Disruptive Mood Dysregulation Disorder (DMDD) Developing Treatment Strategies

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Medication Usage Disclaimer

The following 2 medications that will be discussed in this presentation are being used off-label:

- oxcarbazepine
- amantadine HCl

Learning Objectives

Upon the conclusion of this activity, attendees should have received the knowledge that would allow them to:

1) Distinguish between DMDD and Pediatric Bipolar Disorder.
2) Demonstrate an understanding of the brain dysfunctions underlying the chronic irritability and episodic rage episodes in DMDD.
3) Identify the pharmacologic interventions which have been shown to be effective in DMDD.
4) Describe the target dose ranges and/or blood levels of the anticonvulsant and dopaminergic agonist that resulted in significant reductions of re-hospitalization for uncontrolled aggression in patients with DMDD.
5) Employ the described pharmacological protocol in their medical management of patients with DMDD.

DMDD: What is it?

(McGough, 2014)

A new diagnosis for DSM-V (2013) for children with severe and chronic irritability with explosive temper outbursts.

AREN'T ALL CHILDREN IRRITABLE AT TIMES? Yes but DMDD refers to:

- Temper outbursts - at least three times a week
- Irritable/angry moods almost daily for a year
- Onset at least age 6 but before age 10; may continue as adult, if had childhood onset
- With trouble functioning in multiple settings

DMDD: New DSM-V Diagnosis

(Axelson et al., 2012)

Designed to replace "broad spectrum" Bipolar Disorder in children and adolescence.

- In DSM IV, mania describes discrete episodes of irritated moods (episodic irritability).

- In DSM V, DMDD describes non-episodic (chronic) irritability with frequent temper outbursts.

- DMDD has very little research base, but it is very similar to the concept of Severe Mood Dysregulation proposed by the NIMH (without hyper-arousal).

Epidemic of Bipolar Disorder (BD)?

(Leibenluft, 2011)

- Between 1994 and 2003 there was a 40-fold = 4,000% increase in the diagnosis of BD in children and adolescents. (Moreno, C. et al., 2007)
  - There had been a broadening of the phenotype for pediatric bipolar, to include **chronic** irritability as a subtype of Bipolar Disorder.

- But research does **not** support this change from narrow (episodic) to broad (chronic) phenotype.
  - Non-episodic irritability is unique; not a subtype of Bipolar Disorder (Geller et al. , 2008)

DSM-V & Pediatric Neuropsychiatry

(Fisher et al., 2013; Schieveld et al., 2013)

- The vast majority of the children being diagnosed with Bipolar Disorder were not classic, or narrow phenotype, Bipolar Disorder.
  - They show non-episodic (chronic) irritability, rather than classic (episodic) irritability.

- Non-episodic (or chronic) irritability appears to be a distinct condition, separate from Bipolar.
  - This is the basis for Disruptive Mood Dysregulation Disorder (DMDD) in DSM-V.


It's not fair. Why can't I be diagnosed bipolar like all of my friends?
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DMDD versus Bipolar Disorder

How does DMDD differ from Bipolar?

A) First, it reflects **non-episodic** irritability (chronic) whereas Bipolar Disorder has episodes of irritability associated with mania.
B) Also, it shows **no euphoria or grandiosity**, whereas Bipolar Disorder may show this during mania.
C) Also, it shows **no psychosis**, whereas Bipolar Disorder may show this.

Abnormal Irritability

(Leibenluft, 2011)

Abnormal Irritability:

- Is an impairing, and long-lasting mood disorder with temper outbursts:
  - *"Temper outbursts that are developmentally inappropriate, frequent, and extreme with anger or sadness between outbursts."*

- May occur in association with mental illness*:*
  - *Depression, Anxiety, Post-Traumatic Stress Disorder, Attention Deficit Hyperactivity Disorder, Autistic Spectrum*

Severe Irritability

(Dickstein & Leibenluft, 2012)

- Severe episodic irritability may be a symptom of the manic phase of a Bipolar Disorder.

- If irritability is chronic and severe, with childhood onset (between ages 6 and 10), and very frequent explosive outbursts, with negative moods between outbursts, then consider DMDD.

- Frequent explosive outbursts can undermine academic, family, and social functioning and lead to school dropout, substance abuse, depression, multiple psychiatric hospitalizations or incarceration (Copeland et al., 2014).

DMDD Research

Epidemiologic studies:

- Copeland et al. (2013) showed: that
- Non-episodic (chronic) irritability with rage outbursts (meeting DMDD criteria; age 6-10) are reported in 3% of children.
- Stringaris, et al. (2010) showed that in >2-year follow-up, 1.2% of DMDD subjects experienced a manic episode, whereas 62.4% of narrowly defined BD subjects experienced a manic episode.
- Dougherty et al. (2014) found an 8.2% prevalence for DMDD in 6-year-old children.

Retrospective Study of DMDD

(Copeland et al., 2013)

Used data from existing studies of school age children with mental illness to evaluate DMDD:

- About 50% had temper outbursts, but only 6-7% of these averaged 3 or more per week.
- 8-13% showed negative moods (sad or irritable) but only 1.5%-2.8% had chronic irritability.
- Cumulative prevalence after 4 separate assessments was 4.4% (Close to 1 child in 20 of this sample)
- High rates of other co-existing psychiatric disorders.
- High rates of impairment (family, school, social)
- High rates of mental health service utilization

Exclusionary criteria for DMDD?

- Mania (e.g., full symptom criteria, except duration) lasting more than 1 day.
- Psychosis
- Or better explained by:
  - Post Traumatic Stress Disorder
  - Autism Spectrum Disorder
  - Major Depressive Disorder or Dysthymia

Late in the course of DMDD, child may develop co-morbid depression and/or anxiety (but does not develop Bipolar Disorder) Stringaris, et al., 2010

Disruptive Mood Dysregulation Disorder (DMDD) DSM-V

(Zepf & Holtmann, 2012)

A. Temper Outburst

- Severe recurrent temper outbursts to common stressors
- Beyond provocation
- Not consistent with age (developmental age 6+)
- Onset before age 10
- Never elevated mood or grandiosity

B. Frequency

- Temper outbursts occur, on average, three or more times per week
- Between outbursts:
  - Mood chronically negative
  - Irritable, angry
  - Observed by others such as parents, teachers
  - For at least a year
  - In at least two settings (Home, school, peers)

Neuropathology?
DMDD vs Bipolar Disorder (BD)

Ryan, N.D. (2013) reported:

- DMDD exhibited markedly **decreased** activation of

  paralimbic system (cingulate gyrus, striatal, thalamic, parietal, and parahippocampal regions) after negative feedback (frustrating) trials (not in Bipolar).

Deveney et al. (2013) reported:

- In DMDD, the **prefrontal lobe** tends to show **underactivity** in comparison to Bipolar Disorder which shows over activity.

Neuropathology?

Cause of DMDD is Unknown:

- Possible genetic disorder?

Chen, T., Blum, K, Matthews, D., Fisher, L., et al. (2007).

- Premature birth with hypoxia, drugs/alcohol in pregnancy, difficult birth, malnutrition, abuse?

Fisher, L., Matthews, D., & Matthews, G. (2013). Two Juvenile Cases of Disruptive Mood Dysregulation Disorder (DSM-5). Poster at *Texas Psychological Association*, November, Houston, TX

Biological Markers for DMDD?

(Kowatch et al. , 2009)

- BD rates do not vary by gender, but chronic irritability children are mostly male (66-77%) (suggesting a distinct gender-based disorder).

- Parents of Bipolar children are more likely (33%) to have BD themselves than parents of DMDD children (2.7%), (suggesting a distinct genetic pattern).

- Gene mapping may be a way to find biological markers for DMDD.

TREATMENT FOR DMDD?

- No treatment strategies have been established:

  Deveney et al. (2013); Tourian, Leon, et al. (2015)

- But Bipolar medications may NOT be needed.

  Matthews, D., Fisher, L. & Matthews, G. (2012)

- The selection of medications for the management of maladaptive aggression in youth is a major clinical challenge in pediatric mental health

  Kowatch et al., (2009); Fisher, Matthews & Matthews. (2013); Fisher, W., Johnson, A., Fisher, L., Sharma, S., & Ceballos, N., (2013)

TREATMENT OPTIONS?

- Most experts suggest medication, parent training and psychotherapy.
  Alderman (2003)

- Psychosocial interventions have low risk, but it may require a combination of medication and psychosocial interventions to manage the severity.
  Aman et al. (2014)

- But what medication protocol?
  Matthews, D., Fisher, L., & Matthews, G. (2013)

Medication Protocol:

(Matthews et al., 2006; Matthews et al., 2009, Matthews et al., 2013)

- A Neuropsychiatric approach to DMDD would suggest that medication strategies be based on brain issues.

- If it is true that DMDD represents a combination of top-down and bottom-up brain issues, then:
  - Medications should enhance frontal lobe function (top down) to control irritability, and;
  - Medications should stabilize temporal-limbic (bottom-up) to stop explosive outbursts

Within Case Example of Compliance/Non-compliance

- 8-year-old boy diagnosed with Bipolar Disorder and ADHD at age 5 years. 3 acute admissions over the past 2 years for chronic irritability and frequent uncontrollable severe anger outbursts that resulted in injury to others and property.

- Medication history: valproate sodium, ziprasidone, guanfacine, LiCO3, quetiapine, risperidone, methylphenidate and topiramate in varying doses and combinations over the past 3 years.

- Diagnosed as DMDD and ADHD, combined type on admission.

Treatment Course

1) Instituted oxcarbazepine at 15 mg/kg/day in divided doses and increased by 5 mg/kg/day every fourth day to achieve a total dose of 35-50 mg/kg/day total. Target blood level 30-35 mcg/ml.
2) In parallel, began to decrease the risperidone dosage by 10-20% concurrent with each oxcarbazepine increase, as tolerated, with the goal of discontinuation.
3) Added amantadine HCl 5mg/kg/day and increased to 10 mg/kg/day total in 2 divided doses, am and 8 hours later=mid-afternoon.
4) Methylphenidate added at 0.4 mg/kg/dose 3X daily after other medication adjustments completed.
    - Tolerated the medication regime without adverse events, participated well in cognitive behavioral and skills therapies. Discharged stable to home after 90 days.
    - Unfortunately, patient required readmission 2 years later. The family had moved to another state related to their work, and the medication regime had been significantly altered. “Melt-downs” and chronic irritability had returned, resulting in 2 hospital stays.

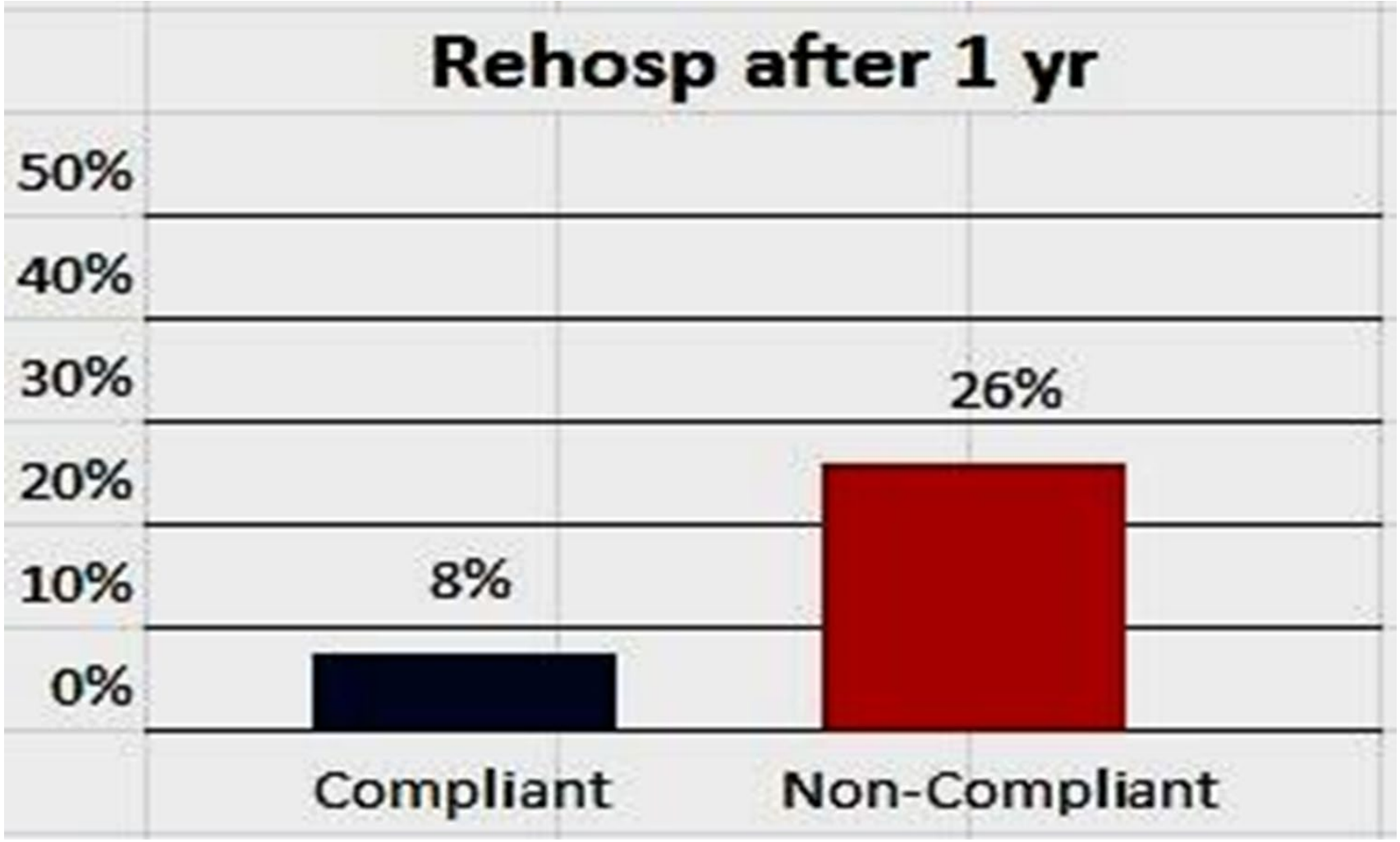
Treatment Course cont'd

Upon transfer from Acute Care was on the following:

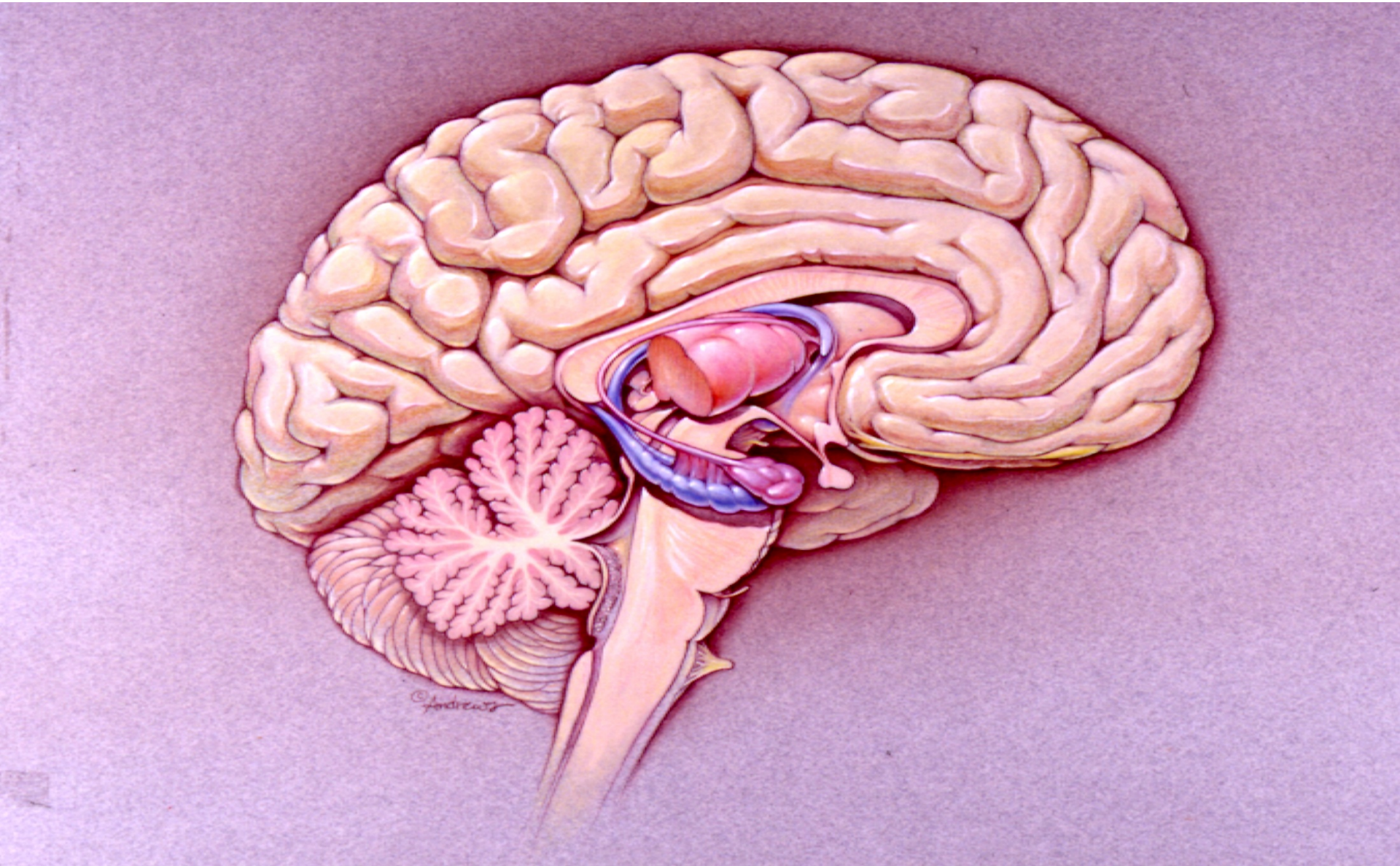
- Risperidone 2 mg 2X daily, clonidine HCl 0.1 mg 3X daily, oxcarbazepine 300 mg 3X daily(level 15 mcg/ml) and haloperidol 2 mg each 6 hours as needed for aggression (being given at least twice daily for the week preceding transfer).

Discharged to home stable on oxcarbazepine (level 35 mcg/ml), amantadine HCl 10 mg/kg/day, and methylphenidate 0.4 mg/kg/day. 1 year follow-up, "Doing well. Meds in place."

Matthews, NEI, (2016)

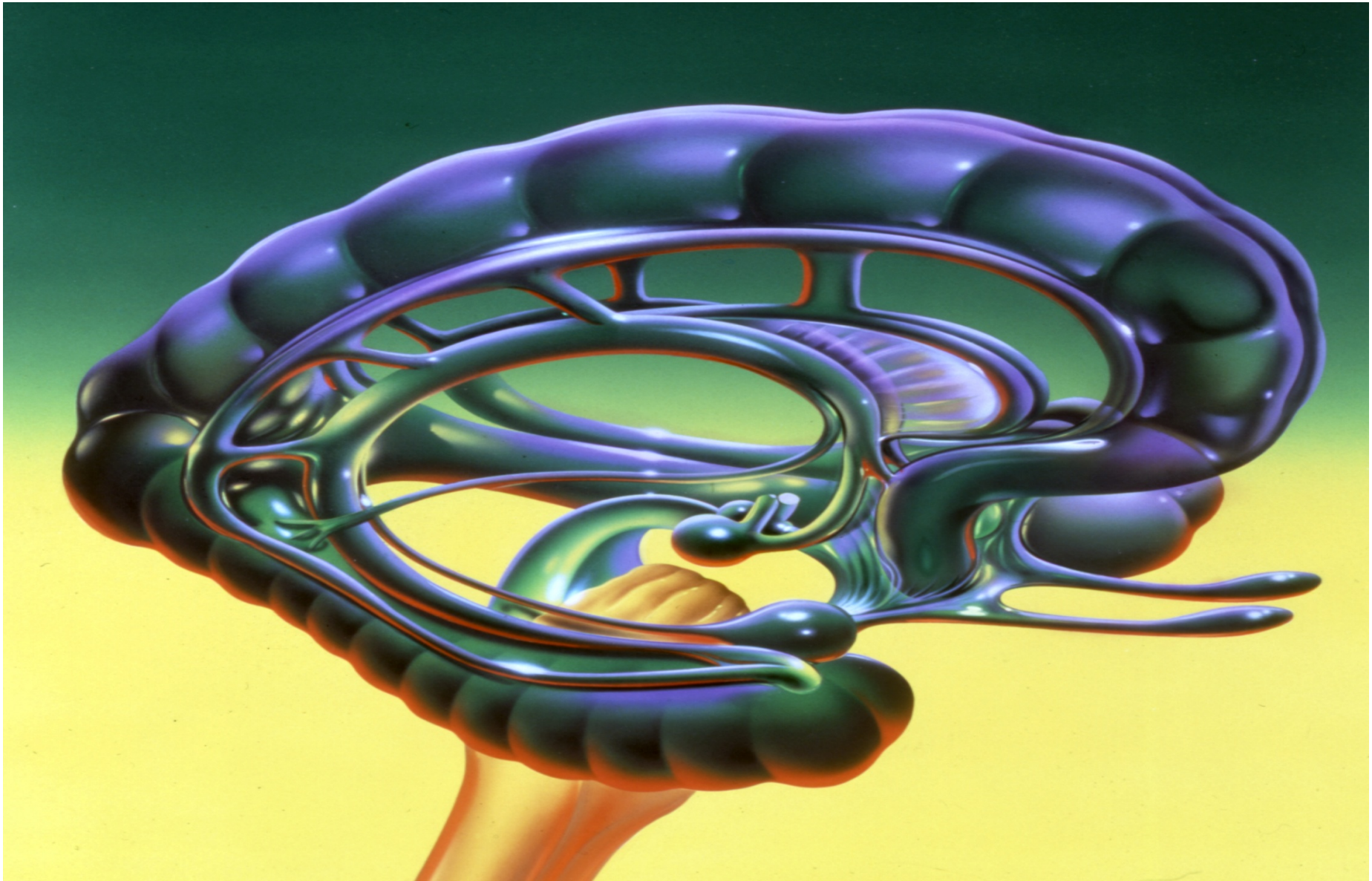


Impulse Control & Concentration



Emotion Generation System

(Limbic Brain)

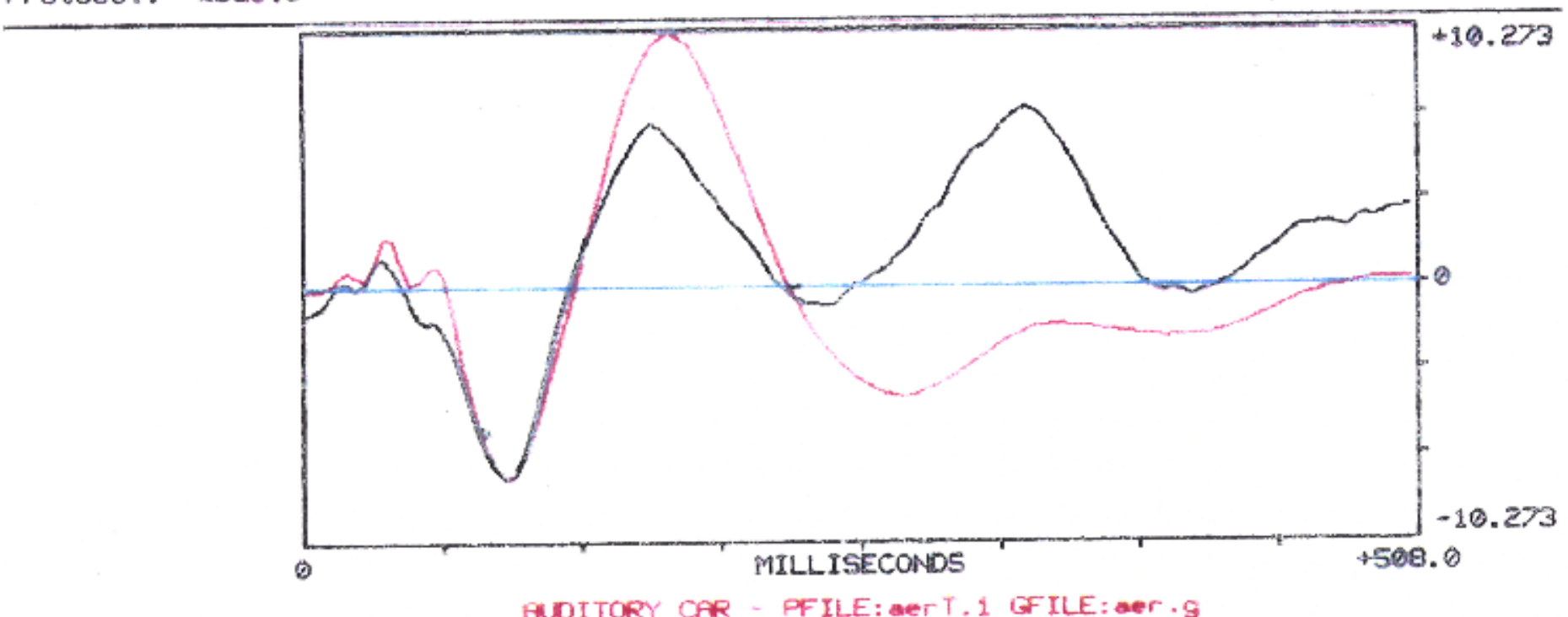


Auditory Evoked Response

Age: 15.114
Visit: 1
Tue Apr 6 1993

Reason: cerebral dysrhythmia
Sensory Deficit: reading glasses

Protocol: xbasic

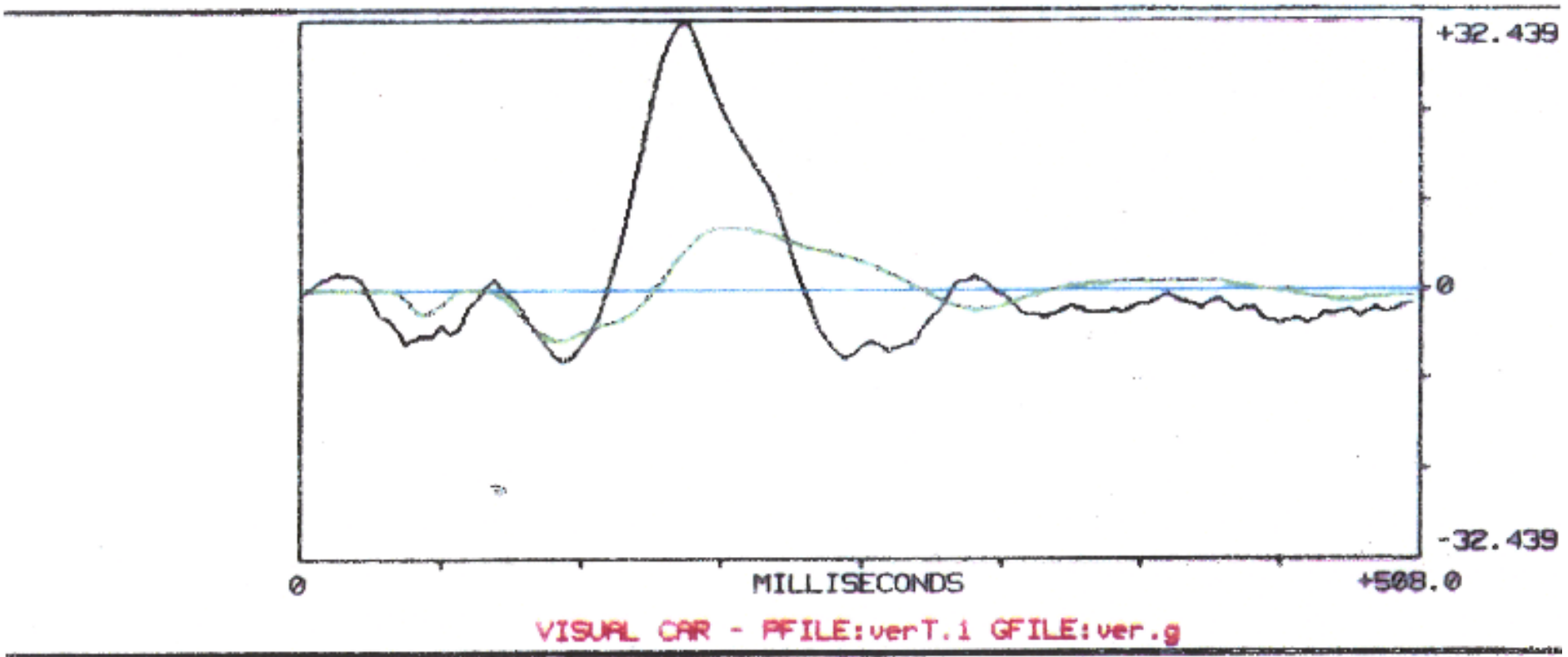


Visual Evoked Response

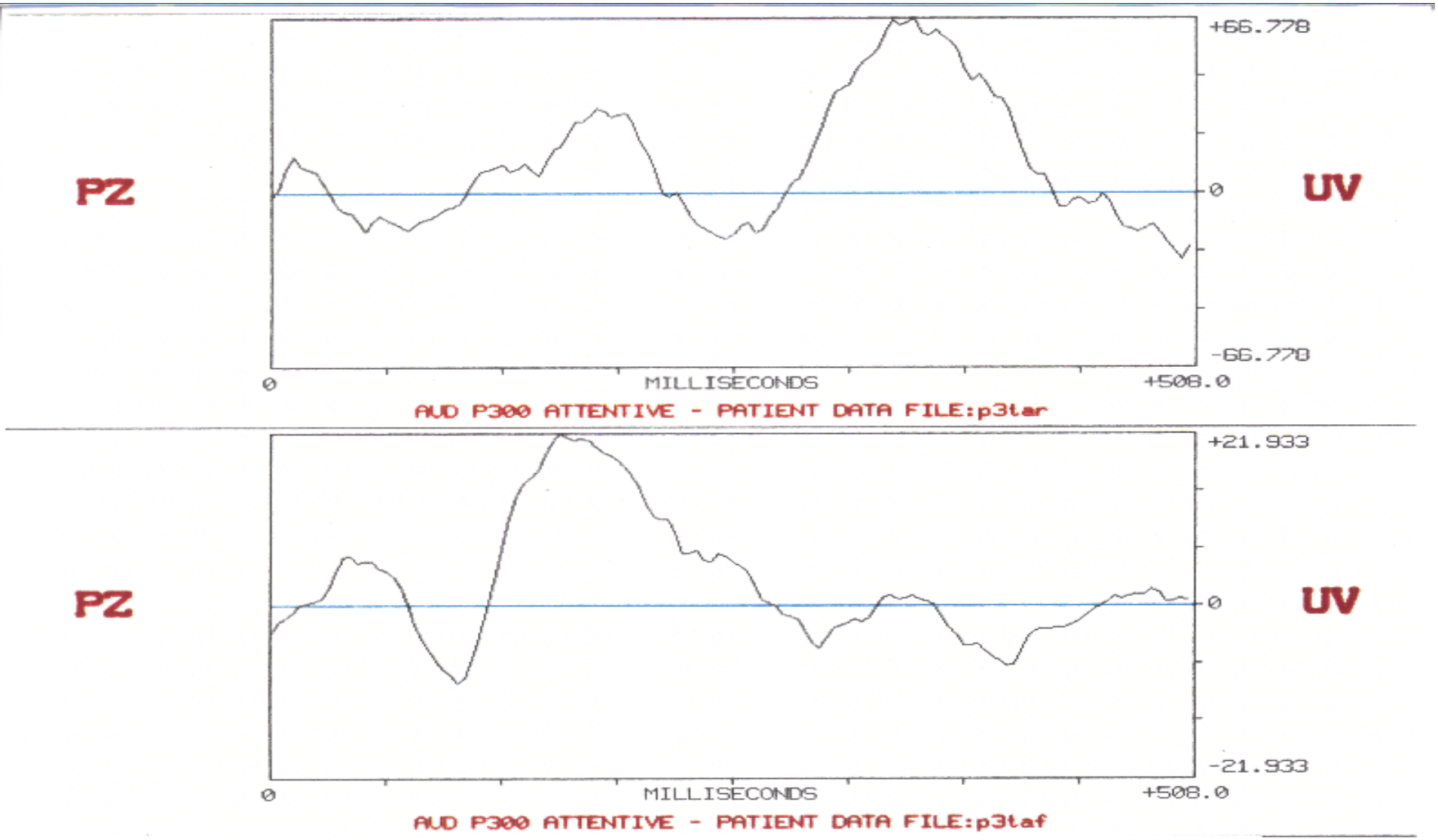
Age: 15.350
Visit: 1
Tue Apr 6 1993

Reason: cerebral dysrhythmia

Protocol: xbasic



P-300's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Treatment Interventions

Neuropsychopharmacological:

- Anticonvulsants - Limbic dysmodulation
- Amantadine HCl or alpha-adrenergic agonists - Frontal lobe dysfunction
- Stimulants - attentional deficits

Psychosocial and Psycho-educational:

- Psychotherapy (family and individual)
- Specialized academic interventions
- Skill-based therapies

Anticonvulsants

Name	Level or Dosage
Carbamazepine	10-12 mcg/ml
Oxcarbazepine	35-50 mg/kg/day ***or***
	25-35 mcg/ml
Levetiracetam	40-60 mg/kg/day (2-4000 mg/day)
Valproate sodium	100-130 mcg/ml
Lamotrigine	5-8 mg/kg/day (300-500mg/day)

[At these levels/dosages they are 65% (++) to 95% (++++) effective in eliminating explosive episodes.]

Anticonvulsants

Name	Effectiveness
Carbamazepine	++++
Oxcarbazepine	++++
Levetiracetam	+++
Lamotrigine	++-+++
Valproate sodium	++
Topiramate	++

(In our experience)

Abnormal Frontal Lobe Function

Evidence of frontal dysfunction clinically, neurophysiologically and/or on neuropsychological testing can be addressed with either:

A. An alpha-adrenergic agonist that is active in the brain, e.g.: clonidine or guanfacine

or

B. Amantadine HCl

- Alpha-adrenergic agonists (competitive) produce decreased norepinephrine stimulation frontally, thus allowing an increased effect of the relatively inadequate dopaminergic activity in the region. This, in turn, produces improved concentration and impulse modulation.
- Amantadine acts by agonistically increasing dopaminergic D-4 activity frontally, while antagonistically decreasing NMDA glutamate activity frontally.
- Usual dose is 50-200 mg/dose, or 10-15 mg/kg/day total, 2x daily (6-8 hours apart).

Abnormal Hippocampal Attention

- Abnormal P-300 (cognitive evoked) responses indicate inadequate Hippocampal attentional function.
- P-300 responses and attentional function are normalized at appropriate dosages of neuro-stimulant medications.
- Dextroamphetamine 0.2-0.3 mg/kg/dose 3x/day.
- Methylphenidate 0.4-0.6 mg/kg/dose 3x/day.
- Stimulants can be transitioned to a long-acting formulation after the most efficacious dosage has been determined.

Angry Child

Explosive Child

What is Crisis Management for Defensive RAGE?

SEE RAGE? Stop VERBAL de-escalation, don't touch him/her

- No more talk, remove others, allow rage (if safe)

SEE RAGE FACE: Slowly, very slowly, back away

- Even if he/she follows, threatens, curses, throws stuff

Don't look threatening – it is a defensive "seizure"

- Make your face, body posture - non-threatening

Don't approach or touch – unless hold must occur,

- but only for absolute imminent danger

SUMMARY

- DMDD is a new diagnosis in DSM-V for 2013

- This severe mood disorder is **relatively** common
  (DMDD at least 3%, versus 1% for BD)

- DMDD is a **distinct condition**, with chronic (non-episodic) irritability, that does not evolve into BD

- No **established** treatment strategies for DMDD

- DMDD **might be manageable** with combination of:
  1) Medication Protocol, 2) Parent Training, 3) Cognitive Behavioral Therapy, 4) Modified crisis management strategies.

Resources

Dan Matthews, MD webinar on Disruptive Mood Dysregulation Disorder:

- https://www.cigna.com

- http://www.neurobehavioralsystems.net/

Dr. Larry Fisher's DMDD Behavioral Management Video:

- http://www.neurobehavioralsystems.net/video/

Behavior and Chores Printable Charts:

- http://www.imom.com
- http://www.kidpointz.com/printable-charts/

Books:

- Ross Greene, PhD http://www.livesinthebalance.org
- Positive Discipline by Jane Nelsen, EdD https://www.positivediscipline.com/

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