



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

Disease State Liver function **Indicator Classification¹** Medication Monitoring

Strength of Recommendation² 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 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 iron) 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 a one prescription for either carbamazepine or valproic acid during the one year period beginning two months prior to the measurement year.
Denominator 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. <i>NB: Appropriate monitoring for CARBAMAZEPINE and VALPROIC ACID differ from each other as defined below.</i>
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	Denominator Filename: neuomed_medlist1_2006.xls, neuomed_medlist2_2006.xls Source: HBI, Master NDC Updated: Annually
References	<ol style="list-style-type: none"> 1. Gajwani, P., et al., <i>Antiepileptic drugs in mood-disordered patients</i>. <i>Epilepsia</i>, 2005. 46 Suppl 4: p. 38-44. 2. Beghi, E., <i>Efficacy and tolerability of the new antiepileptic drugs: comparison of two recent guidelines</i>. <i>Lancet Neurol</i>, 2004. 3(10): p. 618-21. 3. Begley, C.E., et al., <i>The cost of epilepsy in the United States: an estimate from population-based clinical and survey data</i>. <i>Epilepsia</i>, 2000. 41(3): p. 342-51. 4. Johnson, C., <i>Epilepsy Foundation – National Office</i>, E. Falk, Editor. 2006. 5. Bjornsson, E. and R. Olsson, <i>Suspected drug-induced liver fatalities reported to the WHO database</i>. <i>Dig Liver Dis</i>, 2006. 38(1): p. 33-8.

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¹ **Indicator Classification** (Adapted from Health Plan Employer Data Information Set (HEDIS®) technical specifications)

Diagnosis	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)
Effectiveness of Care	
Prevention	Measures applicable to asymptomatic individuals that are designed to prevent the onset of the targeted condition (e.g. immunizations).
Screening	Measures applicable to asymptomatic patients who have risk factors or pre-clinical disease, but in whom the condition has not become clinically apparent (e.g. pap smears; screening for elevated blood pressure).
Disease Management	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).
Medication Monitoring	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)
Medication Adherence	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).
Utilization	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).

² Strength of Recommendation

Strength of Recommendation Based on a Body of Evidence

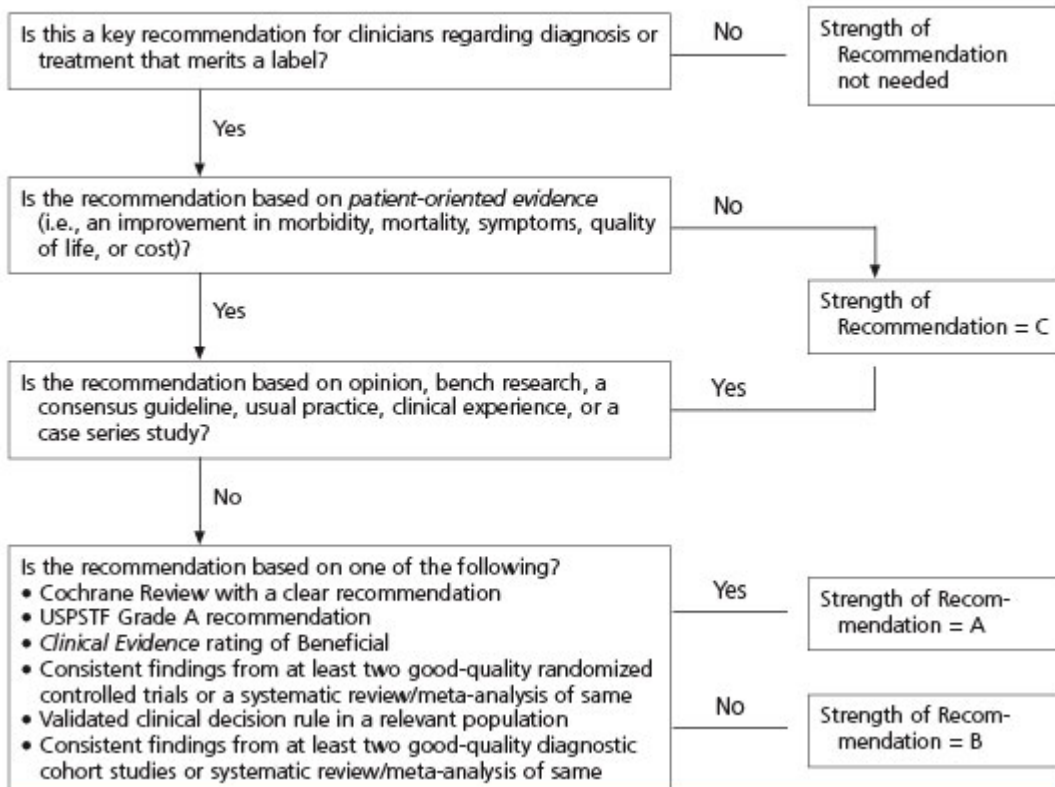


FIGURE 2. Algorithm for determining the strength of a recommendation based on a body of evidence (applies to clinical recommendations regarding diagnosis, treatment, prevention, or screening). While this algorithm provides a general guideline, authors and editors may adjust the strength of recommendation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