Pharmacodynamics of Lithium

Jose de Leon, MD

(04-24-16)

Learning Objectives

After completing this presentation, the participant should be able to:

1) Appreciate the relevance of lithium efficacy, particularly in bipolar disorder, although we have limited understanding of its pharmacodynamics.
2) Summarize frequent lithium adverse drug reactions including a) cognitive, b) gastro-intestinal, and c) weight increases.
3) Remember the need to monitor renal and thyroid function and serum calcium levels and that lithium has been associated with potential for kidney damage.
4) Recall that, besides lithium intoxication, other rare adverse drug reactions associated with potential lethality include the serotonin syndrome and arrhythmias.

Warning

This is a very long presentation (>200 slides):

1) You may need to read it more than once until you have become familiar with key aspects.
2) More importantly, if you have little experience with lithium you need to review it before starting a patient on lithium.
3) The "Do Not Forget" Section tries to summarize things that you must not forget about lithium.

Abbreviations

- ADH: antidiuretic hormone
- ADR: adverse drug reaction
- AED: antiepileptic drugs (or anticonvulsants)
- BDNF: brain-derived neurotrophic factor
- BMI: body mass index
- DDI: drug-drug interaction
- EEG: electroencephalogram
- EPA: Environmental Protection Agency
- EPS: extrapyramidal symptoms
- FDA: Food & Drug Administration (US federal agency that approves drugs)
- GFR: glomerular filtration rate
- GI: gastro-intestinal
- GSK-3: glycogen synthase kinase-3
- HPA: hypothalamic–pituitary–adrenocortical
- ID: intellectual disability
- NMS: neuroleptic malignant syndrome
- PKC: protein kinase C
- PTH: parathyroid hormone
- TDM: therapeutic drug monitoring
- TSH: thyroid stimulating hormone

Statistical Abbreviations

- CI: confidence interval
- NNH: number needed to harm
- NNT: number needed to treat
- HR: hazard ratio
- RR: relative risk
- RCT: randomized clinical trial
- SMD: standardized mean difference
- WMD: weighted mean difference

The presentation “Introduction to Statistical Concepts Needed for Clinical Pharmacology” explains how to interpret these statistical concepts.

Lecture Content

1. Pharmacodynamics of Lithium Efficacy

2. Pharmacodynamics of Lithium Safety

3. Do Not Forget Section

Lecture Content

1. Pharmacodynamics of Lithium Efficacy

- 1.1. Anti-Manic Efficacy
- 1.2. Efficacy for Maintenance Treatment in Bipolar Disorder
- 1.3. Anti-Depressive Efficacy
- 1.4. Anti-Suicidal Efficacy
- 1.5. Possible Efficacy to Control Aggressive Behavior in ID
- 1.6. Possible Efficacy in Schizoaffective Disorder
- 1.7. Possible Neuroprotection
- 1.8. Comments on Efficacy and Pharmacokinetics
- 1.9. Comments on Efficacy and Pharmacodynamic DDIs

2. Pharmacodynamics of Lithium Safety

- 2.0. Comments on Pharmacodynamics and Safety
- 2.1. Brain
- 2.2. Mixed (Brain and Peripheral Components)
- 2.3. Periphery
- 2.4. Comments on Safety and Pharmacokinetics
- 2.5. Comments on Safety and Pharmacodynamic DDIs
- 2.6. Teratogenicity

3. Do Not Forget Section

1. Pharmacodynamics of Lithium Efficacy

1. Pharmacodynamics of Lithium Efficacy

1.1. Anti-Manic Efficacy
1.2. Efficacy for Maintenance Treatment in Bipolar Disorder
1.3. Anti-Depressive Efficacy
1.4. Anti-Suicidal Efficacy
1.5. Possible Efficacy in Controlling Aggressive Behavior in ID
1.6. Possible Efficacy in Schizoaffective Disorder
1.7. Possible Neuroprotection
1.8. Comment on Pharmacokinetics
1.9. Comment on Pharmacodynamic DDIs

1.1. Anti-Manic Efficacy

1.1. Anti-Manic Efficacy

1.1.1. Pharmacodynamics

1.1.2. Meta-Analyses

1.1.1. Anti-Manic Efficacy: Pharmacodynamics

1.1.1. Anti-Manic Efficacy: Pharmacodynamics

- No theory in the literature:
  - unifies anti-manic agent actions and
  - is widely accepted.

  In summary, the pharmacodynamic mechanisms which may explain the action of anti-manic agents are not well understood.
- Two main types of anti-manic agents:
  - antipsychotic drugs: presumably acting by blocking D_2 receptors
  - drugs with complex mechanisms: lithium and two AEDs:
    - carbamazepine
    - valproate

1.1.1. Anti-Manic Efficacy: Pharmacodynamics

- Animal models and in vitro models proposed:
  - ↑ activity of PKC family in mania.
- Lithium and valproate may inhibit PKC activity.
- Tamoxifen:
  - PKC inhibitor
  - A mania RCT: tamoxifen was better than placebo http://www.ncbi.nlm.nih.gov/pubmed/18316672
  - Other RCTs supported some anti-manic effect for tamoxifen.

http://www.ncbi.nlm.nih.gov/pubmed/24441937

1.1.2. Anti-Manic Efficacy: Meta-Analyses

1.1.2. Anti-Manic Efficacy: Meta-Analyses

1.1.2.1. Lithium Monotherapy in Mania
1.1.2.2. Lithium Combinations in Mania

1.1.2.1. Meta-Analyses: Lithium Monotherapy in Mania

1.1.2.1. Meta-Analyses: Lithium Monotherapy in Mania

- Cipriani et al. 2011: http://www.ncbi.nlm.nih.gov/pubmed/21851976
  Meta-analysis of monotherapies

	SMDs (95% CI) (drug versus placebo)
lithium:	-0.37 (-0.50 to -0.25)
Other drugs (SMDs in order from best to worst)	
haloperidol:	-0.56 (-0.68 to -0.43)
risperidone:	-0.50 (-0.63 to -0.38)
olanzapine:	-0.43 (-0.54 to -0.32)
quetiapine:	-0.37 (-0.51 to -0.23)
aripiprazole:	-0.37 (-0.51 to -0.23)
carbamazepine:	-0.36 (-0.60 to -0.11)
valproate:	-0.20 (-0.37 to -0.04)
asenapine:	-0.30 (-0.53 to -0.07)
ziprasiodone:	-0.19 (-0.37 to -0.03)

1.1.2.1. Meta-Analyses: Lithium Monotherapy in Mania

- Yildiz et al. 2015: http://www.ncbi.nlm.nih.gov/pubmed/25036226
  Network meta-analysis of monotherapies[1]

	SMDs[2] (95% CI) (drug versus placebo)
lithium:	0.45 (0.30 to 0.61)
Other drugs (SMDs in order from best to worst)	
risperidone:	0.65 (0.44 to 0.85)
haloperidol:	0.54 (0.38 to 0.70)
olanzapine:	0.48 (0.34 to 0.62)
cariprazine:	0.47 (0.22 to 0.73)
carbamazepine:	0.44 (0.15 to 0.71)
paliperidone:	0.37 (0.08 to 0.66)
aripiprazole:	0.37 (0.20 to 0.55)
asenapine:	0.36 (0.08 to 0.63)
quetiapine:	0.35 (0.14 to 0.56)
ziprasidone:	0.33 (0.08 to 0.59)
valproate:	0.32 (0.15 to 0.50)

[1]Only anti-manic agents significantly superior to placebo are included
[2]Reduction of mania symptoms

1.1.2.1. Lithium Monotherapy in Mania

- Both meta-analyses have similar results
  - Cipriani et al. 2011: http://www.ncbi.nlm.nih.gov/pubmed/21851976
  - Yildiz et al. 2015: http://www.ncbi.nlm.nih.gov/pubmed/25036226

Lithium is intermediate between the best antipsychotics and worst antipsychotics, and similar to carbamazepine and valproate.

- Yildiz et al. 2015: a comparison per drug class vs. placebo:

	SMD (CI)
First-generation antipsychotic (only 1: haloperidol)	0.54 (0.39 to 0.69)
Second-generation antipsychotics	0.44 (0.36 to 0.51)
Mood stabilizers	0.39 (0.28 to 0.49)

- Curran & Ravindran, 2014: http://www.ncbi.nlm.nih.gov/pubmed/25130062
  - lithium's slower onset of action: usually 6-10 days
  - risperidone and olanzapine: usually 2-3 days

1.1.2.2. Meta-Analyses: Lithium in Combination in Mania

1.1.2.2. Meta-Analyses: Lithium in Combination in Mania

- Ogawa et al. 2014: http://www.ncbi.nlm.nih.gov/pubmed/25160685

  Meta-analysis of combinations of antipsychotics and mood stabilizers (including lithium):

  Regarding combinations in patients:

  □ never previously treated: no robust evidence exists that combinations are better than monotherapy

  □ when monotherapy is not successful:

  The combination of mood stabilizer and antipsychotic:

  - is more efficacious and more burdensome,
  - but overall is acceptable, compared to the continuation of monotherapy.

1.2. Efficacy for Maintenance Treatment in Bipolar Disorder

1.2. Efficacy for Maintenance Treatment in Bipolar Disorder

- The definition of a mood stabilizer:
  - is controversial and
  - varies by author.

- To avoid controversy, this section's title is:
  - "Efficacy for Maintenance Treatment in Bipolar Disorder".

  Many authors probably would agree that this title refers to mood stabilizer efficacy.

1.2. Efficacy for Maintenance Treatment in Bipolar Disorder

1.2.1. Pharmacodynamics

1.2.2. Clinical Data

1.2.1. Efficacy for Maintenance Treatment in Bipolar Disorder: Pharmacodynamics

1.2.1. Maintenance Efficacy: Pharmacodynamics

- No theory in the literature:
  - unifies mood-stabilizing actions and
  - is widely accepted.
- Lithium:
  - is usually considered the mood stabilizer of excellence.
  - appears to have 2 major actions:
    - suppressing inositol signaling through depletion of intracellular (noun), and
    - inhibiting GSK-3, a multifunctional protein kinase.

http://www.ncbi.nlm.nih.gov/pubmed/12826261

1.2.1. Maintenance Efficacy: Pharmacodynamics

- Some authors propose that the inositol depletion hypothesis applies well to
  - carbamazepine and
  - valproate http://www.ncbi.nlm.nih.gov/pubmed/12826261
- Rapaport et al. 2009: http://www.ncbi.nlm.nih.gov/pubmed/19555719
  - are critical of the inositol hypothesis
  - propose an "arachidonic acid cascade" hypothesis chronic administration of
    - lithium,
    - carbamazepine,
    - sodium valproate, or
    - lamotrigine

  to rats:
    - downregulated arachidonic acid turnover
    - ↓ formation of prostaglandin E_2, and/or
    - ↓ expression of cascade enzymes

1.2.1. Maintenance Efficacy: Pharmacodynamics

- Malhi et al. 2013: http://www.ncbi.nlm.nih.gov/pubmed/23371914

  Lithium:

  - at a neuronal level:
    - ↓ excitatory neurotransmission: dopamine and glutamate
    - but ↑ inhibitory neurotransmission: GABA

  However, these broad effects are underpinned by complex neurotransmitter systems that strive to achieve homeostasis by way of compensatory changes.

  For example,

  - at an intracellular and molecular level,

    lithium targets second-messenger systems, that further modulate neurotransmission.

    The effects on
    - the adenyl cyclase,
    - phospho-inositide pathways, and
    - protein kinase C,

    may dampen excessive excitatory neurotransmission.

1.2.2. Efficacy for Maintenance Treatment in Bipolar Disorder: Clinical Data

1.2.2. Maintenance Efficacy: Clinical Data

- Lithium is approved by the FDA for:
  - maintenance and
  - mania.

  It is not approved for bipolar depression.

- The next slides review the following:
  - Meta-analyses of RCTs in maintenance treatment for bipolar disorder are limited.
  - Reviews usually recommend lithium for maintenance.
  - Rapid cycling bipolar disorder may have a different drug response than non-rapid cycling bipolar disorder.

1.2.2. Maintenance Efficacy: Clinical Data

1.2.2.1. Meta-Analyses
1.2.2.2. Reviews
1.2.2.3. Rapid Cycling

1.2.2.1. Efficacy for Maintenance Treatment in Bipolar Disorder: Meta-Analyses

1.2.2.1. Maintenance Efficacy: Meta-Analyses

- Meta-analyses of RCTs in maintenance therapy are limited:
  Vieta et al. 2011 http://www.ncbi.nlm.nih.gov/pubmed/21733231
  - Monotherapy:

Lithium monotherapy	RR (95% CI) (vs. placebo)
Any mood episode	0.75 (0.60-0.94) p=0.013
Manic/mixed episode	0.63 (0.39-1.01) p=0.055
Depressive episode	0.87 (0.67-1.15) p=0.35

  - Only 1 Combination: was significant for mania & depression

Quetiapine + mood stabilizer	RR (95% CI) (vs. placebo+MS[1])
Any mood episode	0.38 (0.32-0.46) p<0.001
Manic/mixed episode	0.39 (0.30-0.52) p<0.001
Depressive episode	0.38 (0.29-0.49) p<0.001

[1]Quetiapine + lithium or valproate was compared to placebo + lithium or valproate

1.2.2.2. Efficacy for Maintenance Treatment in Bipolar Disorder: Reviews

1.2.2.2. Maintenance Efficacy: Reviews

- In a comprehensive review: http://www.ncbi.nlm.nih.gov/pubmed/19538682
  Grof & Müller-Oerlinghausen, 2009, proposed that:
  - Lithium has the best demonstrated efficacy.
  - More recent questions of its efficacy are due to its use on the bipolar spectrum, outside the classic diagnosis.
- A review of naturalistic studies and RCTs:
  Frecska et al. 2011 http://www.ncbi.nlm.nih.gov/pubmed/22987729
  - Recurrence within the first year (early relapsers):
    - 48% of patients on monotherapy, and
    - 35% on combination therapy
  - Late relapsers: the rest of the patient population was affected by recurrences at a smaller rate over a more extended period of time.
  - A favorable outcome at 40 months of episode prevention
    - NNT= 6 for monotherapy
    - NNT= 3 combination therapy

1.2.2.2. Maintenance Efficacy: Reviews

- German guideline:
  Pfennig et al. 2013 http://www.ncbi.nlm.nih.gov/pubmed/23451001
  - For maintenance treatment:
    - Lithium should be used preferentially
      NNT = 14 for 12 months of treatment and
      NNT=3 for 24 months of treatment
    - although other mood stabilizers or
      atypical antipsychotic drugs
      can be given as well.
- Review in *Lancet*:
  Geddes & Miklowitz, 2013 http://www.ncbi.nlm.nih.gov/pubmed/23663953
  - For long-term relapse prevention:
    - Lithium has the strongest evidence.
    - Valproate and lamotrigine: less robust evidence
    - Antipsychotics: much uncertainty

1.2.2.2. Maintenance Efficacy: Reviews

- Gershon et al. 2009: http://www.ncbi.nlm.nih.gov/pubmed/19538684 describe the signature of a lithium responder:
  - essential features:
    - recurrent mood disorder
    - episodic course of illness
    - remission is complete between episodes
  - indicative features
    - predominance of depressive episodes
    - absence of rapid cycling pattern
    - episodic course in another family member
    - no significant psychiatric comorbidity
    - classic pattern of mood episodes

  Approximately 1/3 of patients with current definitions of bipolar disorder are lithium responders.

1.2.2.3. Efficacy for Maintenance Treatment in Bipolar Disorder: Rapid Cycling

1.2.2.3. Maintenance Efficacy: Rapid Cycling

- Fountoulakis et al. 2013 http://www.ncbi.nlm.nih.gov/pubmed/23437958
  - limited data from RCTs
  - lithium and AEDs have comparable efficacies

1.3. Anti-Depressant Efficacy

1.3.1. Pharmacodynamics
1.3.2. Bipolar Depression
1.3.3. Augmentation in Major Depression

1.3.1. Pharmacodynamics of Anti-Depressive Effects

1.3.1. Pharmacodynamics of Anti-Depressive Effects

- No agreement on pharmacodynamic explanations:
  - Bauer al. 2014 http://www.ncbi.nlm.nih.gov/pubmed/24590663
    Commenting on antidepressant augmentation,
    lithium has actions:
    - mainly at the HPA axis and the serotonergic systems
    - but also with other systems.

1.3.2. Bipolar Depression

1.3.2. Efficacy: Bipolar Depression

- Treatment of bipolar depression is a controversial issue.
  Three recent meta-analyses:
  - Selle et al. 2014 http://www.ncbi.nlm.nih.gov/pubmed/24549862
    Focus on monotherapy:
    - Lithium requires adequate testing.
  - Taylor et al. 2014 http://www.ncbi.nlm.nih.gov/pubmed/25283309
    Focus on monotherapy:
    - Lithium is worth considering.
  - Ketter et al. 2014: http://www.ncbi.nlm.nih.gov/pubmed/25533911
    Do not review lithium efficacy.
- Malhi et al. 2009: lithium monotherapy can take 6-8 weeks for a discernable antidepressant effect.
  http://www.ncbi.nlm.nih.gov/pubmed/20001408

1.3.3. Augmentation in Treatment-Resistant Depression

1.3.3. Efficacy: Treatment-Resistant Depression

- Meta-analyses on different augmentation strategies:
  - Lithium cannot be compared very well with other drugs.
    - Lithium RCTs augment TCAs.
    - Second-generation antipsychotic RCTs augment newer antidepressants.
  - The next 2 slides describe meta-analyses/reviews.

1.3.3. Efficacy: Treatment-Resistant Depression

- Meta-analyses/reviews focused on lithium augmentation:
  - Nelson et al. 2014 http://www.ncbi.nlm.nih.gov/pubmed/25069082
    9 RCTs using antidepressant augmentation vs. placebo:
    Lithium NNT=5 (3 to 9)
  - Bauer al. 2014 http://www.ncbi.nlm.nih.gov/pubmed/24590663
    Most RCTs using lithium augmentation are old
    and use TCAs.
  - Boschr et al. 2014 http://www.ncbi.nlm.nih.gov/pubmed/25467053
    If there is response, the combination lithium +
    antidepressant should be given for 6-12 months more.
  - Turner et al. 2014 http://www.ncbi.nlm.nih.gov/pubmed/24108407
    describe “a paucity of high-quality data”.

1.3.3. Efficacy: Treatment-Resistant Depression

- The most comprehensive meta-analysis:

  Zhou et al. 2015 http://www.ncbi.nlm.nih.gov/pubmed/25919841

  5 agents are significantly more effective than placebo:

  - Significant ORs ranged from 1.92 to 1.56.
    - Lithium had the lowest efficacy.

      OR = 1.56 (CI, 1.05 to 2.55)
  - 4 of 5 have significantly lower tolerability than placebo.

    ORs ranged from 3.85 to 2.30.
    - Lithium has the best tolerability (with the lowest OR).

      OR = 2.30 (CI, 1.04 to 6.03)

1.4. Anti-Suicidal Efficacy

1.4. Anti-Suicidal Efficacy

1.4.1. In Bipolar Disorder

1.4.2. In the General Population

1.4.1. Anti-Suicidal Efficacy: In Bipolar Disorder

1.4.1. Anti-Suicidal Efficacy: Bipolar Disorder

1.4.1.1. Pharmacodynamics

1.4.1.2. Meta-Analysis

1.4.1.1. Anti-Suicidal Efficacy in Bipolar Disorder: Pharmacodynamics

1.4.1.1. Anti-Suicidal Efficacy in Bipolar Disorder: Pharmacodynamics

- Cipriani et al. 2014 http://www.ncbi.nlm.nih.gov/pubmed/23814104
  Lithium may exert its anti-suicidal effects in clinical samples through:
  - mood-stabilizer properties (↓ relapse)
    This does not completely explain the anti-suicidal effects, which appear to be larger than the mood-stabilizing effects.
  - other effects. There is some evidence that lithium:
    - ↓ aggression and
    - possibly ↓ impulsivity.

1.4.1.1. Anti-Suicidal Efficacy in Bipolar Disorder: Pharmacodynamics

- Beurel & Jope, 2014 http://www.ncbi.nlm.nih.gov/pubmed/25514751 suggest lithium would ↓ suicide by ↓ inflammation:
  - Anti-inflammatory effects of lithium result from its inhibition of glycogen synthase kinase-3 (GSK3).
  - GSK3 has been demonstrated to strongly promote
    - inflammation,
    - aggressive behavior in rodents and
    - depression-like behaviors in rodents,
    - whereas regulation of impulsivity by GSK3 has not yet been investigated.

This theory is highly speculative.

Inflammation is rarely considered important in suicide.

1.4.1.2. Anti-Suicidal Efficacy in Bipolar Disorder: Meta-Analysis

1.4.1.2. Anti-Suicidal Efficacy in Bipolar Disorder: Meta-Analysis

- Cipriani et al. 2014 http://www.ncbi.nlm.nih.gov/pubmed/23814104

  48 RCTs in bipolar/unipolar depression:

  - Lithium rather than placebo:
    - was more effective in reducing:
      number of suicides (OR=0.13, CI 0.03 to 0.66) and
      deaths from any cause (OR=0.38, CI 0.15 to 0.95).
    - made no difference in preventing deliberate self-harm
      (OR=0.60, CI 0.27 to 1.32).
  - In unipolar depression, lithium rather than placebo:
    - was more effective in reducing:
      risk of suicide (OR=0.36, CI 0.13 to 0.98) and
      number of total deaths (OR=0.13, CI 0.02 to 0.76).
  - In comparing lithium with other drugs:
    a significant difference was found only with
    carbamazepine in preventing deliberate self harm.

1.4.1.2. Anti-Suicidal Efficacy in Bipolar Disorder: Meta-Analysis

- Baldessarini & Tondo, 2009

  6 RCTs in bipolar disorder comparing lithium vs. AEDs on suicidal acts/subjects at risk/months of treatment (expressed as %/ year):

  - lithium was better: pooled RR = 2.86 (CI 2.29 to 3.50).

  http://www.ncbi.nlm.nih.gov/pubmed/19308882

1.4.2. Anti-Suicidal Efficacy: in the General Population (lithium in the water)

1.4.2. Anti-Suicidal Efficacy: General Population

1.4.2.1. Pharmacodynamics
1.4.2.2. Meta-Analysis
1.4.2.3. Is Lithium an Essential Nutritional Compound?

1.4.2.1. Anti-Suicidal Efficacy in the General Population: Pharmacodynamics

1.4.2.1. Anti-Suicidal Efficacy in General Population: Pharmacodynamics

- Vita et al. 2015 http://www.ncbi.nlm.nih.gov/pubmed/25025988
  anti-suicidal effects of lithium in water in the general population, may have different pharmacodynamic mechanisms than in clinical samples:
  - The amount of lithium found in drinking water is much lower than therapeutic doses of lithium.
    The mean lithium concentration: around 0.01 mg/l.
    To match a 300 mg tablet of lithium carbonate, you need to drink 1000s of liters of water.
  - According to the US EPA:
    - grains/vegetables can be richer in lithium than water.
    - adult daily intake of lithium ranges from 650-3100 µg.
      2 liters of water/day of 0.01 mg/l provide 200 µg/day.
      This means that water is a small contributor to daily lithium consumption.

1.4.2.2. Anti-Suicidal Efficacy in the General Population: Meta-Analysis

1.4.2.2. Anti-Suicidal Efficacy in General Population: Meta-Analysis

- Vita et al. 2015 http://www.ncbi.nlm.nih.gov/pubmed/25025988
  - reviewed 9 studies in 5 countries
    on suicide in the general population
    and the amount of lithium found in drinking water.
    7/9 found a significant negative association between
    lithium and mortality due to suicide.

1.4.2.3. Is Lithium an Essential Nutritional Compound?

(Dr. de Leon does not know enough on this subject to comment.)

1.4.2.3. Is Lithium an Essential Nutritional Compound?

- Schrauzer, 2002 http://www.ncbi.nlm.nih.gov/pubmed/11838882
  - suggested:
    - a recommended adult dietary allowance: 1000 µg/day
  - reviewed animal data: rats/goats on low-lithium rations had:
    - higher mortalities,
    - reproductive abnormalities, and
    - behavioral abnormalities.
  - reviewed human literature:
    - no deficiency disease was characterized,
    - low water supplies had been associated with ↑ rates of:
      - suicides,
      - homicides,
      - arrests.
    - lithium has a possible role in early fetal development.

1.5. Possible Efficacy in Controlling Aggressive Behavior in ID

1.5. Efficacy: Aggressive Behavior in ID

- Wickham & Reed, 1987 http://www.ncbi.nlm.nih.gov/pubmed/3320183
  reviewed literature on IDs, mainly from open studies:
  - lithium may ↓ self- and heteroaggressive behavior.
  - they recommend waiting 8 weeks until concluding that the patient is not responding.
- More recently, meta-analyses on:
  - mood stabilizers in the treatment of impulsive or repetitive aggression in adults http://www.ncbi.nlm.nih.gov/pubmed/21282779
  - pharmacotherapy of disruptive behavior disorders in children and adolescents: http://www.ncbi.nlm.nih.gov/pubmed/16983542

  suggest that RCT evidence is rather limited.
- Oliver-Africano et al. 2009 http://www.ncbi.nlm.nih.gov/pubmed/19845412
  drug treatment in aggressive behaviors in ID:
  - should be used much more sparingly and
  - reserved for those patients with particular risks.

1.6. Possible Efficacy in Schizoaffective Disorder

1.6. Possible Effects in Schizoaffective Disorder

- Clinicians frequently use lithium when they diagnose schizoaffective disorder.
- Systematic reviews of the literature on treating schizoaffective disorder agree:

http://www.ncbi.nlm.nih.gov/pubmed/21284405 http://www.ncbi.nlm.nih.gov/pubmed/21565468

  - published treatment studies include samples diagnosed using different criteria, and
  - evidence on treatment for schizoaffective disorder is very limited.
- Meta-analysis of lithium in schizophrenia:
  - The significant effect on efficacy disappeared after eliminating schizoaffective patients.

http://www.ncbi.nlm.nih.gov/pubmed/26509923

1.7. Possible Neuroprotective Effects

1.7. Possible Neuroprotective Effects

- Complex subject: http://www.ncbi.nlm.nih.gov/pubmed/17506922
  Literature in animals/humans suggests both:
  - a neuroprotective effect
  - a neurotoxic effect
- Ferensztajn-Rochowiak & Rybakowski, 2016 http://www.ncbi.nlm.nih.gov/pubmed/26922521 Lithium actions:
  - at the cellular level:
    - ↑ proliferation of progenitor cells in the dentate gyrus of the hippocampus and
    - ↑ mitotic activity of Schwann cells.
  - in clinical studies: ↑ cerebral gray matter, in:
    - the frontal lobes,
    - hippocampus and
    - amygdala

1.7. Possible Neuroprotective Effects

1.7.1. Pharmacodynamics
1.7.2. Clinical Data

1.7.1. Neuroprotection: Pharmacodynamics

1.7.1. Neuroprotection: Pharmacodynamics

- Ferensztajn-Rochowiak & Rybakowski, 2016
http://www.ncbi.nlm.nih.gov/pubmed/26922521
  - Neurotrophic effects of lithium:
    - improvement in synaptic plasticity promoting cell survival and
    - inhibiting apoptosis.
- Rybakowski, 2014: http://www.ncbi.nlm.nih.gov/pubmed/25377609
  Lithium pharmacodynamics of neuroprotection:
  - ↑ expression of BDNF and
  - inhibition of the glycogen synthase kinase-3 (GSK-3)

1.7.2. Neuroprotection: Clinical Data

1.7.2. Neuroprotection: Clinical Data

- There are no published prospective clinical studies definitively demonstrating neuroprotection in neurodegenerative diseases.
  There are several promising:
  - naturalistic studies or
  - small controlled studies with biological markers.
- Literature describes ongoing or planned RCTs in:
  - traumatic brain injury,
  - Parkinson disease, and
  - Alzheimer disease.
- RCTs in amyotrophic lateral sclerosis: negative.

http://www.ncbi.nlm.nih.gov/pubmed/23453347

1.8. Efficacy: Comments on Pharmacokinetics

1.8. Efficacy: Comments on Pharmacokinetics

- Pharmacokinetics facilitates pharmacodynamics.
- Efficacy:
  - Sufficient drug concentration may be needed.
  - Once there is sufficient drug concentration, pharmacodynamics determines efficacy.
- Lithium is a narrow therapeutic window drug. See the presentation "Pharmacokinetics of Lithium" for more details.
- The next section presents a summary of the therapeutic concentration ranges for various indications.

1.8.1. Therapeutic Concentration Ranges

1.8.1. Therapeutic Concentration Ranges

1.8.1.1. Bipolar Disorder

1.8.1.2. Other Disorders

1.8.1.3. References

1.8.1.1. Therapeutic Concentration Ranges: Bipolar Disorder

1.8.1.1. Therapeutic Ranges in mEq/l or mM/l: Bipolar Disorder

- Mania: □ up to 1.2 (Hiemke et al. 2012)
  - □ 0.6–1.2 (Lexicomp, 2015)
  - □ 0.8–2.0 (Sproule, 2002)
- Maintenance treatment in adults with bipolar disorder:

	Nonelderly	Elderly[1]
Grandjean & Aubry, 2009	0.6-0.8 0.8-1.0 for ER[3]	Controversial[2]
Hiemke et al. 2012	0.5-0.8	
Lexicomp, 2015	0.8-1.0	0.4-0.6
Severus et al. 2008	0.6-0.75	
Sproule, 2002	0.8-1.0 0.4-0.7 in some[4]	0.5-0.8

[1]Some consider that the elderly may need lower doses.

[2]These authors consider controversial that elderly may need lower doses.

[3]With ER preparations and because of the later peak of serum lithium concentration, this author recommends maintaining serum concentrations within the upper range, 0.8–1.0.

[4]According to this author, some patients can be maintained at this lower range, but these patients cannot be identified a priori.

1.8.1.2. Therapeutic Concentration Ranges: Other Disorders

1.8.1.2. Therapeutic Ranges in mEq/l or mM/l: Other Disorders

- Depression augmentation:
  - 0.6–0.9 (Boschr et al. 2014)
    - Once in this range, observe for 2 weeks.
    - If there is no response, discontinue.

- Self- or hetero-aggressive behavior in adults with ID:
  - 0.7-1.0 (Wickman & Reed,1987)

1.8.1.3. Therapeutic Concentration Ranges: References

1.8.1.3. References for Therapeutic Concentration Ranges

- Boschr et al. 2014 http://www.ncbi.nlm.nih.gov/pubmed/25467053
- Grandjean & Aubry, 2009 http://www.ncbi.nlm.nih.gov/pubmed/19374461
- Hiemke et al. 2012 http://www.ncbi.nlm.nih.gov/pubmed/22053351
- Lexicomp http://www.ncbi.nlm.nih.gov/pubmed/25467053 http://www.amazon.com/Drug-Information-Handbook-Lexicomp/dp/1591953421/ref=sr_1_1?s=books&ie=UTF8&qid=1457718666&sr=1-1&keywords=drug+information+handbook
- Severus et al. 2008 http://www.ncbi.nlm.nih.gov/pubmed/18271901
- Sproule, 2002 http://www.ncbi.nlm.nih.gov/pubmed/12126457
- Wickman & Reed,1987 http://www.ncbi.nlm.nih.gov/pubmed/3320183

1.9. Comments on Efficacy and Pharmacodynamic DDIs

1.9. Efficacy: Comments on Pharmacodynamic DDIs

- Not-well understood pharmacodynamic DDIs may explain ↑ efficacy of combinations with lithium.
- Mania: limited evidence suggests:
  - when monotherapy is not successful:
    the combination of a mood stabilizer (including lithium) and antipsychotics is more efficacious and more burdensome, compared to the continuation of monotherapy.
    http://www.ncbi.nlm.nih.gov/pubmed/25160685
- Maintenance in bipolar disorder:
  - Combination therapies ↓ recurrences.

http://www.ncbi.nlm.nih.gov/pubmed/22987729

- Augmentation for depression:
  - Combining lithium with TCAs ↑ TCA efficacy.

2. Pharmacodynamics of Lithium Safety

2. Pharmacodynamics of Lithium Safety

- Lithium use in bipolar disorder has ↓ substantially, due to:
  - the active marketing of alternative drugs, and
  - the perceived risks of its use, particularly:
    - to renal function,
    - to endocrine function, and
    - the possibility of teratogenicity.

http://www.ncbi.nlm.nih.gov/pubmed/22265701

- No lithium RCTs have provided percentages for ADRs.
- Lamotrigine RCTs reviewed by Seo et al. 2011:

http://www.ncbi.nlm.nih.gov/pubmed/21242744

controls for lamotrigine RCTs: 280 lithium patients

- common lithium ADRs (≥10%):
  - nausea: 16%
  - diarrhea 14%
  - headaches 14% and
  - tremor 11%.

2. Pharmacodynamics of Lithium Safety

2.0. Comments on Pharmacodynamics

2.1. Brain ADRs

2.2. Mixed ADRs (Brain and Peripheral Components)

2.3. Peripheral ADRs

2.4. Comments on Safety and Pharmacokinetics

2.5. Comments on Safety and Pharmacodynamic DDIs

2.6. Teratogenicity

2. Pharmacodynamics of Lithium Safety

2.0. Comments on Pharmacodynamics

2.1. Brain ADRs

- 2.1.1. Tremor
- 2.1.2. Cognitive Impairment
- 2.1.3. EPS
- 2.1.4. Rare Neurological ADRs

2.2. Mixed ADRs (Brain and Peripheral Components)

- 2.2.1. Metabolic Syndrome
- 2.2.2. Serotonin Syndrome

2.3. Peripheral ADRs

- 2.3.1. GI ADRs
- 2.3.2. Leukocytosis
- 2.3.3. Polyuria
- 2.3.4. Kidney Damage
- 2.3.5. Edema
- 2.3.6. Thyroid Abnormalities
- 2.3.7. Calcium Metabolism Abnormalities
- 2.3.8. Cardiac ADRs
- 2.3.9. Dermatological ADRs
- 2.3.10. Ocular ADRs

2.4. Comments on Safety and Pharmacokinetics

2.5. Comments on Safety and Pharmacodynamic DDIs

2.6. Teratogenicity

2.0. Comments on Pharmacodynamics

2.0. Safety: Comments on Pharmacodynamics

- Information on pharmacodynamics for ADRs: limited
- Described pharmacodynamics include (see the ADR for more details):
  - EPS exacerbation: ↓ dopamine activity (see 2.1.3.1)
  - Serotonin syndrome: ↓ serotonin activity (see 2.2.2.1)
  - Leukocytosis: complex actions on stem cells (see 2.3.2.)
  - Polyuria (see 2.3.3.1.):
    - no ADH-mediated insertion of aquaporin-2 (water channels), and
    - ↓ urea transporters in renal medulla (needed for osmotic gradient)
  - Kidney damage (see 2.3.4.1.):
    - prevent renal tubular epithelial cells from apoptosis
    - leading to cysts that ↓ GFR
  - Thyroid abnormalities: complex actions (see 2.3.6.1) interfering with hormone synthesis and release
  - Hypercalcemia: calcium-sensing receptor antagonism (see 2.3.7.1)
  - Arrhythmias: blocker of cardiac sodium channels (see 2.3.8.1)
  - Psoriasis exacerbation: interference with inositol metabolism (see 2.3.9.2)

2.1. Lithium: Brain ADRs

2.1. Lithium: Brain ADRs

2.1.1. Tremor
2.1.2. Cognitive Impairment
2.1.3. EPS
2.1.4. Rare Neurological ADRs

2.1.1. Lithium: Tremor

2.1.1. Lithium: Tremor

- Fine postural and/or action tremors: 4–20% of patients: http://www.ncbi.nlm.nih.gov/pubmed/19453201
- 2 types (http://www.ncbi.nlm.nih.gov/pubmed/10826665):
  - Related to peak serum levels, it can be reduced by
    - using a slow-release preparation or
    - changing to a single bedtime dose.
  - Nonpeak tremors can be managed by:
    - ↓ dose
    - ↓ caffeine intake or contributing co-medications, or
    - adding a β-blocker.
- Propranolol treatment: Labbate et al. 2009 http://www.amazon.com/Handbook-Psychiatric-Therapy-Lippincott-Williams/dp/0781774861/ref=sr_1_1?s=books&ie=UTF8&qid=1458324003&sr=1-1&keywords=handbook+of+psychiatric+drug+therapy
  - as needed: 10–20 mg can be taken 30 minutes prior to an activity in which tremor is a serious problem, or
  - for tremor suppression all day, take 10–20 mg twice a day.

2.1.2. Lithium: Cognitive Impairment

2.1.2. Lithium: Cognitive Impairment

2.1.2.1. Meta-Analyses

2.1.2.2. Review by Experienced Clinicians

2.1.2.3. Other Relevant Studies

2.1.2.1. Lithium and Cognitive Impairment: Meta-Analyses

2.1.2.1. Lithium and Cognitive Impairment: Meta-Analyses

- Pachet &Wisniewski, 2003: http://www.ncbi.nlm.nih.gov/pubmed/14504681
  A comprehensive review of the literature on lithium and cognitive impairment found:
  - impairment in
    - tasks of psychomotor speed
    - the majority of verbal memory studies
  - no impairment in:
    - visual–spatial constructional ability or
    - attention/concentration, and
  - no negative cumulative effect.

- Wingo et al. 2009: http://www.ncbi.nlm.nih.gov/pubmed/19689922
  A comprehensive meta-analysis: lithium associated with:
  - small impairments in
    - verbal learning
    - memory and
    - creativity, and
  - greater impairment in psychomotor performance

2.1.2.2. Lithium and Cognitive Impairment: Review by Experienced Clinicians

2.1.2.2. Lithium and Cognitive Impairment: Expert

- Dunner, 2000 http://www.ncbi.nlm.nih.gov/pubmed/10826665

  Cognitive complaints: leading cause of non-compliance

  - usually manifest as:
    - loss of cognitive executive function (lack of drive/loss of productivity)
    - within the first 6–8 months
  - recommendations:
    - review indications with the patient
    - review alternatives with the patient
    - consider neuropsychological tests to compare in case of worsening
  - Some patients complain of loss of creativity:

    Lithium may:
    - ↓ creativity: by eliminating hypomania
    - ↑ creativity: by eliminating depression

    Recommendation:
    - use lower lithium doses
    - stay within the therapeutic range

2.1.2.2. Lithium and Cognitive Impairment: Expert

- Patients from non-Western cultures may have different lithium complaints:
  - Lee, 1993, described in Chinese:
    - no cultural equivalent for the words “loss of creativity”
    - no complaints of “missing of highs”
    - >1/3 complained of mild “hotness”.

http://www.ncbi.nlm.nih.gov/pubmed/8269711

2.1.2.3. Lithium and Cognitive Impairment: Other Relevant Studies

2.1.2.3. Lithium and Cognitive Impairment: Other Studies

- Bramness et al. 2009: http://www.ncbi.nlm.nih.gov/pubmed/19326366
  - Association between lithium and traffic accidents in Norway, but only in young females
- Gualtieri & Johnson, 2006: http://www.ncbi.nlm.nih.gov/pubmed/17406176

  In a neuropsychology study of cognitive deficits and mood stabilizers in bipolar disorder, 3 profiles are described:
  - best:
    - lamotrigine and
    - oxcarbazepine
  - intermediate:
    - lithium
  - worst:
    - valproate,
    - carbamazepine, and
    - topiramate

2.1.3. EPS

2.1.3. Lithium EPS

2.1.3.1. Pharmacodynamics

2.1.3.2. Clinical Relevance

2.1.3.1. EPS: Pharmacodynamics

2.1.3.1. EPS: Pharmacodynamics

- Animal studies suggest lithium:
  - ↓ dopamine release in the accumbens

    http://www.ncbi.nlm.nih.gov/pubmed/15888507
  - ↓ dopamine-associated behaviors

    http://www.ncbi.nlm.nih.gov/pubmed/15044694
  - interferes with striatal dopaminergic neurotransmission http://www.ncbi.nlm.nih.gov/pubmed/2865683
  - prolongs haloperidol-induced catalepsy

    http://www.ncbi.nlm.nih.gov/pubmed/7200429

2.1.3.2. EPS: Clinical Relevance

2.1.3.2. EPS: Clinical Relevance

- Not well studied in clinical environment, but lithium
  - may ↑ EPS by first-generation antipsychotics

    http://www.ncbi.nlm.nih.gov/pubmed/6126349
  - is associated with many cases of NMS secondary to second-generation antipsychotics

    http://www.ncbi.nlm.nih.gov/pubmed/15119907
- The best study was a prospective study:
  - with first-generation antipsychotics
  - 10 patients single-blindly rated on an EPS scale:
    - in 10/10 patients: ↑ EPS scores
    - in 3/10 patients: EPS were distressing

    http://www.ncbi.nlm.nih.gov/pubmed/2903220

2.1.3.2. EPS: Clinical Relevance

- See the presentation "Acute Dystonic Reaction: Case 2". An acute dystonic reaction occurred:
  - after adding lithium to risperidone
  - is probably explained by a pharmacodynamic DDI:
    Lithium ↑ the effects of risperidone.
    It was equivalent to ↑ the risperidone dose.
  - Personal vulnerability probably contributed, too.
    The patient's vulnerability was suggested
    by two occurrences of dystonia with levo-dopa.

2.1.4. Rare Neurological ADRs

2.1.4. Lithium: Rare Neurological ADRs

2.1.4.1. Pseudotumor Cerebri
2.1.4.2. Residual Symptoms After Intoxication
2.1.4.3. Confusional States

2.1.4.1. Pseudotumor Cerebri

2.1.4.1. Lithium: Pseudotumor Cerebri

- "Pseudotumour cerebri,"
  or idiopathic intracranial hypertension
  - was associated with lithium in 1985.
    http://www.ncbi.nlm.nih.gov/pubmed/3921728
  - is found in 16 published cases, according to a 2012 review:
    http://www.ncbi.nlm.nih.gov/pubmed/22588960
  - is to be ruled out if the lithium patient has a persistent headache.

2.1.4.2. Residual Symptoms After Intoxication

2.1.5. Lithium: Residual Symptoms After Intoxication

- A number of rare, potentially serious neurological ADRs after lithium intoxication include residual:
  - EPS
  - cerebellar symptoms

http://www.ncbi.nlm.nih.gov/pubmed/19453201

2.1.4.3. Lithium: Confusional States

2.1.4.3. Lithium: Confusional States

- Occasionally, lithium has been associated with confusional states without toxic lithium levels, which is explained by
  - a non-convulsive status or
  - an encephalopathy with triphasic waves in EEG, may be confused with Creutzfeldt-Jakob disease.

http://www.ncbi.nlm.nih.gov/pubmed/17201705

2.2. Lithium: Mixed ADRs

(Brain and Peripheral Components)

2.2. Lithium: Mixed ADRs

2.2.1. Metabolic Syndrome
2.2.2. Serotonin Syndrome

2.2.1. Lithium: Metabolic Syndrome

2.2.1. Lithium: Metabolic Syndrome

2.2.1.1. ↑ Weight

2.2.1.2. Peripheral Metabolic ADRs

2.2.1.1. Lithium ↑ Weight

2.2.1.1. Lithium ↑ Weight

2.2.1.1.1. Pharmacodynamics
2.2.1.1.2. Clinical Relevance
2.2.1.1.3. Monitoring

2.2.1.1.1. Lithium ↑ Weight: Pharmacodynamics

2.2.1.1.1. Lithium ↑ Weight: Pharmacodynamics

- The pharmacodynamic mechanism is not well understood. It is usually assumed that lithium may ↑ appetite through pharmacodynamic brain changes.

- Dunner, 2000: http://www.ncbi.nlm.nih.gov/pubmed/10826665
  - emphasized the relevance of lithium pharmacokinetics to weight gain:
    - it may be dose-related and
    - less likely if the patient is maintained on <0.8 mEq/L.
  - stressed that if the patient has polyuria, it is important to recommend avoiding high-calorie beverages.

2.2.1.1.2. Lithium ↑ Weight: Clinical Relevance

2.2.1.1.2. Lithium ↑ Weight: Clinical Relevance

- Meta-analysis of gain >7%: http://www.ncbi.nlm.nih.gov/pubmed/22265699
  - versus placebo: OR=1.89 (CI 1.27-2.82)
  - versus olanzapine: OR=0.32 (CI 0.21-0.49)
- Different reviews provide different weight gain prevalences in patients taking lithium:
  - 11–65% gain some weight http://www.ncbi.nlm.nih.gov/pubmed/2230066
  - 20% gain > 10 kg in http://www.ncbi.nlm.nih.gov/pubmed/3053797
  - 30% gain 4–10 kg http://www.ncbi.nlm.nih.gov/pubmed/19453201
- Two recent lamotrigine RCTs: the mean ↑ weight gain after 52 weeks on lithium:
  - 3.4 kg in the whole sample,
    - 6.1 kg in obese patients, and
    - 1.1 kg in non-obese patients,
  - no differences from placebo in % with gains ≥7%

http://www.ncbi.nlm.nih.gov/pubmed/16816224 http://www.ncbi.nlm.nih.gov/pubmed/16542188

2.2.1.1.3. Lithium ↑ Weight: Monitoring

2.2.1.1.3. Lithium ↑ Weight: Monitoring

- International guidelines http://www.ncbi.nlm.nih.gov/pubmed/19689501

  Baseline: □ waist circumference
  □ weight and height (BMI)
  □ fasting glucose
  □ fasting lipid profile

  Then weight: □ at 6 months
  □ then annually

2.2.1.2. Lithium: Peripheral Metabolic ADRs

2.2.1.2. Lithium: Peripheral Metabolic ADRs

- ↑ weight can secondarily cause: □ hyperglycemia and/or
  □ hyperlipidemias
- No major direct effects on peripheral metabolism:
  - □ although lithium can impair glucose release
    - normalization by compensatory mechanism and
    - lithium-associated diabetes mellitus is rare.

http://www.amazon.com/Lithium-Encyclopedia-Clinical-Practice-Jefferson/dp/0880482303/ref=sr_1_1?s=books&ie=UTF8&qid=1458335570&sr=1-1&keywords=jefferson+and+lithium

  - □ no good studies exist of the effects of lithium on lipid levels, but some recent case reports suggest that occasionally lithium can be associated with hyperlipidemias.

http://www.ncbi.nlm.nih.gov/pubmed/17379021 http://www.ncbi.nlm.nih.gov/pubmed/19375600

2.2.2. Lithium and the Serotonin Syndrome

2.2.2. Lithium and the Serotonin Syndrome

2.2.2.1. Pharmacodynamics
2.2.2.2. Clinical Presentation

2.2.2.1. Lithium and the Serotonin Syndrome: Pharmacodynamics

2.2.2.1. Lithium and the Serotonin Syndrome: Pharmacodynamics

- Mechanism:↑ serotonin activity at
  - the central nervous system, and
  - the periphery
- Usually caused by combinations of several serotonergic drugs. Lithium can be one of them.

2.2.2.2. Lithium and the Serotonin Syndrome: Clinical Presentation

2.2.2.2. Lithium and the Serotonin Syndrome: Clinical Presentation

- Rare, but potentially lethal
- A good article summarizing the diagnosis of serotonin syndrome has a pdf available free of charge in PubMed. http://www.ncbi.nlm.nih.gov/pubmed/20433130
- Recalling some definitions:
  - clonus: exaggerated reflexes
    e.g., ankle dorsiflexion/plantarflexion
    can be
      - spontaneous or
      - inducible by reflex
  - ocular clonus: slow, continuous, horizontal eye movements

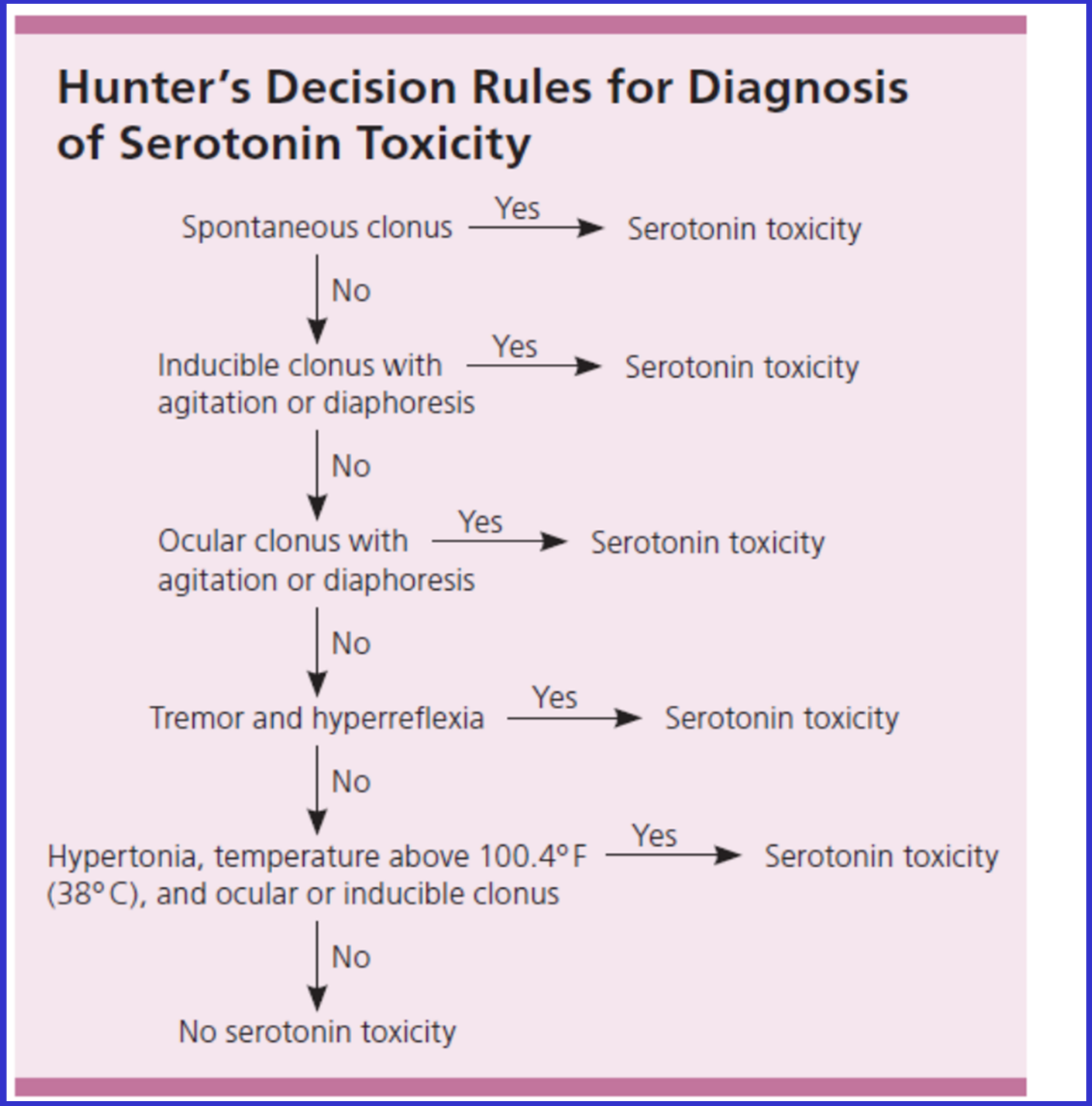
2.2.2.2. Lithium and the Serotonin Syndrome: Clinical Presentation

- The main symptoms that warrant the diagnosis:
  1) spontaneous clonus,
  2) inducible clonus with □ agitation or
     □ diaphoresis,
  3) ocular clonus with □ agitation or
     □ diaphoresis, or
  4) tremor and hyperreflexia.
  5) a combination of □ hypertonia,
     □ T > 38°C (100.4°F), and
     □ ocular or
     inducible clonus

http://www.ncbi.nlm.nih.gov/pubmed/20433130

2.2.2.2. Lithium and the Serotonin Syndrome: Clinical Presentation

Figure 1. Able et al. 2010: http://www.ncbi.nlm.nih.gov/pubmed/20433130



2.3. Peripheral ADRs

2.3. Lithium: Peripheral ADRs

2.3.1. GI ADRs
2.3.2. Leukocytosis
2.3.3. Polyuria
2.3.4. Kidney damage
2.3.5. Edema
2.3.6. Thyroid Abnormalities
2.3.7. Calcium Metabolism Abnormalities
2.3.8. Cardiac ADRs
2.3.9. Dermatological ADRs
2.3.10. Ocular ADRs

2.3.1. Lithium and GI ADRs

2.3.1. Lithium and GI ADRs

2.3.1.1. Pharmacodynamic Mechanisms
2.3.1.2. Clinical Presentation
2.3.1.2. Management

2.3.1.1. Lithium and GI ADRs: Pharmacodynamics

2.3.1.1. Lithium and GI ADRs: Pharmacodynamics

- We have very limited understanding of pharmacodynamic mechanisms behind lithium GI ADRs.

- We have some understanding of pharmacokinetic mechanisms behind lithium GI ADRs:
  - some appear to be dose-related.

2.3.1.2. Lithium and GI ADRs: Clinical Presentation

2.3.1.2. Lithium and GI ADRs: Clinical Presentation

- The main GI ADRs include:
  - nausea
  - vomiting
  - diarrhea, and
  - abdominal pain
- They tend: http://www.ncbi.nlm.nih.gov/pubmed/10826665
  - to be present early in the treatment and
  - can be dose-related.
- Be careful; GI symptoms emerging late in treatment can be a sign of toxicity. http://www.ncbi.nlm.nih.gov/pubmed/19453201 Do TDM.

2.3.1.2. Lithium and GI ADRs: Management

Based on:

http://www.ncbi.nlm.nih.gov/pubmed/10826665

http://www.amazon.com/Handbook-Psychiatric-Therapy-Lippincott-Williams/dp/0781774861/ref=sr_1_1?s=books&ie=UTF8&qid=1458324003&sr=1-1&keywords=handbook+of+psychiatric+drug+therapy

2.3.1.2. Lithium and GI ADRs: Management

- Nausea is the most frequent:

  Manage it by:

  - administering lithium with food,
  - changing the time of day for administration,
  - reducing to a single dose, or
  - changing preparations.

- Vomiting is rare:

  Manage it:

  - in the same way as nausea, or
  - with antacids.

- Diarrhea may be more frequent in ER formulations:

  Manage it by:

  - changes in food intake,
  - changes in preparation, or
  - antidiarrheal agents.

2.3.2.Lithium and Leukocytosis

2.3.2. Lithium and Leukocytosis

- Lithium usually causes:
  - a benign increase in neutrophils : ↑ by 35–40%
  - after one week of treatment.

  http://www.ncbi.nlm.nih.gov/pubmed/3882540
- Ferensztajn-Rochowiak & Rybakowski, in 2016, described lithium may act by improving:
  - the homing of hematopoietic stem cells,
  - the ability to form colonies, and
  - hematopoietic stem cell self-renewal.

  http://www.ncbi.nlm.nih.gov/pubmed/26922521
- The use of lithium to prevent or
  treat

  clozapine-induced neutropenia is highly controversial.

2.3.3. Lithium and Polyuria

2.3.3. Lithium and Polyuria

2.3.3.1. Pharmacodynamics
2.3.3.2. Meta-Analyses and Reviews
2.3.3.3. Management

2.3.3.1. Lithium and Polyuria: Pharmacodynamics

2.3.3.1. Lithium and Polyuria: Pharmacodynamics

- The main pharmacodynamic mechanisms in polyuria:
  - the failure of the ADH-mediated insertion of the water channel protein aquaporin-2, and
  - ↓ urea transporters in the renal medulla needed to maintain the osmotic gradient

  http://www.ncbi.nlm.nih.gov/pubmed/18216143

- A chart review study of 24 hour urine collections suggested that antidepressants that block the serotonin transporter ↑ risk of polyuria. http://www.ncbi.nlm.nih.gov/pubmed/18651340

2.3.3.2. Lithium and Polyuria: Meta-Analyses and Reviews

2.3.3.2. Lithium and Polyuria: Meta-Analyses and Reviews

- Polyuria is accompanied by
  - a secondary polydipsia and
  - sometimes nocturia.
- To verify impairment in concentrating the urine:
  - urine osmolality is better, but
  - specific gravity of the urine is a simpler way.
- A 2012 meta-analysis: http://www.ncbi.nlm.nih.gov/pubmed/22265699
  - ↓ urinary concentrating ability by 15% of normal maximum (WMD -158·4 mOsm/kg, CI -229.8 to -87.1).
- Labbate et al. 2009, estimate that in long-term patients:
  - 50–70% have polyuria, and
  - 10% have urine volume >3 liters/day, which qualifies as nephrogenic diabetes insipidus. http://www.amazon.com/Handbook-Psychiatric-Therapy-Lippincott-Williams/dp/0781774861/ref=sr_1_1?s=books&ie=UTF8&qid=1458324003&sr=1-1&keywords=handbook+of+psychiatric+drug+therapy
- The nephrogenic diabetes insipidus may persist after lithium discontinuation in a small number of patients.

2.3.3.3. Lithium and Polyuria: Management

2.3.3.3. Lithium and Polyuria: Management

- Treatments: http://www.amazon.com/Handbook-Psychiatric-Therapy-Lippincott-Williams/dp/0781774861/ref=sr_1_1?s=books&ie=UTF8&qid=1458324003&sr=1-1&keywords=handbook+of+psychiatric+drug+therapy
  - □ ↓ dose to the minimum effective,
  - □ changing the preparation, or
  - □ adding amiloride.
- Amiloride: □ is started at 5 mg twice a day and
  □ can be ↑ to 10 mg twice a day.

After adding amiloride, it is prudent to monitor weekly for several weeks: □ potassium and
□ lithium levels.

Amiloride inhibits 2 major lithium transporters:

- □ the sodium channel in collecting duct
- □ sodium-proton (H+) exchanger present on many cells

http://www.ncbi.nlm.nih.gov/pubmed/10073618

2.3.4. Lithium and Kidney Damage

2.3.4. Lithium and Kidney Damage

2.3.4.1. Pharmacodynamics
2.3.4.2. Meta-Analyses and Reviews
2.3.4.3. End-Stage Kidney Disease
2.3.4.4. Rare Renal Complications
2.3.4.5. Renal Monitoring

2.3.4.1. Lithium and Kidney Damage: Pharmacodynamics

2.3.4.1. Lithium and Kidney Damage: Pharmacodynamics

- Khan & El-Mallakh, 2015: http://www.ncbi.nlm.nih.gov/pubmed/26459462 proposed:
  - a relationship between renal microcyst formation and a significant ↓ in GFR.
  - that microcysts may be explained by anti-apoptotic effect.
  - that lithium:
    - prevents renal tubular epithelial cells from undergoing apoptosis as part of the normal maintenance process,
    - allows the inappropriate growth of the surface area of tubules to form invaginations and ultimately cysts.

2.3.4.2 Lithium and Kidney Damage: Meta-Analyses and Reviews

2.3.4.2. Lithium and Kidney Damage: Meta-Analyses and Reviews

- A 2010 meta-analysis: http://www.ncbi.nlm.nih.gov/pubmed/19395432
  - The mean creatinine ↑ in the average patient is small and of questionable clinical significance.
- A 2012 meta-analysis: http://www.ncbi.nlm.nih.gov/pubmed/22265699
  - On average, ↓ GFR by -6·22 mL/min (CI -14·65 to 2·20) (p=0·15, not significant)
- A review: http://www.ncbi.nlm.nih.gov/pubmed/19453201
  - GFR falls slightly in about 20% of patients

2.3.4.3. Lithium and End-Stage Kidney Disease

2.3.4.3. Lithium and End-Stage Kidney Disease

- Although the link between lithium and chronic renal failure was long disputed in the past, it is unequivocally established by □ epidemiological,
  □ clinical, and
  □ histopathological studies.
- The nephropathy:
  □ is a chronic tubulointerstitial type and
  □ occurs mostly in patients who took lithium for >10–20 years.

http://www.ncbi.nlm.nih.gov/pubmed/19384328

2.3.4.3. Lithium and End-Stage Kidney Disease

- 2012 meta-analysis: http://www.ncbi.nlm.nih.gov/pubmed/22265699
  - Lithium ↑ risk of renal failure; a small absolute risk. (0.5% of patients received renal replacement therapy.)
- 2015 retrospective review: http://www.ncbi.nlm.nih.gov/pubmed/26003379
  - After adjusting for age, sex, and diabetes, the presence of lithium in serum was associated with an ↑ risk of stage three chronic kidney disease (HR 1.9, CI 1.8 to 2.1).
- Prevalences of end-stage kidney disease:
  - France: lithium accounts for 0.2% of causes http://www.ncbi.nlm.nih.gov/pubmed/12846754
  - Area of Sweden: http://www.ncbi.nlm.nih.gov/pubmed/25735990
    - 1.5% of those who took lithium in the 1960s and 1970s
    - 0% who took lithium for >10 years after the 1980s, but 5% had severe or very severe chronic renal failure.

2.3.4.4. Lithium and Rare Renal Complications

2.3.4.4. Lithium and Rare Renal Complications

- An acute nephrotic syndrome
  - can happen on rare occasions
  - manifests with proteinuria in urinalysis
  - is usually reversible after discontinuation

  These patients should not be re-challenged with lithium.

http://www.amazon.com/Handbook-Psychiatric-Therapy-Lippincott-Williams/dp/0781774861/ref=sr_1_1?s=books&ie=UTF8&qid=1458324003&sr=1-1&keywords=handbook+of+psychiatric+drug+therapy

The biopsy shows "minimal change disease".

http://www.ncbi.nlm.nih.gov/pubmed/2492165

- A recent French study: lithium ↑ renal cancer.

  Lithium standardized incidence ratio vs. general population:
  - ♂: 7.5 (CI 1.5-22.0)
  - ♀: 13.7 (CI 3.7-35.1)

http://www.ncbi.nlm.nih.gov/pubmed/24451323

2.3.4.5. Lithium and Renal Monitoring

2.3.4.5. Lithium and Renal Monitoring

- International guidelines http://www.ncbi.nlm.nih.gov/pubmed/19689501
  recommend :
    - electrolytes
    - urea and
    - creatinine

  at:
    - baseline
    - every 3-6 months
- Jefferson, 2010: http://www.ncbi.nlm.nih.gov/pubmed/20923621
  - recommends estimating GFR with serum creatinine at least twice/year if not provided by the laboratory
  - To get more accurate creatinine values, tell the patient:
    - maintain adequate hydration
    - avoid strenuous exercise
    - avoid excessive meat
    - avoid creatinine dietary supplements

2.3.4.5. Lithium and Renal Monitoring

- Jefferson, 2010: http://www.ncbi.nlm.nih.gov/pubmed/20923621
  - To try to establish the possibility of renal damage:
    - Make a good estimate of GFR by collecting 24-hour urine for creatinine clearance.
    - Neither serum creatinine nor estimated GFR are good methods for establishing early impairment.
  - Consult a nephrologist, but be selective. The decision about whether to stop lithium is a risk-benefit decision.
- Labbate et al. 2009: If serum creatinine significantly ↑, but there is no lithium intoxication or other explanation, consider
  - stopping lithium and
  - obtaining a 24-hour creatinine clearance.

It can be a sign of an interstitial nephritis.

http://www.amazon.com/Handbook-Psychiatric-Therapy-Lippincott-Williams/dp/0781774861/ref=sr_1_1?s=books&ie=UTF8&qid=1458324003&sr=1-1&keywords=handbook+of+psychiatric+drug+therapy

2.3.4.5. Lithium and Renal Monitoring

- Presne et al. 2003: http://www.ncbi.nlm.nih.gov/pubmed/12846754
  Stopping lithium:
  - may be beneficial in patients with moderate impairment (creatinine clearance >40 mL/min),
  - but a point of no return probably exists, after which renal fibrosis continues to progress despite lithium removal.
- Raedler et al. 2008: http://www.ncbi.nlm.nih.gov/pubmed/18155820
  - explored a new non-invasive technique for diagnosis: "capillary electrophoresis coupled to a mass spectrometer" that has been applied to the differential diagnosis of nephropathies.
    3/14 lithium patients with no lab abnormalities showed some degree of pathological findings.

2.3.5. Lithium and Edema

2.3.5. Lithium and Edema

- On rare occasions, patients develop edema.
  - location: • lower extremity or
    • face
  - can resolve spontaneously
  - is unrelated to any changes in renal function
- Management:
  - If medical problems are ruled out and edema is a problem for the individual, it can be treated with spironolactone, but lithium levels need to be monitored since they may ↑

http://www.amazon.com/Handbook-Psychiatric-Therapy-Lippincott-Williams/dp/0781774861/ref=sr_1_1?s=books&ie=UTF8&qid=1458324003&sr=1-1&keywords=handbook+of+psychiatric+drug+therapy

2.3.6. Lithium and Thyroid Abnormalities

2.3.6. Lithium and Thyroid Abnormalities

2.3.6.1. Pharmacodynamics
2.3.6.2. Meta-Analyses and Reviews
2.3.6.3. Management

2.3.6.1. Lithium and Thyroid Abnormalities: Pharmacodynamics

2.3.6.1. Lithium and Thyroid Abnormalities: Pharmacodynamics

- Pharmacodynamic mechanism:
  - Lithium interferes with the
    - synthesis and
    - release

  of thyroid hormones through several mechanisms.

http://www.ncbi.nlm.nih.gov/pubmed/10221287

2.3.6.2. Lithium and Thyroid Abnormalities: Meta-Analysis and Reviews

2.3.6.2. Lithium and Thyroid Abnormalities: Meta-Analysis and Reviews

- Meta-analysis: http://www.ncbi.nlm.nih.gov/pubmed/22265699

  Lithium prevalence compared to placebo:
  - TSH ↑ on average by 4.0 IU/mL (CI 3.9-4.1)
  - clinical hypothyroidism: OR=5.8 (CI 2.0-16.7)
- Review: Dunner, 2000 http://www.ncbi.nlm.nih.gov/pubmed/10826665
  - ↑ TSH elevations: 30% of patients
  - clinical hypothyroidism: 5% of patients (after 6–18 months)
- Review: Kleiner et al.1999 http://www.ncbi.nlm.nih.gov/pubmed/10221287

  Lithium prevalence vs. general population:
  - subclinical hypothyroidism: up to 23% (vs. 10%)
  - overt hypothyroidism: 8–19% (vs. 0.5–1.8%)
- Lithium may also: http://www.ncbi.nlm.nih.gov/pubmed/16174674
  - exacerbate preexisting thyroid autoimmunity
  - be associated with goiter
  - cause hyperthyroidism on rare occasions

2.3.6.3. Lithium and Thyroid Abnormalities: Management

2.3.6.3. Lithium and Thyroid Abnormalities: Management

- International guidelines http://www.ncbi.nlm.nih.gov/pubmed/19689501 recommend TSH:
  - baseline
  - at 6 months
  - then annually
- Obvious hypothyroidism: supplemental thyroid treatment
- Subclinical cases:
  - management is controversial, and
  - different authors offer different recommendations

http://www.ncbi.nlm.nih.gov/pubmed/10221287

http://www.ncbi.nlm.nih.gov/pubmed/16174674

2.3.7. Lithium and Calcium Metabolism Abnormalities

2.3.7. Lithium and Calcium Metabolism Abnormalities

2.3.7.1. Pharmacodynamics

2.3.7.2. Meta-Analyses and Reviews

2.3.7.3. Management

2.3.7.1. Lithium and Calcium Metabolism Abnormalities: Pharmacodynamics

2.3.7.1. Lithium and Calcium Metabolism Abnormalities: Pharmacodynamics

- Lithium interferes with parathyroid gland function, but the precise mechanism is not well-understood; it may antagonize the calcium-sensing receptor.

http://www.ncbi.nlm.nih.gov/pubmed/10221287

2.3.7.2. Lithium and Calcium Metabolism Abnormalities: Meta-Analyses and Reviews

2.3.7.2. Lithium and Calcium Metabolism Abnormalities: Meta-Analyses/Reviews

- Meta-analysis: http://www.ncbi.nlm.nih.gov/pubmed/22265699

  Lithium treatment was associated with:

  - □ ↑ blood calcium: +0·09 mMol/L (CI 0.02 to 0.17)
  - □ ↑ PTH: +7·32 pg/mL (CI 3.42 to 11.23)

- Review: Livingstone and Rampes, 2006:

  http://www.ncbi.nlm.nih.gov/pubmed/10221287

  Usually: □ serum calcium level ↑ mildly

  □ PTH: inappropriately ↑ for calcium level, although it may not necessarily > reference range

  (During hypercalcemia, PTH should be suppressed.)

2.3.7.3. Lithium and Calcium Metabolism Abnormalities: Management

2.3.7.3. Lithium and Calcium Metabolism Abnormalities: Management

- International guidelines http://www.ncbi.nlm.nih.gov/pubmed/19689501 recommend serum calcium:
  - baseline
  - at 6 months
  - then annually
- Differential diagnosis:
  - primary hyperparathyroidism:
    - hypercalciuria is usually present
  - lithium-associated hyperparathyroidism:
    - hypocalciuria and
    - normal serum phosphate levels

http://www.ncbi.nlm.nih.gov/pubmed/10221287

2.3.7.3. Lithium and Calcium Metabolism Abnormalities: Management

- In lithium patients,
  - majority: ↑ calcium levels are mild and do not require treatment
  - rarely: clinical manifestations of hypercalcemia; lithium discontinuation should be considered
- If the hypercalcemia persists after weeks of discontinuation
  - hyperparathyroidism should be investigated.

    It is unknown whether persistent cases are:
    - preexisting cases of hyperparathyroidism, or
    - not.

    http://www.ncbi.nlm.nih.gov/pubmed/19001061

2.3.8. Lithium and Cardiac ADRs

2.3.8. Lithium and Cardiac ADRs

2.3.8.1. Pharmacodynamics
2.3.8.2. Reviews
2.3.8.3. Management
2.3.8.4. Avoid Lithium in Brugada Syndrome

2.3.8.1. Lithium and Cardiac ADRs: Pharmacodynamics

2.3.8.1. Lithium and Cardiac ADRs: Pharmacodynamics

- Lithium is a potent blocker of cardiac sodium channels.
  http://www.ncbi.nlm.nih.gov/pubmed/17347696
- Regarding pharmacokinetics:
  Abnormalities have been described both at:
  - therapeutic lithium concentrations
  - toxic lithium concentrations

  Extrapolating from other psychiatric drug arrhythmias, these abnormalities may be concentration-related within a patient.
- A 9-year hospital study on sinus node dysfunction:
  - 4/5 on carbamazepine
  - adding carbamazepine to lithium may ↑ its risk

  http://www.ncbi.nlm.nih.gov/pubmed/7806689

2.3.8.2. Lithium and Cardiac ADRs: Reviews

2.3.8.2. Lithium and Cardiac ADRs: Reviews

- Several abnormalities:
  - the most frequent are EKG changes,
    which seldom have clinical significance. They include
    - T-wave flattening and
    - possible T-wave inversion, and

    can be similar to those produced by hypokalemia.
  - an occasional ADR is ↓ heart rate.
  - a rare ADR is arrhythmias,
    most frequently:
    - sinus node dysfunction and
    - atrioventricular blockade

2.3.8.3. Lithium and Cardiac ADRs: Management

2.3.8.3. Lithium and Cardiac ADRs: Management

- To avoid arrhythmias:
  - severe bradycardia
  - sinus node dysfunction and
  - atrioventricular blockade
  - lithium intoxications should be avoided, and
  - use lithium with caution in patients with:
    - prior cardiovascular disease, or
    - renal impairment.
- If these arrhythmias occur at therapeutic concentrations:
  - do careful risk/benefit assessment of continuation, and
  - consider cardiological consultation for possibility of pacemaker.

http://www.ncbi.nlm.nih.gov/pubmed/19352146

2.3.8.4. Lithium and Cardiac ADRs: Avoid Lithium in Brugada Syndrome

2.3.8.4. Lithium and Cardiac ADRs: Avoid in Brugada Syndrome

- Brugada syndrome: genetic channelopathy at heart repolarizing channels, either:
  - sodium
  - potassium
  - calcium
- Characterized by:
  - high incidence of ventricular fibrillation and
  - specific ECG pattern:
    - pseudo right bundle branch block and
    - persistent ST elevation in V_1 to V_3.

2.3.9. Lithium and Dermatological ADRs

2.3.9. Lithium and Dermatological ADRs

2.3.9.1. Meta-Analysis and Reviews
2.3.9.2. Management of Acne
2.3.9.3. Management of Psoriasis

2.3.9.1. Lithium and Dermatological ADRs: Meta-Analyses and Reviews

2.3.9. Lithium and Dermatological ADRs

- Meta-analysis: http://www.ncbi.nlm.nih.gov/pubmed/22265699
  - showed no significant ↑ risk of skin disorders or alopecia
  - is in disagreement with reviews by expert clinicians
- Dunner, 2000: http://www.ncbi.nlm.nih.gov/pubmed/10826665
  - most frequent dermatological ADRs:
    - dry skin
    - exacerbation of acne
    - exacerbation of psoriasis
  - hair loss is a rare ADR (rule out hypothyroidism).
- Jafferany, 2008: http://www.ncbi.nlm.nih.gov/pubmed/18986438

  More rare ADRs:
  - maculopapular eruptions
  - folliculitis
  - mucosal lesions
  - exfoliative dermatitis

2.3.9.2. Lithium and Dermatological ADRs: Management of Acne

2.3.9.2. Lithium and Dermatological ADRs: Management of Acne

- Acneiform eruptions:
  - new, or
  - exacerbation of prior case
- Usually begin as a monophormic eruption (all lesions in the same stage) on
  - face
  - neck
  - shoulders
  - back
- Usually respond to standard treatment, but if not, a dermatological consultation is needed

http://www.amazon.com/Handbook-Psychiatric-Therapy-Lippincott-Williams/dp/0781774861/ref=sr_1_1?s=books&ie=UTF8&qid=1458324003&sr=1-1&keywords=handbook+of+psychiatric+drug+therapy

2.3.9.3. Lithium and Dermatological ADRs: Management of Psoriasis

2.3.9.2. Lithium and Dermatological ADRs: Management of Psoriasis

- According to Jafferany, 2008: http://www.ncbi.nlm.nih.gov/pubmed/19287551
  - lithium can cause:
    - onset of new case: 2–6% of patients, or
    - an exacerbation of a prior case.
  - psoriasis may respond to inositol supplementation, according to an RCT http://www.ncbi.nlm.nih.gov/pubmed/15149510 but usually not to conventional treatment.
  - psoriasis usually disappears with the discontinuation of lithium.

2.3.10. Lithium and Ocular ADRs

2.3.10. Lithium and Ocular ADRs

- Rare ocular ADRs include:
  - eye irritation in the first weeks
  - exophthalmos
  - downbeat nistagmus

  Their presentation and management are reviewed in:

  http://www.ncbi.nlm.nih.gov/pubmed/20443647

2.4. Safety: Comments on Pharmacokinetics

2.4. Safety: Comment on Pharmacokinetics

- Pharmacokinetics facilitates pharmacodynamics.
- Safety:
  - Acute ADRs: once the concentration is toxic, pharmacodynamics determines the ADRs in each patient.
  - Chronic ADRs: ADRs are not well-studied for:
    - dose-related (or concentration-related) intoxication
    - non-dose-related intoxication

    Experts agree that some lithium ADRs are dose-dependent.
- Lithium is a narrow therapeutic window drug.

  See the presentation "Pharmacokinetics of Lithium" for more details. That presentation describes overdosing.
- The next 2 slides present a summary of the relationship between safety and serum lithium concentrations/doses.

2.4. Safety: Comment on Pharmacokinetics

- Lithium concentrations in bipolar disorder:
  Malhi & Berk, 2012: http://www.ncbi.nlm.nih.gov/pubmed/22265701
  - Therapeutic range is "reasonably well defined". (0.4–0.8 mmol/L),
  - Greater efficacy of concentrations (>0.6mmol/L)
    - is more necessary for acute mania and,
    - to a lesser extent, for maintenance, but

    comes at a cost in terms of tolerability.
  - Conversely, lower plasma concentrations that
    - might be adequate for depression prophylaxis,
    - and ↓ the risks of long-term toxicity

      might not be optimal to ↓ mania recurrence.

2.4. Safety: Comment on Pharmacokinetics

- Lithium dosing in bipolar disorder:
  Malhi & Berk, 2012: http://www.ncbi.nlm.nih.gov/pubmed/22265701
  Dosing can be used to ↓ ADR risk:
  - once-daily dosing
    - can maintain therapeutic concentrations and
    - carries minimal risk of long-term toxicity
  - several lithium ADRs are dose-dependent:
    - tremor
    - diarrhea
    - weight gain
  - Concentrations indicating incipient intoxication should prompt immediate dose adjustment.

2.5. Comment on Safety and Pharmacodynamic DDIs

2.5. Comment on Safety and Pharmacodynamic DDIs

- DDIs with lithium and antidepressants:
  - **↑ risk of serotonin syndrome**
  - antidepressants that ↑ weight have additive effects in combination with lithium.
  - antidepressants blocking the serotonin transporter may ↑ risk of polyuria
- DDIs with lithium and antipsychotics:
  - **↑ EPS risk**
  - most antipsychotics ↑ weight and have additive effects in combination with lithium.

2.5. Comment on Safety and Pharmacodynamic DDIs

- DDIs with lithium and carbamazepine:
  - ↑ **risk for neurological ADRs**
  - ↑ weight: additive effects in combination with lithium
  - possible ↑ risk of arrhythmias
  - possible additive effects on thyroid abnormalities
  - lithium ↓ the risk of carbamazepine-induced hyponatremia
- DDIs with lithium and valproate:
  - ↑ **risk for neurological ADRs**
  - ↑ weight: additive effects in combination with lithium
  - both lithium and valproate are associated with GI ADRs; it is unknown whether there are additive effects.

2.6. Lithium: Teratogenicity

2.6. Lithium: Teratogenicity

- Meta-analysis: http://www.ncbi.nlm.nih.gov/pubmed/22265699
  No significant ↑ risk of congenital malformations.
- Cardiac abnormalities, including Ebstein's anomaly, were initially associated with lithium in the first trimester.
  Prevalence in lithium pregnancies: very low (0.05–0.1%)
  http://www.ncbi.nlm.nih.gov/pubmed/20385337
- Recent reviews: a "weak" cardiac teratogen
  http://www.ncbi.nlm.nih.gov/pubmed/18378767
  http://www.ncbi.nlm.nih.gov/pubmed/18982835
- Prescribing information:
  Category D: positive evidence of risk

https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=LITHIUM+CARBONATE

2.6. Lithium: Teratogenicity

- Current view of lithium: http://www.ncbi.nlm.nih.gov/pubmed/20385337
  - lithium is considered a first-line alternative for the treatment of bipolar disorder during pregnancy.
  - at 16-18 weeks of gestation, performing high-resolution ultrasound fetal echocardiography to screen for cardiac anomalies is recommended.
  - effects on the newborn:
    - shallow respiration
    - hypotonia,
    - lethargy
    - cyanosis
    - diabetes insipidus
    - goiter
- Pregnancy: need to ↑ dose and then ↓ dose prior to delivery

.http://www.ncbi.nlm.nih.gov/pubmed/10826665

3. “Do Not Forget” Section

3. “Do Not Forget” Section

3.1. Key Issues in Efficacy
3.2. More Importat ADRs
3.3. Risk-Benefit Analysis

3.1. Key Issues in Efficacy

3.1. Key Issues in Efficacy

- Lithium is FDA approved for:
  - mania and
  - maintenance treatment of bipolar disorder
- For mania, lithium may be slower in onset than antipsychotics.
- For long-term maintenance, lithium is both:
  - the best and
  - the most-studied drug
- Remember that lithium's anti-suicidal properties may be very important in bipolar disorder.
- Approximately 1/3 of bipolar patients respond to lithium.
- Patients more likely to respond are those with the classic bipolar phenotype:
  - baseline euthymia, and
  - episodic relapses.

3.2. More Important ADRs

3.2. More Important ADRs

- To avoid ADRs: □ pay close attention to TDM
  □ consider once-daily dosing
- Cognitive complaints: the leading cause of non-compliance.
  Pay attention to them even if they seem vague to you.
- Weight gain: it may be concentration-related.
  Avoiding high-calorie beverages is recommended.
- GI ADRs: □ usually happen at the beginning
  □ late in treatment means possible toxicity
- Get baseline and pay attention to serum: □ TSH and
  □ calcium levels.
- Get baseline and pay attention to renal function.
  Good management is important to avoid kidney damage.
- Besides intoxications, lithium can kill in other ways,
  including: □ arrhythmias and
  □ the serotonin syndrome.

3.3. Risk-Benefit Analysis

3.3. Risk-Benefit Analysis

- In summary:
  - lithium can be life-saving in bipolar disorder, but
  - can be associated with multiple ADRs.

- It is very important to establish a long-term relationship with the patient in order to:
  - collaborate to avoid ADRs and
  - provide a reasonable risk-benefit analysis
    - when serious ADRs happen or
    - when other physicians who do not know the patient as well recommend stopping the lithium.

Questions

- Please review the 10 questions in the pdf titled "Questions on the Presentation Pharmacodynamics of Lithium".
- You will find the answers on the last slide after the "Thank you" slide. No peeking until you have answered all the questions.
- If you do not answer all the questions correctly, please review the Power Point presentation once again to reinforce the pharmacological concepts.

Thank you

Answers

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