Measure Title: LIVER FUNCTION TESTS (LFT) AND COMPLETE BLOOD COUNTS (CBC) FOR PATIENTS INITIATED ON CARBAMAZEPINE OR VALPROIC ACID

Disease State: Liver function

Indicator Classification: Medication Monitoring

Strength of Recommendation: B

Specialties: Family Practice, Gerontology, Internal Medicine, Neurological Surgery, Neurology, Pediatrics, Psychiatry

Clinical Rationale: Disease Burden

- Carbamazepine and valproic acid are commonly used to treat seizure and mood disorders[1, 2].
- Epilepsy and seizures affect 2.7 million Americans of all ages, at an estimated annual cost of $12.5 billion in direct and indirect costs. Approximately 200,000 new cases of seizures and epilepsy occur each year. [3, 4]
- The World Health Organization monitors adverse drug reactions. In a recent systematic investigation of adverse drug reactions leading to liver injury and fatalities (88.3% of cases in the United States), valproate was the third most common drug associated with such fatalities. [5]

Reason for Indicated Intervention or Treatment

- Carbamazepine use can lead to hematological toxicity, such as rare aplastic anemia, persistent leukopenia, and isolated thrombocytopenia [[6-15]].
- Valproic acid use has been associated with multiple hematologic abnormalities, including thrombocytopenia [8, 12, 16].

Evidence supporting Intervention or Treatment

- **Carbamazepine**
  - A review of 13 cases of fatal aplastic anemia developing in patients taking carbamazepine showed that the medication was the probable cause in only 3 patients [17].
  - Clinical trials have shown that approximately 10% of patients taking carbamazepine develop transient leukopenia, usually during the first month of treatment. This resolves despite continuation of the medication [[7, 11, 13].
  - Case reports and clinical trials show that up to 8% of patients taking carbamazepine develop persistent leukopenia. This is usually evident during the first few weeks of therapy, and responds to discontinuation of the medication [9, 10, 14].
  - A case report on four patients developing thrombocytopenia while taking carbamazepine found that all cases appeared 14 to 16 days after the medication was initiated, and all resolved within 7 days after discontinuation. [15]

- **Valproic acid**
  - Several retrospective studies of patients taking valproic acid have shown that fatal hepatotoxicity is a side effect of the medication [18-21]. From 1987 to 1993, 29 patients on valproic acid developed fatal hepatotoxicity [18], and in a study of adverse drug reactions in the UK, anticonvulsants, and more specifically sodium valproate was associated with the greatest number of fatalities and more specifically, hepatotoxicity.
  - Cases of life-threatening pancreatitis have been reported in both children and adults.
and adults receiving valproate. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death.

- There is no evidence that early, presymptomatic detection of hematologic side effects with laboratory testing alters patient outcomes in patients taking carbamazepine or valproic acid.

**Clinical Recommendations**

- The FDA black box warning for Carbamazepine indicates that patients taking this medication have a risk that is 5-8 times greater than the general population for developing aplastic anemia and agranulocytosis. Therefore, they recommend:
  - performing complete pretreatment blood counts (including platelets and possibly reticulocytes and serum ion) and periodic monitoring through therapy.[22]
- The FDA black box warning for Valproic Acid indicates that patients taking this medication have an increased risk for developing hepatotoxicity and pancreatitis. Therefore they recommend:
  - performing pretreatment liver function tests and frequent monitoring through therapy, particularly within the first 6 months.
  - informing patients of the warning signs for pancreatitis.[23]

**Source**
Health Benchmarks, Inc.

**Denominator**
Continuously enrolled members, who had at least one prescription for either carbamazepine or valproic acid during the one year period beginning two months prior to the measurement year.

**Exclusion**
Members who received a prescription for either Carbamazepine or Valproic Acid in the 1-365 days prior to the index prescription.

**Numerator**
Members who have had appropriate monitoring lab work done 0-60 days prior to the index prescription. NB: Appropriate monitoring for CARBAMAZEPINE and VALPROIC ACID differ from each other as defined below.

**Interpretation of Score**
High score implies better performance

**Physician Attribution**
Score all physicians who saw the member 0-60 days prior to the index prescription date.

**External Files Required for Analysis**
neuromed_medlist1_2006.xls, neuromed_medlist2_2006.xls
Source: HBI, Master NDC
Updated: Annually

**References**
**Indicator Classification** (Adapted from Health Plan Employer Data Information Set (HEDIS®) technical specifications)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Measures applicable to patients receiving diagnostic workups for a symptom or condition that delineate appropriate laboratory or radiological testing to be performed (e.g. evaluation of thyroid nodule; pregnancy test in patients with vaginal bleeding or abdominal pain)</td>
</tr>
<tr>
<td><strong>Effectiveness of Care</strong></td>
<td></td>
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<tr>
<td><strong>Prevention</strong></td>
<td>Measures applicable to asymptomatic individuals that are designed to prevent the onset of the targeted condition (e.g. immunizations).</td>
</tr>
<tr>
<td><strong>Screening</strong></td>
<td>Measures applicable to asymptomatic patients who have risk factors or preclinical disease, but in whom the condition has not become clinically apparent (e.g. pap smears; screening for elevated blood pressure).</td>
</tr>
<tr>
<td><strong>Disease Management</strong></td>
<td>Measures applicable to individuals diagnosed with a condition that are part of the treatment or management of the condition (e.g. cholesterol reduction in patients with diabetes; radiation therapy following breast conserving surgery; appropriate follow-up after acute event).</td>
</tr>
<tr>
<td><strong>Medication Monitoring</strong></td>
<td>Measures applicable to patients taking medications with narrow therapeutic windows and/or potential preventable significant side effects or adverse reactions (e.g. thyroid stimulating hormone (TSH) testing after levothyroxine dose change; hepatic enzyme monitoring for patients using antimycotic pharmacotherapy).</td>
</tr>
<tr>
<td><strong>Medication Adherence</strong></td>
<td>Measures applicable to patients taking medications for chronic conditions that are designed to assess patient adherence to medication (e.g. adherence to lipid lowering medication).</td>
</tr>
<tr>
<td><strong>Utilization</strong></td>
<td>Measures applicable to patients receiving treatment for a symptom or condition that advocate appropriate utilization of laboratory and pharmaceutical resources (e.g. conservative use of imaging for low back pain; inappropriate use of antibiotics for viral upper respiratory infection).</td>
</tr>
</tbody>
</table>
2 Strength of Recommendation

Strength of Recommendation Based on a Body of Evidence

Is this a key recommendation for clinicians regarding diagnosis or treatment that merits a label?

Yes

Is the recommendation based on patient-oriented evidence (i.e., an improvement in morbidity, mortality, symptoms, quality of life, or cost)?

No

Strength of Recommendation = C

Yes

Is the recommendation based on opinion, bench research, a consensus guideline, usual practice, clinical experience, or a case series study?

No

Strength of Recommendation not needed

Yes

Is the recommendation based on one of the following?

- Cochrane Review with a clear recommendation
- USPSTF Grade A recommendation
- Clinical Evidence rating of Beneficial
- Consistent findings from at least two good-quality randomized controlled trials or a systematic review/meta-analysis of same
- Validated clinical decision rule in a relevant population
- Consistent findings from at least two good-quality diagnostic cohort studies or systematic review/meta-analysis of same

Yes

Strength of Recommendation = A

No

Strength of Recommendation = B

FIGURE 2. Algorithm for determining the strength of a recommendation based on a body of evidence (applies to clinical recommendations regarding diagnosis, treatment, prevention, or screening). While this algorithm provides a general guideline, authors and editors may adjust the strength of recommendation based on the benefits, harms, and costs of the intervention being recommended. (USPSTF = U.S. Preventive Services Task Force)