



DEPARTMENT OF THE NAVY  
BUREAU OF MEDICINE AND SURGERY  
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IN REPLY REFER TO  
BUMEDINST 6010.34  
BUMED-M5  
12 Aug 2019

BUMED INSTRUCTION 6010.34

From: Chief, Bureau of Medicine and Surgery

Subj: VALPROIC ACID MONITORING PROTOCOL

Encl: (1) Valproic Acid Clinical Decision Reference Algorithm

1. Purpose. To set standards for laboratory monitoring for patients started on valproate or valproic acid.
2. Scope and Applicability. This instruction applies to all budget submitting office 18, 60, 70, and 27 activities inside and outside the continental United States. This instruction applies to all military (active duty and Reserve) and civilian healthcare practitioners and clinical support staff, including those assigned, employed, contracted, or under resource sharing agreements and clinical support agreements with Department of the Navy activities or who are enrolled in a Navy-sponsored training program.
3. Background. Valproic acid is a branched chain organic acid that is used as therapy for epilepsy, bipolar disorders, and migraine headaches. It is a well-known cause of several distinctive forms of acute and chronic liver injury. There is no national consensus on laboratory monitoring for valproic acid-induced hepatotoxicity and the Food and Drug Administration's black box warning states laboratory values should be checked frequently, especially in the first 6 months. Additional information regarding potential hepatotoxicity from valproic acid is available from the National Institutes of Health <https://livertox.nih.gov/>. This instruction is not intended to direct management responsibilities of medical treatment facilities under the authority, command, and control of the Defense Health Agency.
4. Action
  - a. The following monitoring protocols will be implemented when prescribing valproic acid for Navy Medicine's patient population; see enclosure (1) for a reference algorithm:
    - (1) Epilepsy Patients. Perform liver associated enzymes (LAE) testing prior to initiation, then monthly for the first 6 months, and then yearly. If the LAEs (i.e., specifically aspartate aminotransferase (AST) or alanine transaminase (ALT)) become elevated between two and three times the upper limit of normal, increase monitoring to weekly, which should consist of LAEs and an international normalized ratio (INR). If the LAEs rise above triple the upper limit of normal, or if there is any elevation in the INR above the upper limit of normal, seek immediate neurology consultation (as abrupt withdrawal may provoke seizures) along with immediate internal medicine or gastroenterology consultation, and consider stopping the drug after clinical collaboration with these consultants.

(2) Non-Epilepsy Patients. Perform LAEs at initiation, at 3 months, at 6 months, and then yearly. If the LAEs (i.e., specifically AST or ALT) become elevated between two and three times the upper limit of normal, increase monitoring to weekly, which should consist of LAEs and an INR. If the LAEs rise above triple the upper limit of normal, or if there is any elevation in the INR above the upper limit of normal, seek immediate internal medicine or gastroenterology consultation and consider stopping the drug after clinical collaboration with these consultants.

b. Genetic testing for mitochondrial disorders is not recommended in adults except for patients presenting with epilepsy partialis continua without other explanation.

c. Hepatic toxicity due to valproic acid has a variety of clinical presentations, and the key to its detection is vigilance to abnormal laboratory values and sometimes nonspecific symptoms. These clinical presentations take on several different forms:

(1) Asymptomatic Elevation of LAEs. This is the most common type of hepatic dysfunction and is usually transient, reversible, and dose-related.

(2) Vague Symptoms Such as Increasing Somnolence. A high index of suspicion must be maintained when patients receiving valproic acid present with vague symptoms or somnolence, even in the presence of normal LAEs. In such cases, the only evidence of liver dysfunction may be hyperammonemia. Other vague symptoms may include nausea, vomiting, malaise, or abrupt increase in seizure frequency.

(3) Acute Liver Injury and Jaundice with Elevated LAEs. In rare cases, an idiosyncratic, non-dose related, irreversible hepatic failure may occur. Breakthrough seizures or status epilepticus, especially following a febrile illness, may be an indicator of impending liver failure prior to changes in LAEs, and may progress to coma and death.

(4) Reye-type Syndrome. This type of liver dysfunction is most commonly found in children and presents with fever and lethargy and can be followed by stupor and coma or even death. Attention should also be paid to detecting pharmacokinetic interactions which may raise the level of valproate and potentially increase the likelihood of hepatotoxicity.

## 5. Records Management

a. Records created as a result of this instruction, regardless of format or media, must be maintained and dispositioned for the standard subject identification codes (SSIC) 1000 through 13000 series per the records disposition schedules located on the Department of the Navy/ Assistant for Administration (DON/AA), Directives and Records Management Division (DRMD) portal page at <https://portal.secnav.navy.mil/orgs/DUSNM/DONAA/DRM/Records-and-Information-Management/Approved%20Record%20Schedules/Forms/AllItems.aspx>.

b. For questions concerning the management of records related to this instruction or the records disposition schedules, please contact your local records manager or the DON/AA DRMD program office.

6. Review and Effective Date. Per OPNAVINST 5215.17A, Chief Medical Office (BUMED-M5) will review this instruction annually around the anniversary of its issuance date to ensure applicability, currency, and consistency with Federal, Department of Defense, Secretary of the Navy, and Navy policy and statutory authority using OPNAV 5215/40 Review of Instruction. This instruction will be in effect for 10 years, unless revised or cancelled in the interim, and will be reissued by the 10-year anniversary date if it is still required, unless it meets one of the exceptions in OPNAVINST 5215.17A, paragraph 9. Otherwise, if the instruction is no longer required, it will be processed for cancellation as soon as the need for cancellation is known following guidance in OPNAV Manual 5215.1 of May 2016.

  
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Releasability and distribution:

This instruction is cleared for public release and is available electronically only via the Navy Medicine Web site, <https://www.med.navy.mil/directives/Pages/BUMEDInstructions.aspx>

VALPORIC ACID CLINICAL DECISION REFERENCE ALGORITHM

