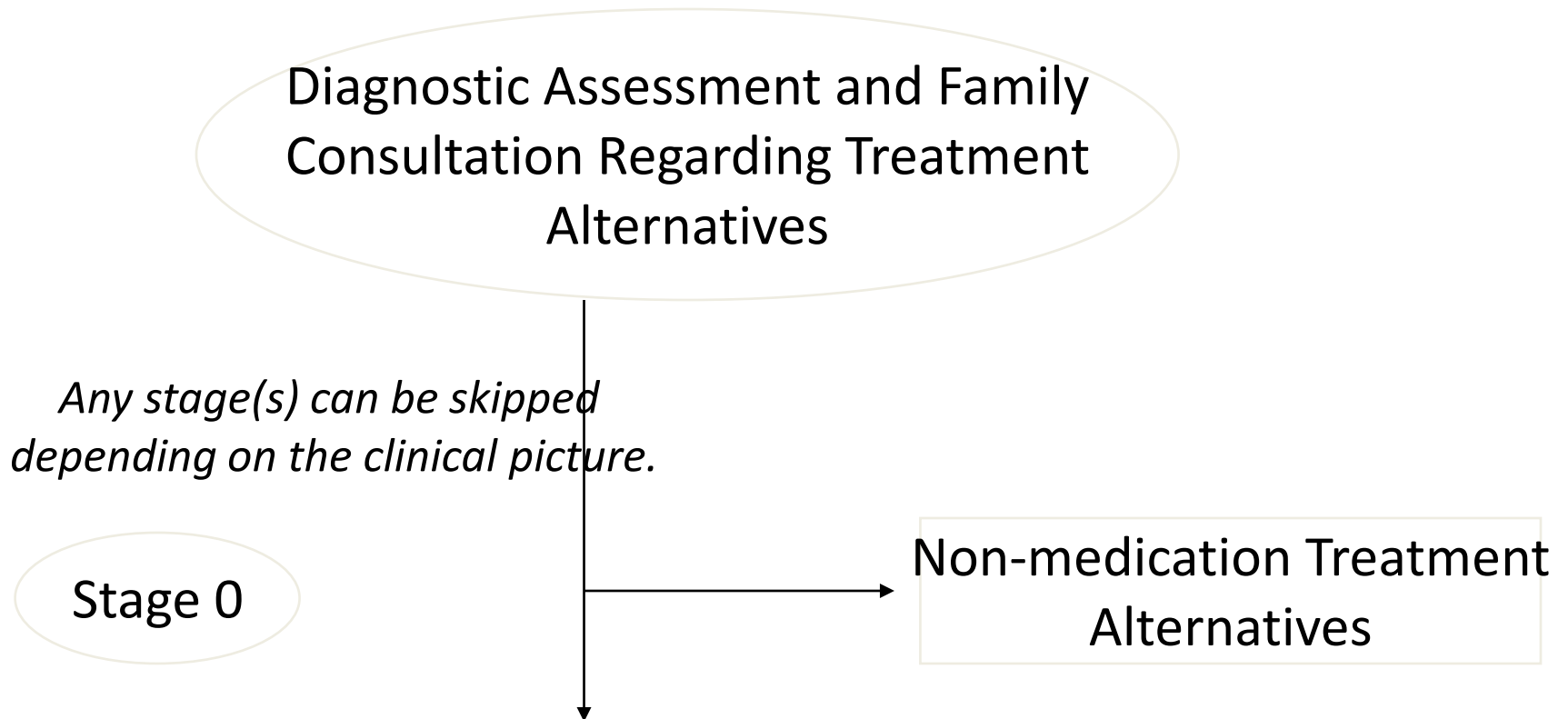




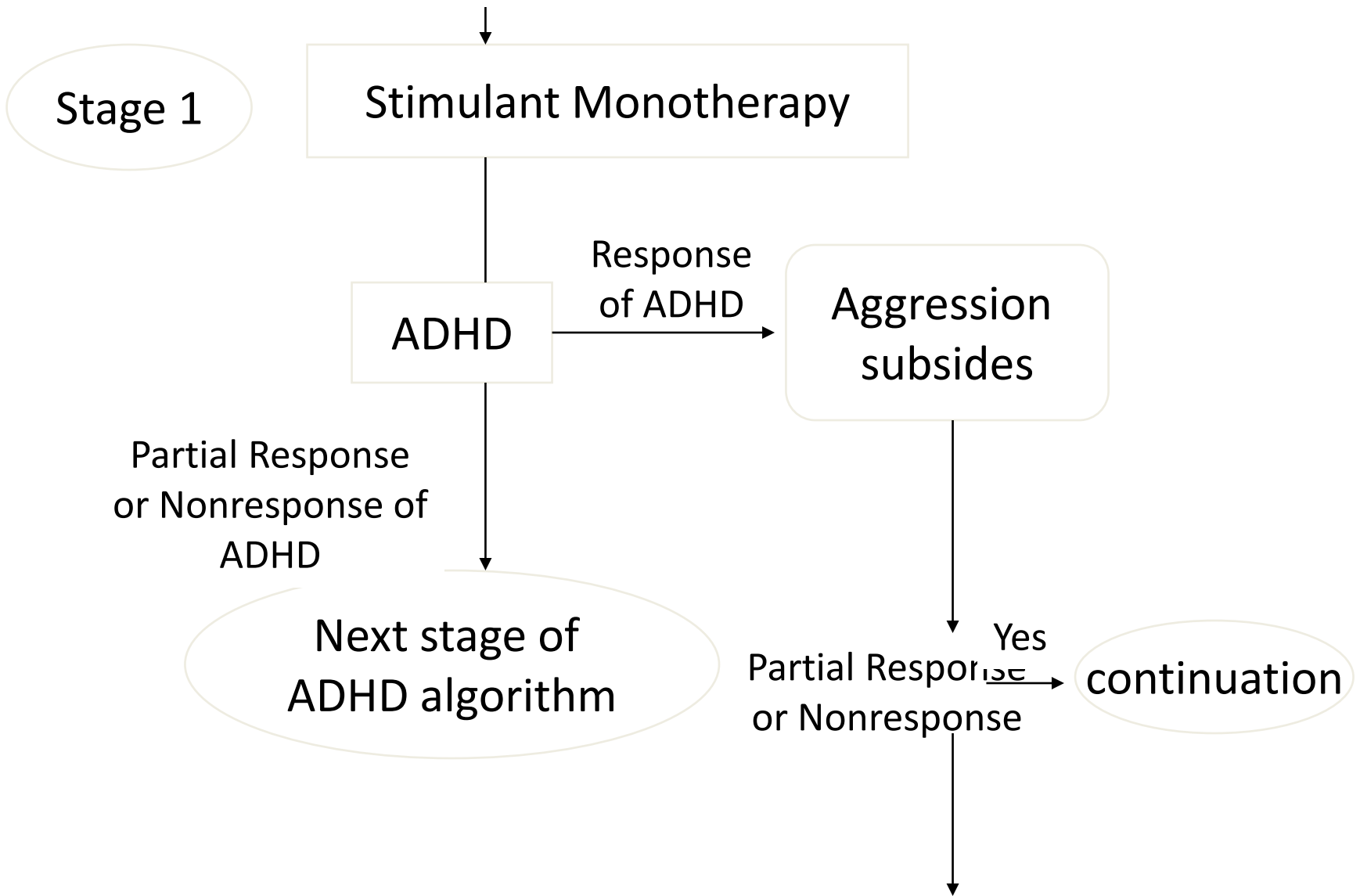
Algorithm for the medication treatment of attention-deficit/hyperactivity disorder (ADHD) with comorbid intermittent explosive disorder. ****Caution: Cardiovascular side effects.**
*****Caution: risk of extrapyramidal symptoms of tardive dyskinesia.**



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.



Comorbid Intermittent Explosive
Disorder is a Proxy for Aggression
and Bipolar Disorder



Mood Stabilizer or
Alpha Agonists**

Response

Partial Response
or Nonresponse

continuation

Medication Not
Used Above

Response

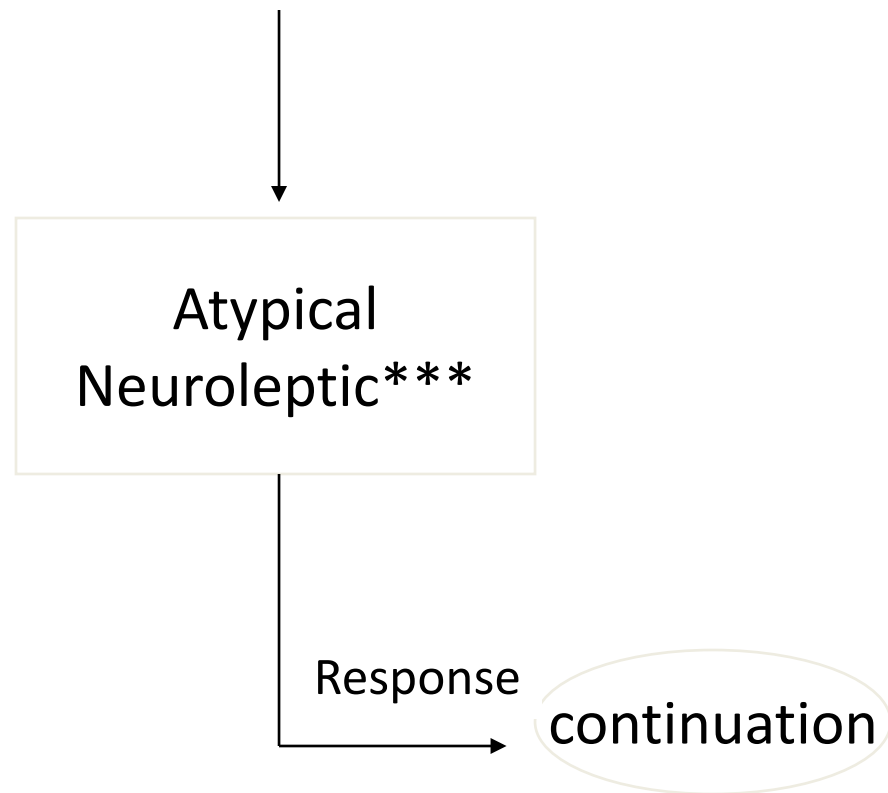
Partial Response
or Nonresponse

continuation

Stage 2

Stage 3

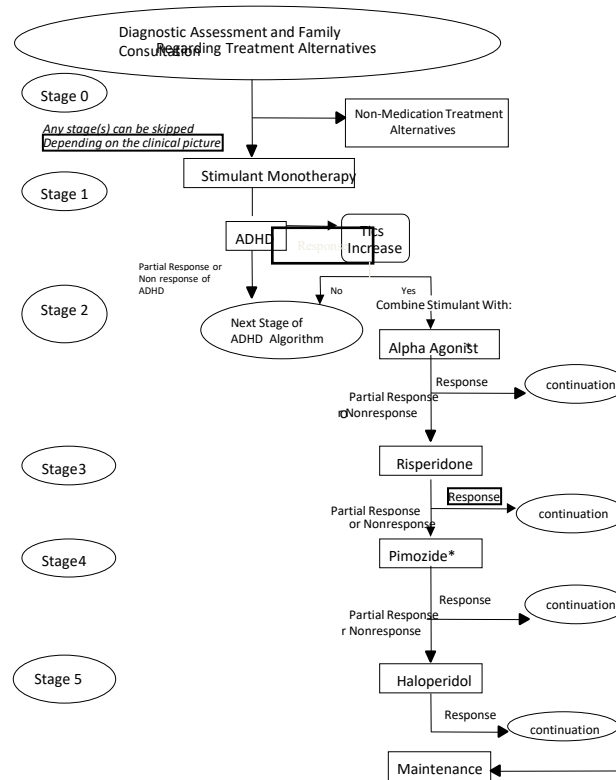
Stage 4



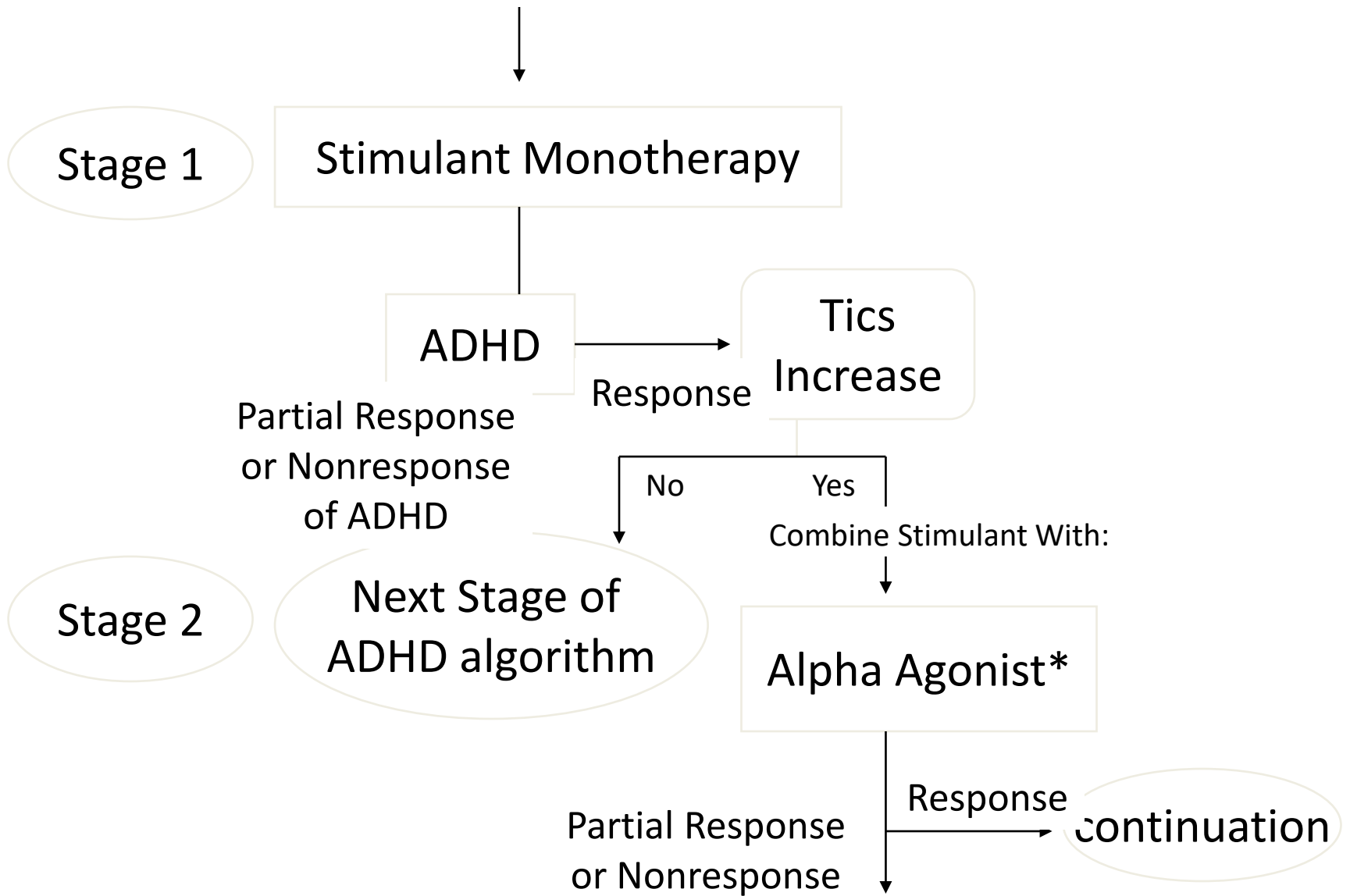
Pliszka SR, AACAP (2000) 39:7, 908-927



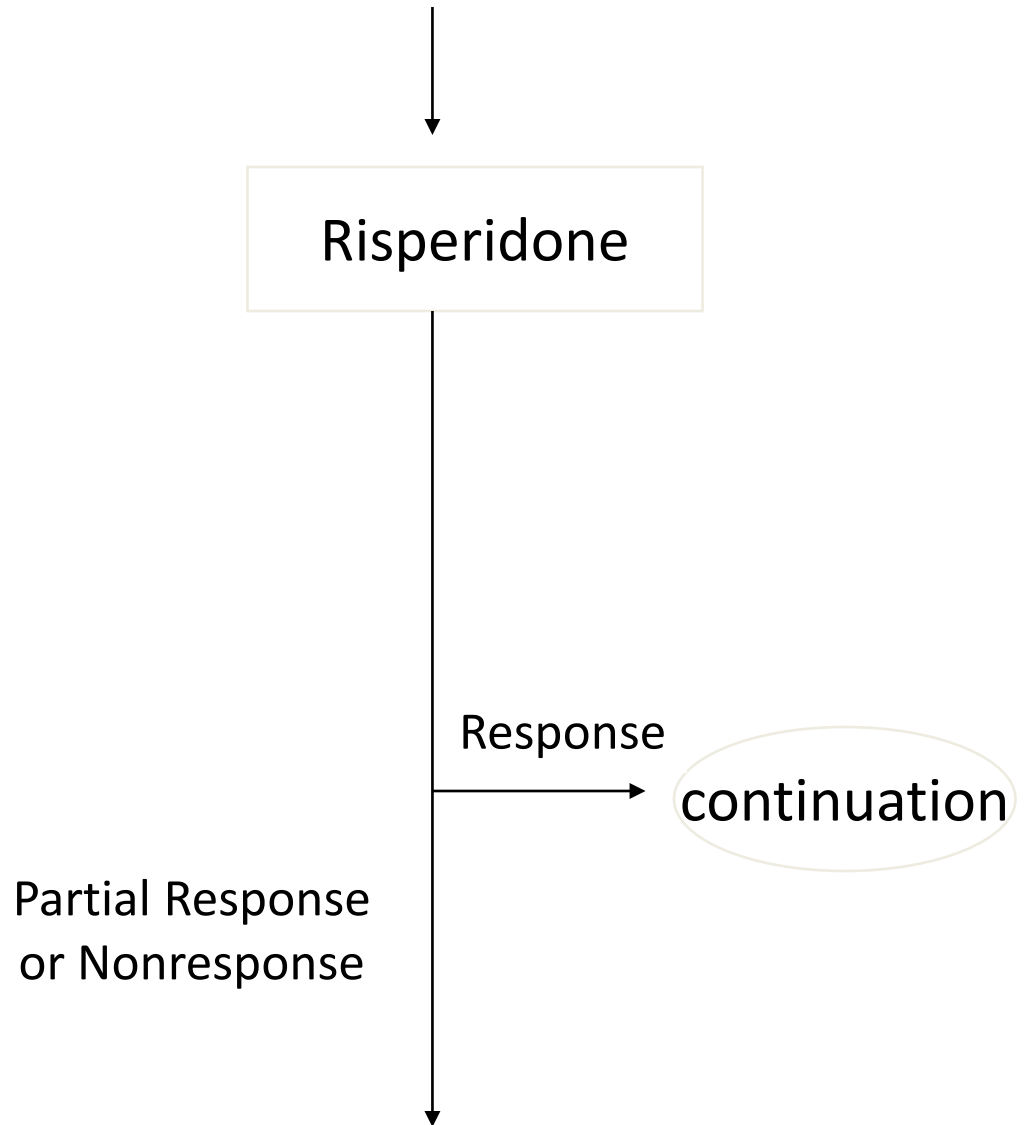
Algorithm for the medication treatment of attention-deficit/hyperactivity disorder (ADHD) with comorbid tic disorder. *Caution: cardiovascular side effects.



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

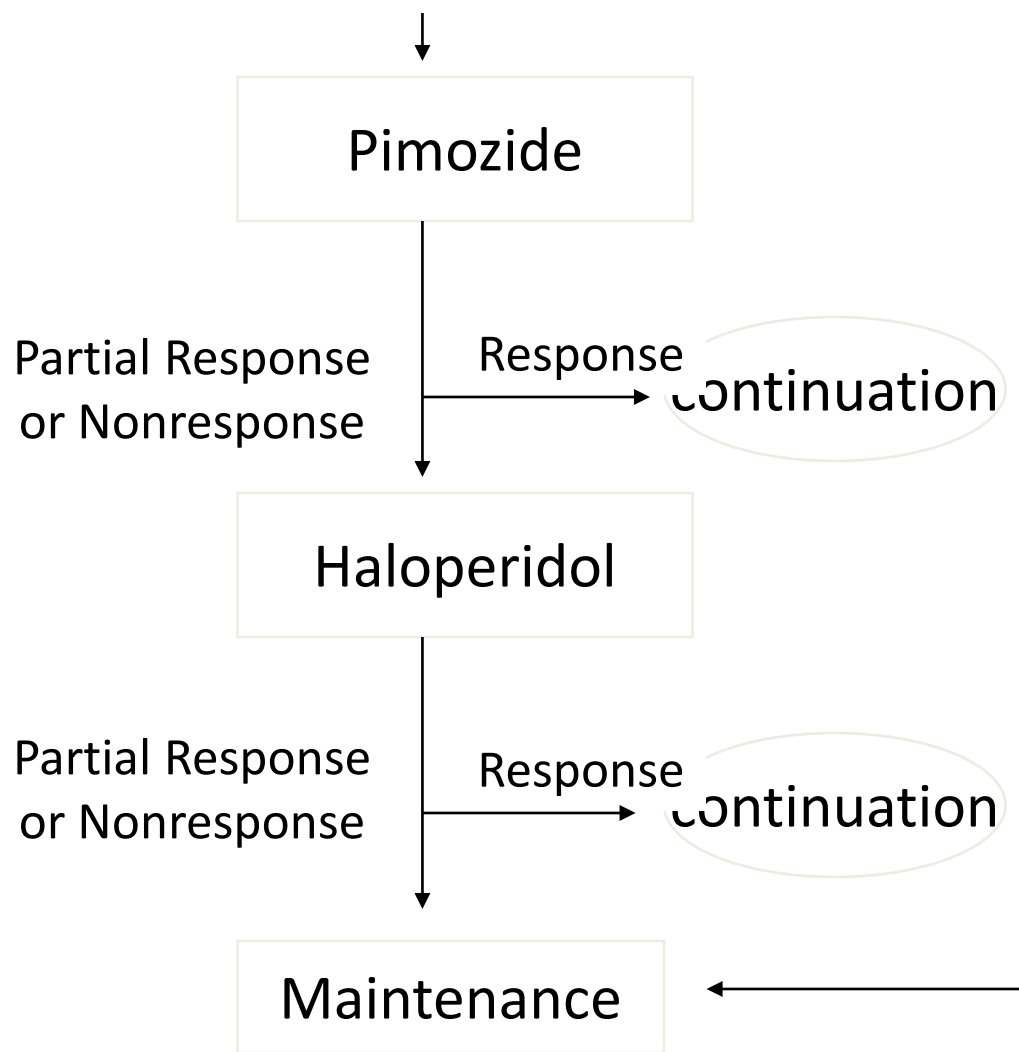


Stage 3



Stage 4

Stage 5



Practical Points

- 1) Optimize ADHD Treatment
- 2) Monitor Target Symptoms
+ Side Effects
- 3) Then Attend to Comorbid
Disorders

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