Learning Objectives

1. Briefly review the most current guidelines for the psychopharmacologic management of pediatric bipolar disorder.

2. Critically examine the existing evidence for the efficacy of lithium in the treatment of pediatric bipolar disorder. Does the research justify lithium’s approval by Health Canada and the FDA for the acute and maintenance treatment of pediatric bipolar disorder?

3. Review the side effects and potential adverse effects of lithium with particular attention to the pediatric population.

Outline

- Overview of psychopharmacology for pediatric bipolar disorder (PBD):
  - Summary of evidence for mood stabilizers
  - ‘Current’ Treatment guidelines
- Lithium:
  - History
  - Indications & clinical use
  - Pharmacodynamics & pharmacokinetics
  - Efficacy
  - Adverse effects
  - Contraindications & drug interactions
  - Monitoring
  - Dosing

Treatment Guidelines for PBD (Kowatch et al., 2005)

- 1st-line for mania without psychosis:
  - Monotherapy with any of Li, DVP, CBZ, OLZ, QUE, or RISP
  - However, most recommend starting with Li or DVP, and it is noted that Li has had the most controlled study in youth

Kowatch et al., 2005 (cont.)

- 1st-line for mania with psychosis:
  - Li + atypical antipsychotic OR
  - DVP + atypical antipsychotic OR
  - CBZ + atypical antipsychotic
  - However, it is noted that a higher level of evidence exists for Li + atypical antipsychotic than for either of the anticonvulsants + atypical antipsychotic
Published DBPC Trials for PBD (April 2011)

<table>
<thead>
<tr>
<th>Li</th>
<th>AED</th>
<th>SGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2*</td>
<td>3**</td>
<td>6***</td>
</tr>
</tbody>
</table>

*1 equivocal study in adolescents with substance dependence + BD (I or II) or MDD with ≥1 risk factor for BD (Geller et al., 1998); 1 negative discontinuation study (Keller et al., 2004); NB – 1 negative unpublished study for mania (Kowatch et al., 2007)

**1 negative study of valproate for mania (Wagner et al., 2009); 1 negative study of oxcarbazepine for mania (Wagner et al., 2007); 1 negative prematurely terminated study of topiramate for mania (DelBello et al., 2006); NB – 1 positive unpublished study of valproate for mania (Kowatch et al., 2007)

***1 positive study of olanzapine for mania (Tohen et al., 2007); 1 positive study of risperidone for mania (Haas et al., 2009); 1 positive adjunctive treatment study of quetiapine for mania (DeHert et al., 2002); 1 negative study of quetiapine for bipolar depression (DelBello et al., 2009); 2 positive studies of aripiprazole for mania (Findling et al., 2009); NB – Several positive unpublished trials of SGAs (e.g. ziprasidone, quetiapine) for mania referred to in the literature.

AED=antiepileptic drug; SGA=second-generation antipsychotic

Treatment of mania in PBD: Changing tides of opinion

- Mood stabilizers less effective that SGAs for mania in youth. Youth have greater reduction in manic symptoms from SGAs than adults. (DeHert et al., 2010 – AACAP annual meeting)
- Until further notice…new AACAP Treatment Guidelines not expected until 2017

Duration of Treatment

- AACAP Practice Parameter for children and adolescents with bipolar disorder (2007):
  - A trial of a mood stabilizer should be continued for 6-8 weeks at an adequate dose before adding or substituting another mood stabilizer
  - Current evidence suggests that the regimen needed to stabilize acute mania should be maintained for 12-24 months
  - A gradual taper of the medication may then be considered after a discussion with the patient and family; this discussion should include weighing the risk of symptom recurrence against current or potential adverse effects of the medication
Lithium

History

• “Latterly I have used the bromide of lithium in cases of acute mania, and have more reason to be satisfied with it than any other medicine calculated to diminish the amount of blood in the cerebral vessels, and to calm any nervous excitement that may be present.”

Willam A. Hammond, 1871

History (cont.)

• In 1949, the Australian physician John Cade was using guinea pigs to study the toxicity of uric acid from patients with manic-depressive illness; he noted that the animals became lethargic after injection with Li carbonate
• The same year, he described marked clinical improvement in 10 patients with mania who were administered Li

History (cont.)

• In 1970, the FDA approved the use of Li for the treatment of acute mania
• In 1974, the FDA also approved the use of Li for maintenance therapy in patients with a history of mania
• Over 28,000 articles have been written about Li’s use in medicine, but few studies in pediatric populations have been conducted

History (cont.)

• The clinical observations of Cade were subsequently substantiated in more rigorous clinical trials conducted by Mogens Schou and others
• Consequently, the effectiveness of Li for acute mania and for the prophylactic treatment of manic-depressive disorder became firmly established, and the use of Li for these purposes increased gradually in the late 1960’s

Indications

• Li is approved by HC and the FDA for acute treatment of mania and for maintenance treatment in bipolar disorder down to age 12 years
• Comparison with other medications:
  – AEDs are not approved by HC or the FDA for any psychiatric indication in youth
  – SGAs are not approved by HC for any psychiatric indication in youth, but risperidone, aripiprazole, quetiapine, ziprasidone have been approved by the FDA for manic/mixed episodes in pediatric bipolar disorder (10-17 years) as has olanzapine (13-17 years)
Clinical Uses in Youth

- Bipolar disorder (manic and depressive phases of the illness)
- Severe mood dysregulation (not a DSM IV diagnosis)
- Augmentation of antidepressants in the treatment of depressive disorders
- Conduct disorder & aggression

Pharmacodynamics

- Li’s precise mechanisms of action are uncertain, but it has numerous pharmacologic effects:
  1. Li has chemical similarities to Na, K, Ca, and Mg. Consequently, ion substitution has been implicated to explain Li’s clinical effects, with considerable attention focused on ion pumps and channels, particularly Na-Li counterexchange.
  2. Li interacts with cyclic adenosine monophosphate (cAMP) second messengers, reducing intracellular concentrations of cAMP. These interactions may be involved in Li’s overall stabilizing effect in neurotransmitter function.

Pharmacodynamics (cont.)

3. Li’s inhibitory action on receptor-mediated signal-transduction pathways reduces myo-inositol levels. Since the phosphoinositide (PI) cycle regulates a wide variety of neuronal functions, Li-induced modification of the PI cycle has been proposed as one of the main potential mechanisms for its mood-stabilizing effect.

4. Rat studies have shown that Li can increase the amphetamine-induced release of 5-HT and the concentrations of 5-HIAA (a serotonin metabolite) in the perifornical hypothalamus. This mechanism may be related to Li’s antidepressant effect.

Pharmacokinetics: Absorption

- Li is rapidly absorbed from the GI tract, with \( T_{\text{max}} = 1-3 \) hours (adults)
- With extended-release tablets (Duralith), absorption is delayed, with \( T_{\text{max}} = 4-12 \) hours (adults)
- Food or antacids do not appear to influence absorption
- [N.B. Duralith was discontinued in 2007, but now Lithmax SR is available]

Pharmacokinetics: Distribution

- Li is initially distributed into ECF and is not bound to plasma proteins
- Li is then distributed into brain, thyroid, bone, and most other body tissues
- Compared with adults, children have larger relative volumes of extracellular water and therefore can be expected to have lower weight-adjusted serum concentrations of Li
- Brain-to-serum Li concentrations have been found to be lower in children (0.58±0.24) than in adults (0.92±0.36) (Moore et al., 2002)

Pharmacokinetics: Metabolism

- Li is **NOT** metabolized

- Rather, Li is excreted almost entirely in the urine
ABSTRACT

BACKGROUND: Lithium is a benchmark treatment for bipolar illness in adults. However, there has been relatively little methodologically stringent research regarding the use of lithium in youth suffering from bipolarity.

METHODS: Under the auspices of the Best Pharmaceuticals for Children Act (BPCA), a Written Request (WR) pertaining to the study of lithium in pediatric mania was issued by the United States Food and Drug Administration (FDA) to the National Institute of Child Health and Human Development (NICHD) in 2004. Accordingly, the NICHD issued a Request for Proposals (RFP) soliciting submissions to pursue this research. Subsequently, the NICHD awarded a contract to a group of investigators in order to conduct these studies.

RESULTS: The Collaborative Lithium Trials (CoLT) investigators, the BPCA-Coordinating Center, and the NICHD developed protocols to provide data that (1) establish evidence-based dosing strategies for lithium, (2) characterize the pharmacokinetics and biodisposition of lithium, (3) examine the acute efficacy of lithium in pediatric bipolarity, (4) investigate the long-term effectiveness of lithium treatment, and (5) characterize the short- and long-term safety of lithium. By undertaking two multi-phase trials rather than multiple single-phase studies (as was described in the WR), the feasibility of the research to be undertaken was enhanced while ensuring all the data outlined in the WR would be obtained. The first study consists of: (1) an 8-week open-label, randomized, escalating dose Pharmacokinetic Phase; (2) a 16-week Long-Term Effectiveness Phase; (3) a 28-week double-blind Discontinuation Phase; and (4) an 8-week open-label Restabilization Phase. The second study consists of: (1) an 8-week, double-blind, parallel-group, placebo-controlled Efficacy Phase; (2) an open-label Long-Term Effectiveness lasting either 16 or 24 weeks (depending upon blinded treatment assignment during the Efficacy Phase); (3) a 28-week double-blind Discontinuation Phase; and (4) an 8-week open-label Restabilization Phase. In December of 2006, enrollment into the first of these studies began across seven sites.

CONCLUSION: These innovative studies will not only provide data to inform the labeling of lithium in children and adolescents with bipolar disorder, but will also enhance clinical decision making regarding the use of lithium treatment in pediatric bipolar illness.

First-Dose Pharmacokinetics (PK) of Lithium Carbonate in Children and Adolescents (Findling et al., 2010)

- N=39 subjects aged 7-17 years
- Oral doses of 600 or 900 mg Lithium
- Multiple serum levels —population PK modelling
- Lithium clearance varied significantly between subjects but not based on age, dose, gender or creatinine clearance
- Clearance most correlated to fat free mass

Pharmacokinetics: Elimination

- Serum concentrations of Li decline in a biphasic manner
- In adults, Li has a fast-phase half-life ($T_{1/2α}$) of 0.8-1.2 hrs and a slow phase half-life ($T_{1/2β}$) of 20-27 hrs
- Findling et al. 2010 showed similar results for children and adolescents with a fast-phase half-life ($T_{1/2α}$) of 2.4 hrs and a slow phase half-life ($T_{1/2β}$) of 27 hrs
- This differs from earlier study by Vitiello (1988)

Elimination – cont.

- Effects of sodium balance on Li levels:
  - Na depletion ↑ Li re-absorption, resulting in higher Li levels
  - Conversely, high Na intake ↓ Li re-absorption, resulting in lower Li levels

Efficacy: Pediatric Bipolar Disorder

- The 2 largest uncontrolled studies of Li in adolescents with acute mania reported relatively high response rates after 4 weeks of treatment:
  - Strober et al., 1998: 28/50 (56%)
  - Kafantaris et al., 2003: 63/100 (63%)
- However, both studies permitted the use of adjunctive antipsychotic medication throughout the open treatment period

Li vs. DVP vs. CBZ for PBD

- Kowatch et al., 2000:
  - Randomized, open study comparing Li, DVP, and CBZ for pediatric bipolar disorder
  - 42 outpatient children and adolescents:
    - 20 with bipolar I disorder, 22 with bipolar II disorder
    - Mixed or manic episode
  - Primary outcome measures: YMRS and CGI-I
  - Response rates:
    - Li=38%, DVP=53%, CBZ=38% (p=0.6)
  - Effect sizes (using YMRS change from baseline)
    - Li=1.1, DVP=1.6, CBZ=1.0
Li+DVP for PBD

• Findling et al., 2003 (Study 1 of 3):
  – **Open**, prospective study of Li+DVP in children and adolescents with bipolar I or II disorder and ≥1 manic or hypomanic episode within the prior 3 months
  – Significant improvement was found on all outcome measures
  – Remission rate: 47%

Li+DVP for PBD (Revisited)

• Findling et al., 2006 (Study 3 of 3):
  – **Open**, prospective study of Li+DVP in subjects who previously remitted with Li+DVP but then relapsed on Li or DVP monotherapy (i.e., whichever drug had been stopped was now added back):
  – 90% restabilized with resumption of Li+DVP
  – The remainder required adjunctive antipsychotic treatment to address residual symptoms

Li Maintenance Treatment for PBD

• Findling et al., 2005 (Study 2 of 3):
  – Randomized, double-blind trial of Li vs. DVP maintenance treatment for up to 76 weeks in subjects who were treated initially with Li+DVP and remitted (i.e., either Li or DVP was discontinued)
  – The 2 groups did not differ significantly in:
    • Median time to relapse: Li=114 days, DVP=112 days (p=0.6)
    • Median time to discontinuation from the study for any reason: Li=91 days, DVP=56 days (p=0.7)

Li Discontinuation Study (Naturalistic)

• Strober et al., 1990:
  – 18-month, naturalistic, prospective, follow-up study of 37 adolescents whose bipolar I illness had been stabilized with Li during inpatient hospitalization
  – In the 13 patients who stopped Li shortly after discharge, the relapse rate was nearly 3x higher than in the 24 patients who continued Li prophylaxis without interruption (92% vs. 38%, p=0.001)

DBPC Trials of Li for Pediatric Bipolar Disorder

• Geller et al., 1998:
  – Not all subjects had bipolar disorder, and all had substance dependence
  – **Equivocal** result
• Kafantaris et al., 2004:
  – Discontinuation study
  – **Negative** result
• Kowatch et al., 2007:
  – Presented but not published
  – **Negative** result (for Li, though not for DVP)

Geller et al., 1998

• 6-week DBPC study of Li for 25 outpatient adolescents with:
  – Substance dependence
  – BD-I, BD-II, mania, or MDD with ≥1 risk factor for BD (few, if any, were in an episode of acute mania)
Geller et al., 1998 (cont.)

- Results:
  - Li > PBO with respect to:
    - % of positive urine samples (p=0.03)
    - CGAS as a continuous variable (p=0.04)
    - Response rate, with response defined as CGAS≥65:
      - 46% vs. 8% (p=0.05 using a one-tailed t-test)
      - NNT=3
  - However, there were no significant differences in the mood or substance dependence items on the K-SADS

Kafantaris et al., 2004

- 85 of 100 adolescents with acute mania completed an open trial of Li for ≥4 weeks, and 45 were considered responders
- In a DBPC continuation phase, 40 of the 45 responders were randomized to continue Li vs. switch to PBO for 2 weeks (the parents of the remaining 5 did not consent to this phase)
- Symptom exacerbation rate was similar in the two groups: Li=53%, PBO=62% (p=0.8)

Kowatch et al., 2007 (Presented but not published)

- NIMH-funded DBPC trial in 154 outpatient youth (7-17 years old) who had bipolar I disorder and were experiencing a manic or mixed episode
- Randomized to Li, DVP, or PBO in a 2:2:1 ratio for 8 weeks
- Primary outcome measures:
  - YMRS
  - CGI-Improvement

Kowatch et al., 2007 (cont.)

- Efficacy results (change in YMRS score):
  - DVP > PBO
  - Li = PBO (but trend favouring Li)
  - DVP = Li
- Percentage with >50% ↓ in YMRS score:
  - DVP = 56%
  - Li = 41%
  - PBO = 30%

Efficacy: Pediatric Bipolar Depression

- Patel et al., 2006:
  - Open study of Li for 6 weeks in 27 adolescents with bipolar depression
  - Mean CDRS-R scores significantly ↓ from baseline to endpoint (p<0.001, effect size=1.7)
  - Response rate: 48%
  - Remission rate: 30%
  - Side effects were generally mild to moderate

Efficacy: Severe Mood Dysregulation

- Dickstein et al., 2009:
  - 45 youths (7-17 years old) with severe mood dysregulation (SMD) were tapered off medications and had a 2-week, single-blind PBO run-in
  - After the PBO run-in, 20 youths no longer met criteria for SMD
  - The 25 who continued to meet criteria for SMD were entered into a DBPC trial of Li
  - Among randomized patients, there were no significant between-group (Li vs. PBO) differences in either clinical or MRS (magnetic resonance spectroscopy) outcome measures
Efficacy: Antidepressant Augmentation

- Ryan et al., 1988:
  - Retrospective review of 14 adolescents with MDD who did not respond to a TCA alone and received Li augmentation
  - 6 patients achieved a good response with TCA+Li
- Strober et al., 1992:
  - 3-week open study of Li augmentation in 24 adolescents who remained depressed after 6 weeks on imipramine (IMI)
  - 2 patients responded dramatically and 8 patients showed partial improvement with IMI+Li

Efficacy: CD & Aggression

- 3 positive DBPC trials of Li for CD & aggression:
  - Campbell et al., 1984:
    - Inpatient children, N=61, 2 weeks
    - Li = haloperidol (HAL) > PBO
    - HAL was associated with more adverse effects than Li
  - Campbell et al., 1995:
    - Inpatient children, N=50, 6 weeks
    - Response rates: Li (68%) > PBO (40%)
  - Malone et al., 2000:
    - Inpatient children & adolescents, N=40, 4 weeks
    - Response rates: Li (70-80%) > PBO (20-30%)

Efficacy: CD & Aggression (cont.)

- 3 negative DBPC studies of Li for CD & aggression:
  - Klein et al., 1991 (presented but not published):
    - Outpatient children and adolescents
    - No clear description of an aggression criterion for entering treatment
  - Silva et al., 1991 (presented but not published):
    - Outpatient children
    - The only long-term study
    - Very small sample (n=11)
  - Rifkin et al., 1997:
    - Inpatient adolescents
    - Treatment period was only 2 weeks

Lithium for CD & Aggression: Pragmatic considerations

Particularly in outpatients...

- Safety
- Compliance
- Monitoring

Adverse Effects

<table>
<thead>
<tr>
<th>Table 31.17-3 Adverse Effects of Lithium</th>
</tr>
</thead>
</table>

**Neurological**
- Benign, nontoxic: dysphoria, lack of spontaneity, slowed reaction time, memory difficulties
- Tremor: postural, occasional extrapyramidal
- Dizziness, course tremor, dysarthria, akathisia, neuromuscular irritability, seizures, coma, death
- Acute hyper trophy, hypothyroidism, myxoedema, cretinism, neuromuscular irritability, postural tremor, coma, death

**Endocrine**
- Thyroid: goiter, hypothyroidism, exophthalmos, hyperthyroidism (rare)
- Parathyroid: hyperparathyroidism, adenoma

**Cardiovascular**
- Seizure, T-wave changes, sinus node dysfunction
- Renal: concentrating defect, morphological changes, polyuria (nephrogenic diabetes insipidus), reduced glomerular filtration rate, nephrotic syndrome, renal tubular acidosis

**Dermatological**
- Acne, hair loss, porosis, rash

**Gastrointestinal**
- Diarrhea, nausea, vomiting, diarrhea

**Miscellaneous**
- Altered carbohydrate metabolism, weight gain, fluid retention

Reference: Kaplan & Sadock’s Comprehensive Textbook of Psychiatry, 8th edition (online)

Adverse Effects (cont.)

- Fewer than 20% of adult patients have no adverse effects from Li
- However, only about 30% of adult patients have more than minor adverse effects from Li (although this may be an underestimate)
- The adverse effect profile of Li is generally the same across age groups, but younger children have been found to have more side effects than older children, even controlling for weight, serum Li level, optimal dose, and duration of optimal dose (Campbell et al., 1991)
Adverse Effects (cont.)

- In children, the most common side effects of Li are enuresis, fatigue, ataxia, vomiting, headache, and stomachache (Silva et al., 1992)
- Certain adverse effects may be more distressing (e.g., acne, weight gain) or impairing (e.g., cognitive dulling) for children and adolescents than for adults
- Studies of pediatric patients on chronic Li therapy have not been conducted

Contraindications

- Significant renal disease
- Significant cardiovascular disease
- Severe debilitation, dehydration, or sodium depletion
- Caution in patients taking diuretics or other drugs that interact with Li
- Pregnancy (relative contraindication)

Pre-treatment Work-up

- Medical history & physical exam
- Labs:
  - BUN & creatinine
  - Electrolytes, including Ca and Ph
  - Fasting blood glucose
  - TFTs
  - CBC (Li can cause a benign ↑ in WBC)
  - Urinalysis with specific gravity
  - Pregnancy test for menstruating females
  - LFTs are NOT necessary
- EKG

Monitoring

- Li levels:
  - Note - single dose profiles in children show marked variability (Findling et al., 2010)
  - ≥ 4 days after initiation or dose change (steady state)
  - 12 hrs after last dose, usually in the morning
  - q1-2 weeks until stable, then q3-6 months (some recommend q1-2 months)
  - Target: 0.6-1.2 mEq/L
    - >1.5 mEq/L (or lower in some children): often associated with toxicity
    - >2.0 mEq/L: the risk of serious toxic effects escalates substantially
    - >3.5 mEq/L: associated with death and will likely require dialysis

Table 31.17-4 Drug Interactions with Lithium

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>Case reports of encephalopathy, worsening of extrapyramidal adverse effects, and neuroleptic malignant syndrome. Inconsistent reports of altered red blood cell and plasma concentrations of lithium, antipsychotic drug, or both.</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Occasional reports of a serotonin-like syndrome with potent serotonin reuptake inhibitors.</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>No significant pharmacokinetic interactions. Occasional reports of neurotoxicity; combinations helpful for treatment resistance.</td>
</tr>
<tr>
<td>Nonsteroidal antiinflammatory drugs</td>
<td>May reduce renal lithium clearance and increase serum concentration. Toxicity reported (exceptions are possibly aspirin and sulindac [Clinoril]).</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Well-documented reduced renal lithium clearance and increased serum concentration. Toxicity reported.</td>
</tr>
<tr>
<td>Potassium-sparing loop diuretics</td>
<td>Limited data, may increase lithium concentration. Occasional reports of increased lithium concentration and decreased lithium clearance.</td>
</tr>
<tr>
<td>Calcium channel inhibitors</td>
<td>Case reports of neurotoxicity; no consistent pharmacokinetic interactions.</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Successes: Reports of prolonged neuromuscular blockade.</td>
</tr>
</tbody>
</table>

Reference: Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 8th edition (online)
Monitoring (cont.)

- Li level, BUN & creatinine, and TFTs:
  - q3 months for the 1st year, then q3-6 months
- Electrolytes, including Ca and Ph:
  - After 2-6 weeks, then at least yearly
- CBC with differential:
  - After ≥6 weeks to determine new baseline WBC
  - Expected leukocytosis occurs after 4-6 weeks of Li, with neutrophils most ↑
- EKG:
  - Yearly, with dose ↑, and as clinically indicated (e.g., ↑ Li level, signs or symptoms of toxicity)

Approaches to Dosing

- Two main approaches:
  - Weight-based schedule (Weller et al., 1986)
  - Single-dose, kinetics-based method (Geller & Fetner, 1989)
- Both approaches result in similar dosage estimates when applied to children 4-6 years old (Hagino et al., 1998)
- Findling et al. 2010 recommend careful selection of initial dosages based on body weight

Weight-Based Approach

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dosage, Day 1–2</th>
<th>Dosage, Day 3–7</th>
<th>Blood Level, Day 7 (Morning)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 kg</td>
<td>150 mg qhs</td>
<td>150 mg qAM, 300 mg qhs</td>
<td>Adjust dose to 0.8–1.0 mEq/L</td>
</tr>
<tr>
<td>25–40 kg</td>
<td>150 mg b.i.d.</td>
<td>300 mg b.i.d.</td>
<td>Adjust dose to 0.8–1.0 mEq/L</td>
</tr>
<tr>
<td>40–50 kg</td>
<td>150 mg qAM, 300 mg qhs</td>
<td>300 mg qAM, 450 mg qhs</td>
<td>Adjust dose to 0.8–1.0 mEq/L</td>
</tr>
<tr>
<td>&gt;50 kg</td>
<td>300 mg b.i.d.</td>
<td>450 mg b.i.d.</td>
<td>Adjust dose to 0.8–1.0 mEq/L</td>
</tr>
</tbody>
</table>

Dosing Frequency

- Regular Li carbonate or citrate:
  - Start with BID-TID, then may consider reducing to QD-BID
- Lithmax SR (extended-release Li carbonate):
  - Start with BID, then may consider reducing to QD
- With QD dosing:
  - 12-hour Li levels may be 10-30% higher compared with divided dosing
  - Consequently, the total daily dose may need to be reduced by about the same percentage

Dosing Comments

- Taking Li with meals, dividing the dosage, or using extended-release tablets (Lithmax SR) may reduce gastrointestinal and other side effects
- Note that serum Li levels were found to be significantly lower with Li citrate than with Li carbonate (Tyrer et al., 1982)
<table>
<thead>
<tr>
<th></th>
<th>Bipolar I Disorder, Manic or Mixed, Without Psychosis</th>
<th>Bipolar I Disorder, Manic or Mixed, With Psychosis</th>
<th>Bipolar Depressive Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>A &amp; B</td>
<td>A &amp; B</td>
<td>B &amp; C</td>
</tr>
<tr>
<td>Divalproex</td>
<td>B &amp; C</td>
<td>B &amp; C</td>
<td>C</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>B</td>
<td>B</td>
<td>ND</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>D</td>
<td>D</td>
<td>ND</td>
</tr>
<tr>
<td>Topiramate</td>
<td>C</td>
<td>C</td>
<td>ND</td>
</tr>
<tr>
<td>Clozapine</td>
<td>C</td>
<td>C</td>
<td>ND</td>
</tr>
<tr>
<td>Risperidone</td>
<td>B &amp; C</td>
<td>B &amp; C</td>
<td>ND</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>B &amp; C</td>
<td>B &amp; C</td>
<td>B</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>B &amp; C</td>
<td>B &amp; C</td>
<td>B</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>B &amp; C</td>
<td>B &amp; C</td>
<td>ND</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>B &amp; C</td>
<td>B</td>
<td>ND</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>NA</td>
<td>NA</td>
<td>C&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bupropion</td>
<td>NA</td>
<td>NA</td>
<td>D</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>C</td>
<td>C</td>
<td>B &amp; D</td>
</tr>
</tbody>
</table>

*Note: Level A data consist of child/adolescent placebo-controlled, randomized clinical trials. Level B data consist of adult randomized clinical trial. Level C data consist of open child/adolescent trials and retrospective analysis. Level D data consist of child/adolescent case reports or the panel consensus as to recommend current clinical practices. ND = no data; NA = not applicable.

<sup>a</sup> May be mood destabilizing.
Bipolar I Disorder, Manic or Mixed, without Psychosis

Stage 1
Monotherapy with Mood Stabilizer or Antipsychotic (Li, VAL, CBZ, OLZ, QUE, RISP)

Stage 1A
Partial Response

Stage 2
Total Nonresponse/Not Tolerated

Stage 2A
No Response

Stage 3
Switch Monotherapy Agent (Li, VAL, CBZ, OLZ, QUE, RISP) (drug class not tried in Stage 1)

Stage 3A
Partial Response

Stage 3B
No Response or Partial Response

Stage 4
Monotherapy (Li, VAL, CBZ, OLZ, QUE, RISP) (drug class not tried in Stages 1 and 2)

Stage 4A
Combination Treatment
- Li + VAL
- Li + OLB
- Li + QUE
- Li + RISP
- VAL + OLB
- VAL + QUE
- VAL + RISP
- CBZ + OLB
- CBZ + QUE
- CBZ + RISP

Stage 4B
Combination 2 Mood Stabilizer + Antipsychotic
- Li + VAL + OLZ
- Li + VAL + QUE
- Li + VAL + RISP
- Li + CBZ + OLZ
- Li + CBZ + QUE
- Li + CBZ + RISP

Stage 5
Alternate Therapy OXC, ZIP, ARI

Fig. 1 Algorithm 1: Bipolar I disorder, manic or mixed, acute, without psychosis. Algorithm 2: Bipolar I disorder, manic or mixed, acute, with psychosis.
Li = Lithium; VAL = valproate; CBZ = carbamazepine; OLZ = olanzapine; RISP = risperidone; QUE = quetiapine; RISP = risperidone; OXC = oxcarbazepine; ARI = aripiprazole; ECT = electroconvulsive therapy.
Bipolar I Disorder, Manic or Mixed, with Psychosis

Stage 1
Mood Stabilizer + Atypical
(e.g., Li + Atypical or VAL + Atypical or CBZ + Atypical)

Total Nonresponse/Not Tolerated

Stage 1A
Augmentation
Li + VAL + Atypical
Li + CBZ + Atypical

Stage 2
Mood Stabilizer + Atypical
Li + Atypical or VAL + Atypical or CBZ + Atypical
(Combination not tried in Stage 1)

Partial Response

Stage 2A
Augmentation
Li + VAL + Atypical
Li + CBZ + Atypical

Stage 3
Alternate Mood Stabilizer + Atypical
Li + Alternate Atypical or VAL + Alternate Atypical or CBZ + Alternate Atypical

No Response

Stage 3A
Li + VAL + Alternate Atypical
Li + CBZ + Alternate Atypical

Stage 4
Combination 2 Mood Stabilizers + Atypical
Li + VAL + Atypical or Li + CBZ + Atypical

No Response

Stage 5
Alternate Monotherapy + Atypical
(UXG, ZIPL, RNI)

Stage 6
Stage 6A
ECT (Adolescents)

Stage 6B
Clozapine

Kowatch et al., 2005
The Collaborative Lithium Trials (CoLT): specific aims, methods, and implementation

Robert L Findling*1, Jean A Frazier2, Vivian Kafantaris3, Robert Kowatch4, Jon McClellan5, Mani Pavuluri6, Linmarie Sikich7, Stefanie Hlastala5, Stephen R Hooper7,8, Christine A Demeter1, Denise Bedoya1, Bernard Brownstein9 and Perdita Taylor-Zapata10

Published: 12 August 2008

ABSTRACT

BACKGROUND: Lithium is a benchmark treatment for bipolar illness in adults. However, there has been relatively little methodologically stringent research regarding the use of lithium in youth suffering from bipolarity. Methods: Under the auspices of the Best Pharmaceuticals for Children Act (BPCA), a Written Request (WR) pertaining to the study of lithium in pediatric mania was issued by the United States Food and Drug Administration (FDA) to the National Institute of Child Health and Human Development (NICHD) in 2004. Accordingly, the NICHD issued a Request for Proposals (RFP) soliciting submissions to pursue this research. Subsequently, the NICHD awarded a contract to a group of investigators in order to conduct these studies.

RESULTS: The Collaborative Lithium Trials (CoLT) investigators, the BPCA-Coordinating Center, and the NICHD developed protocols to provide data that will: (1) establish evidence-based dosing strategies for lithium; (2) characterize the pharmacokinetics and biodisposition of lithium; (3) examine the acute efficacy of lithium in pediatric bipolarity; (4) investigate the long-term effectiveness of lithium treatment; and (5) characterize the short- and long-term safety of lithium. By undertaking two multi-phase trials rather than multiple single-phase studies (as was described in the WR), the feasibility of the research to be undertaken was enhanced while ensuring all the data outlined in the WR would be obtained. The first study consists of: (1) an 8-week open-label, randomized, escalating dose Pharmacokinetic Phase; (2) a 16-week Long-Term Effectiveness Phase; (3) a 28-week double-blind Discontinuation Phase; and (4) an 8-week open-label Restabilization Phase. The second study consists of: (1) an 8-week, double-blind, parallel-group, placebo-controlled Efficacy Phase; (2) an open-label Long-Term Effectiveness lasting either 16 or 24 weeks (depending upon blinded treatment assignment during the Efficacy Phase); (3) a 28-week double-blind Discontinuation Phase; and (4) an 8-week open-label Restabilization Phase. In December of 2006, enrollment into the first of these studies began across seven sites.

CONCLUSION: These innovative studies will not only provide data to inform the labeling of lithium in children and adolescents with bipolar disorder, but will also enhance clinical decision-making regarding the use of lithium treatment in pediatric bipolar illness.

©Daniel Gorman, Amy Cheung, Kate Cochrane-Brink, John Langley
Adverse Effects

Table 31.17-3 Adverse Effects of Lithium

**Neurological**
- Benign, nontoxic: dysphoria, lack of spontaneity, slowed reaction time, memory difficulties
- Tremor: postural, occasional extrapyramidal
- Toxic: course tremor, dysarthria, ataxia, neuromuscular irritability, seizures, coma, death
- Miscellaneous: peripheral neuropathy, benign intracranial hypertension, myasthenia gravis–like syndrome, altered creativity, lowered seizure threshold

**Endocrine**
- Thyroid: goiter, hypothyroidism, exophthalmos, hyperthyroidism (rare)
- Parathyroid: hyperparathyroidism, adenoma

**Cardiovascular**
- Benign T-wave changes, sinus node dysfunction

**Renal**
- Concentrating defect, morphological changes, polyuria (nephrogenic diabetes insipidus), reduced glomerular filtration rate, nephrotic syndrome, renal tubular acidosis

**Dermatological**
- Acne, hair loss, psoriasis, rash

**Gastrointestinal**
- Appetite loss, nausea, vomiting, diarrhea

**Miscellaneous**
- Altered carbohydrate metabolism, weight gain, fluid retention

Reference: Kaplan & Sadock’s Comprehensive Textbook of Psychiatry, 8th edition (online)
### Table 31.17-4 Drug Interactions with Lithium

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>Case reports of encephalopathy, worsening of extrapyramidal adverse effects, and neuroleptic malignant syndrome. Inconsistent reports of altered red blood cell and plasma concentrations of lithium, antipsychotic drug, or both.</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Occasional reports of a serotonin-like syndrome with potent serotonin reuptake inhibitors.</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>No significant pharmacokinetic interactions. Occasional reports of neurotoxicity; combinations helpful for treatment resistance.</td>
</tr>
<tr>
<td>Nonsteroidal antiinflammatory drugs</td>
<td>May reduce renal lithium clearance and increase serum concentration. Toxicity reported (exceptions are possibly aspirin and sulindac [Clinoril]).</td>
</tr>
<tr>
<td>Diuretics</td>
<td>May reduce renal lithium clearance and increase serum concentration. Toxicity reported.</td>
</tr>
<tr>
<td>Thiazides</td>
<td>Well-documented reduced renal lithium clearance and increased serum concentration. Toxicity reported.</td>
</tr>
<tr>
<td>Potassium-sparing Loop</td>
<td>Limited data, may increase lithium concentration. Lithium clearance unchanged (some case reports of increased lithium concentration).</td>
</tr>
<tr>
<td>Osmotic (mannitol, urea)</td>
<td>Increase renal lithium clearance and decrease lithium concentration.</td>
</tr>
<tr>
<td>Xanthine (aminophylline, caffeine, theophylline)</td>
<td>Increase renal lithium clearance and decrease lithium concentration.</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors (acetazolamide)</td>
<td>Increase renal lithium clearance.</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Reports of reduced lithium clearance; increased concentrations and toxicity.</td>
</tr>
<tr>
<td>Angiotensin II receptor type–1 antagonists</td>
<td>Reports of increased lithium concentrations and toxicity.</td>
</tr>
<tr>
<td>Calcium channel inhibitors</td>
<td>Case reports of neurotoxicity; no consistent pharmacokinetic interactions.</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Reports of prolonged neuromuscular blockade.</td>
</tr>
<tr>
<td>Succinylcholine, pancuronium</td>
<td>Increased lithium concentration.</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Few reports of neurotoxicity.</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Increased renal lithium clearance.</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>Additive antithyroid effects.</td>
</tr>
<tr>
<td>Iodides</td>
<td>Used for lithium tremor. Possible slight increase in lithium concentration.</td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
</tr>
</tbody>
</table>

Reference: Kaplan & Sadock’s Comprehensive Textbook of Psychiatry, 8th edition (online)