Use of Tegretol and Trileptal in Psychiatric Practice

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Bipolar disorder in general

- Bipolar disorder is a mood disorder that is characterized by episodes of mania, hypomania, and major depression. The subtypes include bipolar I and bipolar II.
  - Bipolar I disorder: patients experience manic episodes, and nearly always experience hypomanic and major depressive episodes.
  - Bipolar II disorder: marked by at least 1 hypomanic episode, at least 1 major depressive episode, and the absence of manic episodes.

- Goal of treatment: The goal of treating acute mania and hypomania is remission (resolution of mood symptoms or improvement to the point that only one or two symptoms of mild intensity persist). If psychotic features (delusions or hallucinations) are also present, resolution of the psychosis is required for remission.

- Drug classes used: Lithium, **Anticonvulsants**, Antipsychotics, Benzodiazepines

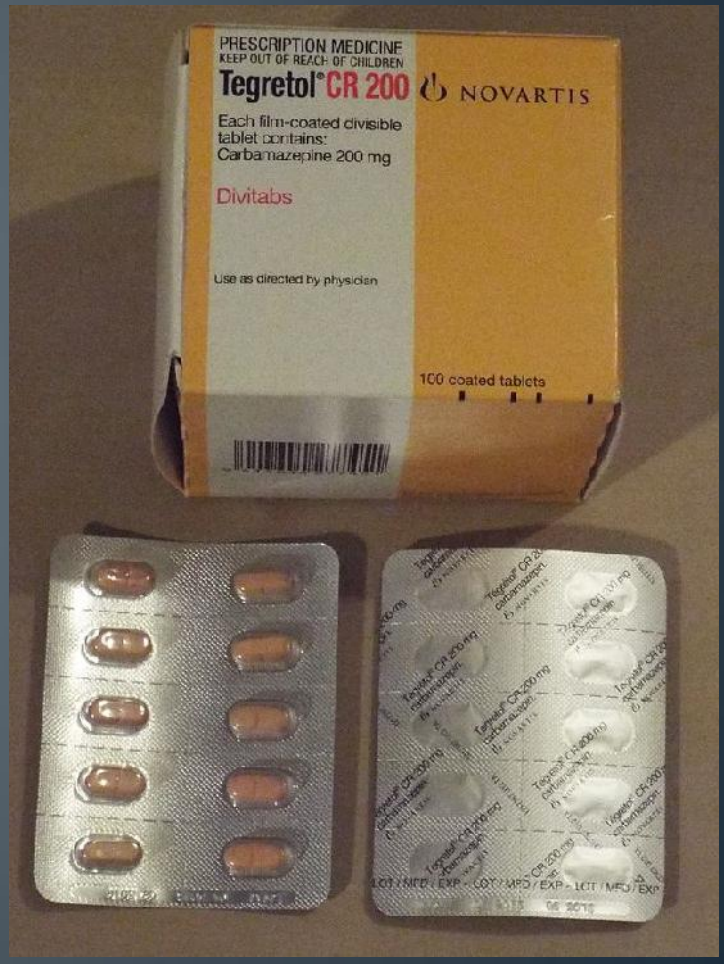
- Anticonvulsants that are efficacious for acute mania and hypomania ("ceiling" drugs):
  - valproate (Depakote)
  - **carbamazepine**
  - **oxcarbazepine**

Tegretol (carbamazepine)

- **Class**: Anticonvulsants

- **Indications**:
  - Epilepsy (partial seizures, generalized tonic-clonic seizures and mixed seizures)
  - 2nd line treatment for **manic and mixed episodes of bipolar I disorder**.
  - Trigeminal neuralgia
  - Neuropathic pain
  - In combination with an antipsychotic in some cases of **schizophrenia**.

- It is usually only used in people who have been unresponsive to lithium, however it may be better for rapid cycling bipolar illness.
- Pregnancy Class D



Tegretol: Pharmacokinetics

- Metabolism/Clearance:
  - >90 % metabolized by CYP3A4 to active metabolite, carbamazepine epoxide, which has anticonvulsant activity and can be measured in the serum.
- Mechanism of action:
  - Stabilizes inactivated state of voltage-gated Na channels, which leaves the affected cells less excitable until the drug dissociates.
  - Also a GABA receptor agonist, which may contribute to its efficacy in neuropathic pain and manic-depressive illness.
- In addition to anti-convulsant effects, carbamazepine has anti-cholinergic, anti-neuralgic, anti-diuretic, muscle relaxant, anti-manic, anti-depressive, and anti-arrhythmic properties.
- Half-life:
  - 25-65 hours (initial use, enzyme inducing naive patient),
  - 8-22 hours (after several weeks due to auto-induction)

Tegretol: Adverse effects

Common:

- Nausea, vomiting, diarrhea, rash, pruritus, dizziness, blurred vision, lethargy, headache, motor coordination impairment
- Less common: increased risk of seizures and arrhythmias
- Men may have higher rates of sexual dysfunction and low testosterone levels
- increased risks of suicide
- risks to the fetus in pregnant women: congenital malformations: spina bifida, and developmental disorders

Rare but serious:

- Aplastic Anemia/Agranulocytosis:
  - non-dose-related side effect that is most likely to occur within the first 3-4 months after initiating therapy
  - decrease of platelet or WBC counts but majority of leukopenia cases do not progress to aplastic anemia or agranulocytosis;
  - perform baseline and periodic hematological testing
  - WBC <3000/mcL or neutrophil counts <1000/mcL warrant either a decrease in dose with frequent WBC monitoring, or discontinuation of medication.

Tegretol: Pharmaco-genetics

- The FDA has informed health-care professionals that serious and life-threatening fatal skin reactions (Stevens–Johnson syndrome and toxic epidermal necrolysis) caused by carbamazepine therapy are significantly more common in patients with a particular human leukocyte antigen allele, HLA-B*1502., especially during the first 8 weeks of therapy.
- HLA-B*1502 occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians, but has a very low or absent frequency in European, Japanese, Korean and African populations.
- The FDA recommends screening for this allele in patients of these ethnic groups prior to starting carbamazepine.
- Patients testing positive should not be treated w/ carbamazepine unless benefit clearly outweighs risk

Tegretol: Interactions with other drugs

- Carbamazepine, as a CYP450 inducer, may increase clearance of many drugs, decreasing their concentration in the blood
  - Benzodiazepines, warfarin, phenytoin, theophylline, and valproic acid.
  - Birth control pills
  - Lamotrigine: May decrease level and increase carbamazepine level
  - Lithium: May increase CNS toxicity of Lithium. Avoid using together
  - MAO Inhibitors: May increase depressant and anti-cholinergic effects. Avoid using together.
- Grapefruit juice raises the bioavailability of carbamazepine by inhibiting CYP3A4 enzymes in the gut wall and in the liver
- Contraindicated
  - Hypersensitivity to this drug or tricyclic antidepressant
  - History of bone marrow suppression
  - MAO inhibitor use within 14 days
  - Mixed seizure disorder diagnosis (may experience increase in seizures)
  - Hepatic dysfunction
- Drugs that decrease the metabolism of carbamazepine or otherwise increase its levels include:
  - erythromycin, cimetidine, propoxyphene, and calcium channel blockers.

Tegretol: Management of therapy

- Bipolar disorder:
  - 800-1200 mg/day PO divided bid-qid
  - Start: 200 mg PO bid
  - Then, increase by 200 mg/day q3-4 days until therapeutic response is achieved
  - Max: 1600 mg/day
  - taper dose gradually to D/C
- Blood levels:
  - Initially measured at 3, 6, and 9 weeks
  - Therapeutic Drug Levels: 4-12 mcg/mL
  - Toxic Levels: >12 mcg/mL
  - Timing: before morning dose
  - Time to Steady State: >1mo
- Available forms
  - Capsules (extended-release): 100mg, 200mg, 300mg
  - Oral suspension: 100mg/5ml
  - Tablets: 200mg
- Monitoring Parameters q 6-12 months:
  - BUN/Cr
  - Serum Na
  - CBC w/ diff
  - Liver function tests
  - Urinalysis
  - Eye exam at baseline, then periodically
  - Symptoms of depression, behavior changes, suicidality

Trileptal (oxcarbazepine)

- Class: Anticonvulsants

- Compound with a similar chemical structure to carbamazepine, thus with a similar mechanism of action.
- Has less potential to affect other medications, therefore may sometimes be used instead.

- Indications:
  - Epilepsy
  - Chronic pain
  - Trigeminal Neuralgia
  - Bipolar disorder

- Pregnancy Class C

Trileptal: Pharmacokinetics

- Metabolism/Clearance:
  - occurs in the liver, but minimally affects the CYP system.
    - major advantage over carbamazepine, particularly in patients who require poly-therapy
  - activated to eslicarbazepine in the liver
  - 70 percent of active 10-monohydroxy metabolite (MHD) form undergoes UGT-glucuronidation
  - 30 percent is renally excreted as unchanged active drug
  - Half-life: 9 hours (active metabolite, prolonged in renal insufficiency)
  - The half-life does not change significantly with chronic administration due to a lack of autoinduction

- Mechanism of Action:
  - Oxcarbazepine and MHD block voltage-sensitive Na channels, stabilizing hyperexcited neuronal membranes, inhibiting repetitive firing, and decreasing the propagation of synaptic impulses.
  - Oxcarbazepine and MHD also increase K conductance and modulate the activity of high-voltage activated Ca channels.

Trileptal: Adverse effects

- Common:
  - Dizziness, headache, N/V, diplopia, balance disorder, tremor, nystagmus, abdominal pain, dyspepsia, gastritis, diarrhea/constipation, cognitive dysfxn, impaired concentration, rash, nervousness, insomnia, acne, photosensitivity
- Serious Reactions:
  - Hyponatremia, anaphylaxis, angioedema, drug rash w/ eosinophilia and systemic sx, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, suicidality, agranulocytosis, aplastic anemia, pancreatitis, withdrawal seizures if abrupt D/C

- The difference in structure helps reduce the impact on the liver of metabolizing the drug, and also prevents the serious forms of anemia or agranulocytosis associated with carbamazepine.

- Asian ancestry: Consider screening patients of Asian descent for HLA allele B*1502 prior to initiating therapy.
  - increased risk of developing Stevens-Johnson syndrome and/or toxic epidermal necrolysis in patients receiving carbamazepine or oxcarbazepine due to structural similarities
  - Screening is not recommending in low-risk populations or in current oxcarbazepine patients (risk usually during first few months of therapy).

Trileptal: Drug Interactions

- Alcohol: May enhance the CNS depressant effect of oxcarbazepine.
- Carbamazepine: May decrease serum concentrations of the active metabolite(s) of oxcarbazepine.
- Contraceptives (Estrogens/Progestins): oxcarbazepine may decrease the serum concentration of contraceptives
- Dolutegravir/Elvitegravir: oxcarbazepine may decrease the serum concentration. Consider using an alternative antiepileptic when possible.
- Eslicarbazepine: May enhance the adverse/toxic effect of oxcarbazepine. Risk X: Avoid combination
- Phenytoin: May decrease serum concentrations of the active metabolite(s) of oxcarbazepine. Consider increasing the initial adult oxcarbazepine extended release tablet dose to 900 mg/day.
- Hydrocodone: CYP3A4 Inducers may decrease the serum concentration of Hydrocodone.
- Phenobarbital: May decrease serum concentrations of the active metabolite(s) of oxcarbazepine.
- Selegiline: Oxcarbazepine may enhance the serotonergic effect of Selegiline. Risk X: Avoid combination
- Thiazide Diuretics: May enhance the adverse/toxic effect of oxcarbazepine. Specifically, there may be an increased risk for hyponatremia.
- Valproic Acid: May decrease the serum concentration of oxcarbazepine.

Trileptal: Management of therapy

- Dosing (*bipolar disorder):
  - 600-1200 mg PO bid
  - Start: 300 mg PO bid
  - Then increase by 300 mg/day q3 days or by 600 mg/day q wk
  - Info: taper dose gradually to D/C
- renal dosing:
  - CrCl <30: start 150 mg bid
  - Info: titrate dose slowly until response
- Blood levels:
  - MHD concentrations for efficacy may range from 2 to 55 mcg/mL
  - however, a clear correlation between plasma concentrations and therapeutic response has not been demonstrated
  - Therapeutic drug monitoring of MHD is not routinely warranted; but beneficial in:
    - optimizing seizure control in the following situations: extremes of age, pregnancy, renal impairment, to identify potential drug interactions, to assess reasons for therapeutic failure, or to rule out noncompliance
- Available forms:
  - Film-coated Tablets: 150 mg, 300 mg and 600 mg
  - Oral Suspension: 300 mg/5 mL (60 mg/mL)
- Monitoring Parameters:
  - Cr at baseline
  - CBC
  - Serum Na (first 3 months of therapy)
  - Periodic thyroid function tests (particularly pediatric patients)
  - Signs of depression
  - Behavior changes
  - Suicidality
  - Seizure frequency
  - Symptoms of CNS depression (dizziness, headache, somnolence)
  - Hypersensitivity reactions

Sidenote: Hyponatremia

- Hyponatremia associated with oxcarbazepine and carbamazepine is due to increased responsiveness of collecting tubules to antidiuretic hormone, and it is considered to be one of the forms of SIADH
- The incidence of hyponatremia associated with oxcarbazepine may be higher than with carbamazepine.
  - Elderly patients, particularly those on concomitant natriuretic drugs, are significantly more likely to develop hyponatremia.
  - Hyponatremia typically develops gradually in the first few months of therapy, which may explain why most patients are asymptomatic
- For patients with mild-moderate asymptomatic hyponatremia, the oxcarbazepine can be continued and water restriction and a high salt intake can be initiated in an attempt to raise the serum sodium concentration.
- Symtoms:
  - headache shortly after a dose is taken and tend to fade within 60 to 90 minutes;
  - Fatigue, stomach pain, tremor, rash, diarrhea, constipation, decreased appetite and dry mouth
  - craving for salty foods;
- Acute hyponatremia can cause cerebral edema, which can lead to encephalopathy and seizures.
  - Because of a cerebral adaptation, the degree of cerebral edema is less with chronic hyponatremia, and most patients seem to be asymptomatic.

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