Juvenile-onset Bipolar Disorder:

Case Experience

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Pre-Lecture Exam Question 1

1. **An 8-year-old girl has an episode of Major Depressive Disorder (MDD). She is more likely to develop a Manic Depressive Illness (MDI) if one of the following statements is true:**

A. Her depression is mild but prolonged.

B. Her depression is nonpsychotic.

C. There is no family history of MDI.

D. She is a girl, and girls are more at risk than boys.

E. Her depression is severe.

Question 2

2. Is this statement true or false? The Young Mania Scale was specifically developed for use in youth.

A. True
B. False

Question 3

3. A significant pharmacokinetic drug-drug interaction can occur between one of the following psychotropic combinations:

A. Gabapentin and lithium

B. Lithium and lamotrigine

C. Lamotrigine and gabapentin

D. Valproate and lamotrigine

E. Valproate and lithium

Question 4

4. One of the following statements is true about lithium in pre-teen children:

A. Lithium has a lower clearance and a longer half-life in children than in adults

B. Lithium has a lower clearance and a shorter half-life in children than in adults

C. Lithium has a higher clearance and a longer half-life in children than in adults

D. Lithium has a higher clearance and a shorter half-life in children than in adults

E. Lithium has the identical clearance and half-life in children as adults

Question 5

5. A 12-year-old boy has been started on lithium. When should his blood be drawn for an accurate blood level?

A. After 3 days, the blood should be drawn after his morning dose

B. After 2 days, the blood should be drawn before his morning dose

C. After 5 days, the blood should be drawn after his morning dose

D. After 5 days, the blood should be drawn before his morning dose

E. After 5 days, the blood can be drawn at any time

Question 6

6. A 17-year-old girl is being considered to start on valproate. When discussing possible side effects with her and her parents, which of the following should be discussed?

A. Valproate is always associated with weight loss

B. Valproate is very alerting

C. Fatal liver disease is most common in girls over the age of 13 years

D. Valproate helps normalize menstrual irregularities

E. Valproate may cause neural tube defects in a baby if a girl is pregnant

Question 7

7. If one were using carbamazepine to treat MDI in a 14-year-old boy, which of the following statements would be true?

A. If should be dosed hs only to prevent drowsiness

B. It induces CYP2D6 and therefore it will induce imipramine and desipramine

C. Induction occurs at CYP3A4 and occurs at each dose increase

D. Inhibition occurs at CYP3A4 and occurs at each dose increase

E. Because it is a substrate of CYP2D6, CYP3A4 inhibitors should as nefazodone will not increase its concentration

Question 8

8. The boy in the last question has been started on carbamazepine. A trough level of 2 mcg has been reported on day 5 after initiation of treatment. Which statement is true?

A. This is a good level and drug dosing should not be increased

B. This is too high and dosing should be decreased

C. The usual range for carbamazepine is 2-6 mcg/ml

D. The usual range for carbamazepine is 14-20 mcb/ml

E. Dosing should be increased

Question 9

9. Carbamazepine is partially metabolized to its epoxide. Which of the following statements are true about this metabolite?

A. It is active and is measured as part of the usual carbamazepine plasma level

B. It is inactive and it is not measured as part of the usual carbamazepine plasma level

C. It is active and it is not measured as part of the usual carbamazepine plasma level

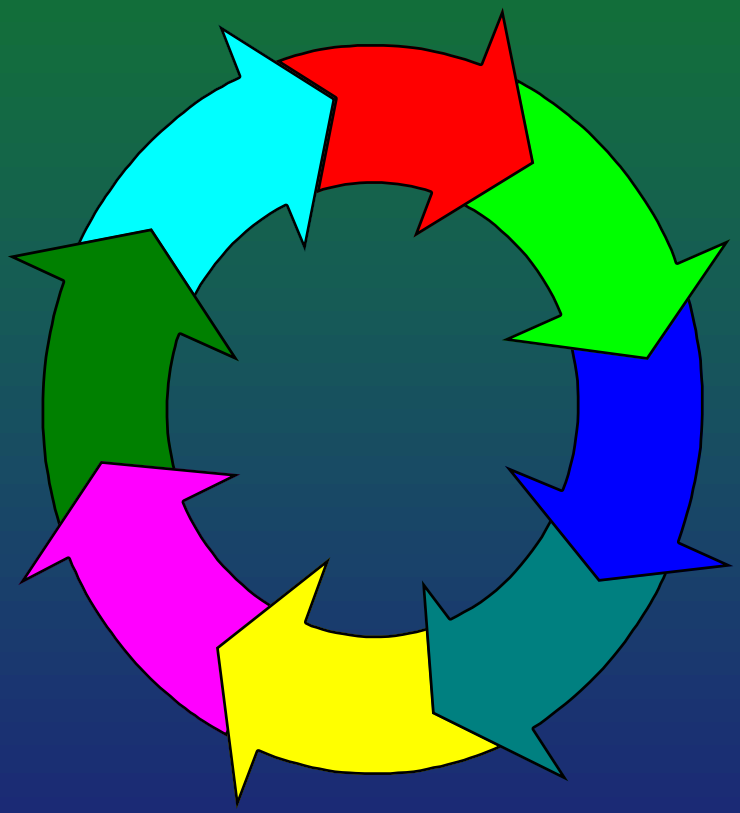
D. It is inactive and it is not measured as part of the usual carbamazepine plasma level

E. None of these statements is true

Juvenile BPD: Case Experience

"Every time I prematurely conclude from the parent history that I know what is wrong with the child [lucid histories of well-defined entities], I have regretted it".

(Carlson G, J Affect Dis , 51:177-187, 1998)



> school visits

> classroom observations

Juvenile Bipolarity: Outline

- Phenomenology
- Assessment
- Relevant studies
- Treatment

Juvenile Bipolar Disorder: Rate

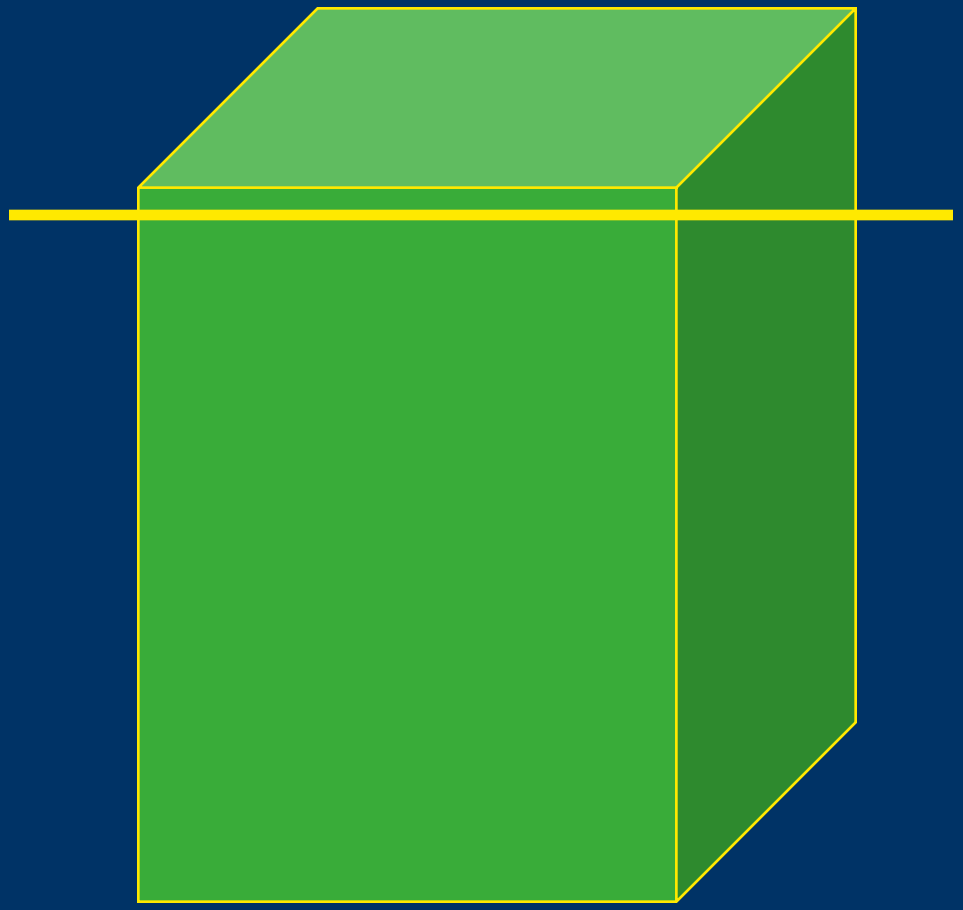
Kraepelin (1921):	0.4% (4/900)
	onset < age 10
Weller et al (1986):	21% (33/157)
	mania

Definition of Mania (Carlson & Kashani, 1988)

- n=150 adolescents
- 0.6% (RDC)

  1 wk mania
  +impairment
- 7.3% (DSM-III)

  1 wk mania +
  depressive episode
- 13.3% symptoms
  mania or hypomania



Juvenile Bipolar Disorder: Diagnosis

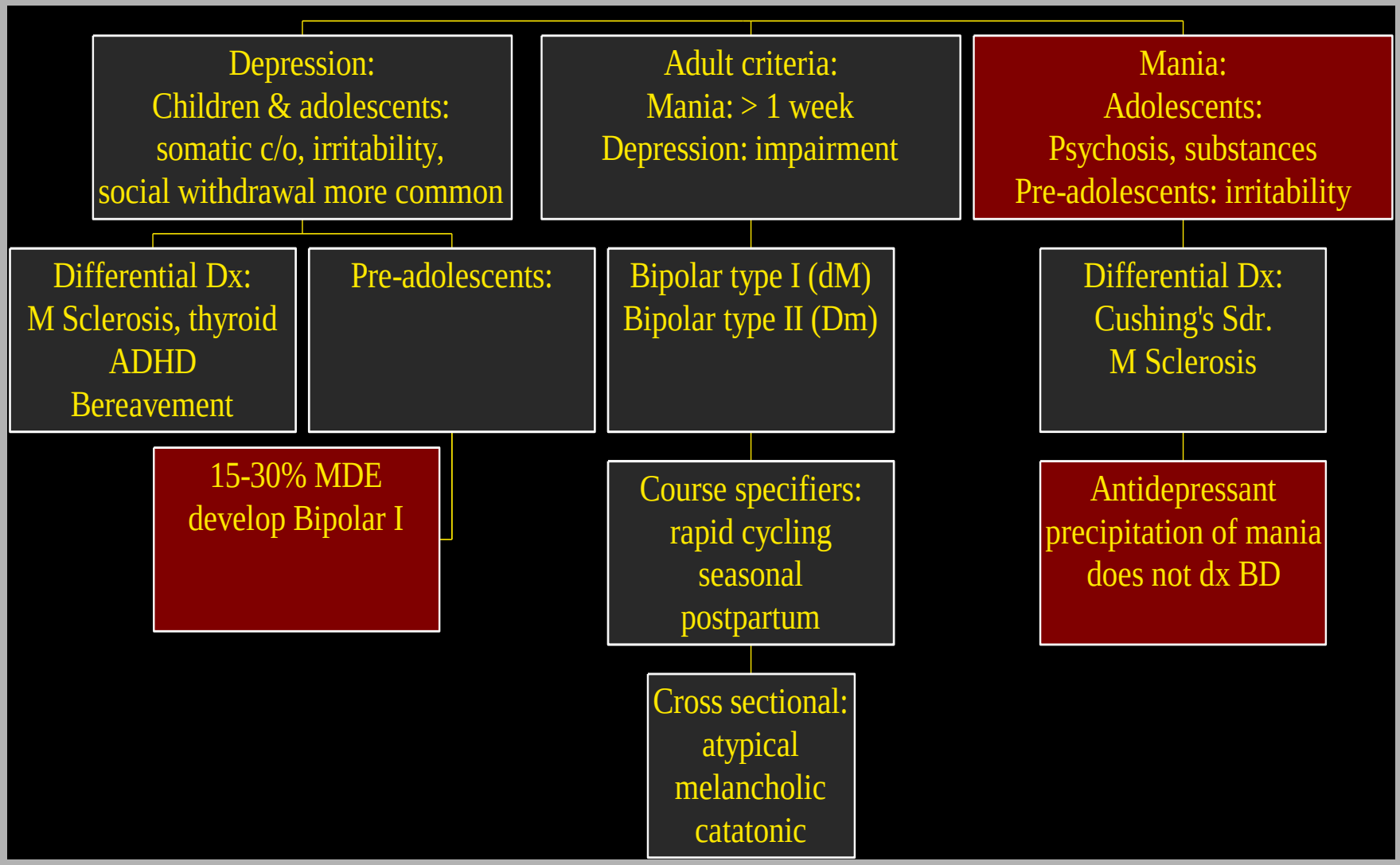
Anthony & Scott (1960):

- adult criteria + fm Hx
- diphasic
- 2 or > episodes
- endogenous
- severe

Weinberg & Brumback (1976):

- euphoria
- irritability
- and 3 or >
  - pressured speech
  - flight of ideas
  - grandiosity
  - sleep disturbance
  - hyperactivity
  - distractibility

Juvenile Bipolar Disorder: DSM-IV Diagnosis



Diagnosis of Bipolar Disorder in Adolescents and Children : *Confounders*

1. Symptoms may differ from those in adulthood BPD
   »non-mood comorbidity

2. Mania in children can be a manifestation of more than one disorder

(Lewinsohn P, Klein D, Seeley J. Bipolar Disorders, 2:281-293, 2000)

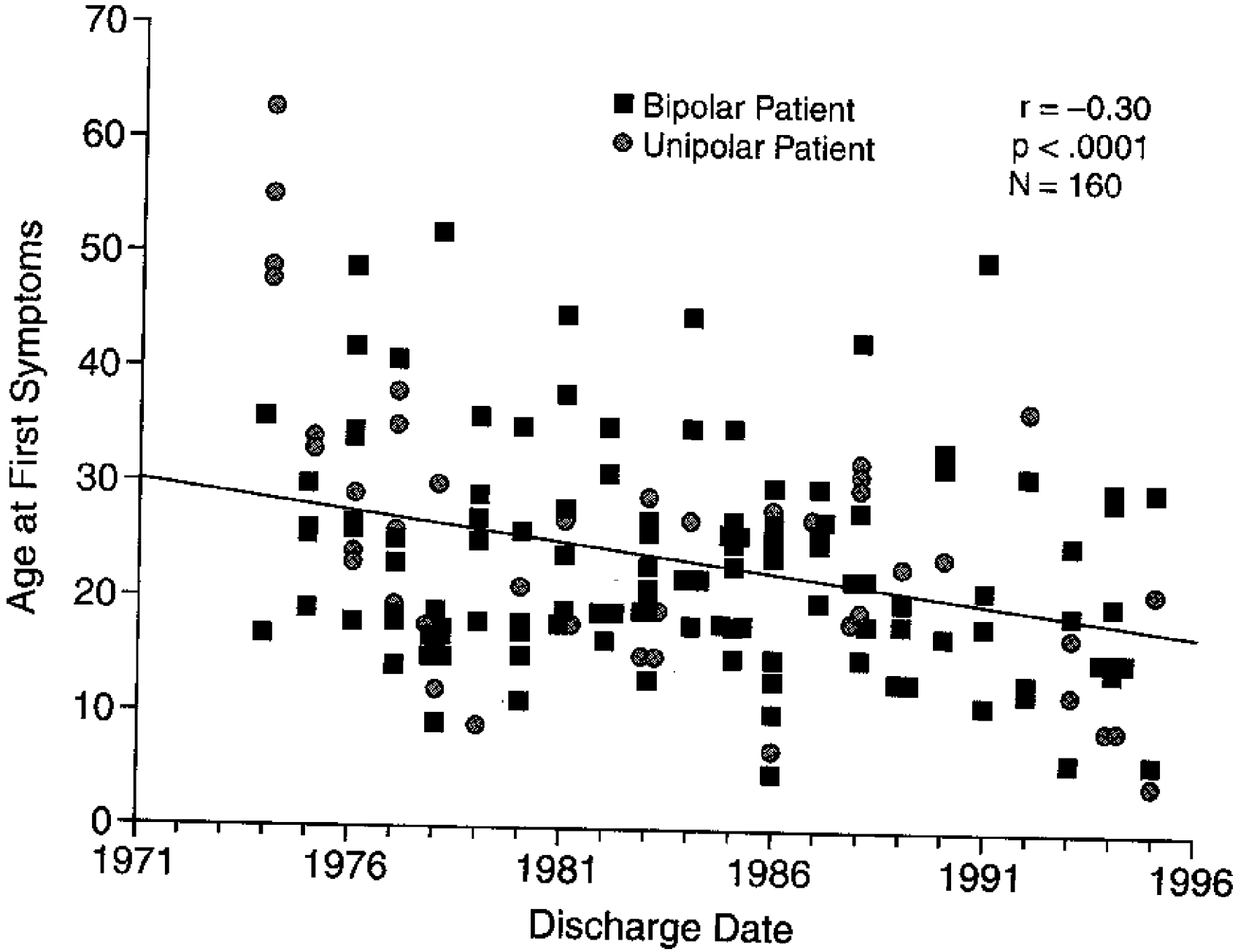
Evolution of the Template of MDI Over 30 Years

(Carlson G, J Affect Dis, 51:177-187, 1998)

Discrete episodes of mania, depression and euthymia with mood-congruent psychotic symptoms

to

a disorder with mixed states of affective dysregulation, mood-incongruent psychotic symptoms and considerable comorbidity


Bipolar Patient
Unipolar Patient
r = –0.30
p < .0001
N = 160
Age at First Symptoms
70
60
50
40
30
20
10
0
1971
1976
1981
1986
1991
1996
Discharge Date

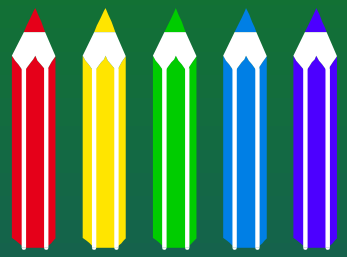
Assessment

- DSM-IV evaluation: structured interview
  - CHIPS; DISC; K-SADS
- Vineland-Adaptive Behavior Scales (IQ)
- Behavior Scales: CBCL; YMRS; CDRS
- Parent & Child + multiple informants
- Video Tapes
- Labs: T3, T4, TSH, Urine toxic screen

Differential Diagnosis

- CNS pathology
- PTSD
- Schizophrenia (VEOS)
- Hyperthyroidism
- ADHD + Conduct Disorder
- Borderline Personality Disorder
- Drug Abuse

»non-mood comorbidity



- ADHD
- Conduct Do
  - Kovacs & Pollock, (1995): 69% referred sample
  - Kutcher, (1989): 42% of CD in hospitalized youth with mania
- PTSD (Wozniack, 1997, 21% PTSD c sxs of mania)

Studies of Childhood Mania and ADHD

(Carlson G, J Affect Dis, 51:177-187, 1998)

	Faraone et al., 1997	Biederman et al, 1998	Biederman et al, 1998	Geller et al., 1998
N	68	15 (ADHD+mania)	102 (mania+ADH)	33
Source	Outpatient psychopharmacology clinic			Outpatients
Assessment	K-SADS-E, 1987, DSM-III-R; CBCL			WASH-U-K-SADS
X Age	6.1	10.4	10.8	9.1
%Mixed/Rapid	59/19	-	-	87/83
%Chronic/episodic	-	60/40	80/20	100
%Euphoria/irritability	-	7/80	6/71	87/97

Studies of Adolescents with Bipolar Disorder

(Carlson G, J Affect Dis, 51:177-187, 1998)

	Strober et al., 1988	Faraone et al, 1997	Kafantaris et al, 1998	Kutcher et al., 1998
N	60	17 (teen onset)	48	28
Source	Clinical historical	Outpt. Psychopharm	Li study	Clinical BPD
Assessment	K-SADS 1985	K-SADS-E 1987	K-SADS-1993	Mini SCID1990
X Age	Mid-teen	15.1	16	16.7 (mania)
%Mixed/Rapid	0	56/10	-	74
% ADHD-DBD	30	59	29	22
%Euphoria/irritability	-	-	-	-

Less elated/expansive mood?

Geller's* sample differs from Biederman's*, identifying higher rates of euphoria (87% Vs 7%)

Definition: Infectious mood; incongruent with text, ie elevator vignette

* (Biederman et al, 1998; Geller et al, 1995)

Phenomenology: 18 months - 8 years (Carlson, 1984)

* (Davis, 1979)

Lack of clear-cut episodes? ie. chronicity

- Geller's sample concurs with Biederman's sample
- Both groups report high rates of chronicity (60-80%)*

Hard to reconcile with rates of chronicity (5%) in adolescent and adult samples (Strober et al 1995; Winokur et al 1993)

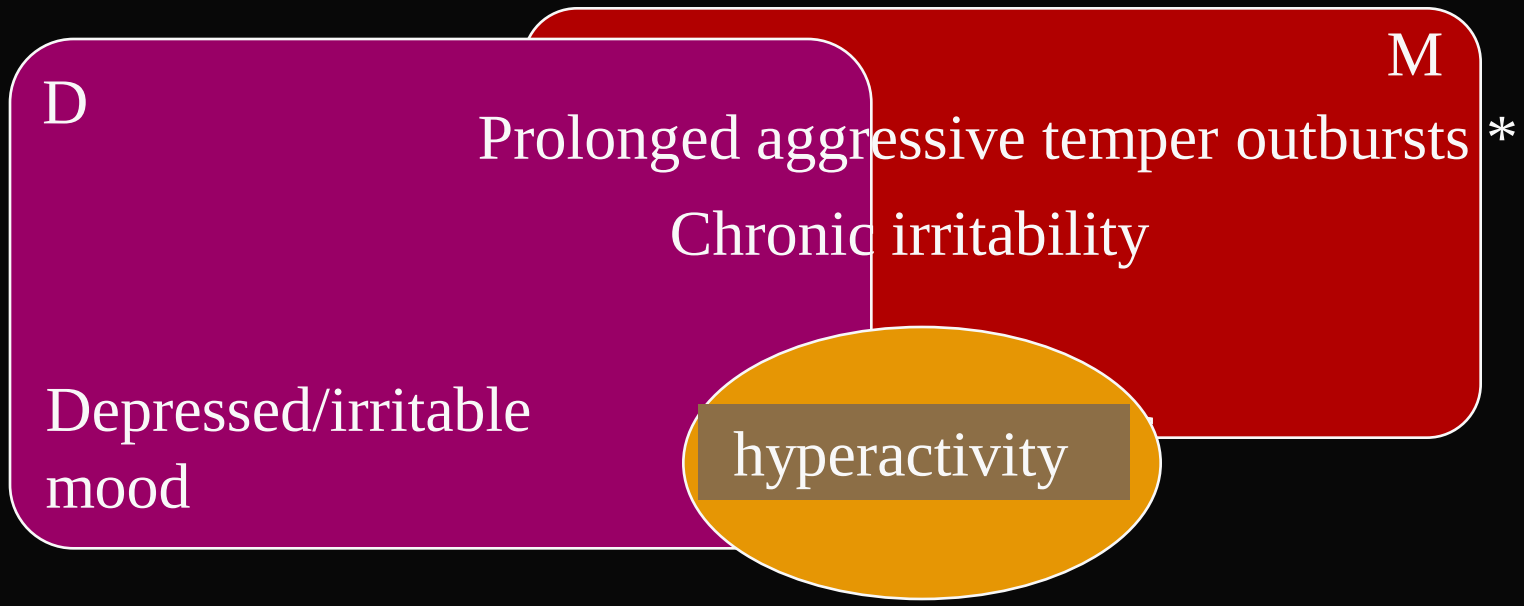
Suggesting perhaps a different phenotype in preadolescents compared to adolescents

* (Biederman et al, 1998; Geller et al, 1995)

Phenomenology: 18 months - 8 years (Carlson, 1984)

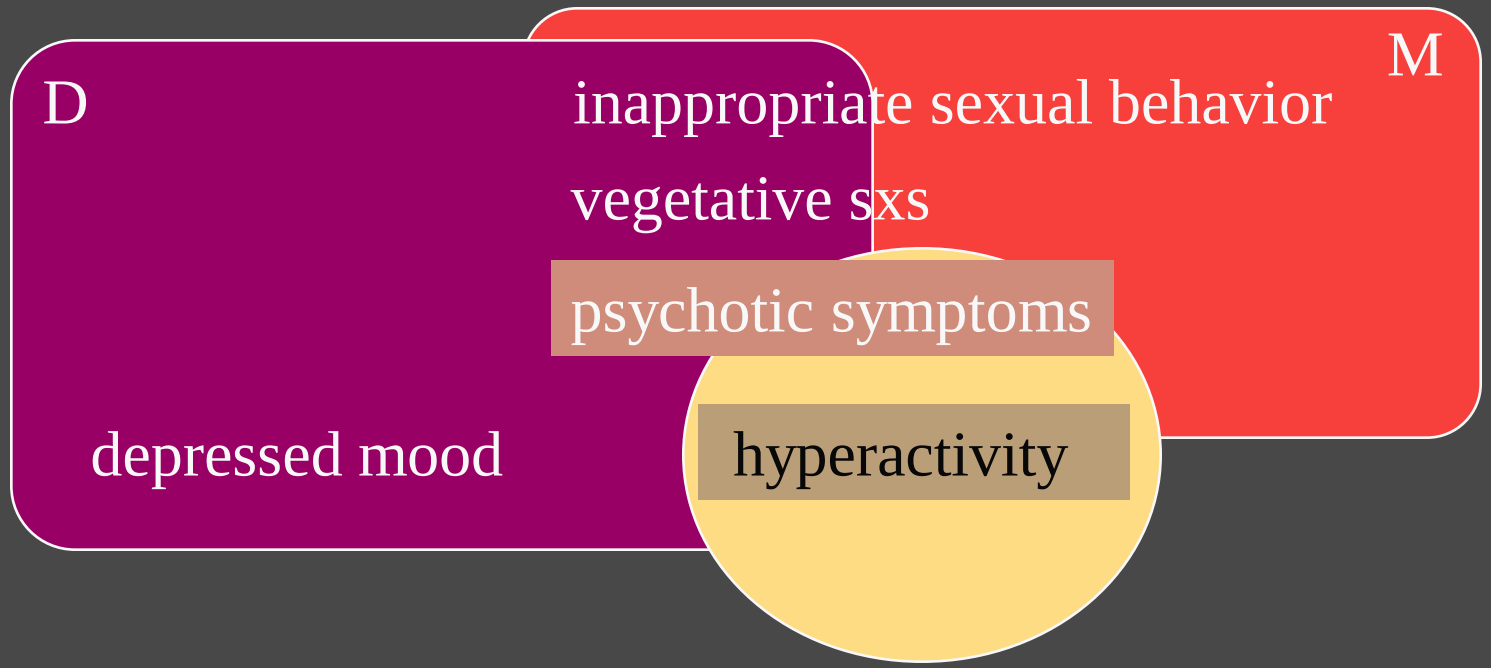
* (Davis, 1979)

Phenomenology: 18 months - 8 years (Carlson, 1984)



* (Davis, 1979)

Phenomenology: adolescents (Bashir, 1987; Carlson, 1984)



Clinical Features of Children with both ADHD and Mania: Does Ascertainment Source Make a Difference?

(Biederman J, et al, 1998)

- **Logistic regression, modeling outcome variables as a function of ascertainment source (ADHD Vs mania study), mania (yes or no), and their interaction (if significant = Δ)**

- **Results**: manic and ADHD sxs were similar in both groups. One ADHD sx ("fidgety") > prevalent in mania study; Two manic sx (>social activity, physical restlessness) were > prevalent in mania study

Clinical Features of Children with both ADHD and Mania: Does Ascertainment Source Make a Difference?

(Biederman J, et al, 1998)

	ADHD + mania (n=15)	MANIA + ADHD (n=102)
Mixed (n) %	(10) 100	(62) 95
Episodic (n) %	(7) **50***	(24) 24
CBCL		>inattention; aggression;
Comorbidity	Lower rates	Higher rates
MDD precedes mania	(7) 70	(51) 78

*p=0.021

Original Article

Bipolar disorder during adolescence and young adulthood in a community sample

Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample.
Bipolar Disord 2000: 2: 281–293. © Munksgaard, 2000

Peter M Lewinsohn[a], Daniel N Klein[b] and John R Seeley[a]

[a] Oregon Research Institute, Eugene, OR, USA; [b] Department of Psychology, State University of New York at Stony Brook, N USA

Objectives: To compare the incidence and prevalence of bipolar disorder (BD) between adolescence and young adulthood; to explore the stability and consequences of adolescent BD in young adulthood; to determine the rate of switching from major depressive disorder (MDD) to BD; and to evaluate the significance of subsyndromal BD (SUB).

Methods: A large, randomly selected community sample (n = 1507) received diagnostic assessments twice during adolescence, and a stratified subset (n = 893) was assessed again at 24years of age. In addition, direct interviews were conducted with all available first-degree relatives. Five mutually exclusive groups, based on diagnoses in adolescence, were compared: BD (n = 17), SUB (n = 48), MDD (n = 275), disruptive behavior disorder (n = 49), and no-disorder (ND) controls (n = 307).

Results: Lifetime prevalence of BD was approximately 1% during adolescence and 2% during young adulthood. Lifetime prevalence for SUB was approximately 5%. Less than 1% of adolescents with MDD 'switched' to BD by age 24. Adolescents with BD had an elevated incidence of BD from 19 to 23 years, while adolescents with SUB exhibited elevated rates of MDD and anxiety disorders in young adulthood. BD and SUB groups both had elevated rates of antisocial symptoms and borderline personality symptoms. Compared to the ND group, adolescents with BD and SUB both showed significant impairment in psychosocial functioning and had higher mental-health treatment utilization at age 24 years of age. The relatives of adolescents with BD and SUB had elevated rates of MDD and anxiety disorders. The relatives of SUB

Key words: bipolar – epidemiology – fam

Bipolar Disorder during Adolescence and Young Adulthood in a Community Sample

(Lewinsohn P, Klein D, Seeley J. Bipolar Disorders, 2:281-293, 2000)

- Randomly selected community sample (n=1507)
- Diagnostic assessments during adolescence
- Stratified subset (n=893) again at 24 years of age

» **BPD (n=17)** » **SUB (n=48)** » **MDD (n=275)**

» **DBD (n=49)** » **ND (n=307)**

SUBsyndromal Group

(Lewinsohn P, Klein D, Seeley J. Bipolar Disorders, 2:281-293, 2000)

- experiencing a distinct period of abnormally and persistently elevated, expansive, or irritable mood (ie. manic)
- **without meeting full criteria for BPD**

Incidence of psychiatric disorders in young adulthood by adolescent diagnostic group

(Lewinsohn P, Klein D, Seeley J. Bipolar Disorders, 2:281-293, 2000)

	BPD (n=17)	SUB (n=48)	DBD (n=49)
Recurrence rate of BPD in adulthood*	27%	2%	0%
ETOH Abuse/depend	**27%**	17%	33%
MDD	NA	41%	35%
Antisocial (% PDE** elevation)	**27%**	11%	24%

*p <0.05

** Personality Disorder Exmaination

DBD = Disruptive Behavior Disorder

Additional Conclusions

(Lewinsohn P, Klein D, Seeley J. Bipolar Disorders, 2:281-293, 2000)

	BPD	SUB	DBD
Prevalence	low	high*	N/a
Females	>	>	<
MDD→BPD	1%	→MDD	
New cases 19-23 vs 0-18	6/17	8/48**	N/a

*Concordant with Angst J, 1998 and ECA, 1991, 4.5% ages 18-29

**Suggesting that the period of maximum risk for SUB may precede the risk for BPD by several years among adolescents and y adults

Expert Consensus Guidelines for the Medication treatment of Bipolar Disorder

Subtype	DVP	LI	CBZ	GAB	LTG	TOP	TGB
Euphoric Mania	**1**	**1**	**2**	**2**	**3**	**2**	**3**
Dysphoric Mania	**1**	**1**	**2**	**2**	**3**	**2**	**3**
Mixed Mania	**1**	**1**	**2**	**2**	**3**	**2**	**3**
Mania c Psychosis	**1**	**1**	**2**	**2**	**3**	**N/A**	**N/A**
Rapid Cycling	**1**	**1**	**2**	**2**	**2**	**N/A**	**N/A**
Bipolar Depression	**1**	**1**	**2**	**2**	**2**	**N/A**	**N/A**

Sachs GS et al. *Postgrad Med Special Report* 2000

1 = First-line treatment; 2 = Second-line treatment; 3 = Third-line treatment

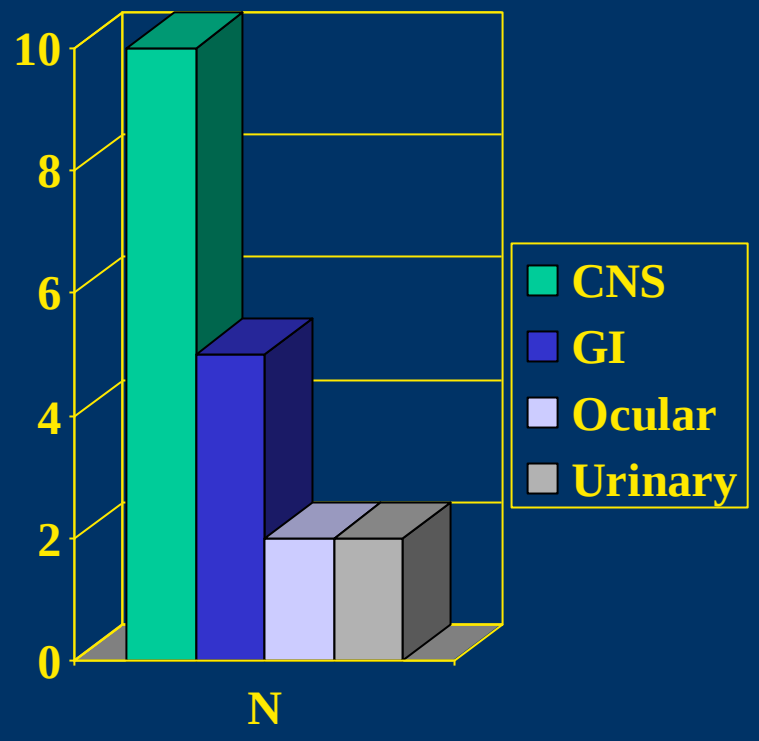
NA = Not evaluated

Geller B, Cooper TB, Sun K, Zimerman B, et al., Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. J Am Acad Child Adolesc Psychiatry 1998 Feb (37), 2: 171-8

- adolescents with bipolar disorders and temporally secondary substance dependency disorders: mean age at onset: 9.6 +/- 3.9
- 16.3 +/- 1.2 years old ; 6-week protocol
- 30mg/kg/day starting dose
- intent-to-treat group: 46.2% response

Lithium: side effects

- (Hagino et al., 1995):
- n=20 inpatients, ages 4-6
- test dose: 600 mg
- 0.6-1.2 mEq/L in 2 wk..
- 39 ± 9.5 mg/kg/d, dose preceding side effects
- initial dose: 30 mg/kg/d
- > 1.2 mEq/L not good



Studies of Mood Stabilizers in Children and Adolescents with Bipolar Disorder

	Controlled	Uncontrolled
CBZ	0	0
Lithium	1 (Geller et al, 1996)	Many
Na^+ DVPX	0	3 case reports 4 case series 1 open randomized (Kowatch et al., 2000)

(Kowatch R et al., JAACAP, 39:6, June 2000)

Effect Size of Lithium, Divalproex Sodium, and Carbamazepine in Children & Adolescents with Bipolar Disorder (Kowatch R et al., JAACAP, 39:6, June 2000)

	All	Pre/post pubertal	Bipolar II
N (%)	42	26 (62) / 16 (38)	22 (52%)
Age	11.4	9.4 / 14.7	11.2
Male n (%)	26 (62)	19 (73) / 7 (44)	17 (77)*
Age onset BIP	7.1	6.1 / 8.8	7.3
Onset ADHD	5.5	4.7 / 6.5	5.8
CGAS	48.2	47.8 / 48.8	52*

* $p \leq .03$, χ^2

Intent-to-treat Analysis, n=32, Monotherapy x 5 Weeks
(Kowatch R et al., JAACAP, 39:6, June 2000)

	CGI Δ ≥ 1,2 % (n)	*≥ 50% Δ From Baseline YMRS*	*Mean CGI & YMRS Response Rate*
CBZ	31 (4/13)	38 (5/13)	34%
Lithium	46 (6/13)	38 (5/13)	42%
Na^+ DVPX	40 (6/15)	53 (8/15)	46

TREATMENT GUIDELINES FOR MOOD STABILIZERS IN CHILDREN AND ADOLESCENTS

Medication	Initial Daily Dose (given bid or tid)		Titration	Half Life (hours)	Target Dose (daily)	Desired Serum Level	Plasma Binding	Monitoring
Lithium	<25 kg	300 mg	Q 3-5 days	10-12	600 mg	1.0-1.4 mEq/l	0%	Serum lithium every 4-6 days during acute phase; every 1-2 months during continuation phase
	25-40	600 mg			750-900 mg			
	>40 kg	900 mg		20-24	1200 mg			
DVP	<25 kg	250 mg	Q 3 days	8-20	500 mg	50-125 µg/ml	80-90% at plasma concentrations of 80 µg/ml	Liver function tests; Androgenism in female adolescents
	25-40	375 mg			750 mg			
	>40 kg	500 mg			>1000 mg			
CBZ	<25 kg	100 mg	Q 5 days	12-60	400 mg	4– 14 µg/ml	75-90 % at therapeutic plasma concentrations	Autoinduction Skin Rash Neutropenia (d/c < 1500) SIADH
	25-40	200 mg			800 mg			
	>40 kg	400 mg			1200 mg			

Davanzo P, McCracken J. "Mood Stabilizers in Pediatric Psychopharmacology of Bipolar Disorder: Advances and Controversies". Child Psychiatric Clinics of NorthAmerica; January 2000.

New Anticonvulsants as Potential (Third Generation) Mood Stabilizers

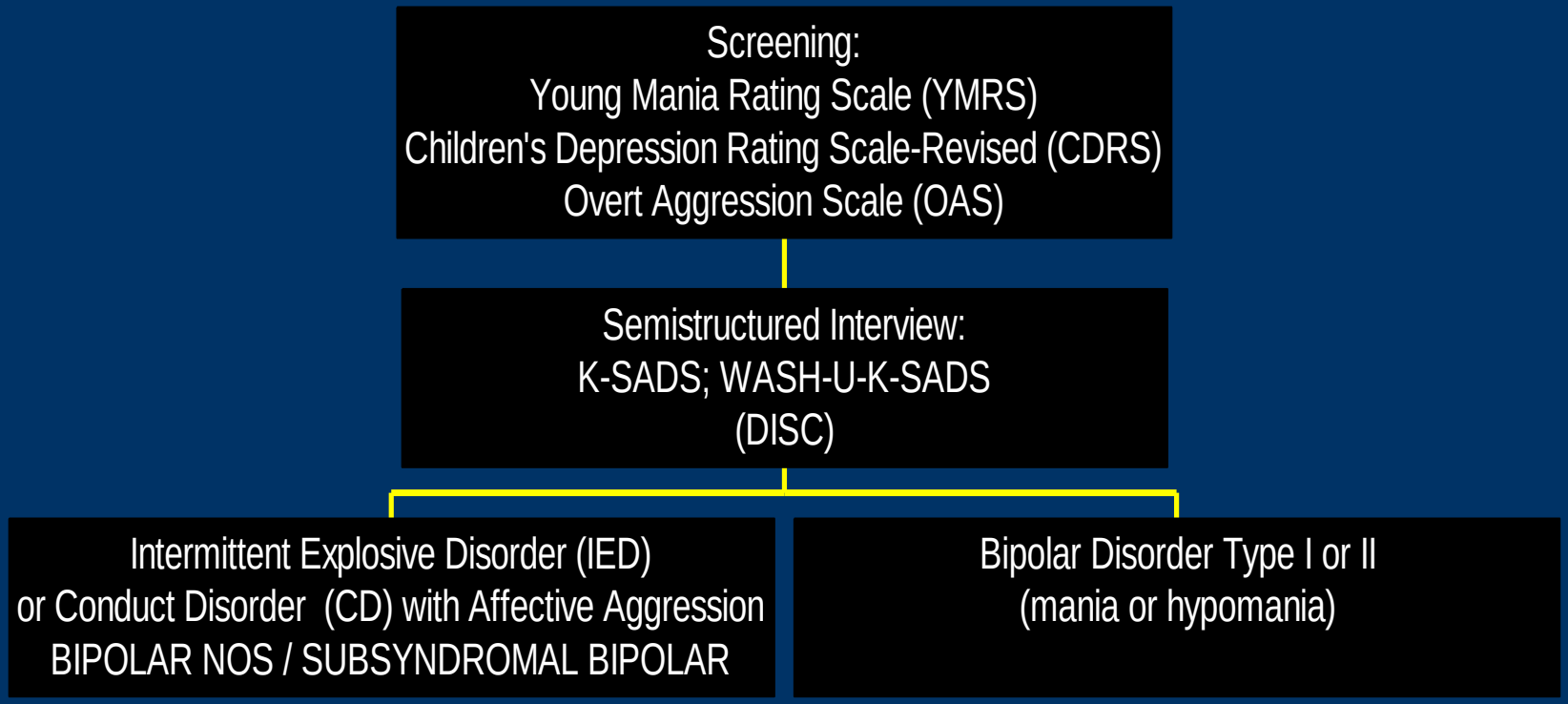
- Lamotrigine
- Gabapentin
- Topiramate

Lamotrigine

- bimodal spectrum of efficacy in the treatment of BPD
- refractory bipolar depression [1] and rapid cycling BPD [2]
- Kusumakar and colleagues [3] studied 22 adolescents with BPD during their depressed phase, refractory to treatment with DVP + mood stabilizer or antidepressant; 6 weeks openly, addition of lamotrigine to DVP. 16/22 (72%) responded by the end of week 4

1. Bowden et al, 2000 2. Fatemi, 1997 3. Kusumakar, 1997

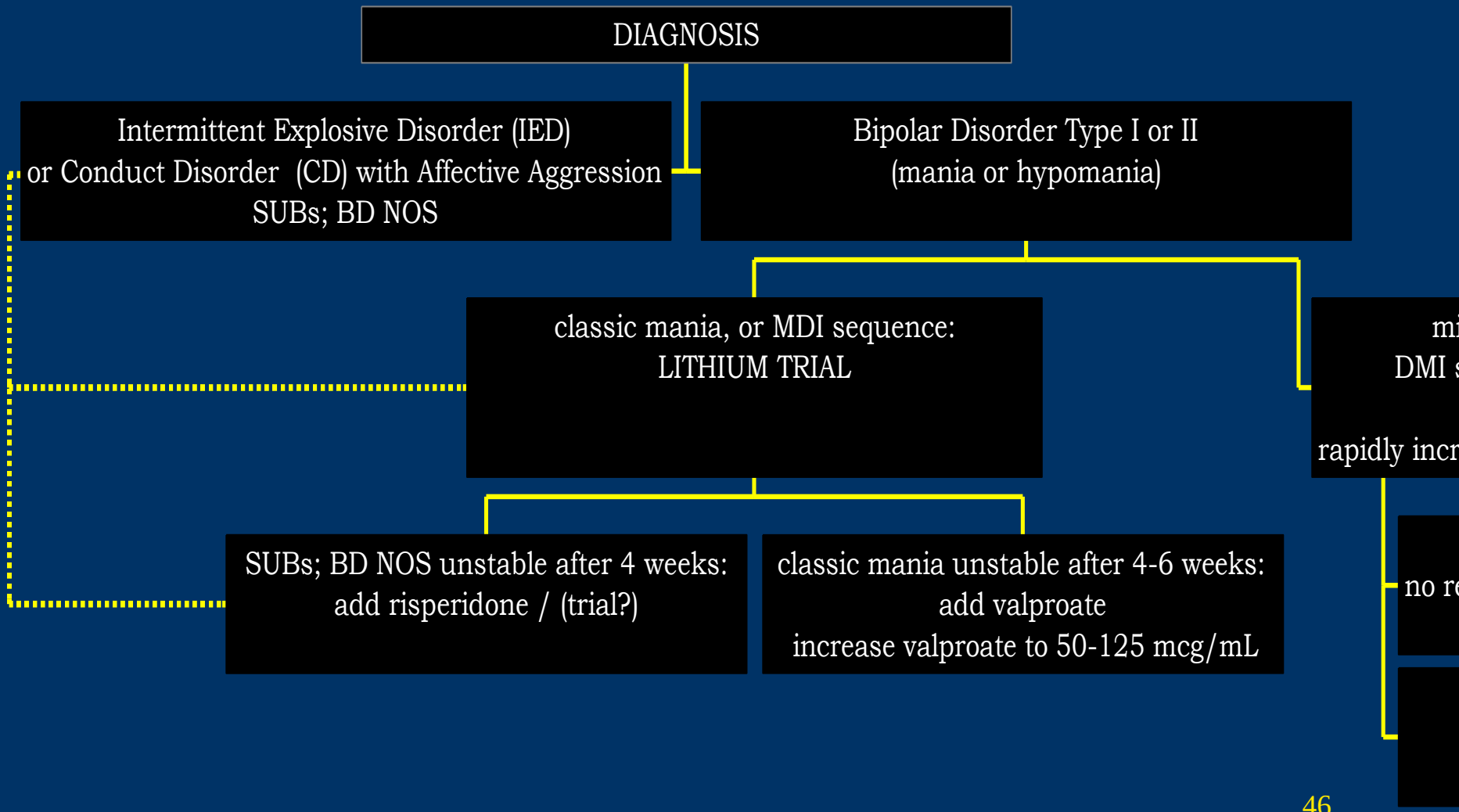
Suggested Algorithm for the Psychotropic Treatment of Children with Manic-like Symptoms



Davanzo P, McCracken J. "Mood Stabilizers in Pediatric Psychopharmacology of Bipolar Disorder: Advances and Controversies".

Child Psychiatric Clinics of NorthAmerica; January 2000.

Original Algorithm: Lithium - Divalproex



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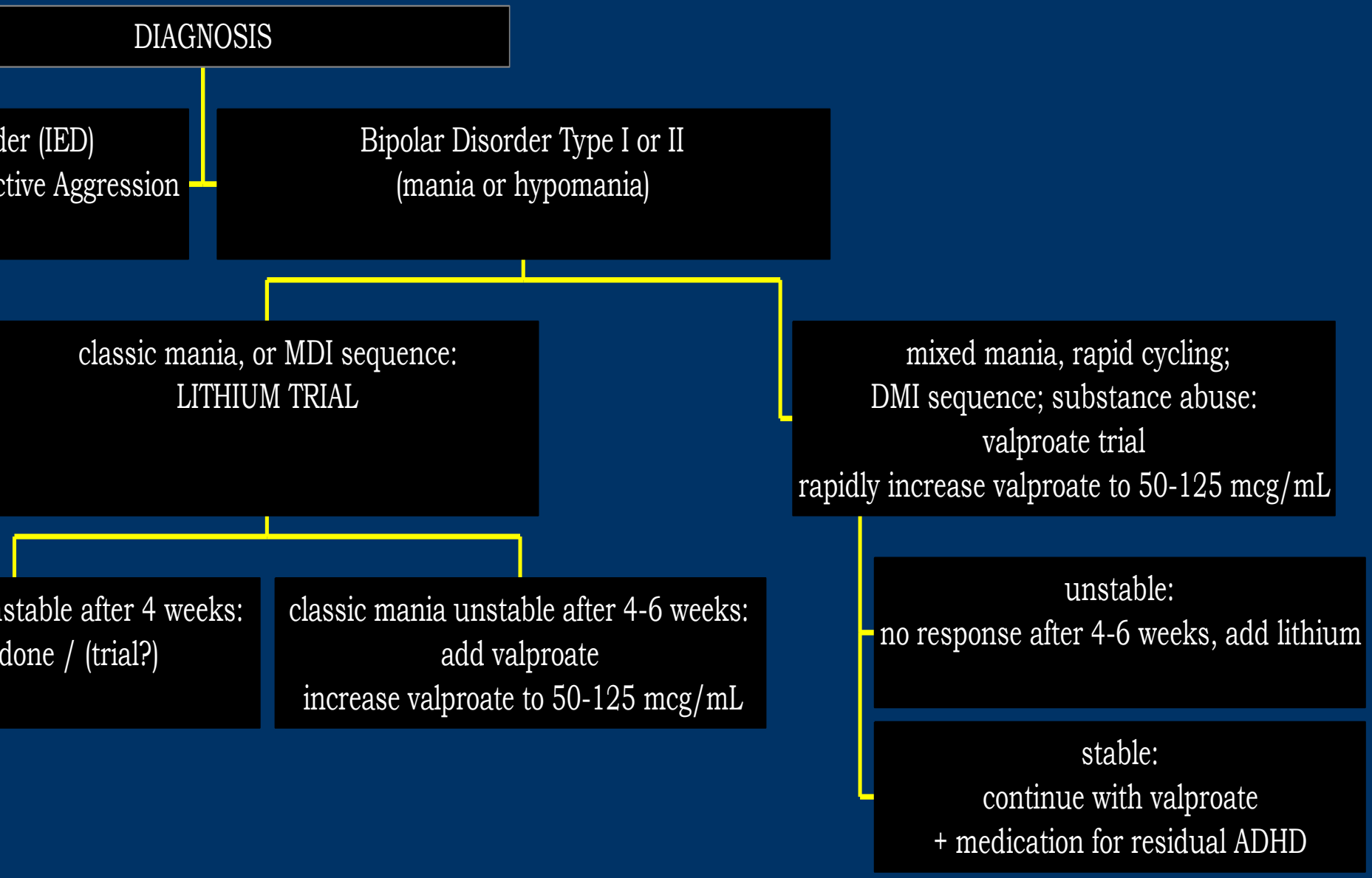
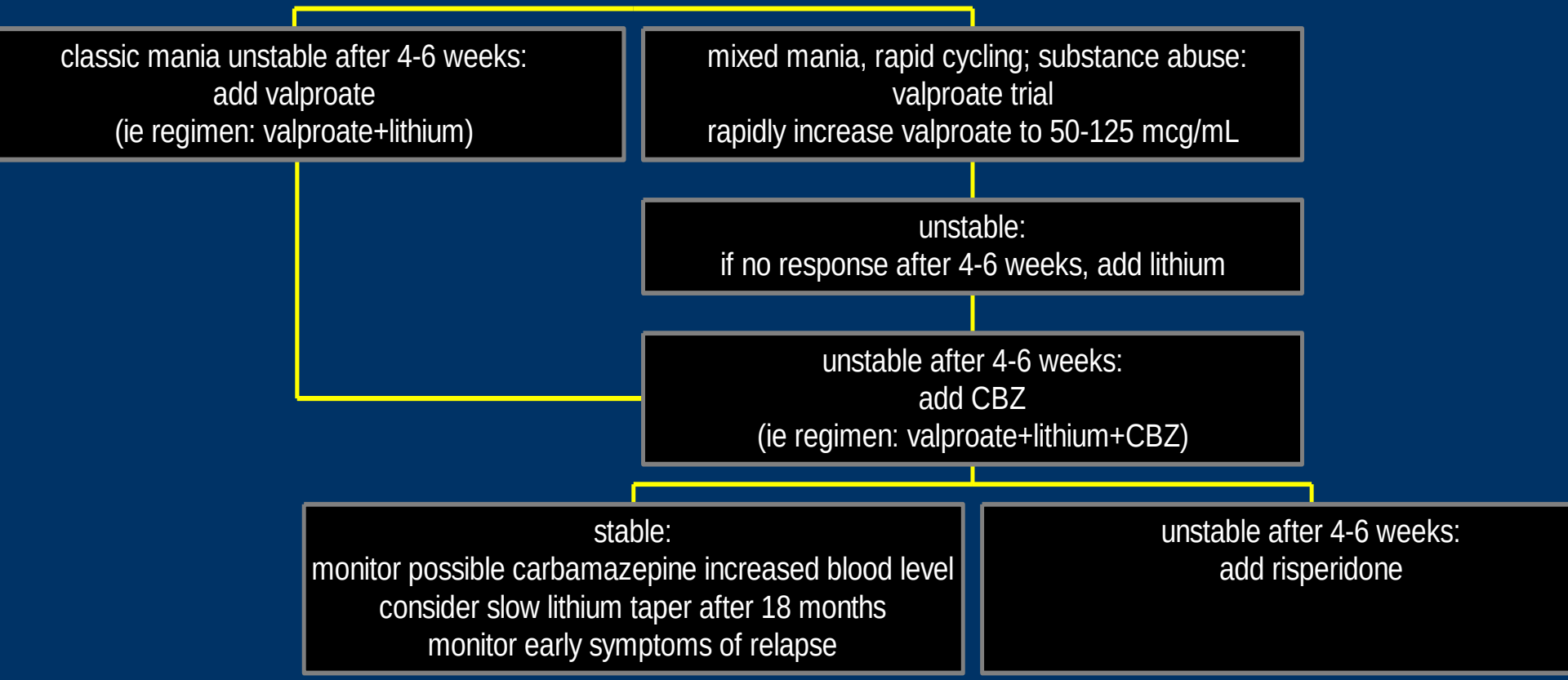
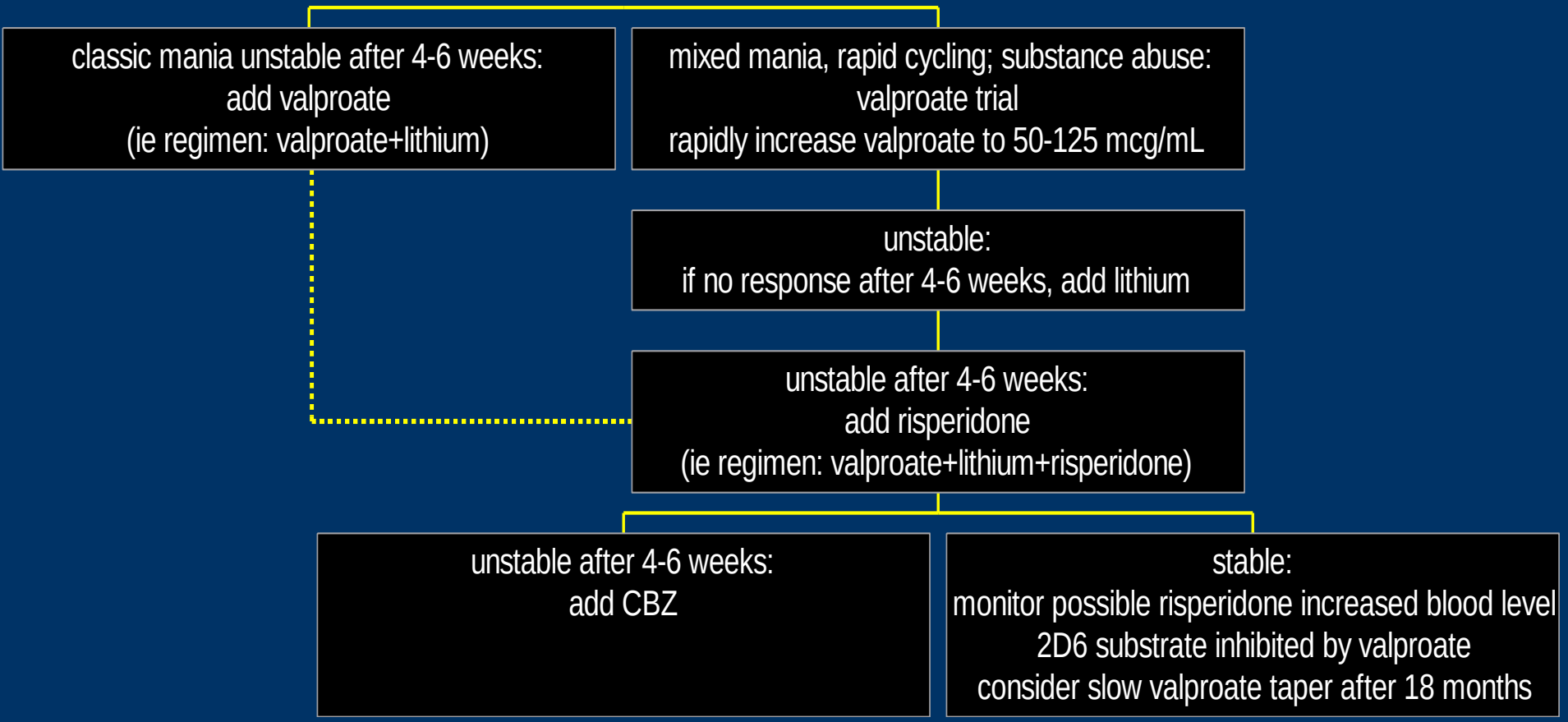


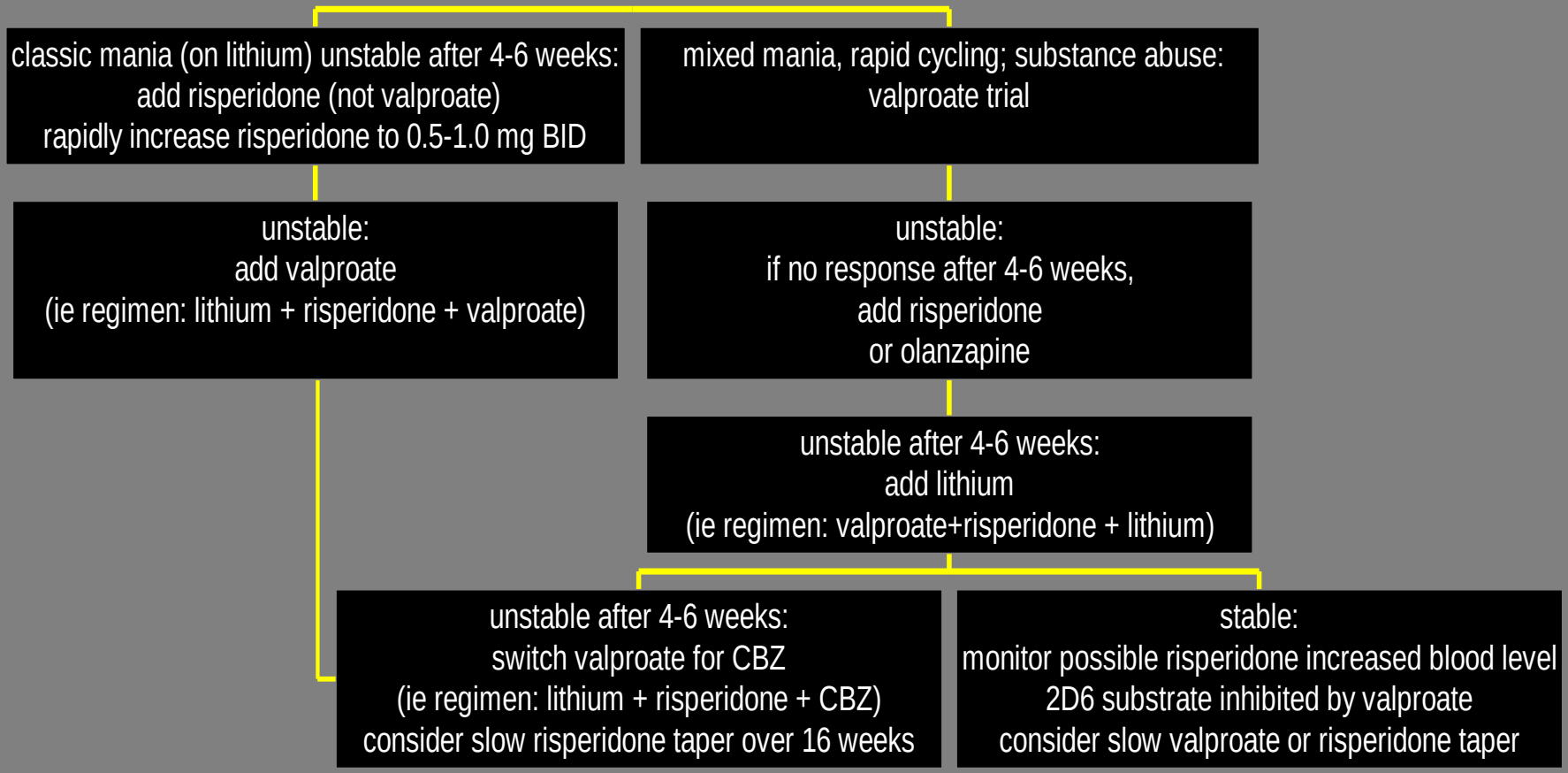
Original Augmentation Sequence: Li/DVP + CBZ



New Sequence ? : Li + DVP + Risperidone/Olanzapine



New Sequence ? : Li *or* DVP + Risperidone/Olanzapine



New Anticonvulsants as Potential (Third Generation) Mood Stabilizers

- Lamotrigine
- Gabapentin
- Topiramate

Lamotrigine

- bimodal spectrum of efficacy in the treatment of BPD
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1. Bowden et al, 2000 2. Fatemi, 1997 3. Kusumakar, 1997

Psychotherapy of Persons with Bipolar Disorder

- **mastering a narrower range of emotions**
- **learning to unravel what is personality**
- **developmental tasks**
- **mood charting**
- **no med split**
- **support groups**

Psychotherapy of Persons with BD

- **thin line: too much control / too little**
  - **–lithium: the power struggle**
- **anger: lifetime course; Rx rejection**
- **denial; exploring meaning; education**
- **realistic losses: energy, euphoria, libido**
- **compliance: competes with + intermittent reinforcement schedule**

Summary

- Rare disorder; 5% subsyndromal phenotype
- Developmental variant in pre-adolescent
- High co morbidity (ADHD, CD, ODD)
- Meticulous (longitudinal) diagnosis
- Pharmacotherapy; Risperdone; LiCO3, Divalproex, Carbamazepine, combinations
- Psychotherapy: compliance issues

Post Lecture Exam
Question 1

1. **An 8-year-old girl has an episode of Major Depressive Disorder (MDD). She is more likely to develop a Manic Depressive Illness (MDI) if one of the following statements is true:**

A. Her depression is mild but prolonged.

B. Her depression is nonpsychotic.

C. There is no family history of MDI.

D. She is a girl, and girls are more at risk than boys.

E. Her depression is severe.

Question 2

2. Is this statement true or false? The Young Mania Scale was specifically developed for use in youth.

A. True
B. False

Question 3

3. A significant pharmacokinetic drug-drug interaction can occur between one of the following psychotropic combinations:

A. Gabapentin and lithium

B. Lithium and lamotrigine

C. Lamotrigine and gabapentin

D. Valproate and lamotrigine

E. Valproate and lithium

Question 4

4. One of the following statements is true about lithium in pre-teen children:

A. Lithium has a lower clearance and a longer half-life in children than in adults

B. Lithium has a lower clearance and a shorter half-life in children than in adults

C. Lithium has a higher clearance and a longer half-life in children than in adults

D. Lithium has a higher clearance and a shorter half-life in children than in adults

E. Lithium has the identical clearance and half-life in children as adults

Question 5

5. A 12-year-old boy has been started on lithium. When should his blood be drawn for an accurate blood level?

A. After 3 days, the blood should be drawn after his morning dose

B. After 2 days, the blood should be drawn before his morning dose

C. After 5 days, the blood should be drawn after his morning dose

D. After 5 days, the blood should be drawn before his morning dose

E. After 5 days, the blood can be drawn at any time

Question 6

6. A 17-year-old girl is being considered to start on valproate. When discussing possible side effects with her and her parents, which of the following should be discussed?

A. Valproate is always associated with weight loss

B. Valproate is very alerting

C. Fatal liver disease is most common in girls over the age of 13 years

D. Valproate helps normalize menstrual irregularities

E. Valproate may cause neural tube defects in a baby if a girl is pregnant

Question 7

7. If one were using carbamazepine to treat MDI in a 14-year-old boy, which of the following statements would be true?

A. If should be dosed hs only to prevent drowsiness

B. It induces CYP2D6 and therefore it will induce imipramine and desipramine

C. Induction occurs at CYP3A4 and occurs at each dose increase

D. Inhibition occurs at CYP3A4 and occurs at each dose increase

E. Because it is a substrate of CYP2D6, CYP3A4 inhibitors should as nefazodone will not increase its concentration

Question 8

8. The boy in the last question has been started on carbamazepine. A trough level of 2 mcg has been reported on day 5 after initiation of treatment. Which statement is true?

A. This is a good level and drug dosing should not be increased

B. This is too high and dosing should be decreased

C. The usual range for carbamazepine is 2-6 mcg/ml

D. The usual range for carbamazepine is 14-20 mcb/ml

E. Dosing should be increased

Question 9

9. Carbamazepine is partially metabolized to its epoxide. Which of the following statements are true about this metabolite?

A. It is active and is measured as part of the usual carbamazepine plasma level

B. It is inactive and it is not measured as part of the usual carbamazepine plasma level

C. It is active and it is not measured as part of the usual carbamazepine plasma level

D. It is inactive and it is not measured as part of the usual carbamazepine plasma level

E. None of these statements is true

Answers to Pre & Post Competency Exams

1. E
2. B
3. C
4. D
5. D
6. E
7. C
8. E
9. C