University of Washington
Department of Psychiatry

FCAP
Depression

April 19, 2004

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DEPRESSION IN YOUTH
CLINICAL FEATURES

Prevalence

General Population 2 - 5%

Clinical Population 13-34%

Clinical Presentation: Clinical Features

Children/Adolescents

- -Somatic complaints
- -Irritability: can be primary mood symptom
- -Guilt
- -Low self-esteem
- -Suicide attempts

Adults

- Endogenicity
  - AM sleeplessness
  - Weight Loss
  - Diurnal Mood Changes
- Psychosis
- Impairment of functioning

Clinical Presentation: Comorbidity

- 40% to 70% have comorbid dx
- Most common:
  - -Anxiety disorders-20% to 40%
  - -Disruptive disorders-10% to 80%
  - -Substance abuse-20% to 30%
- MDD presents after anxiety and disruptive disorder
- Substance abuse secondary to depression

Clinical Presentation: Course of Disorder

- Mean length of episode: 7 to 9 months
- 90% remitted by 1.5 to 2 years
- 6% to 10% become protracted
- Recurrence: 70% by 5 years
- Approximately 20% develop bipolar disorder

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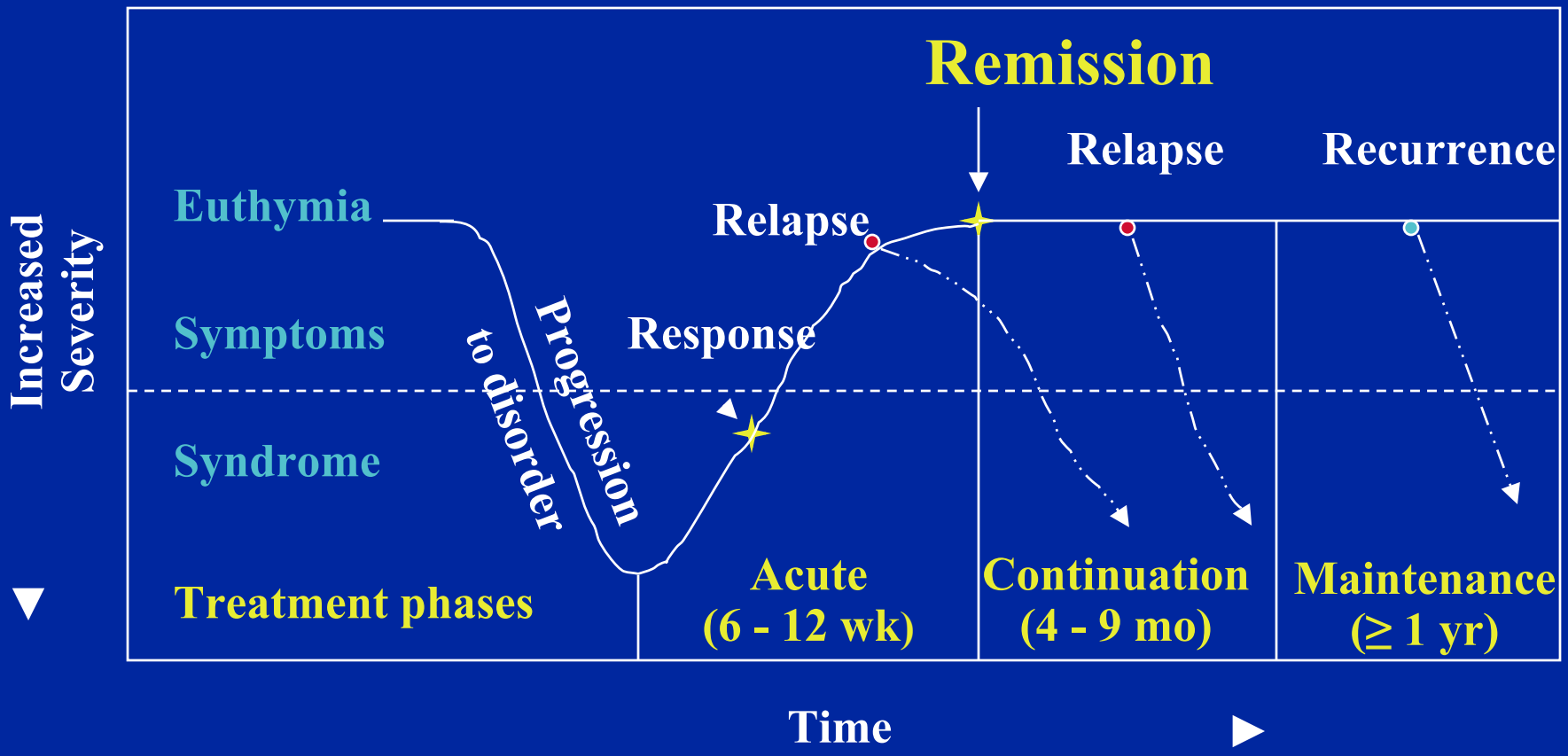
Phases of Treatment for Depression



Kupfer DJ. *J Clin Psychiatry*. 1991;52(suppl5):28.

Assessment of Depression

1. This is a clinical diagnosis
2. Rating Scales: Beck, Childhood Depression Inventory, Hamilton, Zung, Child Behavior Checklist
3. Recent physical examination
4. Laboratory Tests: Thyroid screen and others as indicated (e.g. pregnancy test, drug toxicology screen)
5. Need to assess for Drug/Alcohol Abuse
6. Family assessment: Particularly depression, anxiety, suicide, drug, alcohol problems, abuse history, support systems
7. Specific assessment of risk of suicide

SUICIDE

1. A leading cause of death in adolescents: 2nd or 3rd
2. 12% of teen deaths are suicide
3. Suicidal ideation very common in adolescents: 20% per year
4. Suicide attempts: 10% per year
   a. More common in females
   b. More often completed in males

PRIMARY RISK FACTORS FOR SUICIDE

Prior Suicide Attempt
Drug and Alcohol Abuse
Affective Illness
Antisocial/Aggressive Behavior
Family History of Suicidal Behavior
Availability of a Firearm
Homosexuality

Suicide Risk Reduction

- Do it 100% of the time if you see a parasuicidal child
  - -Get rid of GUNS (and other lethal means)
  - -Change positive EXPECTANCIES (Actively create doubt) about Suicide
  - -Tell them not to harm themselves

Formulation

How did the patient get this way?

Biopsychosocial Model

Biological: (e.g., genetics, drug abuse, thyroid disorder)

Psychological: (e.g., abuse, losses)

Sociological: (e.g., poverty)

Summary Informs Treatment

Clinical Management: S***evere impairment, recurrent, + neurovegetative sx, significant decline in functioning***

- Psychoeducation, **AND**
- Psychotherapy,
  - Cognitive Behavioral
  - Interpersonal
  - Family/Group **AND**
- Pharmacotherapy

RESEARCH

1) Fluoxetine
   Two positive controlled trials with adolescents with major depression with fluoxetine

1) Emslie - Arch Gen Psych (1997) 54:1031-1037
2) Emslie, J Am Acad Child Adolesc Psych (2002)41:1205-1215.

RESEARCH

Fluoxetine #1

Fixed dose of 20mg – 97 subjects, 56% positive response vs 33% on placebo

RESEARCH

Fluoxetine #2

20mg – 219 subjects – 41% remission

versus 20% placebo

RESEARCH

2) Paroxetine

- One positive trial with adolescents with major depression with paroxetine

	Paroxetine	Imipramine	Placebo
• Dose	***10-40mg/day***	***200mg/day***	
• Response rate	***63%***	***50%***	***46%***

- High dropout rate on imipramine
- Considered a negative trial by some, not all, as primary indicators didn't show a difference

Keller J. - American Acad Child Adoles Psychiatry (2001): 40:762-772

Paroxetine versus Clomipramine

- 212 Adolescents (ages 12-20) with major depression
- 8 week trial
- 58 treated with Clomipramine
- 63 treated with Paroxetine
- No placebo arm

Braconnier – J. Amer Acad Child Adolesc Psych (2003);42:22-29

Dosing

Begun at 20mg of Paroxetine or 75mg of Clomipramine

At 21 days, clinicians could double the dose

Results

Intent to treat analyses
Clomipramine responders
- **48% on MADRS**
- **58% of CGI**

Paroxetine responders
- **65% on MADRS**
- **58% CGI**

No significant difference between groups

RESEARCH

Paroxetine

- **2 large, unpublished placebo controlled trials with no difference between paroxetine versus placebo**

- **Possible increased risk of suicidal ideation and suicide attempts**

RESEARCH

3) Citalopram Treatment for Depression in Children and Adolescents

- 174 outpatients, ages 7-17 years, with major depression
- Double-blind, placebo-controlled 8 week trial
- Randomized to citalopram, 20-40 mg (mean 23 mg) or placebo
- Evidence of benefit vs. placebo
- Presented at a scientific meeting, under review for publication

Wagner KD, Robb AS, Findling R, Tiseo PJ. ACNP, Walkoloa, Hawaii 2001. P158 (Science abstract)

RESEARCH
Citalopram

One unpublished study with no difference from placebo

RESEARCH

4) Sertraline Treatment of Major Depression in Children

- 2 multicenter studies of 376 children and adolescents, ages 6-17 years, with major depression
- Double-blind, placebo-controlled 10-week trials
- Randomized to sertraline (50-200 mg/day) or placebo

Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder. JAMA 2003:290.8.1033-1041.

Sertraline Treatment of Major Depression in Children

Results

- Significantly greater improvement in depression (CDRS-R scores) with sertraline versus placebo
- 69% responded to sertraline vs 59% to placebo
- Vomiting, diarrhea, agitation and anorexia more common in sertraline group than placebo group

RESEARCH

Nefazodone

- **Double blind placebo controlled 8-week study**
- **195 subjects aged 12-17**
- **99 on active drug; 98 on placebo**

RESEARCH
Nefazodone
Results

- Change from baseline p=.055, NS
- CGI much or very much improved:
  - 62% on Nefazodone
  - 42% on placebo
  - P = .005
- No safety data available

RESEARCH
Nefazodone

- **Results presented at a scientific meeting, not published in a referred journal**
- **Another large double blind placebo controlled trial with negative results not published**

Emslie 2002

RESEARCH

Several negative trials:
Nortriptyline, imipramine, amitriptyline, venlafaxine, MAOI

RESEARCH

Many agents with no controlled trials for depression in youth

- fluvoxamine
- bupropion *(currently underway)*
- trazodone

RESEARCH

No Data on dysthymia, minor depression or adjustment disorder in youth

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Recent Safety Concerns Regarding Antidepressants in Children and Adolescents

Pooled Paroxetine Data Reviewed in Great Britain: Findings in June 10, 2003:

1) No evidence of benefit in major depression
2) Mood-related side effects were 1.5 to 3.2 times higher on Paroxetine as compared to placebo, including suicide attempts (no deaths reported)
3) Statement: Paroxetine contraindicated in children and adolescents for treatment of major depression

FDA Action
June 19, 2003

1) Announcement that the matter was being reviewed
2) Recommended that Paroxetine not be used in children and adolescents while this was being reviewed

Paroxetine Study
Keller, et al

Serious adverse events

- **11 patients on Paroxetine**
- **5 patients on imipramine**
- **2 patients on placebo**
- **Not statistically significant**

Paroxetine Study - Keller

Adverse reactions on paroxetine

- Worsening of depression(n-2)
- Emotional lability, including suicidal ideation and gestures (n-5)
- Aggressiveness (n-2)
- Euphoria (n-1)

Venlafaxine

Wyeth notice August 22, 2003

- In pediatric clinical trials, there were increased reports of hostility and especially in Major Depressive Disorder, suicide-related adverse events such as suicidal ideation and self-harm
- No FDA indication in youth

Epidemiologic Data

When antidepressant use rose in various regions, the suicide rate in youths 10-19 decreased

Olfson, Archives General Psychiatry 10/2003

FDA Position as of 10/14/03

1) Unclear if there is a signal Thomas Laughlen FDA team leader on the psychopharmacology drug group
2) Scrutinizing clinical trial data
3) Asked for data from all eight drug companies doing pediatric trials in exchange for extension of patent exclusivity
4) Analysis to include assessment of co-variance
5) Presentation to an expert advisory panel in February 2004

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Great Britain update December 10, 2003

Expert Working Group of the Committee on Safety of Medicines (CSM) has completed its review of the safety and efficacy of the SSRI class in the treatment of paediatric major depressive disorder.

December 10, 2003 www.mhra.gov.uk

Summary of Advice
In patients under 18 years old:

*Paroxetine, venlafaxine, sertraline, citalopram and escitalopram are now contraindicated in paediatric MDD in the under 18s

*There are no data on the safety and efficacy of fluvoxamine in paediatric MDD. Safety and efficacy in adults cannot be extrapolated to those under 18 and therefore this product should not be used in this age group.

*The balance of risks and benefits of fluoxetine in the treatment of MDD in under 18s appears to be favourable.

General prescribing advice for paroxetine, venlafaxine, sertraline, citalopram escitalopram and fluvoxamine:

1. These products should not be prescribed as a new therapy for patients under 18 years of age with depressive illness
2. If your patient is being successfully treated with any of these products, then the normal completion of the planned treatment course should be considered as an option in the management of the illness
3. If your patient is not doing well on any of these products, change of treatment should be considered
4. A decision to prescribe any of these for paediatric MDD, for example if a patient is intolerant to fluoxetine, should only be made with specialist advice and after careful consideration of all available information

Fluoxetine does not have a marketing authorisation for MDD in under 18 year olds. However the CSM has considered the clinical trail data and advised that the balance of risks and benefits is favourable. Again, a decision to prescribe fluoxetine for paediatric MDD in a patient under 18 should be made with specialist advice.

WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE – DUP BOARD RECOMMENDATIONS

12/18/2003

1. MAA to provide educational guidance to Medicaid providers regarding antidepressant treatment for youth with MDD. The guidelines should parallel the position of the FDA.
2. No new starts in children under the age of 18 with paroxetine or venlafaxine for treatment of MDD
3. No change of therapy for youth stabilized on these medications

Russell Katz, M.D.
FDA Director of the division of neuropharmacological drug products

Finding whether such a link exists was no easy task.

"Our view at the moment is that the risk is not particularly well-understood or defined. It is not at all a straightforward matter to figure this out."

New York Times December 11, 2003

Dr. David Shaffer, a professor of psychiatry and peadiatrics at Columbia University

Letter on the issue at Pfizer's request to the British drug agency concluding that there was insufficient data to restrict the use of the drugs in adolescents

"The bottom line is that suicidal ideation and suicide attempts are very common in depressed kids," he said.

Dr. Jeffrey A. Lieberman, a professor of psychiatry and pharmacology at the University of North Carolina.

“I think they’re really overreacting”

“This is really going way too far, and in the process doing more harm than good.”

FDA Hearing – February 2, 2004

Conclusions

- Signal present, meaning not clear
- A warning will be issued with this purpose, for clinicians to take this issue more seriously

FDA Action
March 22, 2004

- Warning to be added or strengthened for children and adults for SSRI's, venlafaxine, mirtazepine, nefazodone and bupropion
- Monitor patients for risk of suicide, especially at initiation of treatment or dose change
- Special awareness when symptoms of activation, mania, irritability

Commentary:
British position does not recognize evidence of statistically significant benefit plus no statistically significant difference in side effects between active drug and placebo

Brent and Birmaher. Amer Acad Child Adolesc Psychiatry. April 2004

Brent and Birmaher don’t address statistical strategy of pooling the sertraline data plus the non published studies

FDA

Next hearing planned for the end of summer 2004

Issues

- Is there a signal?
- Short term versus long term effects
- Definition of adverse events – one was a child who slapped self in face and others with minor cutting on self
- Illness vs medication effects

Issues

- **Further analysis of suicide ideation/attempts by assessment of lethality**
- **Patients at high risk for suicide are generally excluded**
- **Were patients on what was prescribed? (49 adolescents suicides) – 24% had been prescribed antidepressant, but zero tested positive at the time of death**

Conclusions

1) Story far from clear
2) Attention to suicide risk and side effects **essential**
3) Informed consent crucial

Level of Care

1) Majority Managed on an Outpatient Basis

2) When to Refer

3) When to Hospitalize
   a) Safety re suicide or aggression
   b) Presence of psychosis
   c) Outpatient failures

Collaboration + Team Approach

1. Critically important
2. Clear communication and definition of roles of physician, therapist, teacher, patient, parent
3. Specific charting which gets to all of mental health care providers is essential

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Psychotherapies for Depression with Efficacy in Controlled Trials

Interpersonal Psychotherapy

Cognitive Behavioral Therapy

GUIDELINES FOR THE TREATMENT OF DEPRESSION (ADULTS)

Treat until better

Continue treatment for 9-12 months after normalization

Maintenance treatment for recurrent depression: five years plus

Maintenance treatment for chronic depression:

two to five years (?)

Maintenance treatment for dysthymic disorder:

one to five years (?)

Treatment of Depression

1. Five controlled trials have demonstrated efficacy in depressed children and adolescents (fluoxetine (2); paroxetine; citalopram; sertraline). FDA approval only for fluoxetine.
2. Antidepressants have precipitated mania in children and adolescents.
3. Concern re possible mood related side effects
4. Given these findings, what makes sense?

TREATMENT:

1. Treat depression in parents
2. Address family conflict
3. Build support systems
4. Provide cognitive behavioral therapy or interpersonal psychotherapy
5. Treat cautiously with SSRI's

OFF LABEL USE

Fluoxetine is the only FDA approved medication (January 2003) as safe plus effective in children 8 and over for treatment of depression

Fluvoxamine and sertraline (Obsessive Compulsive Disorder) and imipramine (enuresis) are the only antidepressant otherwise approved for any indication in childhood and adolescence

Requires careful attention to informed consent

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Trends in Treatment of Depression

	1987	1997
Number of Americans treated for depression	1.7 million	6.3 million
% of patients with depression treated with antidepressants	37%	75%
% of patients with depression treated with psychotherapy	71%	60%
Projection of # of patients who would benefit from antidepressant medication treatment		14 million

JAMA: 1/9/02

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

Use of Antidepressants in Youth - 2002

2.7 million prescriptions for children 1-11
8.1 million for youth 12-17
- SSRI's
- Nefazodone
- Venlafaxine and
- Mirtazapine

IMS Health report

SSRIs in Foster Children for FY 2003 – Washington State

Drug	Total number of children	Total number of prescriptions	Total dollars spent
ZOLOFT	602	3,344	
PAXIL	370	1,978	
PAXIL CR	48	160	
CELEXA	275	1,426	
FLUOXETINE HCL	205	1,134	
PROZAC	28	118	
PROZAC WEEKLY	11	30	
LEXAPRO	89	284	
FLUVOXAMINE MALEATE	59	340	
LUVOX	2	6	
Total	1,689	8,820	

Total number of children screened for this data collection was 20,300

No data available re numbers of prescriptions of antidepressants in youth after June 2003

Selective Serotonergic Re-uptake SSRI's

1. Fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram
2. Relatively long half life of fluoxetine
3. Activation and sedative potential
4. Dose range is broad: often lower with panic symptoms and higher with OCD symptoms

fluoxetine	10-50mg/day
paroxetine	10-50mg/day
sertraline	25-200 mg/day
fluvoxamine	50-300mg/day
citalopram	10-50mg/day
escitalopram	5-30mg/day

Fluoxetine (Prozac)

1. Dose 5 to 60mg/day. Typical dose 10-30mg
2. Available in 10mg and 20mg pulvules, in solution, and Prozac Weekly (90mg) [New]
3. Side Effects: Agitation, Sleep Disturbance, Nausea, Sedation, Decreased Libido, Sexual Dysfunction
4. Elimination half-life 84 hours
5. Inhibits Cytochrome P450 IID6

Paroxetine (Paxil)

1. Dosage 10 to 50mg/day - Typical dose 10-30mg/day
2. Available in tablets of 10-20-30 and 40mg, controlled release tablets of 12.5, 25 and 37.5mg, and in solution
3. Side effects: Agitation, Insomnia, Somnolence, Decreased Libido, Sexual Dysfunction, Withdrawal Syndrome, Mood Related Symptoms, Possible Association with Suicide Ideation/Attempts
4. Elimination half-life 24 hours
5. Inhibits Cytochrome P-450 IID6 Isoenzyme
6. Withdrawal syndrome

Sertraline (Zoloft)

1. Dose 25-200mg/day, Typical Dose 100mg/day.
2. Available in 25, 50 and 100mg tablets
3. Side effects: Insomnia, Nausea, Somnolence, Decreased Libido, Sexual Dysfunction
4. Elimination half life 26 hours
5. Comparatively less inhibition of Cytochrome P-450IID6

Fluvoxamine (Luvox)

1. Dosage 50mg to 300mg/day
2. Available in 25, 50 and 200mg tablets
3. Side Effects: Nausea, Sedation, Irritability, Decreased Libido, Sexual Dysfunction
4. Elimination half-life 15 hours
5. Inhibits cytochrome P450 IIA2
6. Requires B.I.D. dosing

Citalopram (Celexa)

1. Most recently approved SSRI in the United States
2. Available in 10, 20, 40 mg tablets and oral solution
3. Extensive European experience
4. Side Effects: Nausea, Somnolence, Decreased Libido, Sexual Dysfunction
5. Weak effect on Cytochrome P450
6. Slowed cardiac conduction (↑ QTc)
7. Elimination half-life – 36 hours

Escitalopram (Lexapro)

1. S-enantiomer of citalopram
2. One-half the dose of citalopram
3. Unclear advantage vs. citalopram
4. No pediatric data

HETEROCYCLIC ANTIDEPRESSANTS

1. Imipramine (Tofranil), desipramine, (Norpramin), doxepin (Sinequan), clomipramine (Anafranil), nortriptyline (Pamelor), amitryptiline (Elavil)
2. Sudden Death Controversy
3. Baseline EKG: PR interval; QTc
4. Begin at 1mg/kg/day; increase by 1mg/kg/day every 5-7 days (1/2 for nortriptyline)
5. EKG + blood level at 3 mg/kg/day
6. Ceiling dose 5mg/kg/day
7. Question of therapeutic window
8. Don’t exceed 450 ng/ml
9. Controlled trials for depression positive only for adults

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

OTHER ANTIDEPRESSANTS

1. Venlafaxine (Effexor)
2. Bupropion (Wellbutrin)
3. Nefazodone (Serzone)
4. Trazodone (Desyrel)
5. Mirtazapine (Remeron)
6. Monamine Oxidase Inhibitors
   - Phenelzine (Nardil)
   - Tranylcypromine (Parnate)

Venlafaxine (Effexor)

1. Dosage: Starting dose 37.5 mg/day; typical dose = 75mg to 225 mg/day; range 37.5 to 300
2. Available in 25, 37.5, 50, 75 and 100mg tablets and in extended release capsules of 37.5, 75 and 150mg
3. Side effects: Nausea (less with XR form) somnolence, dizziness, increased blood pressure, sexual dysfunction, irritability, mood related symptoms
4. Combined effects on 5HT (+)NA at greater than 150mg/day

Venlafaxine *(Continued)*

One negative double blind placebo controlled trial with no efficacy established for Major Depressive Disorder.

There have been reports of increased hostility and suicide related adverse events such as suicidal ideation and self harm in controlled trials of children and adolescents with depression on venlafaxine

Bupropion (Wellbutrin, Zyban)

1. Noradrenergic effect
2. Benefits with ADHD
3. Dosage, starting at 75mg/day. No single dose greater than 150mg. Given t.i.d., typical dose 75-300mg
4. Available in tablets of 75 and 100mg, sustained release (SR) tablets of 100 and 150mg, and extended release (XL) tablets 250 AND 300mg
5. Side effects: activation, 0.4% with seizures (reportedly lower with SR and XL forms)

Bupropion

Open label trial 16 children and adolescents with major depression

12/16 Comorbid for ADHD

9/16 Responded

Dose of SR 100-200

Current randomized controlled trial

Nefazodone (Serzone)

1. Dosage: 200 to 600mg/day optimal 300 to 500mg/day (?therapeutic window). Begin at 50mg bid
2. Available in tablets of 50, 100, 150, 200 and 250mg. The 100 and 50mg tablets are scored
3. Side Effects: low order nausea, drowsiness, weakness
4. **Important warning:** reports of serious but rare liver toxicity

Trazodone (Desyrel)

1. Agonist and Antagonist of serotonin
2. Less potent Antidepressant Effect
3. Hypnotic Effect
4. Dosage 50-400 - Typical dose 250-300mg/day
5. Available in scored 50mg and 100mg tablets and 150 and 300mg tablets
6. Side Effects: Sedation, priapism

Mirtazapine (Remeron)

Effects on serotonin and norepinephrine receptors
Dosage: Begin at 15mg po hs, dose range 15 to 45mg
Available in scored 15mg and 30mg tablets and a 45mg tablet
Side effects: Drowsiness, dizziness, weight gain
Elimination half life 20-24 hours

Augmentation

Mood Stabilizers - lithium, valproic acid, carbamazepine

Thyroid

Additional antidepressants

Effect of combination medication treatment such as for augmentation and specific target symptoms not established in youth

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Texas Children's Medication Algorithm Project

Hughes, J Am Acad Child Adolesc Psych (1999) 38:1442-1454

Medication algorithm for treating children and adolescents who meet DSM-IV criteria for major depressive disorder.

- SSRI = selective serotonin reuptake inhibitor
- BUP = bupropion
- MIRT = mirtazapine
- NEF = nefazodone
- TCA = tricyclic antidepressant
- VLF = venlafaxine
- ECT = electroconvulsive therapy

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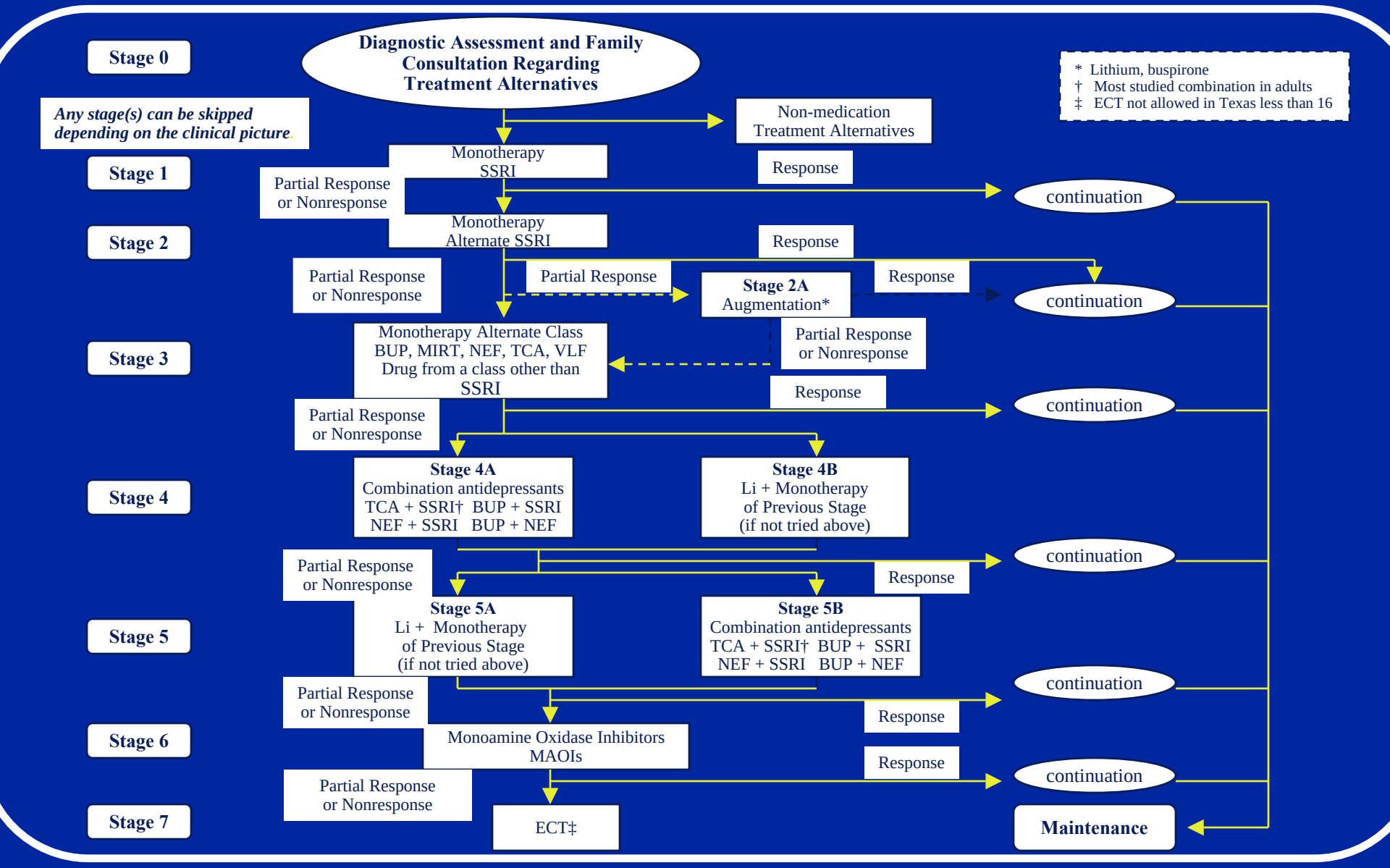

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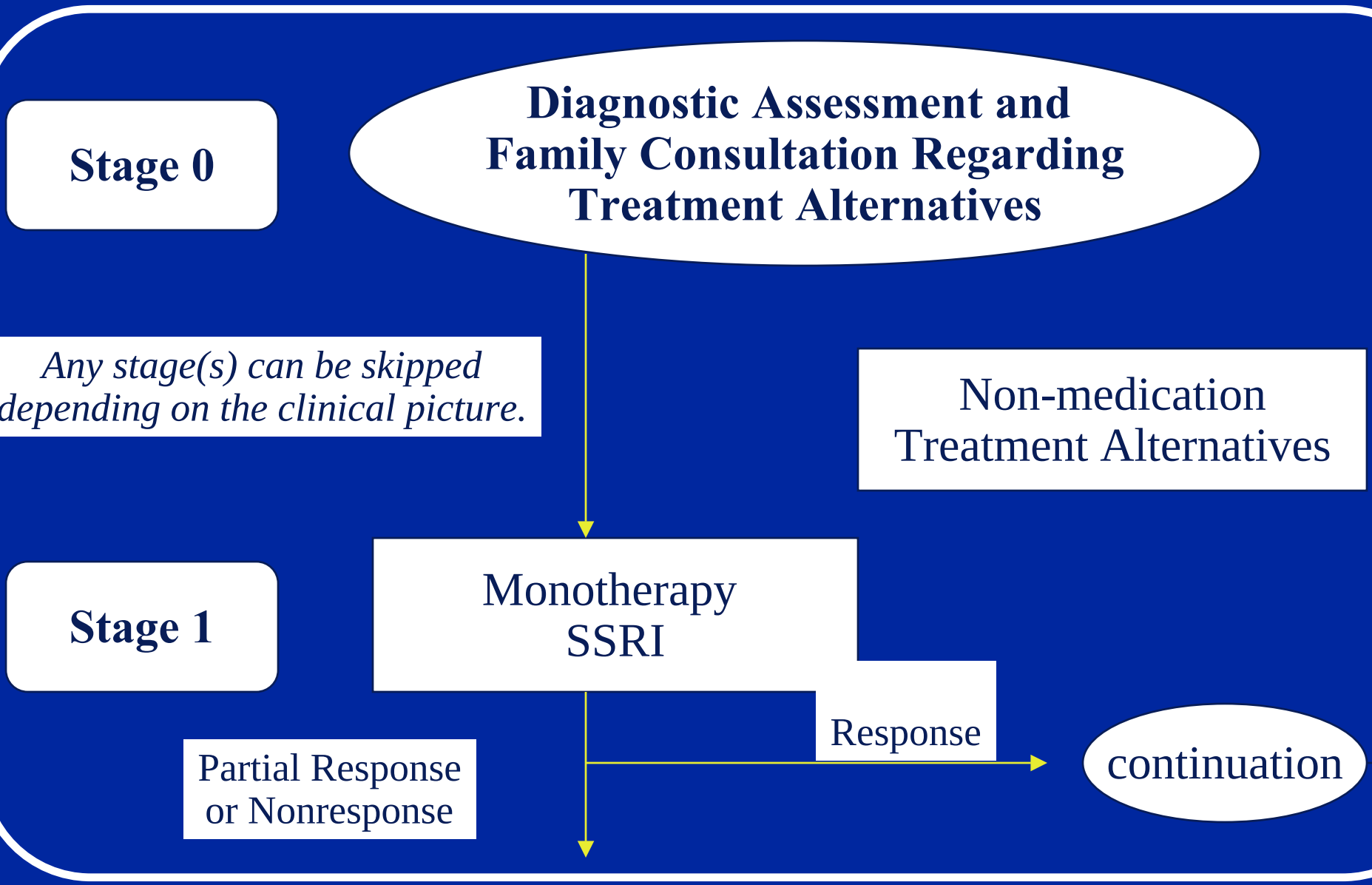
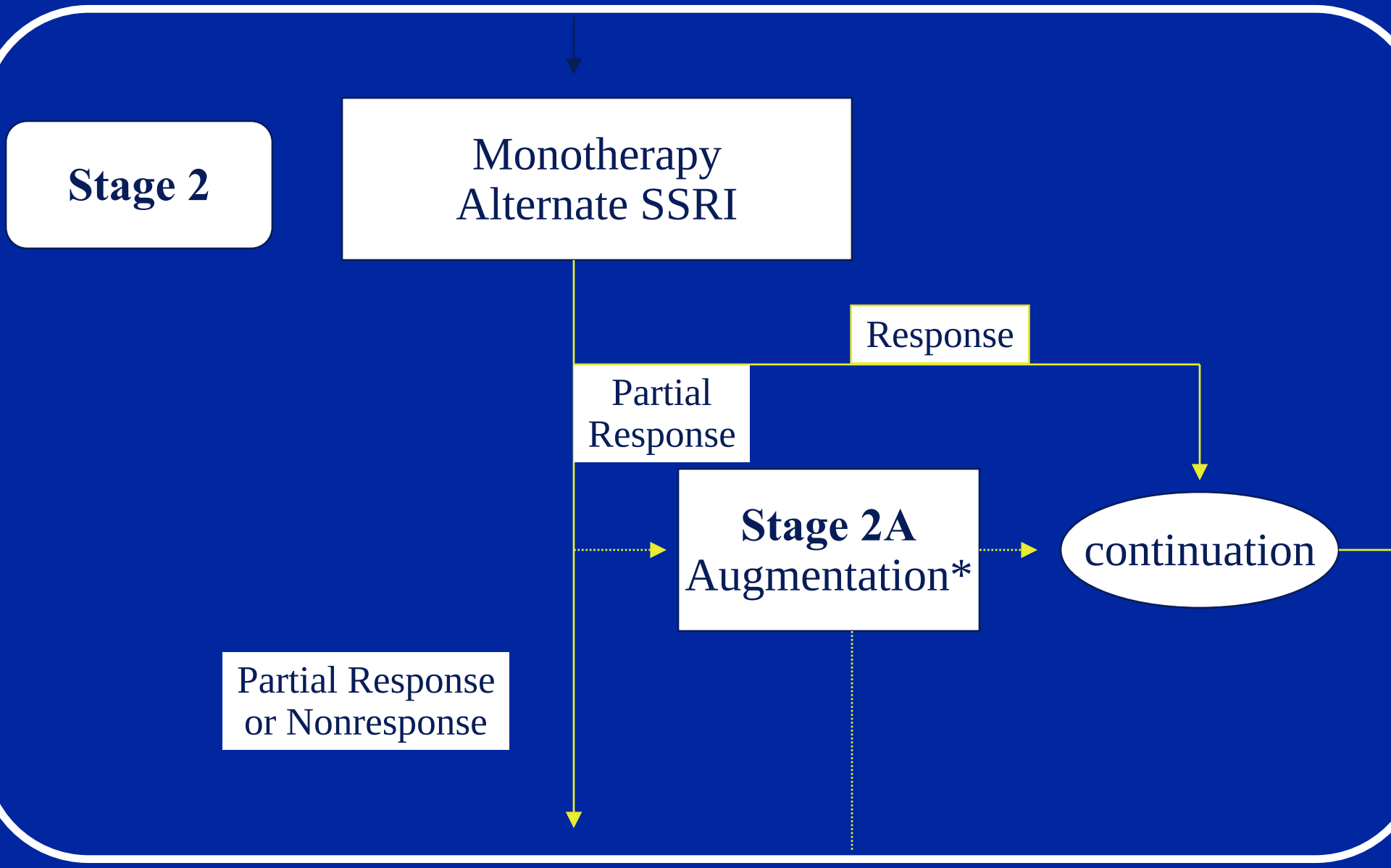
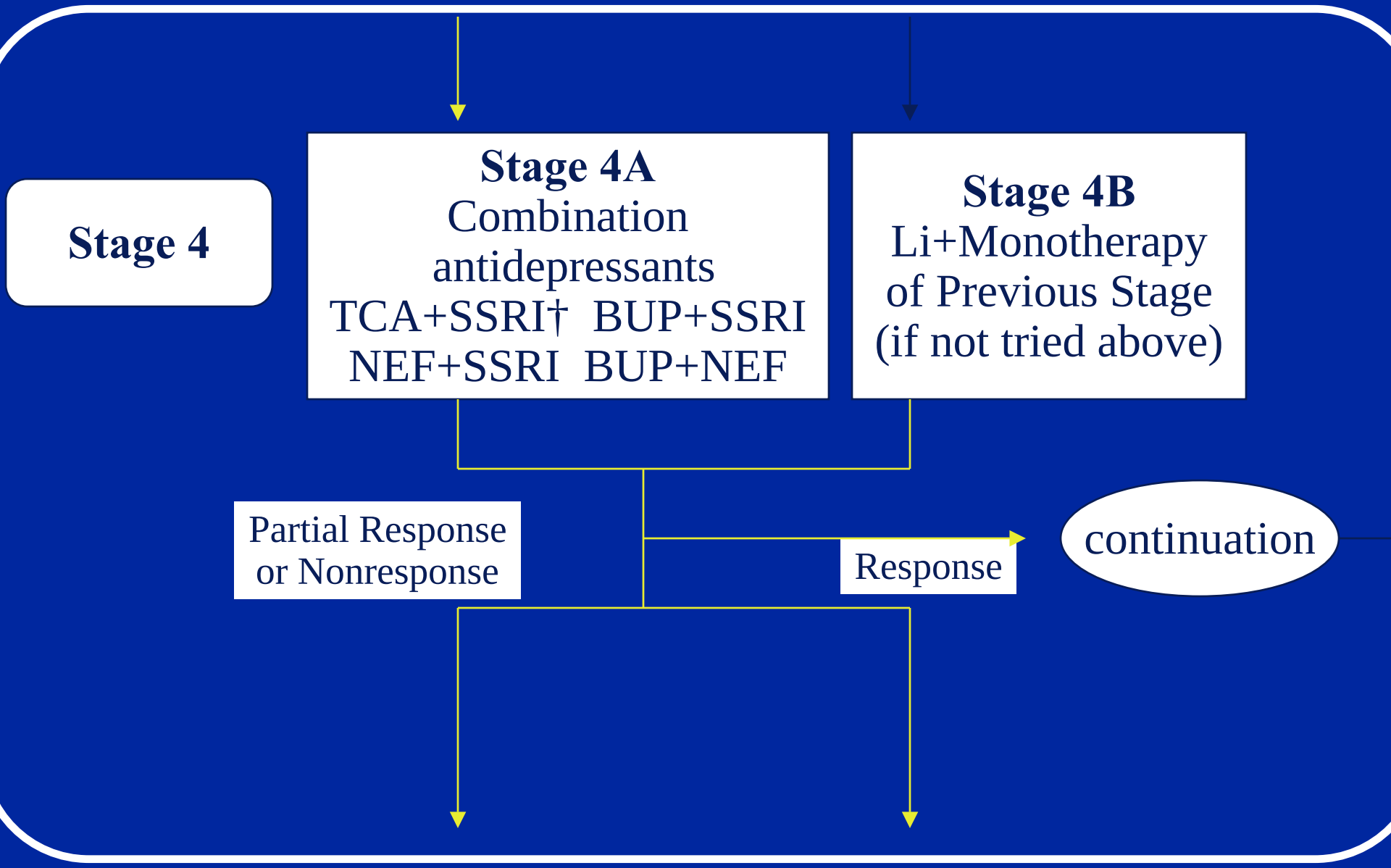



Stage 2
Monotherapy
Alternate SSRI
Response
Partial
Response
Stage 2A
Augmentation*
continuation
Partial Response
or Nonresponse

Stage 3

Monotherapy
Alternate Class
BUP, MIRT, NEF,
TCA, VLF
Drug from a class
other than SSRI

continuation


Stage 4
Stage 4A
Combination antidepressants
TCA+SSRI† BUP+SSRI
NEF+SSRI BUP+NEF
Stage 4B
Li+Monotherapy of Previous Stage (if not tried above)
Partial Response or Nonresponse
Response
continuation

Stage 5

Stage 5A
Li + Monotherapy
of Previous Stage
(if not tried before)

Stage 5B
Combination
antidepressants
TCA+SSRI† BUP+SSRI
NEF+SSRI BUP+NEF

Partial Response
or Nonresponse

Response

continuation

Stage 6

Monoamine Oxidase Inhibitors
MAOIs

Response → continuation

Partial Response
or Nonresponse

Stage 7

ECT‡

Maintenance

* Lithium, buspirone
† Most studied combination in adults
‡ ECT not allowed in Texas less than 16

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5. *Hughes CL, Emslie GJ, Crismon ML, et al. The Texas Children's Medication Algorithm Project: report of the Texas Consensus Conference panel on medication treatment of childhood major depressive disorder. J Amer Acad Child Adoles Psych 1999;38:1442-1454.*

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