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<b>(21) International Application Number:</b> PCT/US97/06712 <b>(22) International Filing Date:</b> 23 April 1997 (23.04.97) <b>(30) Priority Data:</b> 60/016,140                      24 April 1996 (24.04.96)                      US <b>(71) Applicant (for all designated States except US):</b> BRIGHAM AND WOMEN'S HOSPITAL [US/US]; 75 Francis Street, Boston, MA 02115 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> STOLL, Andrew, L. [US/US]; 35 Old Winter Street, Lincoln, MA 01773 (US). SEVERUS, Wolfram, E. [DE/DE]; Badensche Strasse 7, D-10825 Berlin (DE). <b>(74) Agent:</b> SANZO, Michael, A.; Vinson & Elkins, 1455 Pennsylvania Avenue, N.W., Washington, DC 20004 (US).		<b>(81) Designated States:</b> AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> OMEGA-3 FATTY ACIDS AND OMEGA-3 PHOSPHATIDYLCHOLINE IN THE TREATMENT OF BIPOLAR DISORDER		
<b>(57) Abstract</b>  <p>The present invention is directed to a method of treating patients with bipolar disorder by administering omega-3 fatty acids. These may be administered in a substantially purified form, as part of a pharmaceutical composition, or as part of a larger molecule, e.g. a triacylglycerol, which releases free fatty acid after ingestion by a patient. The present invention is also directed to triacylglycerols which are esterified at the gamma carbon of glycerol to phosphocholine and at either the alpha or beta carbon of glycerol to an omega-3 fatty acid. These "omega-3 phosphatidylcholines" are also used in the treatment of patients with bipolar disorder.</p>		

Petition for Inter Partes Review  
Of U.S. Patent 8,278,351

Exhibit

**ENZYMOTEC - 1010**

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# Omega-3 Fatty Acids and Omega-3 Phosphatidylcholine in the Treatment of Bipolar Disorder

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## *Field of the Invention*

The present invention relates to medical treatments for psychiatric disorders. More specifically, it is concerned with novel methods and compositions for treating patients with bipolar disorder.

## *Background of the Invention*

Patients with bipolar disorder suffer recurrent, alternating cycles of mania and depression. In a controlled clinical study performed more than a decade ago, it was reported that lecithin (phosphatidylcholine) has anti-manic properties when administered to such patients (Cohen *et al.*, *Am. J. Psychiatry* 139:1162-1164 (1982); see also Cohen *et al.*, *Am. J. Psychiatry* 137:242-243 (1980); Schreier, *Am. J. Psychiatry* 139:108-110 (1982)). More recent reports, have suggested that the beneficial effects observed for lecithin are due primarily to the metabolic release of free choline (Stoll *et al.*, *Biol. Psychiatry* 37:170-174 (1995)).

Although effective in reducing mania, lecithin is not widely used in treating bipolar patients. One of the main reasons for this is that 15-30 grams of lecithin per day must typically be given to a patient in order to obtain a beneficial effect and the intake of such a large quantity of lipid would, over time, tend to promote cardiovascular disease. An ideal solution to this problem would be to administer a therapeutic agent that has the same beneficial effect as lecithin in controlling mania but which does not have the same adverse effect with respect to cardiovascular disease.

The present invention is directed to phosphatidylcholines in which the  $\alpha$  or  $\beta$  carbon of glycerol is esterified to an omega-3 fatty acid. These fatty acids are unique among dietary fats in that they inhibit thrombosis and platelet aggregation and can lower blood pressure (see Dimmitt, *Clin. Exp. Pharmacol. Physiol.* 22:204-208 (1995)). Thus, the "omega-3 phosphatidylcholines" disclosed herein produce the same effects as lecithin in bipolar patients due to the release of free choline but reduce, rather than increase, the risk that a patient will suffer a stroke or coronary thrombosis.

In addition, the present invention is directed to a method of treating bipolar disorder using omega-3 fatty acids themselves, *i.e.* apart from phosphatidylcholine. These may be administered in a purified state, as part of a composition containing other therapeutic agents or

as part of another compound, e.g. a triacylglycerol, which is metabolized to release free fatty acid *in vivo*.

### *Summary of the Invention*

5 An evaluation of mood stabilizing agents indicates that all such agents presently used to treat bipolar patients have an inhibitory effect on neuronal signal transduction systems. The present invention is based, in part, upon this discovery and the upon the recognition that omega-3 fatty acids are useful in treating pathological conditions involving excessive cell signal transduction (see e.g., Sperling, *Rheum. Dis. Clinics* 17 (1991); Sperling, *et al.*, *J. Clin. Invest.* 91:651-660 (1993)).

10 Thus, a method has been developed for treating a human patient for bipolar disorder by administering omega-3 fatty acids at a dosage sufficient to reduce or eliminate the symptoms associated with the disorder, i.e. at a dosage sufficient to reduce the frequency of mood fluctuations or lessen the severity of the mania or depression experienced by such patients. The omega-3 fatty acids should be administered at a dosage of between about 1 and about 30 grams per day. The two most preferred omega-3 fatty acids are eicosapentanoic acid and docosa-  
15 hexanoic acid and these should typically be administered at daily dosages of 2-10 grams and 1-5 grams respectively. The fatty acids may be administered as the sole therapeutic agent or in conjunction with other agents known to be useful in the treatment of bipolar patients. In particular, the fatty acids may be administered either with a source of lithium or choline. In  
20 addition, omega-3 fatty acids may be taken by patients as a component of another molecule, e.g. a triacylglycerol, and be metabolically released after ingestion.

The present invention is also directed to an omega-3 phosphatidylcholine useful in the treatment of bipolar disorder, consisting of glycerol esterified at both its  $\alpha$  and  $\beta$  carbons to fatty acids. At least one, and preferably both, of these fatty acids is an omega-3 fatty acid and the  $\gamma$   
25 position of the glycerol must be esterified to phosphocholine. It is preferred that at least one of the esterified fatty acids be either eicosapentanoic acid or docosahexanoic acid. Omega-3 phosphatidylcholines with eicosapentanoic acid esterified to the  $\alpha$  carbon and docosahexanoic acid esterified to the  $\beta$  carbon and vice versa are the most preferred. In all cases, the  $\gamma$  position of the triacylglycerol is esterified to phosphocholine.

In another aspect, the present invention is directed to a pharmaceutical composition comprising one or more of the omega-3 phosphatidylcholines discussed above. The composition should contain sufficient triacylglycerol so that one or more unit doses provides enough agent to reduce or eliminate the symptoms associated with bipolar disorder. In some instances, lithium may be also incorporated into the composition in order to improve therapeutic effects.

The present invention is also directed to a method for treating bipolar disorder in a human patient by administering an omega-3 phosphatidylcholine. It is expected that this phosphatidylcholine will typically be administered at a dosage sufficient to provide between 1 and 30 (preferably between 2 and 8) grams of free omega-3 fatty acid to the patient. Again, administration may be carried out concurrently with the administration of other therapeutic agents such as lithium.

### *Detailed Description of the Invention*

In the following description, reference will be made to various methodologies well-known to those skilled in the art of medicine and pharmacology. Such methodologies are described in standard reference works setting forth the general principals of these disciplines. Included among the relevant references are: Goodwin, F.K. and Jamison, K.R., Manic Depressive Illness, Oxford University Press (1990); and Bloom, F. and Kupfer, D., Psychopharmacology. The Fourth Generation of Progress, Raven Press (1994).

#### **A. Definitions**

Bipolar disorder: Bipolar disorder refers to a form of psychosis characterized by abnormally severe mood swings. The patient alternates between episodes of mania and episodes of depression.

Omega-3 fatty acids: Fatty acids are long chain aliphatic molecules beginning with a methyl group and ending with a carboxyl group. Omega-3 fatty acids contain a double bond in the third position from the methyl group. Two common, long chain omega-3 fatty acids are eicosapentanoic acid (20 carbons in length) and docosahexanoic acid (22 carbons in length). These are both found in fish oils

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