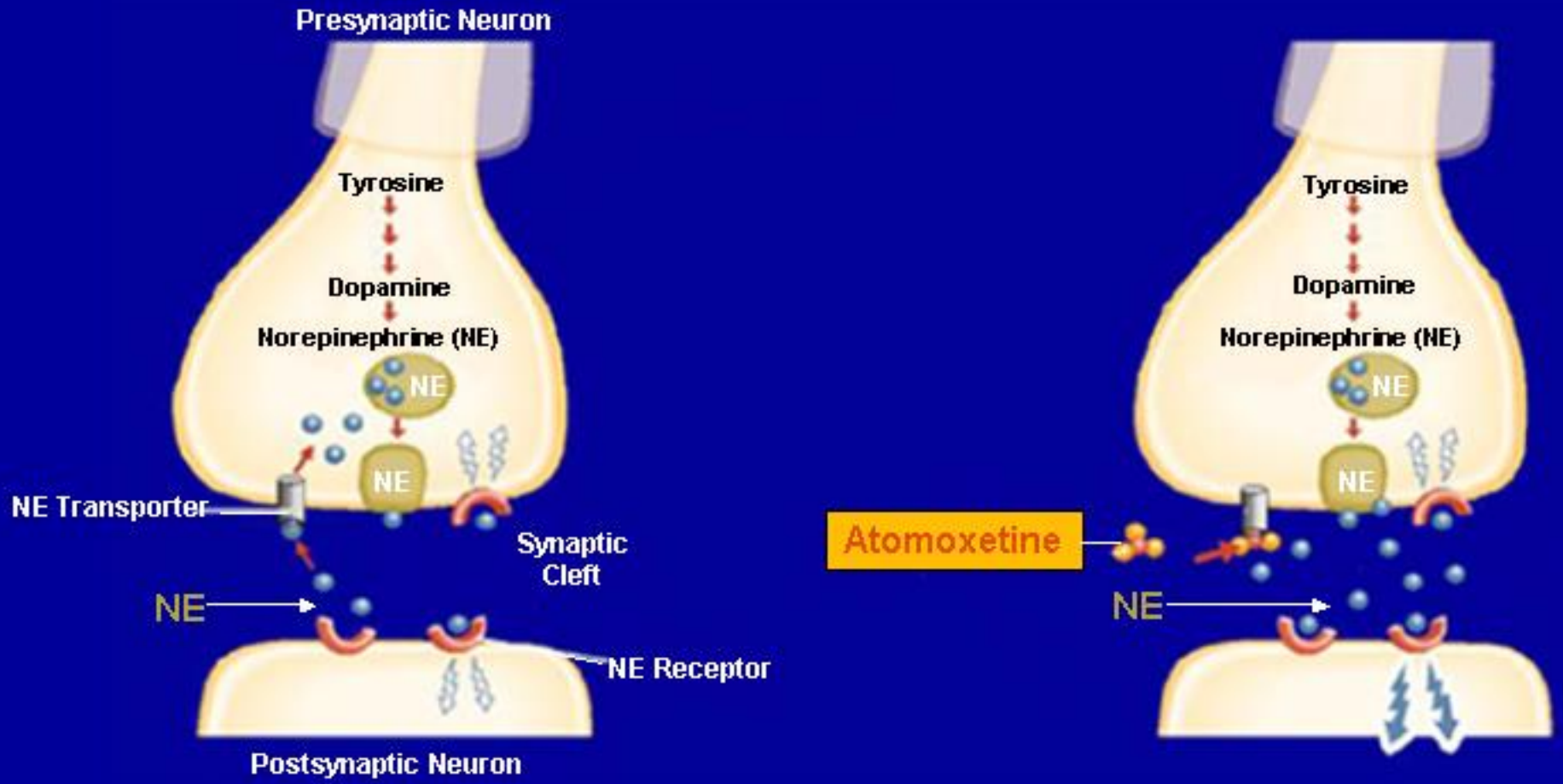
ADHD Treatments* (other medication options)

- Atomoxetine
  - Potent norepinephrine (NE) reuptake inhibitor
    - highly selective
    - inhibits presynaptic NE transporter

Atomoxetine: Site of Action



ADHD Treatments (medication options)

- Atomoxetine *(not to be confused with Tamoxifen)*
  - Michelson, et al (2001) : n=297, ages 8-18, 71 % male; 67% ADHD-CT; 8-week randomized prospective controlled study
  - Participants were moderately -to-severely impaired prior to tx.
  - Results showed superior response to placebo (65% response rate)
    - ADHD symptoms
    - Measures of social and family functioning

ADHD Treatments* (medication options)

- Atomoxetine
  - Total database (Lilly) of several thousand pediatric and adult patients with ADHD
  - Common side effects: Dizziness, drowsiness, dyspepsia, decreased appetite
  - Less common, but not rare (>2%)
    - Depression, tremor, early AM awakening, pruritus (generalized itching)
  - Adult patients: Possible Sexual dysfunction; No abuse potential (no activation of dopamine in nucleus accumbens)

Atomoxetine*, cont'd

- CYP2D6 substrate
  - Use cautiously when other medicines are used (eg. paroxetine, fluoxetine, quinidine)
  - Dose: 0.5 mg/kg/day—1.2 mg/kg/day; Max dose 1.4 mg/kg/day or 100mg (whichever is less)
  - Assessment of liver function prior to start is optional; monitor for hepatotoxicity
- **Black Box warning** re: teen patients with suicidal thinking
    - 5/1357 patients with suicidal thinking during initial trials
      - 1 of these 5 actually attempted suicide (unsuccessfully)
- Monitor height, weight, pulse and BP
    - Potential exists for decreases in growth (up to 0.5cm per year, and increases in HR and BP)
- May be used QD or BID
  - Time to Cmax is 1-2 hours
  - Duration of action is 6-10 hours (may be up to 24 hours)
  - Allow 6-8 weeks for full effect!

ADHD Treatments* (other medication options)

- Tricyclic Antidepressants (TCAs)
  - 30+ randomized controlled studies show efficacy in children
    - imipramine, amitryptiline, desipramine, clomipramine
  - uncontrolled studies show benefit of nortryptiline, protryptiline

ADHD Treatments* (medication options)

- Tricyclic Antidepressants (TCAs)
  - strong effects on H/I symptoms
  - weaker cognitive benefits than stimulants
  - Dosing/ monitoring
    - Use grad dose elevation/ LOTSA drug interax!
    - Imipramine most widely used
    - Most will respond to less than 5mg/kg/day
      - many to 1-2mg/kg/day
      - start at 50 mg @ HS// level @ 7-10 days
      - Do not exceed 300 ng/ml
    - Monitor BP, EKGs:
      - QTc < 0.44ms, PR< 200ms, QRS < 120ms

Cardiovascular parameters for TCAs: When to Call A Cardiology Consult *!

	Resting heart beats/min = or >	Resting BP = o r>	PR = or >	QTc = or >
< 10 yrs	110	140/90 or 135/85 > 1/2 time 3 wks	0.18	0.44
>10 yrs	100	150/95 or 140/85 > 1/2 time 3 wks	0.20	0.44

Adapted from Rye and Ryan: *Child and Adolesc Psychiatric Clinics NA* 4:275, 1995

Tricyclic Antidepressants (TCAs)

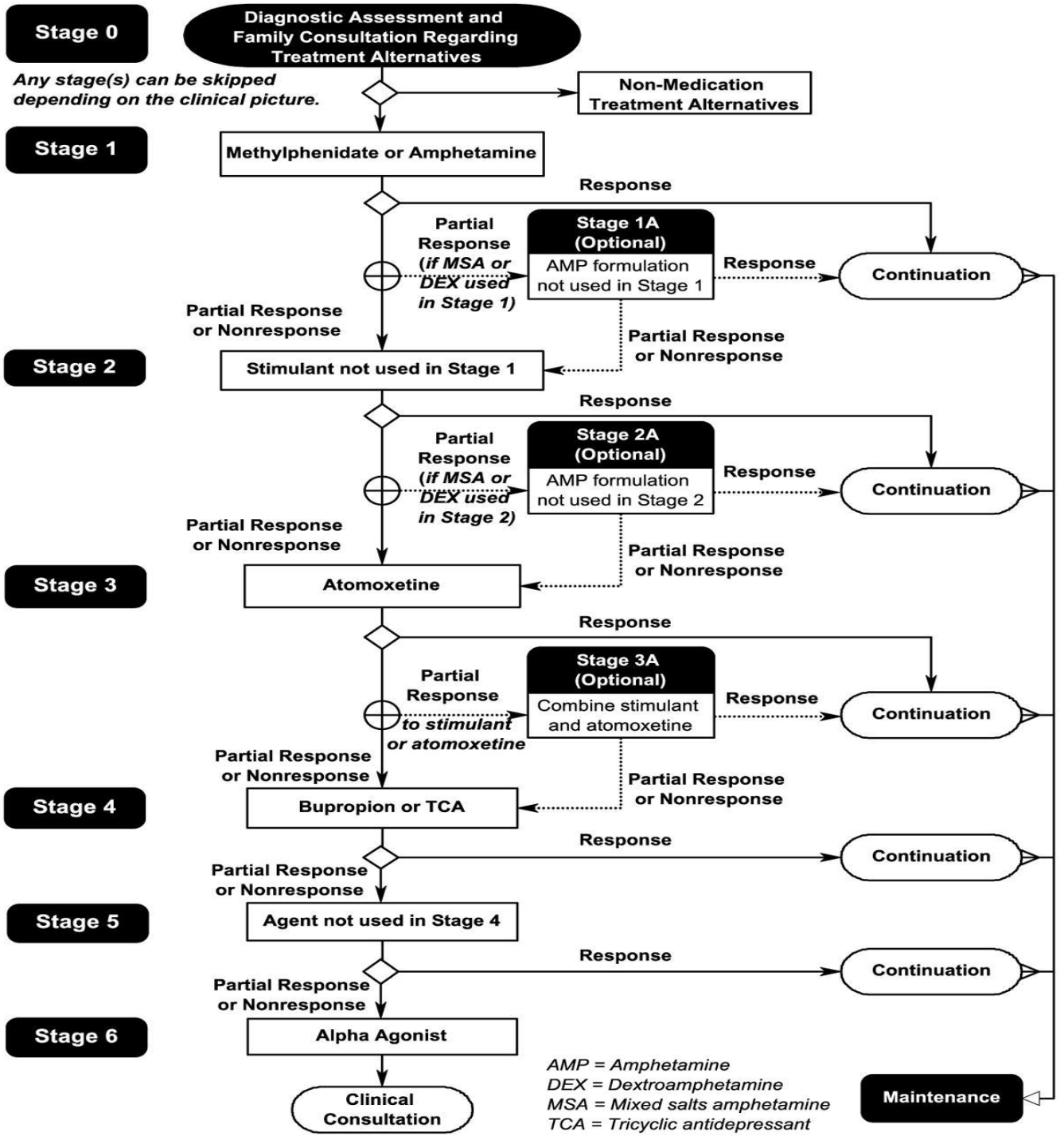
- Clomipramine (*non-routine in kids*)
  - non-selective SRI
  - data to show efficacy, but side effects limit use
  - possible use in co-morbid OCD
  - High seizure risk (1.5% annual risk in adults)
- Desipramine
  - Still used in adults
  - 6 published cases of sudden death in children

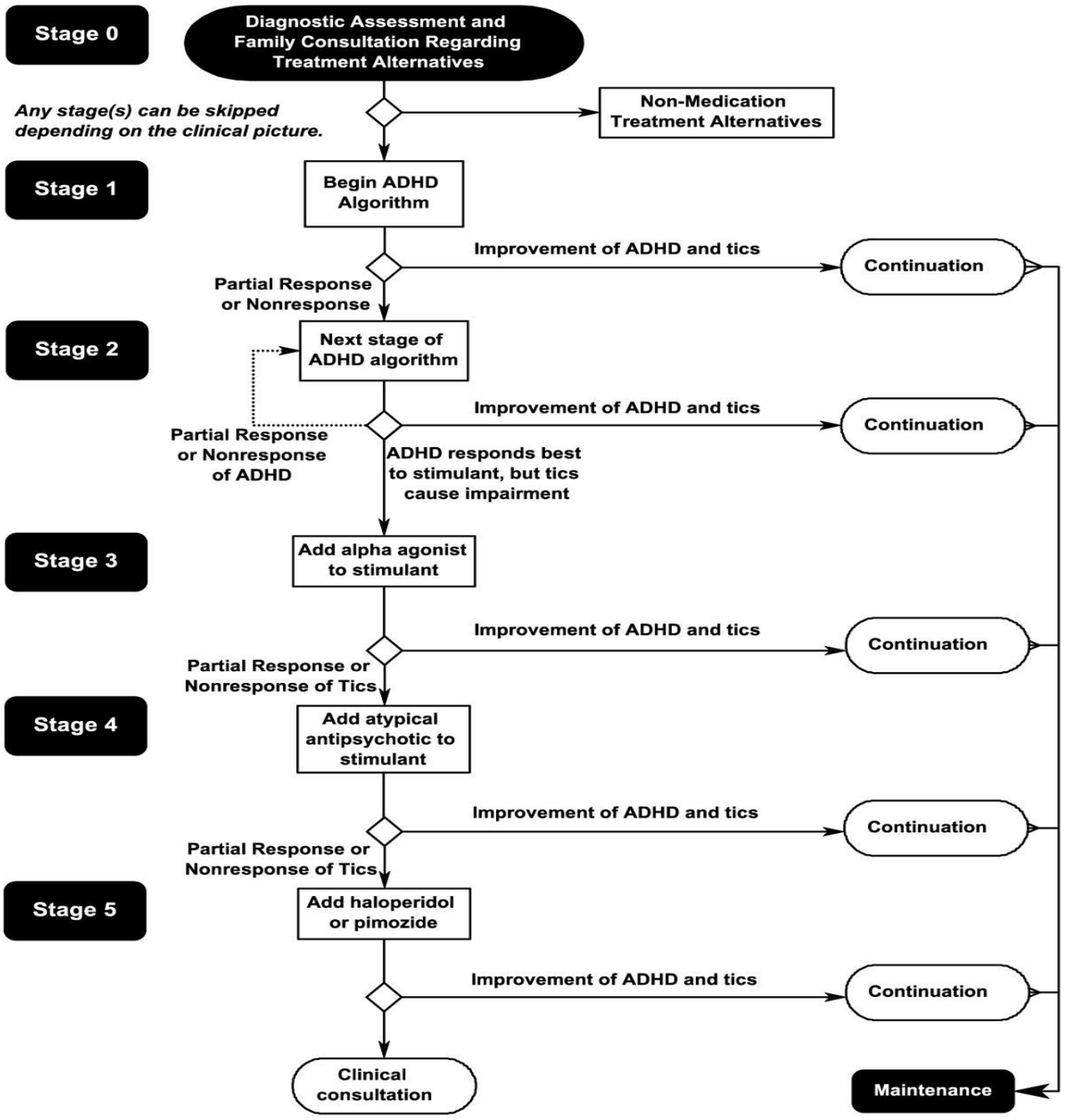
TCAs drug interactions

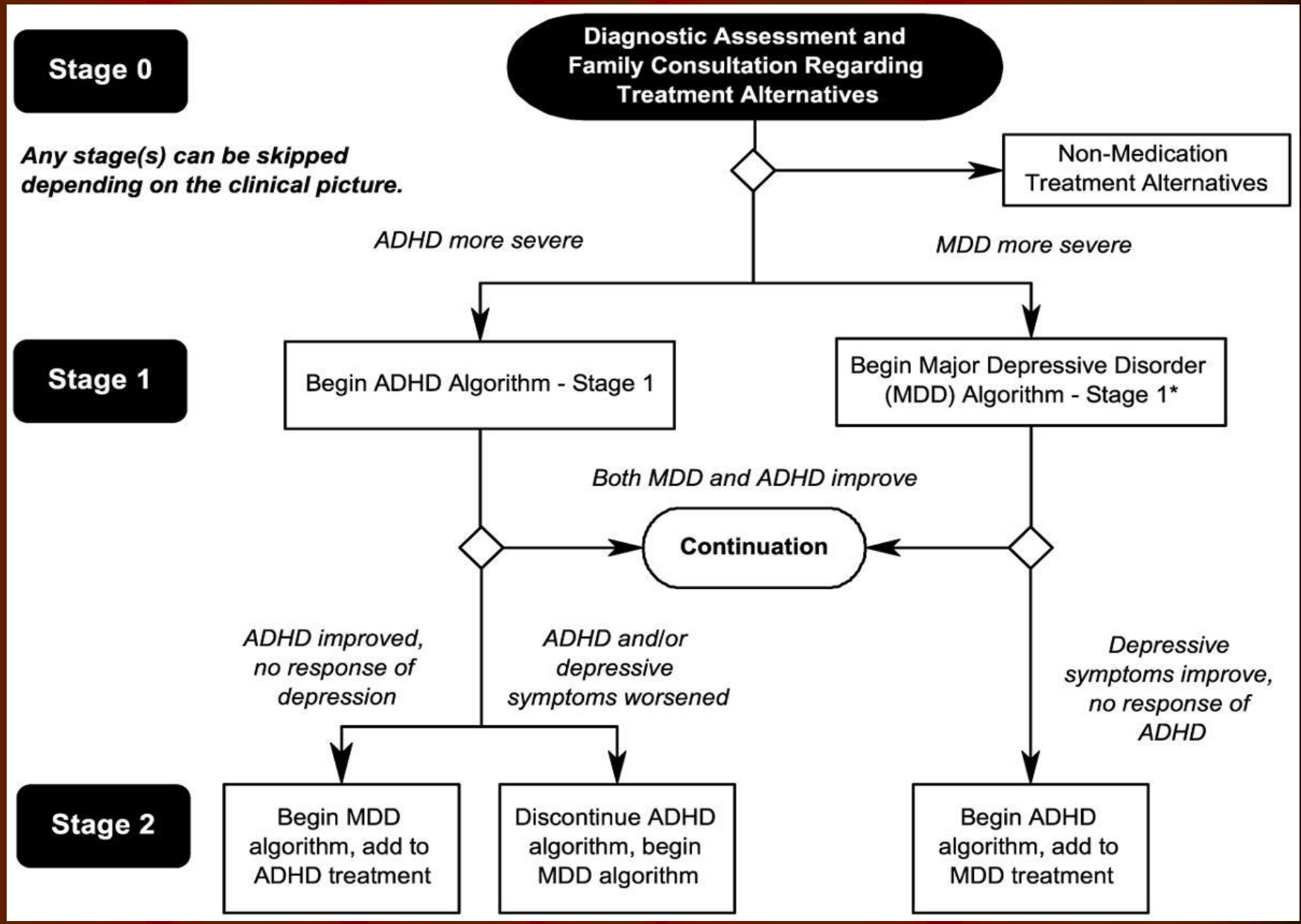
- Very complicated, must be vigilant when using polypharmacy
- TCAs demethylated by variety of CYPs and then hydroxylated via CYP2D6
- Paroxetine/ fluoxetine inhibit CYP2D6, thus decrease clearance up to 400% of CYP2D6 substrates, including TCAs
- Sertraline/citalopram decrease clearance 25% of CYP2D6 substrates

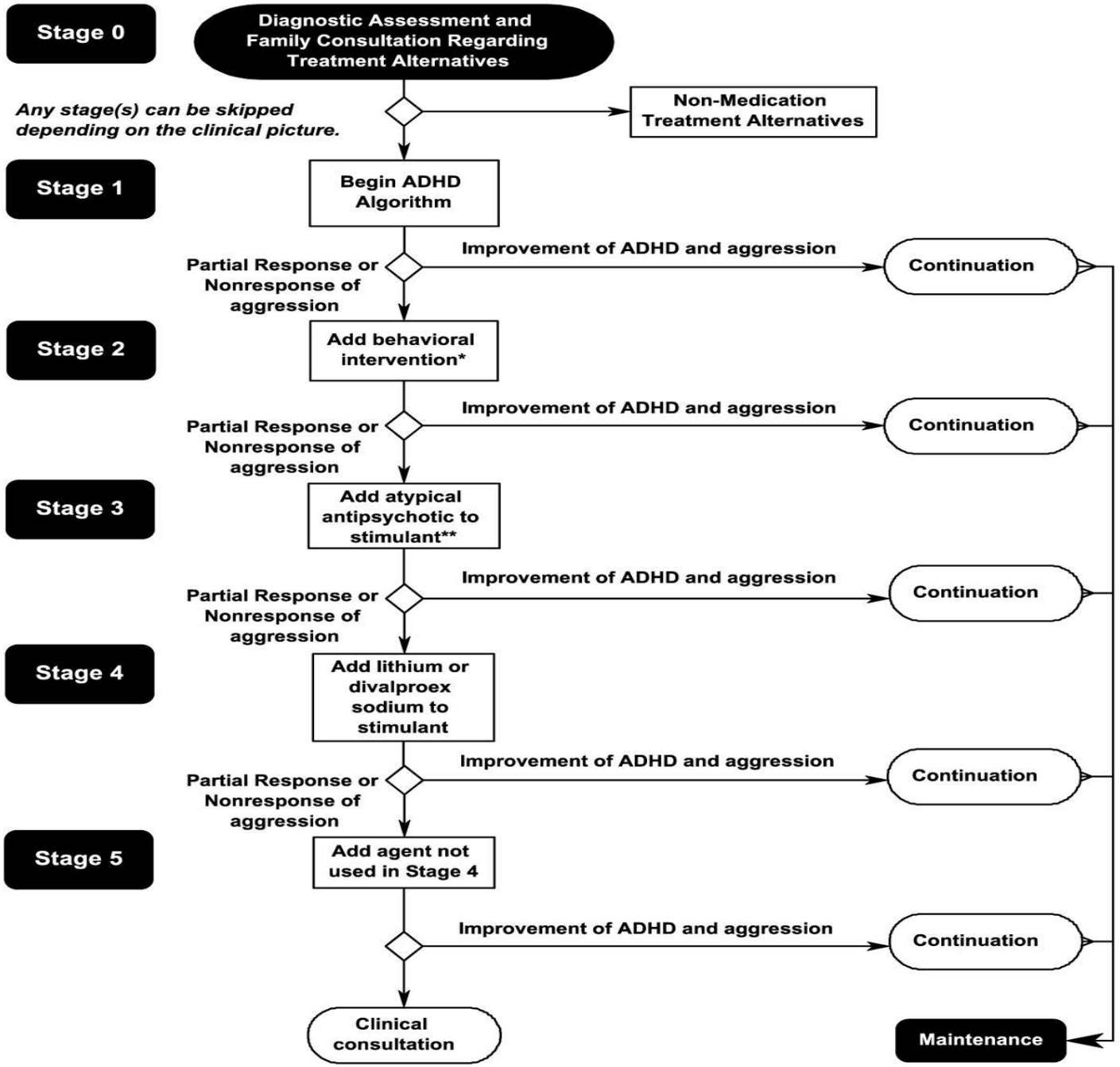
CMAP-ADHD*

- http://www.mhmr.state.tx.us/centraloffice/medicaldirector/adhdalgo.pdf
- 4 algorithms*: ADHD, with tics, with MDD and with IED
- Tactic Tables: Dosing schedules for Stimulants,TCAs,Bupropion, Alpha Agonists and SSRIs


Stage 0
Diagnostic Assessment and Family Consultation Regarding Treatment Alternatives
Any stage(s) can be skipped depending on the clinical picture.
Non-Medication Treatment Alternatives
Stage 1
Methylphenidate or Amphetamine
Response
Partial Response (if MSA or DEX used in Stage 1)
Stage 1A (Optional)
AMP formulation not used in Stage 1
Response
Continuation
Partial Response or Nonresponse
Partial Response or Nonresponse
Stage 2
Stimulant not used in Stage 1
Response
Partial Response (if MSA or DEX used in Stage 2)
Stage 2A (Optional)
AMP formulation not used in Stage 2
Response
Continuation
Partial Response or Nonresponse
Partial Response or Nonresponse
Stage 3
Atomoxetine
Response
Partial Response to stimulant or atomoxetine
Stage 3A (Optional)
Combine stimulant and atomoxetine
Response
Continuation
Partial Response or Nonresponse
Partial Response or Nonresponse
Stage 4
Bupropion or TCA
Response
Continuation
Partial Response or Nonresponse
Stage 5
Agent not used in Stage 4
Response
Continuation
Partial Response or Nonresponse
Stage 6
Alpha Agonist
Clinical Consultation
AMP = Amphetamine
DEX = Dextroamphetamine
MSA = Mixed salts amphetamine
TCA = Tricyclic antidepressant
Maintenance


Stage 0
Diagnostic Assessment and Family Consultation Regarding Treatment Alternatives
Any stage(s) can be skipped depending on the clinical picture.
Non-Medication Treatment Alternatives
Stage 1
Begin ADHD Algorithm
Improvement of ADHD and tics
Continuation
Partial Response or Nonresponse
Stage 2
Next stage of ADHD algorithm
Improvement of ADHD and tics
Continuation
Partial Response or Nonresponse of ADHD
ADHD responds best to stimulant, but tics cause impairment
Stage 3
Add alpha agonist to stimulant
Improvement of ADHD and tics
Continuation
Partial Response or Nonresponse of Tics
Stage 4
Add atypical antipsychotic to stimulant
Improvement of ADHD and tics
Continuation
Partial Response or Nonresponse of Tics
Stage 5
Add haloperidol or pimozide
Improvement of ADHD and tics
Continuation
Clinical consultation
Maintenance


Stage 0
Diagnostic Assessment and Family Consultation Regarding Treatment Alternatives
Any stage(s) can be skipped depending on the clinical picture.
Non-Medication Treatment Alternatives
ADHD more severe
MDD more severe
Stage 1
Begin ADHD Algorithm - Stage 1
Begin Major Depressive Disorder (MDD) Algorithm - Stage 1*
Both MDD and ADHD improve
Continuation
ADHD improved, no response of depression
ADHD and/or depressive symptoms worsened
Depressive symptoms improve, no response of ADHD
Stage 2
Begin MDD algorithm, add to ADHD treatment
Discontinue ADHD algorithm, begin MDD algorithm
Begin ADHD algorithm, add to MDD treatment



* Evaluate adequacy of behavior treatment after inadequate response at any stage.
**If patient is an imminent threat to self or others, atypical antipsychotic may be started with behavioral teatment.

Other medication options*

- Bupropion (Wellbutrin / Zyban)
  - Minimal 5-HT effects
  - Inhibits NE, DA uptake
  - May have special use with comorbid depression or substance abuse
  - 1 open and 3 controlled studies in children
    - not quite as robust an effect as stimulants

Bupropion, cont'd.*

- Side effects
  - skin rash
  - seizures (lower with SR preparation)
    - 0.3%-0.4%; risk increases with doses> 450 mg Total Daily Dose
  - psychosis, agitation
  - sleep problems
  - appetite suppression
    - May have paradoxical beneficial effect on appetite when combined with stimulants
      - Callaghan, *JAACAP*, July 1999

Venlafaxine (Effexor)*

- Selective Inhibition of NE and 5-HT
- Adults: 3 open series and a case report suggest therapeutic effects
- Youths: 1 case series (n=16), 1 case report
  - more benefits on behavioral than cognitive symptoms
  - anecdotal reports: useful in OCD, perseveration, depression, anxiety, agitation
  - Recently fallen out of favor due to concerns about suicidal thinking

Clonidine (Catapres)*

- alpha-2 adrenergic agonist
- may have role for H-I symptoms and aggression (not inattention)
  - special utility in DD population
- placebo-med differences have been found in small controlled studies
- side effects often limit its usefulness
  - CV, sedation

Clonidine (Catapres)

- Dose:
  - Start with 0.05 mg @ HS
  - Typical range is 0.05-0.2 mg, BID-QID
  - max daily dose 0.9 mg
- Must monitor BP, other CV parameters
  - Possible bradycardia
  - rebound tachycardia and HTN
    - children between doses
    - if d/c'd abruptly
  - *if tx'd for more than 1 month, d/c at a rate of 0.05 mg q3-7 days*

Clonidine (Catapres)

- Relative contraindication : Depression
- MPH/ CLON combination
  - may be very helpful, esp. w/ comorbid insomnia
  - 1994: 40% of pts w/ ADHD tx'd with CLON were also on stimulants.
  - 3 fatalities, 1 LTE in kids on MPH/ CLON
    - See *JAACAP* 38:5, May 1999, pp614-622, for debate on this often-used combination
- Recent prospective studies from the Neurology literature MPH/CLON combo for tx of ADHD and tics *Neurology* 2002;58:527-536
  - Total n= 160; no major safety issues in cross-over studies of up to 4 months
  - Mean daily doses CLON 0.25 mg; MPH 25 mg

Pre-treatment workup for Clonidine

- Check for history of arrhythmias, relatives' early sudden death
- Check for Raynaud's Disease, Diabetes Mellitus
- ECG if indicated (Biederman 1999, Kofoed 1999, Oesterheld 1996)
- Orthostatic blood pressure
- Pulse

Clonidine:Side effects

Common

- Sedation, dry mouth, dizziness
- Nighttime awakenings, nightmares, night terrors

Serious

- Idiosyncratic aggravation of cardiac arrhythmias
- Danger of rebound hypertension if stopped suddenly
- Depression in about 5%
- *Hyper*glycemia

- ***No contraindication to use with psychostimulants***, as of 2008

Guanfacine (Tenex)*

- Similar MOA to clonidine, with some impt receptor diffs:
  - alpha 2A agonist, but weaker alpha 1, alpha 2B, alpha 2C activity
  - less beta-adrenergic, histamine, 5-HT, beta-endorphin, and DA effects
- Less hypotension, sedation, rebound HTN
- Longer duration, so less frequent dosing necessary (T 1/2= 17 hrs.); pks in 2-3 hrs
  - start with 0.5 mg qD, then increase 0.5 mg q3-4 days if necessary
  - optimal dosing: 2.5-3.5 mg TDD, div TID or QID.
  - MDD=4 mg/day
- May have role in inattention, impulsivity, tics

Guanfacine (Tenex)

- Sedation , BP changes are common (25-30%), but usually transient
- No reports of sudden death thus far.
- Monitor for behavioral activation/ disinhibition
- Controlled studies underway
  - See Scahill, et al: *Am J Psychiatry* 158:7, July 2001
- Long-acting form of guanfacine (Intuniv) will be available as a non-stimulant drug for ADHD for children aged 6-17 years, possibly in 2008.

Modafinil (Provigil)*

- Wakefulness promoter
- MOA: Possible modulation of glutamate and GABA, and/or an effect on orexin/hypocretin receptors
  - Results in an increase in extracellular DA, NE, 5-HT
  - Different MOA than stimulants
- Schedule IV (cf. schedule II), thus fewer prescribing restrictions
- Therapeutic Dose range: 100-400 mg qAM

Modafinil (Provigil)

- Benefits: Improved mood, reaction time, logical reasoning, short term memory
- Side effects: Headache, nausea, rhinitis, pharyngitis, dizziness, dry mouth, anorexia, insomnia
- Current FDA Indications: Narcolepsy in Pts 16 and older
- Duration 12-15 hours
- Rugino Study (2003): 6 weeks; n=22; RPCT
  - 100mg QD: Significant improvement vs. placebo; minimal side effects; no anorexia
  - Independent study (No Cephalon funding)