Neuropharmacologic Agents for Agitation after Traumatic Brain Injury
Disclosures

• Most, it not all, of the medications discussed have not been tested in pediatric populations.
• Most, if not all, the medications discussed are being used off-label in pediatric populations.
• No financial disclosures
Neuropharmacology in Pediatric Brain Injury: A Review

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Update on Pharmaceutical Intervention for Disorders of Consciousness and Agitation After Traumatic Brain Injury in Children

Stacy J. Suskauer, MD, Melissa K. Trovato, MD

Pharmacological management for agitation and aggression in people with acquired brain injury (Review)

Fleminger S, Greenwood RRJ, Oliver DL
Agitation after TBI: Impact

- Adults 3x more likely in first 6 months after head injury to show aggression than those with multiple traumatic injuries without head injury
- 25% of adults showed aggressive behavior 60 months after discharge from inpatient rehabilitation unit for TBI
- 70% of adults during inpatient TBI rehabilitation experience agitation
- Agitation has been shown to negatively affect rate of recovery in acute inpatient rehabilitation
Agitation after TBI

- Symptoms:
  - Physical and verbal aggression
  - Explosive anger
  - Akathisia
  - Irritability
  - Mood lability
  - Maladaptive behavior
  - Disorientation
Management of Post-TBI Agitation

- Identify and address possible cause/contributors including:
  - Sleep disruption / alteration of sleep wake cycle
  - Sources for discomfort
    - Lines/catheters
    - Unidentified injury (fracture, etc)
    - Inadequate pain control
    - Gastrointestinal distress (reflux, constipation, ileus)
  - Seizures
    - subclinical epilepsy can present as intermittent aggression
  - Disorientation, post-traumatic amnesia
  - Neuroendocrine dysfunction
  - Post-traumatic hydrocephalus
  - Drug withdrawal (pain medications, other meds from ICU)
  - Polypharmacy
Pharmacologic Management: Measure Intervention Response

• Identify symptom that causes disruption:
  – Aggression
  – Dis-inhibition
  – Akathisia
  – Disorientation
  – Acquired mood disorder (depression/anxiety)
  – Mood lability

• Monitor frequency of disruptive behavior/symptom through close observation
• Monitor frequency of activity disruption
• Use outcome measures . . .
Agitated Behavior Scale (ABS)

1. Short attention span, easy distractibility, inability to concentrate.
2. Impulsive, impatient, low tolerance for pain or frustration.
3. Uncooperative, resistant to care, demanding.
4. Violent and or threatening violence toward people or property.
5. Explosive and/or unpredictable anger.
6. Rocking, rubbing, moaning or other self-stimulating behavior.
7. Pulling at tubes, restraints, etc.
8. Wandering from treatment areas.
9. Restlessness, pacing, excessive movement.
10. Repetitive behaviors, motor and/or verbal.
11. Rapid, loud or excessive talking.
12. Sudden changes of mood.
13. Easily initiated or excessive crying and/or laughter.
14. Self-abusiveness, physical and/or verbal.

Total Score

1 = absent: the behavior is not present.
2 = present to a slight degree: the behavior is present but does not prevent the conduct of other, contextually appropriate behavior. (The individual may redirect spontaneously, or the continuation of the agitated behavior does not disrupt appropriate behavior.)
3 = present to a moderate degree: the individual needs to be redirected from an agitated to an appropriate behavior, but benefits from such cueing.
4 = present to an extreme degree: the individual is not able to engage in appropriate behavior due to the interference of the agitated behavior, even when external cueing or redirection is provided.
Non-Pharmacological Management of Post-TBI Agitation

• Environmental Controls
  – Reduce Noise (turn off TV, monitors if possible)
  – Reduce interruptions (minimize and cluster vitals/med administration/nursing care)
  – Limit number of visitors at a time
  – Allow for down-time for patient

• Reduce contributors to agitation
  – Orientation/Memory strategies
  – Identify and treat pain
  – Eliminate unnecessary medications

• Behavioral management
  – Coordinated program to address specific behaviors
  – Incorporate entire care team (family members, psychology, nursing, therapists)
Pediatric Research on Pharmacologic management of Agitation after TBI

- Extremely Limited
- 1 prospective study
- Few case series/reports

**Table 2. Medication dosing parameters used in cited literature for treating agitation**

<table>
<thead>
<tr>
<th>Author</th>
<th>Subject’s age (y)</th>
<th>Drug</th>
<th>Reported Range of Treatment Doses After Titration for Effect; All Medications Given Enterally</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott et al, 2009 (16)</td>
<td>&lt;2</td>
<td>Ziprasidone</td>
<td>1.8 mg/kg divided bid or tid</td>
</tr>
<tr>
<td></td>
<td>2-12</td>
<td>Ziprasidone</td>
<td>1.5 mg/kg divided bid</td>
</tr>
<tr>
<td></td>
<td>&gt;12</td>
<td>Ziprasidone</td>
<td>0.7 mg/kg divided bid</td>
</tr>
<tr>
<td>Chatham Showalter and Kimmel 2000 (17)</td>
<td>13-89</td>
<td>Divalproex</td>
<td>250 mg to 2000 mg total daily dose; mean 1257 mg</td>
</tr>
</tbody>
</table>

*bid = twice daily; tid = 3 times daily.*
Adult Research on Pharmacologic management of Agitation after TBI

- Cochrane review last updated 2008
- 6 studies met criteria (RCT’s) for meta-analysis
  - Propranolol (2)
  - Pindolol (2)
  - Methylphenidate (1)
  - Amantadine (1)
- Research supports use of β-Blockers
- Effect seen within 2-6 weeks
- Response similar in both subacute and chronic timeframe
Benzodiazepines

• Work on GABA molecule to create:
  – Anxiolytic, sedative, antispasticity, anticonvulsant and AMNESIC effects
• Effect duration varies based on medication
  – Short (1-8 hour half life) – e.g. midazolam, alprazolam
  – Intermediate (8-40 hour half life) – e.g. lorazepam
  – Long (>40 hours) – e.g. Diazepam, clonazepam
# Benzodiazepines

## Table 4. GABA agonists

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Approval In Pediatric Patients</th>
<th>FDA Pediatric Dosages</th>
<th>Mechanism of Action</th>
<th>FDA Indications</th>
<th>TBI Usage</th>
<th>Serious Reactions</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen</td>
<td>Yes, 12 y and older</td>
<td>Oral: start 5 mg TID, gradually titrate to maximum 60 mg/d; intrathecal patient dependent</td>
<td>GABA-B agonist</td>
<td>Spasticity</td>
<td>Spasticity</td>
<td>Seizures, death with abrupt withdrawal</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Yes</td>
<td>Age and weight based</td>
<td>Facilitation of the GABA</td>
<td>Sedation, anesthesia induction</td>
<td>Acute agitation</td>
<td>Respiratory arrest, cardiac arrest</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>No</td>
<td>0.25-3 mg</td>
<td>Facilitation of the GABA</td>
<td>Anxiety, panic disorder</td>
<td>Agitation, anxiety</td>
<td>Syncope, tachycardia, seizures, respiratory depression</td>
<td>Dependence</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Yes</td>
<td>0.05 mg/kg</td>
<td>Facilitation of the GABA</td>
<td>Anxiety, insomnia, status epilepticus</td>
<td>Agitation</td>
<td>Respiratory depression, seizures, depression</td>
<td>Dependence</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Safety in age &lt;6 mo not established</td>
<td>2-10 mg</td>
<td>Facilitation of the GABA</td>
<td>Anxiety, preoperative sedation, EtOH withdrawal, seizure disorder</td>
<td>Agitation</td>
<td>Respiratory depression, seizures, depression</td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>age &gt;10 y or &gt;30 kg weight</td>
<td>0.01-0.03 mg/kg/d, not to exceed 0.05 mg/kg/d</td>
<td>Facilitation of the GABA</td>
<td>Seizure disorder, panic disorder</td>
<td>Agitation</td>
<td>Respiratory depression, Hepatotoxicity seizures, depression</td>
<td></td>
</tr>
</tbody>
</table>

EtOH = ethanol; FDA = Food and Drug Administration; GABA = γ-aminobutyric acid; TBI = traumatic brain injury.
Benzodiazepines: Side Effects

- Side effects include the following:
  - Amnesia/memory loss
  - Increased daytime fatigue
  - Decreased concentration
  - Decreased alertness
- **TBI** causes the above effects as well
- Repeated use of benzodiazepines may slow/impair neuronal recovery after focal injury
Benzodiazepines: Research

• Pediatric Research:
  – None
Benzodiazepines: Take Home Points

• Use of benzodiazepines is discouraged due to side effects confounding and even delaying recovery after brain injury
• Limited use on an as needed basis may be appropriate
β-Blockers

- Proposed mechanism of reducing hyperadrenergic activity
- Commonly used for periodic autonomic instability and dystonia (Storming)
- In retrospective studies shown to improve survival when used acutely after ABI
- Current prospective placebo study looking at effect of adrenergic blockade acutely after brain injury on survival and functional outcomes (clonidine and propranolol)
β-Blockers: Side Effects

• Bradycardia
• Orthostatic Hypotension
• Fatigue
• Sedation
**β-Blockers: Research**

- **Pediatric Research:**
  - None

- **Adult Research:**
  - 2 randomized placebo-controlled trials (Brooke 1992, Greendyke 1986) show benefit with propranolol for agitation in the weeks after injury (Brooke) and for aggressive behavior months and years after injury (Greendyke).
β-Blockers: Take Home Points

• Research supports use in adults for agitation
  – Reduces intensity and frequency of agitation, as well as need for use of restraints
  – Doses studied in adults are relatively high, no research guidance for effective dosing in children

• No FDA indication for children
• No research in children
• Monitor closely for side effects
Clonidine

• $\alpha_2$-adrenergic receptor agonist
  – Decreases sympathetic tone
• No studies for agitation after TBI in adults or children
• Current uses:
  – FDA approval for ADHD in children >6
    • RCTs in children with ADHD show decreased impulsivity/hyperactivity, and decreased inattention
  – Emergence agitation after anesthesia
  – Drug and alcohol withdrawal (adults)
  – Akathisia associated with withdrawal (adults)
• May be useful as treatment for akathisia induced agitation or for inattention
Anticonvulsants

• Various mechanisms based on medication:
  – Decrease excitatory neurotransmitter activity
  – Increase inhibitor neurotransmitter activity
  – Reduce sub-clinical epileptic activity
    • Seizures can be a source for aggression/confusion/disorientation
  – Provide mood stabilization
## Anticonvulsants

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Approval in Pediatric Patients</th>
<th>FDA Pediatric Dosages</th>
<th>Mechanism of Action</th>
<th>FDA Indications</th>
<th>TBI Usage</th>
<th>Serious Reactions</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproex</td>
<td>Yes, children &gt;10 y old</td>
<td>Initial dosage 10-15 mg/kg/d</td>
<td>Suggested to increase brain concentrations of GABA</td>
<td>Mania, epilepsy, migraine</td>
<td>Agitation, headache</td>
<td>Teratogenicity, pancreatitis</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Yes, children &gt;10 y old</td>
<td>Initial dosage 10-15 mg/kg/d</td>
<td>Suggested to increase brain concentrations of GABA</td>
<td>Seizure, mania, migraine</td>
<td>Agitation</td>
<td>Teratogenicity, pancreatitis</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Yes, children &gt;12 y old</td>
<td>Age based</td>
<td>Suggested to increase GABA</td>
<td>Bipolar disorder, epilepsy, trigeminal neuralgia</td>
<td>Agitation, chronic headache</td>
<td>Aplastic anemia, agranulocytosis</td>
<td>Toxic epidermal necrolysis and Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Yes, patients ≥2 y old</td>
<td>Age and weight based</td>
<td>Unknown</td>
<td>Seizure, bipolar disorder,</td>
<td>Agitation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*FDA = Food and Drug Administration; GABA = γ-aminobutyric acid; TBI = traumatic brain injury.*
Anticonvulsants: Side Effects

- Varied based on medication
- In children with epilepsy, adverse effects on cognitive and motor function have been reported

<table>
<thead>
<tr>
<th>Medication</th>
<th>TBI Usage</th>
<th>Serious Reactions</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproex</td>
<td>Agitation, headache</td>
<td>Teratogenicity, pancreatitis</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Agitation</td>
<td>Teratogenicity, pancreatitis</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Agitation, chronic headache</td>
<td>Aplastic anemia, agranulocytosis</td>
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</tr>
<tr>
<td>Lamotrigine</td>
<td>Agitation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Anticonvulsants: Research

• Pediatric research:
  – Valproic acid – 1 study included patients age 13-89.

• Adult Research (all studies without controls)
  – Valproic Acid
    • Retrospective study of 28 patients with age range 13-89 demonstrated reduction of agitation symptoms with valproic acid in 26 (90%) patients
    • Authors concluded it may be appropriate for alert, labile, impulsive, and disinhibited patients (Chatham Showalter et al, 2000)
  – Carbamazepine
    • Prospective open trial in 8 patients (400-800 mg daily) had improved Agitated Behavior Scale (Azouvi et al, 1999)
    • 7 patients showed reduction in combativeness within 4 days (Chatham Showalter et al, 1996)
Anticonvulsants: Take Home Points

- Used frequently in adults to address symptoms of agitation: mood lability, dis-inhibition, and aggression
- Studies are limited even in adults to support use
- No evidence for efficacy in pediatrics
## Antidepressants

### Table 6. Antidepressants

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Approval in Pediatric Patients</th>
<th>FDA Pediatric Dosages</th>
<th>Mechanism of Action</th>
<th>FDA Indications</th>
<th>TBI Usage</th>
<th>Serious Reactions</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Yes, children &gt;12 y old</td>
<td>10 mg</td>
<td>Inhibits norepinephrine and serotonin reuptake</td>
<td>Depression</td>
<td>Depression, agitation, chronic pain</td>
<td>Ventricular arrhythmias, torsades de pointes</td>
<td>Suicidality</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Yes</td>
<td>Maximum of 200 mg/d</td>
<td>Selective serotonin reuptake inhibitor</td>
<td>Depression, OCD, panic disorder, PTSD, PMDD Depression</td>
<td>Depression, agitation</td>
<td>Neuroleptic malignant syndrome, serotonin syndrome</td>
<td>Suicidality</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Yes</td>
<td>Maximum 40 mg/d</td>
<td>Selective serotonin reuptake inhibitor</td>
<td>Depression</td>
<td>Depression, agitation, anxiety, OCD, stuttering</td>
<td>Neuroleptic malignant syndrome, serotonin syndrome</td>
<td>Suicidality</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>No</td>
<td>N/A</td>
<td>Serotonin reuptake inhibitor</td>
<td>Depression, OCD, panic disorder, PTSD, GAD PMDD</td>
<td>Depression, agitation</td>
<td>Neuroleptic malignant syndrome, serotonin syndrome</td>
<td>Suicidality</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>No</td>
<td>N/A</td>
<td>Inhibition of CNS neuronal uptake of serotonin</td>
<td>Depression, OCD, panic disorder</td>
<td>Depression, agitation</td>
<td>Neuroleptic malignant syndrome, serotonin syndrome</td>
<td>Suicidality</td>
</tr>
</tbody>
</table>

N/A = not applicable; OCD = obsessive compulsive disorder; PTSD = post-traumatic stress disorder; PMDD = premenstrual dysphoric disorder; GAD = generalized anxiety disorder; CNS = central nervous system; FDA = Food and Drug Administration.
Antidepressants

- Proposed mechanism for decreasing agitation:
  - Treatment of depression/anxiety that contribute to agitation/irritability
  - Mood stabilization
Antidepressants: Side Effects

- TriCyclic Antidepressants: arrythmia, convulsions, confusion, suicidality
- SSRI’s: Behavior changes, sleeplessness, AGITATION, social withdrawal, suicidality, neuroleptic malignant syndrome, serotonin syndrome
Antidepressants: Research

• No pediatric studies
• Very few studies looking at use of antidepressants with primary outcome of reduction of agitation
• Multiple studies (including one prospective RCT) in adults addressing post-TBI depression noted reduction in symptoms of depression as well as reduction in agitation with treatment
• A pilot study demonstrated improved mood, and improved attention and working memory with fluoxetine
Antidepressants: Take Home Points

• Use cautiously in children due to risk of suicidality
• Avoid polypharmacy (NMS, Serotonin syndrome)
• Might be appropriate to address anxiety and depression after TBI which contribute to agitation
• MORE RESEARCH NEEDED
Antipsychotics

• Mechanism of Action
  – Typical antipsychotics block $D_2$-dopamine receptor
  – Atypical antipsychotics have less $D_2$ receptor activity
    • Atypicalss likely act on other neurotransmitter pathways,
      including serotonin, dopamine, $\alpha_1$-adrenergic, muscarinic,
      and histamine pathways
Antipsychotics: Side Effects

• Movement disorders
  – Akathisia – one of more common movement disorders seen with antipsychotics
    • a subjective sense of restlessness often accompanied by involuntary movements of the limbs or trunk
    • Can worsen agitation
  – Extrapyramidal Symptoms
  – Tardive Dyskinesia – choreoathetotic or other involuntary repetitive movement

• Weight gain
• Neuroleptic Malignant Syndrome (NMS)
• Seizures
• Prolonged QT
# Antipsychotics: Side Effects

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Approval in Pediatric Patients</th>
<th>FDA Pediatric Dosages</th>
<th>Mechanism of Action</th>
<th>FDA Indications</th>
<th>TBI Usage</th>
<th>Serious Reactions</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>No</td>
<td>N/A</td>
<td>D1, D2, D3, D4, D5 receptor antagonism</td>
<td>Recurrent suicidal behavior, treatment-resistant schizophrenia</td>
<td>Agitation</td>
<td>Seizures, myocarditis orthostatic hypotension</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Yes, 13-17 y of age</td>
<td>Initiated at 0.5 mg once daily; titrate to a recommended dose of 2.5 mg/d</td>
<td>D2 and serotonin (5HT2) receptor antagonism</td>
<td>Schizophrenia, acute manic, or mixed episodes associated with bipolar I</td>
<td>Agitation</td>
<td>Cognition and motor impairment, tardive dyskinesia seizures</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Yes, 10-17 y old</td>
<td>25-400 mg</td>
<td>D2 and serotonin (5HT2) antagonist</td>
<td>Schizophrenia, bipolar mania</td>
<td>Agitation, insomnia</td>
<td>NMS, tardive dyskinesia</td>
<td>Suicidality</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>No</td>
<td>N/A</td>
<td>D2 and serotonin (5HT2) antagonist</td>
<td>Schizophrenia, bipolar mania</td>
<td>Agitation, insomnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Yes, 13-17 y old</td>
<td>Start at 2.5-5 mg once daily; target: 10 mg/d</td>
<td>Dopamine and serotonin (5HT2) antagonist</td>
<td>Schizophrenia, acute manic or mixed episodes associated with bipolar I</td>
<td>Agitation</td>
<td>NMS, tardive dyskinesia</td>
<td>Suicidality</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>No</td>
<td>N/A</td>
<td>Not been clearly established</td>
<td>Schizophrenia, vocal utterances of Tourette’s Disorder Antiemetic</td>
<td>Agitation</td>
<td>NMS, tardive dyskinesia</td>
<td>Suicidality</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Yes, children &gt;2 y old</td>
<td>Initial dose 0.1mg/kg</td>
<td>Antagonism of apomorphine (in dogs)</td>
<td>Agitation</td>
<td>Prolonged QT interval, NMS, tardive dyskinesia</td>
<td>Suicidality</td>
<td></td>
</tr>
</tbody>
</table>

D = dopamine; FDA = Food and Drug Administration; NMS = neuroleptic malignant syndrome; TBI = traumatic brain injury.
Antipsychotics: Side Effects

• Cognitive impact
  – Multiple animal studies have demonstrated either slowed cognitive improvement or reduced cognitive return with use of antipsychotic medications (both typical and atypical)
  – One human study demonstrated negative cognitive impact with use of antipsychotics after TBI that improved with discontinuation of medication (Stanislav et al, 1997)
Antipsychotics: Research

• Typical Antipsychotics
  – Adult studies suggest may be safe if used sparingly
  – None have FDA approval for use in children <10 (varies depending on medication)
  – No studies in children

• Atypical Antipsychotics
  – Adult studies demonstrate efficacy for multiple medications in this class, but caution use due to side effects
  – Pediatric prospective study with oral ziprasidone, no control (Level of evidence = 4) (Scott et al, 2009)
    • 20 consecutive patients (age 9 months to 17 years) treated with ziprasidone as sole agent for agitation (in acute setting 3-8 days of treatment)
    • Showed reduction in agitation symptoms
    • Increase in symptoms of sedation
Antipsychotics: Take Home Points

• Though atypicals may be safer, likely all antipsychotic medications have detrimental effects with long term use (NMS, Tardive Dyskinesia, etc)

• May be appropriate to use atypical antipsychotics for short-term limited use in agitation after TBI during the acute period when sedation is not a barrier
Summary: Approach to Pharmacologic Intervention for Agitation after Pediatric TBI

• Little evidence to guide us so:
  – Identify and treat contributors to agitation when possible
  – Treatment should include non-pharmacologic environmental and behavioral management
  – Monitor response to intervention
    • Identify symptom of concern and monitor frequency
    • Agitated Behavior Scale (may be most appropriate for adult patients)
  – Avoid Polypharmacy
    • if something doesn’t work, stop it before adding more (based on adult research, anticipate effect within 2-6 weeks of medication initiation)
  – Monitor closely for side effects
References

Propranolol: Research

Table 2. Brookes 1992b (average number of agitated episodes)

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>Active drug</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4</td>
<td>3.3</td>
<td>0</td>
</tr>
<tr>
<td>Week 1</td>
<td>8</td>
<td>9.5</td>
<td>60</td>
</tr>
<tr>
<td>Week 2</td>
<td>9.3</td>
<td>8</td>
<td>180</td>
</tr>
<tr>
<td>Week 3</td>
<td>7.5</td>
<td>4</td>
<td>300</td>
</tr>
<tr>
<td>Week 4</td>
<td>6.7</td>
<td>4.5</td>
<td>420</td>
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<tr>
<td>Week 5</td>
<td>3.5</td>
<td>1.8</td>
<td>420</td>
</tr>
<tr>
<td>Week 6</td>
<td>4</td>
<td>2.5</td>
<td>120</td>
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<tr>
<td>Week 7</td>
<td>2.3</td>
<td>2.4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Active drug</td>
<td>Dose (mg)</td>
</tr>
<tr>
<td>--------</td>
<td>---------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.45</td>
<td>1.35</td>
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<td>3.55</td>
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<tr>
<td>Week 2</td>
<td>4.75</td>
<td>3.55</td>
<td>180</td>
</tr>
<tr>
<td>Week 3</td>
<td>4.5</td>
<td>3</td>
<td>300</td>
</tr>
<tr>
<td>Week 4</td>
<td>4.5</td>
<td>2.3</td>
<td>420</td>
</tr>
<tr>
<td>Week 5</td>
<td>3.50</td>
<td>0.63</td>
<td>420</td>
</tr>
<tr>
<td>Week 6</td>
<td>4</td>
<td>1.2</td>
<td>120</td>
</tr>
<tr>
<td>Week 7</td>
<td>1.25</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Anticonvulsants adverse effects on cognitive function

• Topiramate
  – Studies in epilepsy demonstrate:
    • Behavior problems (15%), decreased alertness (15%), drowsiness (5%), disorientation (5%), unsteadiness (5%)
    • Language impairment
      – Word-finding difficulty
      – Decreased expressive output
      – Decreased verbal fluency and working memory
Table 2. Catecholaminergic agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Approval in Pediatric Patients</th>
<th>FDA Pediatric Dosages</th>
<th>Mechanism of Action</th>
<th>FDA Indications</th>
<th>TBI Usage</th>
<th>Serious Reactions</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>No</td>
<td>N/A</td>
<td>β-Adrenergic receptor blocker</td>
<td>HTN, angina, A-fib, MI, migraine, essential tremor, headache</td>
<td>Agitation</td>
<td>Diabetes, thyrotoxicosis</td>
<td>Angina pectoris</td>
</tr>
</tbody>
</table>

N/A = not applicable; A-fib = atrial fibrillation; HTN = hypertension; MI = myocardial infarction; FDA = Food and Drug Administration; NMDA = N-methyl-D-aspartate; TBI = traumatic brain injury; QD = once a day; BID = twice a day.
Agitation: Definitions

- “Disturbed behavior as a result of overactivity”
- “Episodic dyscontrol”
- “subjective evidence of one or more of the following behaviors: restlessness, derogatory or threatening demands, verbal abusiveness, sexually inappropriate comments or actions, or attempts at physical violence of sufficient severity to disrupt nursing care or therapy.”