Table: FDA Approval Status and Research Evidence Quality - Psychotropic Medications in Children

II. MOOD STABILIZING ANTICONVULSANT AGENTS AND LITHIUM

SECTION CONTRIBUTORS: Robert Kowatch, M.D., Boris Lorberg, M.D., Yana Turkowski, M.D., Julie Zito, Ph.D.

A. LITHIUM

<table>
<thead>
<tr>
<th>Generic Name (Trade Name) and Class</th>
<th>Indicated Age (Yrs) for Mood Stabilization</th>
<th>Labeled Psychiatric Indication for Mood Stabilization (Month/Year if available)</th>
<th>Grade for How Well Medication is Studied for Pediatric Mood Stabilization</th>
<th>Comments/ Pediatric Psychiatric Research References/ Other Indications</th>
<th>Pregnancy Category</th>
</tr>
</thead>
</table>
| Lithium Carbonate (Eskalith, Eskalith-CR, Lithobid), Lithium Citrate Mood stabilizer/ Anti-mania/ Antidepressant | 12+ | Bipolar Disorder - Manic episode  
Bipolar Disorder - Maintenance therapy | A | FDA indication for age 12+ appears to be extrapolated from research among patients older than 18.  
(Findling et al, 2005, 2011, 2013)  
(Geller et al., 1998, 2012)  
(Kowatch, Strawn, et al., 2009)  
(Dickstein et al., 2009)  
(Kafantaris et al., 2003, 2004)  
In TEAM study, 2nd effective of 3 agents for pediatric Bipolar I mania or mixed mood: risperidone>lithium>valproic acid  
(Geller et al., 2012), (Vitiello et al., 2012). | D |

B. MOOD STABILIZING ANTICONVULSANT AGENTS

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<tr>
<th>Generic Name (Trade Name) and Class</th>
<th>Indicated Age (Yrs) for Mood Stabilization</th>
<th>Labeled Psychiatric Indication for Mood Stabilization (Month/Year if available)</th>
<th>Grade for How Well Medication is Studied for Pediatric Mood Stabilization</th>
<th>Comments/ Pediatric Psychiatric Research References/ Other Indications</th>
<th>Pregnancy Category</th>
</tr>
</thead>
</table>
| Carbamazepine (Carbatrol, Epitol, Tegetrol,Tegetrol XR, Equetro) Anticonvulsant/ Anti-mania/ Na Channel Antagonist | 18+ | Bipolar I Disorder - Acute manic and mixed episodes | C | Off-label for pediatric Bipolar Disorder.  
(Ginsberg, 2006)  
(Kowatch et al., 2000)  
FDA-approved 0+ for Epilepsy.  
Black Box Warning for aplastic anemia and agranulocytosis, severe dermatologic reactions. | D |

This table does NOT provide recommendations on which medications to use, nor on their relative efficacy or safety. It is NOT a comprehensive list of the medicines that are currently used in the field of child/adolescent psychiatry.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Off-label</th>
<th>Bipolar I Disorder</th>
<th>A/B/C/D</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Divalproex sodium</strong>&lt;br&gt;(Depakote, Depakote Sprinkles, Depakote ER, Depakote DR), Valproate sodium (Depacon), Valproate/Valproic Acid (Depakene, Stavzor)&lt;br&gt;Anticonvulsant/ Anti-mania/ Antimigraine/ Modulates Voltage-Sensitive Na Channel</td>
<td>Off-label for pediatric Bipolar Disorder.&lt;br&gt;(West et al., 2011)&lt;br&gt;(Pavuluri et al., 2010)&lt;br&gt;(Kowatch et al., 2009)&lt;br&gt;(Wagner, Redden, et al., 2009) – RCT, N=150: negative&lt;br&gt;(Barzman et al., 2006)&lt;br&gt;(DelBello et al., 2006, 2002)&lt;br&gt;(Findling et al, 2005)&lt;br&gt;(Wagner et al., 2002)&lt;br&gt;FDA-approved 10+ for seizures.&lt;br&gt;Black Box Warning for hepatotoxicity, pancreatitis, teratogenic effect.</td>
<td>18+&lt;br&gt;Bipolar I Disorder – Manic episode</td>
<td>A</td>
<td>FDA-approved 10+ for seizures. Black Box Warning for hepatotoxicity, pancreatitis, teratogenic effect. In TEAM study, least effective of 3 agents for pediatric Bipolar I mania or mixed mood: - risperidone- lithium-valproic acid. (Geller et al., 2012), (Vitiello et al., 2012)</td>
</tr>
<tr>
<td>Ethosuximide (Zarontin)&lt;br&gt;Anticonvulsant</td>
<td>Off-label for pediatric and adult Bipolar Disorder.&lt;br&gt;FDA-approved 3+ years for Absence seizure.</td>
<td>None</td>
<td>D</td>
<td>Not assigned by the FDA</td>
</tr>
<tr>
<td>Ethotoin (Peganone)&lt;br&gt;Anticonvulsant</td>
<td>No pediatric or adult psychiatric research available at this time.&lt;br&gt;FDA-approved 1+ years for Complex partial epileptic seizure, Grand mal seizure.</td>
<td>None</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Gabapentin (Neurontin, Gabarone)&lt;br&gt;Anticonvulsant/Anti-neuralgic/ Ca Channel Effects</td>
<td>Off-label for pediatric and adult Bipolar Disorder.&lt;br&gt;(Soutullo et al., 1998, case study)&lt;br&gt;FDA-approved 3+ years for Partial seizure.</td>
<td>None</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine&lt;br&gt;(Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR)&lt;br&gt;Anticonvulsant/ Blocks Na Channels/ Inhibits Release of Glutamate</td>
<td>Off-label for pediatric Bipolar Disorder.&lt;br&gt;(Biederman et al., 2010)&lt;br&gt;(Pavuluri et al., 2009)&lt;br&gt;(Chang et al., 2006)&lt;br&gt;Pediatric add-on trial for manic, mixed, or depressed states was completed, results pending.&lt;br&gt;FDA-approved 2+ for seizures. Black Box Warning for life-threatening skin rash.</td>
<td>18+&lt;br&gt;Bipolar I Disorder</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam&lt;br&gt;(Keppra, Keppra XR)&lt;br&gt;Anticonvulsant</td>
<td>No pediatric or adult Bipolar indication. Should be further studied for potential use in the treatment of Bipolar Disorders (Kaufman, 2004).&lt;br&gt;FDA-approved 1+ month for</td>
<td>None</td>
<td>D</td>
<td></td>
</tr>
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<tr>
<th>Medication</th>
<th>Indication</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mephobarbital (Mebaral) Anticonvulsant</td>
<td>None</td>
<td>None</td>
<td>D</td>
<td>No pediatric or adult Bipolar indication or psychiatric research. FDA-approved for any age for seizures.</td>
</tr>
<tr>
<td>Methsuximide (Celontin Kapseals) Anticonvulsant</td>
<td>None</td>
<td>None</td>
<td>D</td>
<td>No pediatric or adult Bipolar indication or psychiatric research. FDA-approved for any age for seizures. Not assigned by the FDA</td>
</tr>
<tr>
<td>Oxcarbazepine (Trileptal) Anticonvulsant/Antimania/Na Channel Antagonist</td>
<td>None</td>
<td>None</td>
<td>B</td>
<td>Off-label for pediatric, adult Bipolar Disorder. (Wagner, Kowatch, et al., 2006) - RCT N=116 trial: negative FDA-approved 2+ for Partial seizure.</td>
</tr>
<tr>
<td>Phenobarbital (Luminal) Anticonvulsant/Hypnotic/Increases GABA Transmission</td>
<td>None</td>
<td>None</td>
<td>D</td>
<td>No pediatric, adult Bipolar indication. FDA-approved for any age for Epilepsy, Sedation.</td>
</tr>
<tr>
<td>Phenytoin (Dilantin, Dilantin Infatabs, Dilantin-125) Anticonvulsant</td>
<td>None</td>
<td>None</td>
<td>D</td>
<td>No pediatric, adult Bipolar indication. Off-label for adult Bipolar Disorder. Should be further studied for potential use in the treatment of Bipolar Disorder. (Mishory, 2000) FDA-approved for any age for seizures</td>
</tr>
<tr>
<td>Primidone (Mysoline) Anticonvulsant</td>
<td>None</td>
<td>None</td>
<td>D</td>
<td>No pediatric, adult Bipolar indication. Should be further studied for potential use in the treatment of Bipolar Disorder (Schaffer, 1999). FDA-approved for any age for Epilepsy</td>
</tr>
<tr>
<td>Tiagabine (Gabitril) Anticonvulsant/GABA Reuptake Inhibitor</td>
<td>None</td>
<td>None</td>
<td>D</td>
<td>No pediatric, adult Bipolar indication. Should be further studied for potential use in the treatment of Bipolar Disorder. (Carta, 2002) FDA-approved 12+ for Partial seizure.</td>
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</tbody>
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