Food for Thought: Review of Nutritional Modalities Used for the Treatment of Mental Illness

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Introduction
As technology in food preparation and processing has advanced, so has society’s food consumption pattern. Greater emphasis is placed on foods that complement the busy lifestyle of many people. This has resulted in the increasing popularity of energy-dense and nutrient-poor diets. In combination with a lack of physical activity, this has caused a vast increase in cardiovascular disease (CVD), such as coronary (or ischemic) heart disease (heart attack), cerebrovascular disease (stroke), hypertension (high blood pressure), heart failure, and rheumatic heart disease (WHO 2003).

Chronic noncommunicable diseases such as CVD, diabetes, obesity, cancers and respiratory disease account for 59% of the 57 million deaths annually and 46% of the global burden of disease. Risk factors for the diseases, including high blood pressure, high cholesterol, obesity, physical inactivity, and insufficient consumption of fruits and vegetables, are related to diet and physical activity (WHO, 2003). Thus, the growing importance of nutrition and physical health is a key determinant to one’s well-being.

These alterations in food consumption and diet have not only influenced chronic physical conditions, but also have had an impact on cognitive and emotional well-being. There is a strong link between what one consumes and one’s feelings. Inadequate eating habits can aggravate mental illness and prevent general good mental and emotional health (Somer 1999).

The brain is one of the most metabolically active organs in the body. It requires essential nutrients, vitamins, minerals, and essential fatty acids as cofactors for maintenance. Without the adequate intake of all these nutrients, the brain cannot function optimally (Horrobin 2002).

Through research, the scope of treatment options, including that of vitamins, minerals, and various nutrients, has increased. This article presents a brief overview of some recent studies involved in mental health and nutrition, particularly as it relates to depression. A specific dietary supplement, which has been the focus of much research for its nutritional benefits, is omega-3 fatty acid. This fatty acid will be discussed in more depth later in this article, as an example of a treatment for mental disorders.

Nutritional Supplements in Depression
Depression is characterized by feelings of sadness that last two weeks or longer. Depressed individuals tend to feel helpless and hopeless and to blame themselves for having these feelings. People who are depressed may become overwhelmed and exhausted and may stop participating in their routine activities. They may withdraw from family and friends. Some may even have thoughts of death or suicide (Strock 1994). Within the US, as many as 18.8 million adults, or 9.5% of the entire population,
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suffer from depression (APA 2005). Many theories have emerged for the treatment of depression. Here we will focus on the use of tryptophan in relation to the monoamine theory; SAMe, folate, and B12 from the methylation process; and, finally, the usage of minerals.

Tryptophan
A fundamental theory in understanding depression is the monoamine hypothesis. It is based on the presumption that essential amino acid supplementation will increase neurotransmitter levels and improve brain functioning. The essential amino acid tryptophan is obtained from diet and converted to 5-hydroxytryptophan (5-HTP), which is converted to serotonin, a neurotransmitter required for mood and psychological health, and thus used to treat depression. It has also been useful in treating fibromyalgia, binge eating, chronic headaches, obesity, and insomnia (Shannon 2001).

The benefits of tryptophan were demonstrated in a randomized, double-blind, placebo-controlled trial. Patients had met the criteria for nonpsychotic major depressive disorder based on the DSM-IV. All subjects were given 20 mg of fluoxetine every morning for eight weeks and assigned to one of two protocols: either 4 g of tryptophan or placebo 20 to 40 minutes before bedtime. Depression levels were assessed using the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI). Sleep study assessments were done at weeks 4 and 8 using electrophysiological recordings. It was hypothesized that individuals receiving the tryptophan and fluoxetine would have greater improvements in mood than the placebo and fluoxetine group. It was also believed that tryptophan might provide an antidepressant effect with the fluoxetine. Finally, it was also thought that tryptophan would improve sleep measures (Levitan, Shen, Jundal, Driver, Kennedy, and Shapiro 2000).

It was found that those in the fluoxetine plus tryptophan group showed a significant decrease in depression scores (BDI) compared to those using the fluoxetine and placebo, in the first week of treatment. Those in the tryptophan-fluoxetine group had greater improvements in mood than those receiving placebo (as shown by HDRS scores). Tryptophan also appeared to lessen the impact of fluoxetine-induced decrements in slow-wave sleep, resulting in better sleep (Levitan, Shen, Jundal, Driver, Kennedy, and Shapiro 2000).

SAMe
Other nutritional supplements, such as S-adenosyl-methionine (SAMe), have been used to treat depression, dementia, and other neurological disorders. SAMe is “a modified amino acid ubiquitous throughout the body, manufactured by cells using methionine. It is an essential amino acid found in high-protein foods like meat and fish.” (Shannon 2001).

SAMe has the ability to limit the accumulation of homocysteine, which can lead to increased arterial plaque formation; blood clotting; and elevated risk of heart disease, stroke, female reproductive cancers, colon cancer, Alzheimer's disease, fibromyalgia, and depression. SAMe is required in methylation, where a methyl group is transferred from one molecule to another. SAMe donates methyl groups in 35 different reactions to DNA, proteins, lipids, and hormones. It is believed that depression may be related to a weakening methylation (Shannon 2001).

A recent open trial was conducted to examine the use of SAMe as an adjunctive treatment for major depression. Outpatients met DSM-IV criteria for current major depressive disorder and were on medication to treat their mental illness. Subjects were started on 400 mg b.i.d. of SAMe tosylate and increased to 800 mg b.i.d. after two weeks. The study was conducted for a total of six weeks. The patients were assessed using the Hamilton Depression Rating Scale (HAM-D-17), the Montgomery Asberg Depression Rating Scale (MADRS), BDI, the CGI – Severity and Improvement scales, the Kellner Symptom Questionnaire (SQ), and the Massachusetts General Hospital Sexual Function Questionnaire. Pre- and posttreatment serum homocysteine levels were measured. Also, baselines for B12, homocysteine, serum, and red blood cell folate were determined (Alpert et al. 2004).

The study showed that there was a small but significant decrease in pretreatment to posttreatment homocysteine levels. The Massachusetts General Hospital Sexual Function Questionnaire scores also indicated improvement. There was also a significant reduction in depression severity from baseline to endpoint, as measured by the MADRS, HAM-D-17, and BDI. There was also a significant decrease in scores for the CGI-S scores. There was no statistical significance with the SQ scores. Folate, B12, and homocysteine levels were not associated with positive clinical response to SAMe augmentation. These improvements in depression suggest that there is a beneficial relationship with SAMe augmentation (Alpert et al. 2004).

B12, Folate and Folinic Acid
Other critical methyl donor groups, besides SAMe, include vitamin B12 (cyanocobalamin and folate [folic acid]). Often patients with major depressive disorder are also low in plasma and red cell folate levels, which causes them to respond less well to antidepressants (Shannon 2001). A study completed by Coppen and Bailey (2000) examined this hypothesis through the benefits of folic acid when augmented with the antidepressant fluoxetine. A randomized, double-blind, placebo-controlled study was completed in a multicenter general practice setting. Subjects were enrolled in the study and diagnosed with depression, according to the DSM-III-R. Each was
prescribed 20 mg/day of fluoxetine. Subjects were assigned either 500 μg of folic acid or matching placebo, in addition to their medication, for ten weeks. Hamilton Rating Scale (HRSD) and laboratory tests measuring vitamin B12, homocysteine, and plasma folate levels were utilized.

The results showed that the folic acid group had a significantly better response at week ten than the patients in the placebo group. However, this applied only to the women subjects. The patients in the folic acid group had significantly increased plasma folic acid concentration at 10 weeks. There was a significant decrease in homocysteine levels in the women only (21.0%) (Coppen and Bailey 2000).

This study suggested that only in female depressed patients did the augmentation of folic acid significantly improve the response to fluoxetine. Improvements were related to plasma homocysteine levels and not plasma folate. The smaller increase in plasma folate in men, which did not change the plasma homocysteine levels, may indicate their lack of clinical response. It was assumed that analyzing the results with a higher dosage of folic acid in men may be useful in future studies (Coppen and Bailey 2000).

Moreover, Alpert, Mischoulon, Rubenstein, Bottonari, Nierenberg, and Fava (2002) examined whether folinic acid, which is metabolized to methylfolate, the major physiological form of folate, could enhance selective serotonin reuptake inhibitor (SSRI) response among depressed normofolaticem adults with major depressive disorder with an inadequate response to SSRIs. Patients who met DSM-IV criteria for major depressive disorder, and had shown a partial or no response to SSRIs or venlafaxine after at least four weeks of treatment, were enrolled in an eight-week open trial. Folinic acid (leucovorin) was given as 15 mg/day for two weeks, followed by 30 mg/day for 6 weeks. Leucovorin was added to a stable SSRI regimen of adequate dosage (e.g., fluoxetine 20 mg/day, sertraline 50mg/day). Response to treatment was determined using the HAM-D-17 and the CGI.

Those who completed the study had a decreased mean HAM-D-17 and CGI score from the baseline visit. At screening, all subjects had folate levels greater in the moderate to high range, which rose significantly at the end of the trial. Thus, adjunctive folinic acid may represent a desirable approach to refractory/recurrent depression in some depressed patients with normal or high folate levels (Alpert et al. 2002).

Minerals

Minerals are also important in treating depression. One, zinc, is an important bioelement in the immune and nervous systems; and imbalances may accompany mood disturbances. Nowak, Siwek, Dudek, Zieba, and Pilc (2003) examined the effect of zinc supplementation on antidepressant therapy in unipolar depression. Patients meeting DSM-IV criteria for depression participated in a randomized, double-blind, placebo-controlled trial. Subjects received antidepressant medication and were randomly assigned to either zinc supplements (25mg Zn2+) or placebo for 12 weeks. Patients' psychological status was assessed using the HDRS and the BDI.

Initially, after the second week, the antidepressant therapy reduced the HDRS score in both groups. However, the zinc supplementation significantly reduced the HDRS scores at the sixth and twelfth week of treatment, when compared to the placebo group. The zinc group had also significantly reduced the BDI scores at the twelfth week of treatment, when compared to the placebo supplementation. There is a delay in the effect of zinc co-treatment; however, the results do indicate it to be beneficial in treating unipolar depression (Nowak et al. 2003).

Bipolar disorder, also known as manic-depressive disorder, is related to depression, and thus similar treatment modalities have been used to treat patients with this illness. This disorder causes unusual shifts in a person's mood, energy, and ability to function. Different from the normal ups and downs that everyone goes through, the symptoms of bipolar disorder are severe. They can result in damaged relationships, poor job or school performance, and even suicide.

One study used a combination of vitamins and minerals adjunctively with current medication to treat bipolar disorder. Kaplan, Simpson, Ferre, Gorman, McMullen, and Crawford (2001) examined the therapeutic effects of 36 ingredients, primarily chelated minerals. Subjects who had met the DSM-IV criteria for bipolar I, bipolar II, or bipolar disorder not otherwise specified (NOS) participated in an open-label trial. Subjects were administered 32 capsules consisting of a mineral and vitamin formulation, which were distributed 4 times throughout the day, in addition to their psychotropic medications. Patients were assessed by their own psychiatrists for 6 months using various measures such as, HAM-D, Young Mania Rating Scale (YMRS), and the Brief Psychiatric Rating Scale (BPRS).

Among the intention-to-treat (ITT) subjects (those who entered the study), there was a 55% symptom reduction in the HAM-D, 60% reduction on the BPRS, and 66% reduction on the YMRS. For those who completed the study, psychotropic medication was reduced by more than 50% after they began taking the supplement. These preliminary data indicate that nutritional supplements have a beneficial psychotropic effect (Kaplan et al. 2001).

These studies indicated the importance of proper food and nutrition in the diet, particularly for those who suffer from mental illness. Further, it appears that nutrition is a key determinant in the outcome and prevalence of various mental disorders.
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Omega-3 Polyunsaturated Fatty Acids

Fatty acids play a dominant role in the formation of a cell membrane's phospholipid bilayer. Each phospholipid molecule is made up of a 3-carbon glycerol backbone. At the Sn3 position is a phosphorus atom and a head group. The properties of the phospholipid depend on the nature of the head group and the fatty acids attached at the Sn1 and Sn2 positions. The membrane varies in physical properties according to the wide variety of saturated and unsaturated fatty acids that attach to the Sn1 and Sn2 positions. Altering the phospholipid environment affects the functional activity of the neurotransmitter receptors and other proteins embedded inside the protein (Peet 2002).

Fatty acids can be subdivided into saturated, monounsaturated, and polyunsaturated. There are two main types of polyunsaturated fatty acids, omega-6 and omega-3. Arachidonic acid (AA) and docosahexaenoic acid (DHA) are the most abundant fatty acids in the brain. AA, dihomogamma-linolenic acid, and eicosapentaenoic acid (EPA) are also important cell-signaling and enzyme-regulating molecules. The parent precursors to these acids, linolenic (omega-6) and ω-linolenic (omega-3), are known as "essential" fatty acids because they cannot be created by humans. The omega-3 fatty acids are primarily obtained from marine and vegetable sources and the omega-6 fatty acids from animal and plant sources (Peet 2002).

In the past, humans consumed a low-fat diet containing a large amount of omega-3 fatty acids and much less omega-6. Currently, the fatty acid consumption is generally reversed, whereby a disproportionately high amount of omega-6 fatty acids is consumed. This imbalance is associated with a greater increase in some major mental illnesses (Somer 1999).

With a firm understanding of the background and purpose of essential polyunsaturated fatty acids, the next step is to be able to use them in treatment. In the case of depression, it is evident that omega-3 deficiency plays a major role in its prevalence. Various studies have been conducted to analyze omega-3 benefits when used in a clinical setting. Marangell, Martinez, Zboyan, Kertz, Kim, and Puryear (2002) conducted a randomized, double-blind, placebo-controlled trial of the omega-3 fatty acid DHA in treating patients with major depression. The patients were assigned either 2 g/day DHA or placebo for 6 weeks. Subjects were assessed using the MADRS, the HDRS, and the Global Assessment of Functioning Scale.

There was no significant difference between the DHA and the placebo group. The results suggest, that while omega-3 has proven effective in treating depression, it is not DHA fatty acid that is beneficial; thus EPA must be further examined. A variety of other studies have closely studied the influence of EPA in treating depression (Marangell et al. 2002).

Peet and Horrobin (2002) conducted a randomized, double-blind study using a mixture of doses of ethyl-EPA in patients with chronic depression despite ongoing treatment with an adequate dose of a standard antidepressant. Subjects were randomized to placebo, 1 g/day, 2 g/day, or 4 g/day of ethyl-EPA for 12 weeks. Subjects were assessed using the MADRS, the HDRS, and the BDI. Two populations were assessed: the ITT, which included all those who were randomized, and the per-protocol (PP), which included the patients who had completed the 12 weeks of treatment.

The results demonstrated over 90% compliance in all treatment conditions. The majority of the adverse events recorded were due to gastrointestinal events, which affected 4 of the 18 in the placebo group and 20 of the 52 in the ethyl-EPA groups. These events were attributable to the intake of 4 g/day of an oily substance. The 1 g/day group showed a significant improvement in scores on the MADRS, HDRS, and the BDI when compared to the placebo. In the 2 g/day group, none of the measures approached significance. In the 4 g/day group, the comparisons approached significance in the PP population but not the ITT population. Thus, the study suggests that 1g/day of ethyl-EPA is an effective dosage to treat for the symptoms of depression (Peet and Horrobin 2002).

Peet, Brind, Ramchand, Shah, and Vankar (2001) had conducted a series of trials to investigate this fatty acid influence. The first was an open-label study investigating the influence of fish oil in treating schizophrenia in patients who were symptomatic despite using antipsychotic medication. Patients were given 10 g/day of concentrated fish oil (containing 1.1g DHA and 1.7g EPA) for 6 weeks. Outcome measures consisted of the Positive and Negative Syndrome Scale (PANSS) and the Abnormal Involuntary Movement Scale (AIMS). By the end of 6 weeks, patients had shown significant improvement in their symptoms, as indicated by their scores on the PANSS and AIMS. From these results, the next step was to conduct a pilot double-blind trial to compare EPA and DHA with a placebo.

For the second trial, again, patients diagnosed with schizophrenia and on a stable dosage of medication were selected. They were also symptomatic despite medical treatment with antipsychotics. Patients continued taking their medication while being randomly allocated to treatment of 2g EPA, 2g DHA, or equivalent corn oil placebo. Patients were rated on the PANSS scale at the beginning and end of the three-month treatment (Peet et al. 2001).

After treatment, the PANSS scores were significantly lower in the EPA group than in the other groups. This indicated that subjects in this group were less symptomatic after the three months. There was a significant treatment effect favoring EPA over DHA on the positive PANSS score but...
not for the negative symptoms. Further, those with higher baseline EPA levels had the most improvement on the PANSS scores. The study authors assumed that those with particularly low levels of polyunsaturated fatty acid levels, which responded less well to EPA treatment, perhaps had a more serious underlying metabolic abnormality that cannot be treated through EPA administration. The next step was to determine whether EPA alone was sufficient in treating schizophrenia (Peet et al. 2001).

Patients diagnosed with schizophrenia, on no medication, and presented as either new or relapsed cases were randomly assigned to either 2g/day EPA or equivalent placebo for three months. The purpose of this study was to use EPA as the sole treatment, if possible, but antipsychotics were permitted if clinically necessary (Peet et al. 2001).

In the placebo group, every subject required conventional antipsychotic medication by the end of the trial period. However, six patients on EPA were not taking antipsychotic medication at the end of the study. Four of the six went through the entire period without antipsychotic medication, one received medication for the first week only, and one received a single dose of depot antipsychotic medication at the start of the trial. Furthermore, the EPA group had a significantly lower PANSS scores by the end of the study compared to the placebo group. Again, this difference applied predominantly to the positive symptom subscale (Peet et al. 2001). The results of this study suggest that the application of EPA in the treatment of schizophrenia presents promising results.

To further the development of combination supplements in treating schizophrenia, Arvindakshan, Ghate, Ranjekar, Evans, and Mahadik (2003) examined vitamins E and C with omega-3 to use adjunctively with medication. Outpatients diagnosed with schizophrenia according to DSM-IV criteria were tested and compared with normal, healthy controls. Pretreatment, posttreatment, and four-month posttreatment washout assessments included the PANSS, BPRS, Heinrichs Quality of Life (QOL), and the General Psychiatry Cluster Score (GTOT). Treatment for the schizophrenia group involved a mixture of EPA/DHA (180:120 mg), and a mixture of antioxidants (400 IU Bio E:500 mg Celin) for four months. Blood levels were drawn at posttreatment and at the four-month washout.

Blood samples confirmed that EPA and DHA levels were lower in the pretreatment schizophrenic patients when compared to the normal controls. However, the levels had significantly increased posttreatment. The psychological assessments showed an improvement in the schizophrenic patients’ scores from the posttreatment and washout scores when compared to pretreatment scores. This was the first study to show that combination supplementation was effective in improving psychopathology with a concomitant increase in both DHA and EPA. These improvements were evident after the washout period as well. This study presents promising results using a combination of fatty acids and nutrients to treat schizophrenia.

Stoll, Severus, Freeman, Ruef, Zboyan, Diamond, Cress, and Marangell (2003) studied the use of omega-3 in the treatment of bipolar disorder, by conducting a double-blind, placebo-controlled trial. It was hypothesized that omega-3 fatty acids would be an effective mood stabilizer in bipolar disorder. Patients with bipolar disorder on constant medication were randomized to receive either omega-3 fatty acid (7 capsules, 2 times/day with each capsule containing 6.2 g EPA and 3.4 g DHA) or an olive oil placebo for 16 weeks. At baseline, a psychiatric and medical history was obtained. The following rating scales were performed at this time: Structured Clinical Interview for DSM-IV screening for current mania and depression, Young Mania Scale, HDRS, investigator- and patient-rated CGI scale, the Global Assessment Scale, and adverse-effects scale. The main outcome measure of the study was the duration of time to exit the treatment because of bipolar disorder symptoms becoming severe enough to cause a change in medication.

Stoll et al. (1999) noted that the patients in the omega-3 trial remained in the study longer than the placebo group. A post hoc analysis was conducted on a subgroup of eight subjects who did not receive any mood-stabilizing drugs upon entering the study. Those in the omega-3 group remained in remission significantly longer than the subjects who received the placebo monotherapy. According to the secondary measures, the omega-3 group performed much better than the placebo group. This showed that omega-3 fatty acids used as an adjunctive treatment in bipolar disorder resulted in a significant symptom reduction and a better outcome compared with placebo.

Borderline personality disorder (BPD) is a serious mental illness characterized by pervasive instability in moods, interpersonal relationships, self-image, and behavior. This instability often disrupts family and work life, long-term planning, and the individual’s sense of self-identity. Originally thought to be at the “borderline” of psychosis, people with BPD suffer from a disorder of emotion regulation. There is a high rate of self-injury without suicide intent, as well as a significant rate of suicide attempts and completed suicide in severe cases (NIMH 2001).

Zanarini and Frankenburg (2003) examined the influence of ethyl-EPA as monotherapy in a double-blind, placebo-controlled pilot study of female patients with borderline personality disorder. Subjects were given either 500 mg ethyl-EPA or an equivalent placebo for 8 weeks. They were assessed on the MDRS and the Modified Overt Aggression Scale.

The ethyl-EPA treatment group showed a significantly greater decrease
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in psychological assessment scores than the placebo group. This indicated an improvement in their condition. Thus, the results show that ethyl-EPA may be a safe and efficacious monotherapy for moderately disturbed women with borderline personality disorder (Zanarini and Frankenburg 2003).

The trend surrounding the lack of omega-3 consumption and rates of illness can be seen occurring internationally. The relevance of polyunsaturated fatty acids for their effects on mental disorders has been emphasized through national epidemiological studies. Noaghiul and Hibbeln (2003) conducted an epidemiological study examining the relationship of lifetime prevalence of bipolar disorder in various countries to differing rates of seafood consumption. Prevalence rates of schizophrenia were used as a control measure. The Cross-National Collaborative Group epidemiological study of ten countries, and other studies identified through MEDLINE and Psychinfo were analyzed for rates of bipolar disorder and schizophrenia. National seafood consumption rates were obtained from National Marine Fisheries Service and the Food and Agriculture Organization of the United Nations.

The results showed that higher national seafood consumption predicted lower prevalence rates of bipolar spectrum disorder, bipolar I disorder, and bipolar II disorder. The greatest rise in prevalence rates for bipolar disorder generally occurs in countries having a seafood consumption of less than 50 lb. per person annually. These results assume that an insufficient dietary intake of omega-3 essential fatty acids increases the risk of affective disorders (Noaghiul and Hibbeln 2003).

Dietary practices taken in relation to schizophrenia and depression were assessed by Peet (2004). He rationalized that physical illness, particularly diabetes and coronary heart disease, was occurring with increased frequency in patients with major mental illness, such as schizophrenia and depression. Therefore, he performed an ecological analysis of international variations of food supply in relation to epidemiological data on the outcome of schizophrenia and on the prevalence of depression.

A robust relationship was found between the high dietary consumption of seafood and reduced prevalence of depression, and less strongly with the intake of starchy roots. The seafood consumption provided the strongest independent predictor of depression prevalence. The data indicated that greater consumption of refined sugar was associated with a worse outcome of schizophrenia and a greater prevalence of depression. Thus, the study determined that dietary patterns that influence insulin resistance and result in diseases associated with metabolic disturbances are reflected by the dietary patterns of those with the mental illness (Peet 2004).

These results suggest a wide potential for using omega-3 fatty acids either adjunctively or independently in treatment approaches to various mental illnesses. It also appears that the increase in mental disorders reflects the changes in international food consumption habits. Thus, the importance of a diet containing all essential antioxidants and fatty acids is essential to consider when planning treatment for mental disorders.

Conclusion

When considering treatment options for mental illnesses, it is important to include the influence of diet. For instance, with depression, tryptophan was found to be an important regulator of serotonin; SAMe, folic (or folinic) acid; vitamin B12 and key nutrients regulate the methylation cycle; and the use of zinc or chelated minerals to regulate symptoms. Omega-3 presented the value of particular nutritional supplements showing promise in treating many different mental disorders, such as depression, schizophrenia, bipolar disorder, and borderline personality disorder, either adjunctively or as a sole treatment.

This article has presented highlights on some recent studies being conducted in nutrition and mental health. These studies show much promise for the management of mental illness, and future researchers can consider this food for thought when studying nutritional supplements as adjunctive treatment.

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