DSH PSYCHOTROPIC MEDICATION
Operational Procedures
CARBAMAZEPINE PROTOCOL

I. Indications:

A. The individual cooperates with monitoring required for carbamazepine treatment.

B. At least 1 of the following clinical indications is present:

1. Complex partial, tonic-clonic, or mixed seizure type.

2. DSM bipolar mood disorder, including rapid cycling and mixed mood states.

3. DSM schizophrenia, especially if characterized by positive symptoms, psychomotor agitation, or mood lability.

4. DSM schizoaffective disorder.

5. DSM intermittent explosive disorder, as well as other impulse control disorders.

6. DSM major depression when used as an adjunct to recognized antidepressant medications. Reported response rates in samples refractory to antidepressant medication alone have been 25% to 33%.

7. DSM PTSD, especially if characterized by irritability and angry or violent outbursts.

8. Trigeminal neuralgia.

9. Alcohol and benzodiazepine withdrawal states, especially if withdrawal seizures are present or have been identified as occurring previously in the treated individual. Carbamazepine may have benefit in other sedative-hypnotic withdrawal states, however, no controlled data exist for these latter circumstances.

II. Contraindications:

A. History of sensitivity to carbamazepine, tricyclic compounds, or any components of the prescribed preparation.

B. History of blood dyscrasia due to carbamazepine.

C. History of inappropriate secretion of antidiuretic hormone (SIADH) due to carbamazepine or oxcarbazepine.

D. Presence of absence seizures (may induce status epilepticus).

E. Breast feeding.

III. Precautions (documented risk/benefit analysis supports use):

A. Cardiovascular disease, especially affecting cardiac conduction.

B. Anemic, thrombocytopenic, or leukopenic disorders.

C. Acute intermittent porphyria.

D. Known hepatic or pancreatic disease.

E. Concurrent use of medications which carry significant risks of blood dyscrasias, e.g. clozapine or antineoplastics.

F. Diabetes mellitus.

G. Renal disease.

H. Glaucoma.

I. Pregnancy associated with neural tube defects. Breast feeding is contraindicated (see previous section).

IV. Pretreatment screens include:

A. Informed consent or alternate legal authorization.

B. History of current pregnancy or planned pregnancy. History of current or planned breast feeding.

C. Workup includes:

1. CBC with differential, including platelets within 30 days.

2. Electrolytes within 30 days.

3. LFTs within 30 days.

4. Serum amylase within 30 days.

5. Urinalysis, BUN, and creatinine within 30 days.

6. Pregnancy test in women of child bearing potential within 30 days.

7. ECG within past 12 months.

8. HLA B1502 genotyping in patients of Asian ethnicity to address increased risk of hypersensitivity reactions in persons positive for this allele.

V. Monitoring includes:

A. Weekly – does not apply to individuals admitted on a chronic stable dose (i.e., monitoring defaults to semi-annual requirements):

1. Plasma carbamazepine concentration (first 4 weeks).

2. Electrolytes (first 4 weeks).

3. CBC with differential, including platelets (first 4 weeks).

B. Biweekly (does not apply to individuals admitted on a chronic stable dose, i.e. monitoring defaults to semi-annual requirements):

1. Plasma carbamazepine concentration (during months 2 and 3).

2. Electrolytes (during months 2 and 3).

3. CBC with differential, including platelets (during months 2 and 3).

C. Monthly – does not apply to individuals admitted on a chronic stable dose (i.e., monitoring defaults to semi-annual requirements):

1. Electrolytes (during months 4 – 6).

2. CBC with differential, including platelets (during months 4 – 6).

D. Semi-annually:

1. Electrolytes after first 6 months.

2. CBC with differential, including platelets after first 6 months.

3. LFTs.

4. Serum amylase.

E. Annually:

1. ECG.

F. Miscellaneous

1. Carbamazepine should be discontinued if SIADH results in plasma sodium <125 mg/dl.

2. Carbamazepine should be discontinued if platelets decline to <100,000 cells/mm^3.

3. Carbamazepine should be discontinued if WBC declines to < 3500 cells/mm^3 or ANC declines to < 1500 cells/mm^3.

4. Carbamazepine should be discontinued if RBC declines to <4,000,000 cells/mm^3, reticulocytes decline to <0.3%, or serum iron declines to <150 g/dL.

5. Finally, treated individuals should be educated to report any persisting or worsening skin rash, signs and symptoms of hepatotoxicity (e.g., nausea, vomiting, jaundice, or tenderness in the right upper quadrant of the abdomen), persisting sore throat, persisting infection, or increased bruising or bleeding, as longer monitoring periods are statistically unlikely to observe rare late adverse responses to carbamazepine.

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VI. Dosing:

A. Carbamazepine should be initiated at a dose of 200 mg BID to TID.

B. In the elderly or medically fragile, the initial dose should be reduced to 100 mg BID.

C. If tolerated, carbamazepine can be increased by as much as 200 mg per day, however, a slower titration rate of 200 mg every 3 to 4 days is likely to be better tolerated, especially in the medically fragile or elderly. Note that carbamazepine will increase its own rate of metabolism across the first 4 to 6 weeks of treatment, requiring dose adjustment to maintain adequate plasma concentrations. Optimal concentrations for seizure control are thought to range from 4 ng/mL to 12 ng/mL. Optimal plasma concentrations for treatment of mood disorders are thought to range from 8 ng/mL to 12 ng/mL.

D. Carbamazepine should not be given concurrently with monoamine oxidase inhibitors (MAOIs) and at least 14 days should elapse after discontinuing an MAOI before initiating carbamazepine.

E. Doses of > 2000 mg per day of carbamazepine for more than 15 days require Medication Review Committee (MRC) or Therapeutic Review Committee (TRC) consultation or review.

F. Carbamazepine induces a number of hepatic enzymes, resulting in a 30 to 80% decline of medications metabolized by the liver across the first 4 to 6 weeks of carbamazepine treatment (e.g., first- and second-generation antipsychotics, antidepressants, etc.). Conversely, discontinuation of carbamazepine will result in an increase of 30 – 80% in plasma concentrations of hepatically metabolized drugs. That is, induction may require dose adjustment to avoid loss of efficacy, including of birth control pills, while discontinuation may require dose reductions to avoid drug toxicities.

Like other tricyclic compounds, carbamazepine is metabolized via cytochrome P450 2D6. Potent inhibitors of this enzyme (e.g., fluoxetine or paroxetine) may produce a several-fold increase in carbamazepine plasma concentrations.

VII. Adverse risks:

A. Aplastic anemia.

B. Leukopenia and agranulocytosis.

C. Thrombocytopenia with increased petechial hemorrhage, increased bruising, or increased bleeding.

D. SIADH.

E. Delayed cardiac conduction, which may be associated with CHF, syncope, and bradycardia.

F. Nausea and vomiting, associated with either diarrhea or constipation.

G. Ataxia, nystagmus, sedation, headache, and confusion (sometimes including visual hallucinations).

H. Increased intraocular pressure.

I. Eosinophilia, sometimes associated with dermatitis, conjunctivitis, chills, fever, myalgia, and arthralgia.

J. Genitourinary dysfunction, increased BUN, and oliguria.

K. Cholestatic jaundice.

L. Decreased diabetic control.

M. Skin rash.

N. Suicide.

VIII. Drug Interactions:

A. **Anticonvulsants:** Decrease in serum concentrations and half-life of anticonvulsants and/or carbamazepine due to the induction of liver enzymes that metabolize these drugs. Monitoring via blood levels is recommended, especially when anticonvulsant medication is added to or deleted from a drug regimen that includes carbamazepine.

B. **Erythromycin:** Increased carbamazepine blood levels with potential toxicity. Alternate therapy is preferred. **Fluoxetine and paroxetine** also increase carbamazepine plasma concentrations, requiring dose adjustments**. Other SSRIs may increase carbamazepine plasma concentrations to a lesser extent.**

C. **Doxycycline:** Half-life of doxycycline is decreased.

D. **Warfarin:** Decreased blood level and half-life of warfarin.

E. **Oral Contraceptives (OCP):** Breakthrough bleeding or pregnancy may occur due to lower OCP blood levels. A nonhormonal method of birth control is advised to prevent conception or adjust via adequate increase in OCP.

F. **Monoamine Oxidase Inhibitors:** Potential hypertensive crisis if a MAOI washout period of at least 14 days is not allowed prior to carbamazepine. Alternate antidepressant medication advised.

G. **Clozapine:** Increased potential for bone marrow depression.

*****Please see table of drug-drug interactions with carbamazepine on next page. *****

CLINICALLY IMPORTANT INTERACTIONS BETWEEN CARBAMAZEPINE AND OTHER DRUGS		
Influences of Other Drugs on Carbamazepine		
Increased carbamazepine levels and toxicity produced by:	Danazol Diltiazem (not Nifedipine) Erythromycin (and Analogues) Influenza vaccine Isoniazid (not Tranylcypromine) Nafimidone Triacetyloleandomycin Verapamil Viloxazine	
Decreased carbamazepine levels produced by:	Phenobarbital Phenytoin Primidone Theophylline Tricyclic drugs	
Increased carbamazepine levels not associated with marked toxicity:	Cimetidine (mild acute ↑; none after one week) Nicotinamide Valproic acid	
Influences of Carbamazepine on Other Drugs		
Carbamazepine decreases levels or effects of:	Clonazepam Clozapine Cyclosporine Dexamethasone Dicoumarol Doxycycline Ethosuximide Haloperidol Olanzapine Phenothiazines Pregnancy Tests Theophylline Tricyclic Drugs Valproate Warfarin	

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