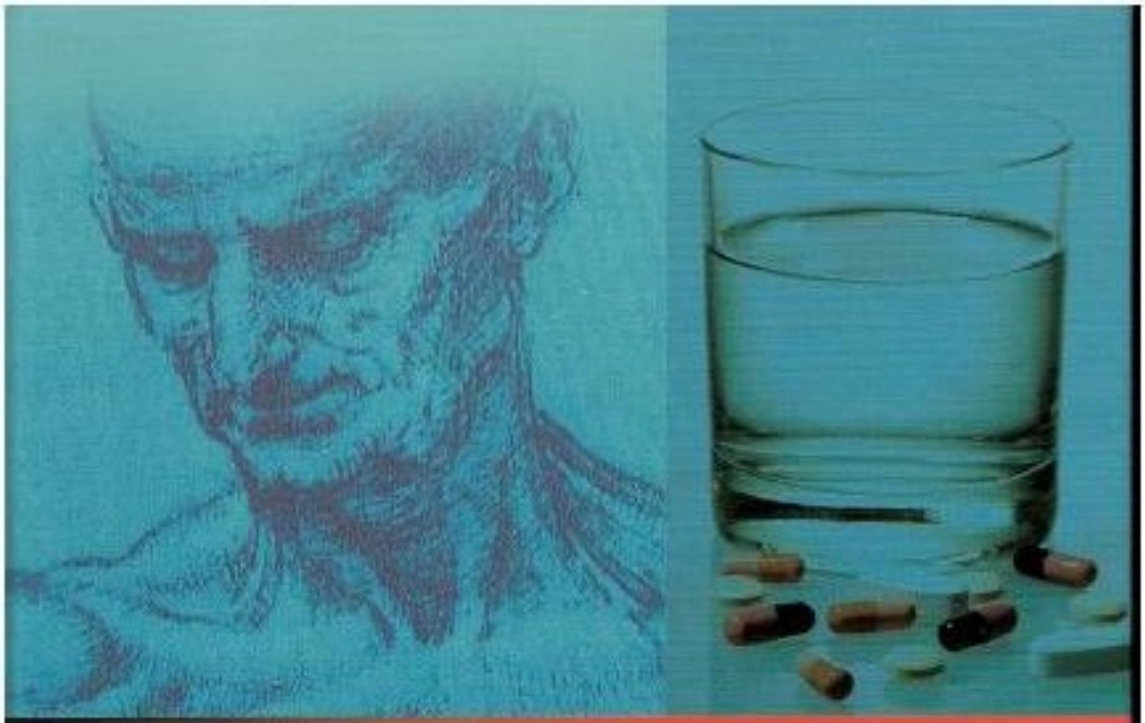
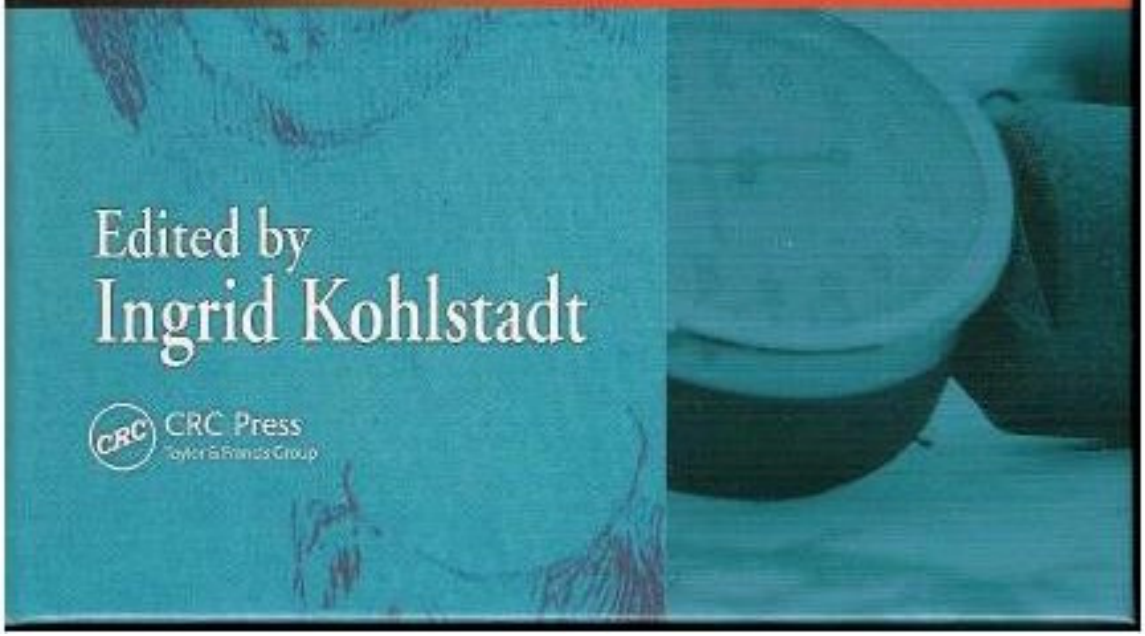


Food and Nutrients in Disease Management



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29 Depression

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I. INTRODUCTION

Since amino acids obtained from dietary sources are the precursors of mood-regulating neurotransmitters such as serotonin and dopamine, amino acids are considered to hold potential in treating depression. Neurotransmitter precursors are the subject of ongoing research.

So why is this topic relevant to primary care medicine? Patients have taken matters into their own hands. Patients are self-treating their depression with amino acid supplements and appear to be motivated by a perceived benefit in their mood and overall health. The amino acid precursors tryptophan, tyrosine, 5-hydroxytryptophan, and L-dopa are readily available as supplements at doses that exceed feasible dietary intake. Amino acids supplements have less potential for harm and larger therapeutic effect when their use is physician-guided.

This chapter presents the bundle damage theory of depression to probe the biologic basis of amino acid therapy. It offers primary care physicians a treatment protocol that implements laboratory testing to guide dosing; explains the potential side effects and how these can be minimized; offers quality regulation in product selection; and presents a protocol for simultaneous use of medication and nutrients in the treatment of clinical depression.

II. EPIDEMIOLOGY

Depression is a global problem. The World Health Organization notes:[32]

> Nearly 5–10% of persons in a community at a given time are in need of help for depression. As much as 8–20% of persons carry the risk of developing depression during their lifetime. The average age of the onset for major depression is between 20 and 40 years. Women have higher rates of depression than men. Race or ethnicity does not influence the prevalence of depression. World wide depression is the fourth leading cause of disease burden, accounting for 4.4% of total Disability-Adjusted Life-Years (DALYs) in the year 2000. It causes the largest amount of non-fatal burden. Disability from depression world wide is increasing. In 1990, the total years lived with disability (YLD) was 10.7%. By 2000, the YLD had increased to 12.1% worldwide.[33] Mental health conditions have a tendency to move upwards in ranking, while ranked as the fourth leading cause of disease burden in 2000, it is expected that depression will move to second place by 2020, second only to heart disease.[34]

Population surveys suggest that while the incidence of depression is higher in the developed countries of North America and Europe than in other regions, it is nonetheless a common condition throughout the world.[38] The rate difference is often attributed to underdiagnosis, but newer data suggest that the Western diet, stressful lifestyle, and higher toxicant exposures contribute to the prevailing high rates in Westernized countries.[32]

The monoamine theory fails to explain why the incidences of depression are increasing on a worldwide basis and is more prevalent in developed countries.[1]

III. PATHOPHYSIOLOGY

The Monoamine Theory

The monoamine theory of depression has long been the major framework against which the treatment of depression has been examined and developed due to the fact that the theory attempts to provide a pathophysiologic explanation for depression and the actions of antidepressants. The central premise of the monoamine theory states that it may be possible to restore normal function in depressed patients by targeting the catecholamine and/or serotonin systems with antidepressants. This theory is based on evidence that depression symptoms can be improved by administering compounds that are capable of increasing monoamine concentrations in the nerve synapses. Early research focused on deficits in the catecholamine system with specific emphasis on noradrenalin as a potential cause for depression. With further research, the theory was expanded to include the serotonin system as a cause for depression. This research has led to the use of drugs for treatment of depression that affect changes in monoamine uptake and enzymatic metabolism.[1]

While many of the depression treatments based on the monoamine theory appear to be initially useful, many of them lack the short-term and long-term efficacy needed for relief of symptoms in most patients. In several studies of reuptake inhibitors administered, only 8% to 13% of subjects obtained relief of symptoms greater than placebo. Remission rates for escitalopram compared to placebo in adults was studied (48.7% vs. 37.6%, P = 0.003). Here, 11.1% of subjects obtained relief greater than placebo.[35] Remission rates for citalopram versus placebo in another study were studied (52.8% vs. 43.5%, P = 0.003). Here, 9.4% of patients obtained relief greater than placebo.[35] Venlafaxine-XR was similar to escitralopram and citalopram (P = 0.03).[35]

Treatment of the elderly in the primary care setting under the monoamine theory reveals no relief of symptoms versus placebo. In the elderly (79.6 years, SD = 4.4, N = 174), it was concluded that citalopram, "was not more effective than placebo for the treatment of depression."[27] In treatment of depression in patients over 60 years of age with a mean age of 68 years, "Escitalopram treatment was not significantly different from placebo treatment" (N = 264).[29]

Depression treatment of children and adolescents ages 7 to 17 (N = 174) with citalopram, under a double-blind 20 mg/day, 40 mg/day option, found 24% of patients treated with placebo showed improvement versus 36% of patients taking citalopram.[28]

Other studies of other reuptake inhibitors revealed similar results.[50–55]

Reuptake inhibitors are effective in treating other disorders than those for which they were initially developed, such as obesity, panic disorder, anxiety, migraine headaches, ADHD/ADD, premenstrual syndrome, dementia, fibromyalgia, psychotic illness, insomnia, obsessive-compulsive disorder, and bulimia/anorexia; yet not all drugs that increase serotonin or catecholamine transmission are effective when treating depression.[1]

Treatment with reuptake inhibitors is based on the monoamine theory, which does not explain why most subjects studied achieve results no better than placebo and why treatment is much less efficacious in the elderly. Neither does it explain the efficacy of treating other conditions. In sum, the mechanism and corresponding medication for the treatment of depression suggest there may be more to the underlying pathophysiology.

Parkinsonism Model

Insights into the pathophysiology of depression can be gained from understanding another monoamine neurotransmitter disease, Parkinson's disease. Parkinsonism is caused by damage to the dopamine postsynaptic neurons of the substantia nigra at levels that result in clinical compromise of fine motor movement.

Parkinson's disease has a study model of neurotoxin damage.[49] A great deal of understanding about Parkinson's disease has resulted from research and case studies involving the neurotoxin MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine). In 1982, the first writings on MPTP appeared in the medical

literature after several heroin addicts administered synthetic heroin (MPPP) that contained the byproduct of synthesis, MPTP.[9] Since that time, the MPTP mechanism of action has become the prototype in the study of Parkinson's disease. At present, most medical school students study the ability of MPTP to quickly induce advanced Parkinson's symptoms in patients without prior history of the disease.

MPTP is a free radical neurotoxin, which interferes with mitochondrial metabolism and leads to cell death (apoptosis). It freely crosses the blood-brain barrier and has an affinity for the postsynaptic dopamine neurons of the substantia nigra, which it destroys. MPTP is chemically similar to MPPP (synthetic heroin) and may be produced as a byproduct during the illegal manufacturing of MPPP and other narcotics.[9] The MPTP model of Parkinson's disease has taught us a lot about the dopamine neurons of the substantia nigra. The main point is that if enough dopamine neurons are damaged, the flow of electrical impulses is compromised and Parkinson's symptoms will occur. The way to compensate for neurotoxin-induced damage is to increase neurotransmitter levels higher than is normally found in the system.[9]

Consistent with the findings of the MPTP model, the pharmacologic treatment is dopamine agonists, which raise the existing levels of this neurotransmitter above population norms in order to boost damaged neurons. Dopamine agonists, such as bromocriptine, pergolide, ropinirole, pramipexole, and cabergoline can be used as a monotherapy or in combination with L-dopa. L-dopa crosses the blood-brain barrier and is freely synthesized into dopamine without biochemical regulation.[3] The elevation of dopamine in the central nervous system stimulates the remaining viable dopamine neurons of the substantia nigra by increasing the electrical flow, which results in restoration of the regulator function of the dopamine bundles and improvement of disease symptoms.[7] The shortcoming is tachyphylaxis, where the dopamine agonist and/or L-dopa become ineffective.

With Parkinson's patients, establishing dopamine levels in the reference range reported by the laboratory does not provide relief of symptoms. For example, the reference range of urinary dopamine reported by the laboratory is 40 to 390 micrograms of dopamine per gram of creatinine (the neurotransmitter-creatinine ratio compensates for dilution of the urine). In our years of research, we have not observed a patient with Parkinson's who was able to achieve relief of symptoms with dopamine levels in this range. For treatment of patients with Parkinson's, the therapeutic range of urinary dopamine is 6000 to 8000 micrograms of dopamine per gram of creatinine. Dopamine levels of this magnitude can be achieved by administration of the amino acid precursor, L-dopa. Amino acid supplementation can reduce the tachyphylaxis generally associated with pharmacologic interventions. Once the synaptic levels of dopamine are high enough and the flow of electricity is once again adequate to regulate fine motor control, clinical resolution of the Parkinsonian tremor and other symptoms are seen.[40]

As with Parkinsonism, the damage to other neuron bundles of the serotonin/catecholamine pathways as seen in depression can be dealt with effectively by increasing the neurotransmitter levels higher than is normally found in the system. This has led our group to propose the Bundle Damage Theory of Depression.

The Bundle Damage Theory

The bundle damage theory states:

> Neurotransmitter dysfunction disease symptoms, such as symptoms of depression, develop when the electrical flow through the neuron bundles that regulate function is compromised by damage to the individual neurons or the neuron components composing the neuron bundle which conducts electricity to regulate or control function. In order to optimally restore neuron bundle regulatory function, synaptic neurotransmitter levels of the remaining viable neurons must be increased to levels higher than is normally found in the system, which restores adequate electrical outflow resulting in relief of symptoms and optimal regulatory function.

Bundles of neurons convey electricity that regulates and/or controls numerous functions in the body. If enough of the individual neurons of a bundle become damaged the flow of electricity through

the bundle is diminished, leading to the function being controlled and/or regulated not controlling properly, causing symptoms of disease to develop. Technically synaptic neurotransmitter levels prior to treatment in patients with disease due to neuron bundle damage are in the normal range for the population.

The bundle damage theory and the monoamine theory are not mutually exclusive of each other. Instead these two theories can be viewed a complementary in that they address different mechanisms of action leading to neurotransmitter dysfunction and compromised electrical flow out of the postsynaptic neuron. The monoamine theory addresses low levels of neurotransmitters in the synapse as the etiology of impedance of electrical flow needed to regulate function and keep disease symptoms under control. The bundle damage theory addresses damage to the primarily postsynaptic neuron structures that impede the flow of electricity needed to regulate function and keep disease symptoms under control. With the monoamine theory and the bundle damage theory the flow of electrical energy needed to regulate function is not adequate. Differentiation of the two theories lies in the etiology of the dysfunction. Under monoamine theory returning neurotransmitter levels to normal will relieve disease symptoms. Under the bundle damage theory synaptic neurotransmitter levels need to be established that are higher than the reference range of the population.

It is the mechanical damage to the postsynaptic neurons as suggested by the bundle damage theory and not the synaptic neurotransmitter levels that is the primary cause of monoamine disease. This subset is composed of about 88% of adult patients and 100% of the elderly patients with depressive symptoms—the nonresponders from the depression studies above.

Neurons are intended to function for life. Loss of a neuron to apoptosis is permanent, although in limited areas of the brain neurons may regenerate to replace the neurons that have undergone apoptosis.[58] As neurons go into apoptosis in the postsynaptic neuron and become completely nonfunctional they tend to go through an agonizing death where the electrical brilliance with which they function slowly fades until the electrical flow through the neuron regulating function decreases and stops over time.

The only way to increase neurotransmitter levels in the central nervous system is to administer amino acid precursors that cross the blood-brain barrier and are then synthesized into neurotransmitters. Increasing neurotransmitter levels in the synapse is analogous to increasing the voltage in an electrical wire, whereby turning up the voltage you get more electricity out of the other end of the wire. Turning up the voltage increases the electrical potential (pressure) of the electrons entering a partially damaged wiring connection, leading to more electrons (electricity) flowing out of the other end. In the case of neurotransmitter disease where the neurons of the neuron bundles are damaged to the point that the electricity flowing out of the neuron bundles is diminished disease develops. Increasing neurotransmitter levels will effectively increase voltage in the remaining viable neurons in the bundle, causing electrical flow out of the damaged neuron bundles to increase to the point that normal regulation and/or control is once again observed. In this state, from a clinical standpoint, the symptoms of disease are under control.

Etiology of Bundle Damage

Bundles of monoamine neurons can be impaired from neurotoxin exposures, trauma, or biological insult.[56] Neurotoxin exposures are poorly defined and ongoing exposures are in contrast to the MPTP study model of Parkinsonism. The most comprehensive listing located reveals 1179 known neurotoxins.[39] Susceptibility of individuals based on genetic predisposition, environmental influences, synergy between chemicals or other predisposing factors suggest that some individuals may experience neurotoxicity from many unlisted substances and at lower than threshold doses of known neurotoxins, and so was not considered. Under the bundle damage theory it is assumed that neurotoxins are the leading cause of monoamine bundle damage leading to the following speculation:

The bundle damage's theory of repeated insult during a lifetime can explain the lack of efficacy seen in the treatment of elderly with reuptake inhibitors who presumably have greater cumulative lifetime effects from neurotoxins and other events that cause neuron damage. In the end these patients need to have neurotransmitter levels established that are much higher than can be achieved with reuptake inhibitors alone.

With repeated insult more damage occurs, which is cumulative. When the damage is at the point where the neurotransmitter levels needed to control disease symptoms cannot be achieved with the use of reuptake inhibitors alone, from a clinical standpoint it appears that the drug is not working. This may explain why about 90% of adults treated with reuptake inhibitors achieve results no better than placebo.

The bundle damage theory may also explain why developed countries have a higher rate of depression as the population is exposed at a higher rate to neurotoxins.

Since insult exposure may be ongoing in patients with depression, optimizing nutritional status is important. Improving neuronal ability to minimize and recover from toxic insult form the basis of the antioxidant nutrients Dr. David Perlmutter explains in Chapter 28, "Parkinson's Disease," and the membrane-stabilizing nutrients Dr. Patricia Kane explains in Chapter 24, "Seizures."

IV. PHARMACOLOGY

Amino Acids

Treatment of depression, as well as any other monoamine neurotransmitter diseases, is not possible through the direct administration of monoamine neurotransmitters. This is due to the fact that monoamine neurotransmitters do not cross the blood-brain barrier, as depicted in Figure 29.1.[2,3,4,5] The only way to increase the levels of central nervous system monoamine neurotransmitter molecules is to provide amino acid precursors, which cross the blood-brain barrier and are synthesized into their respective neurotransmitters by presynaptic neurons.[6,7]

Reuptake Inhibitor Depletion of Monoamine

The National Institute of Drug Abuse presents a detailed discussion on its website on how reuptake inhibitors deplete neurotransmitters.[22] Medicines used to treat depression are not the only drugs that block reuptake; cocaine and amphetamines block reuptake as well.[22] Reuptake inhibitors block

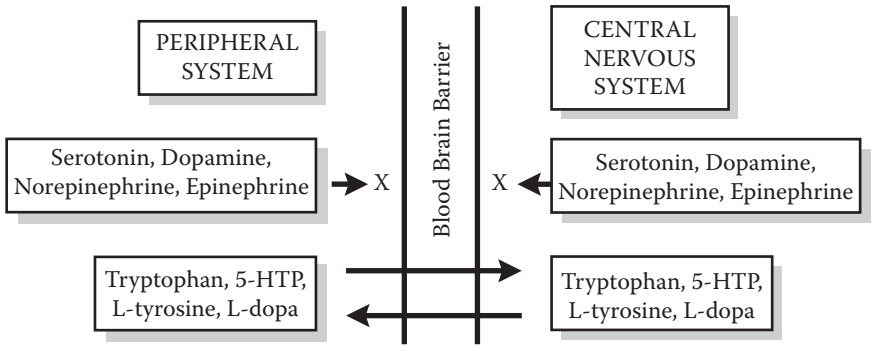

FIGURE 29.1 The monoamine neurotransmitters serotonin, dopamine, norepinephrine, and epinephrine do not cross the blood-brain barrier; therefore, peripheral administration of these neurotransmitters will not increase central nervous system neurotransmitter levels. The amino acid precursors of these neurotransmitters do cross the blood-brain barrier. The only way to increase central nervous system neurotransmitter levels is through administration of amino acid precursors.

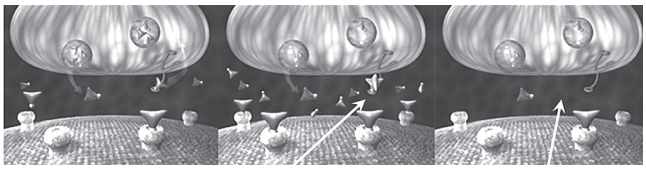

FIGURE 29.2 The effects of reuptake inhibitors on neurotransmitter levels, reuptake inhibition may deplete neurotransmitters. In the left picture, prior to treatment, neurotransmitter levels are not high enough to prevent symptoms of disease. In the center picture, reuptake is blocked, neurotransmitters move from the vesicles of the presynaptic neuron to the synapse. In the right picture, the neurotransmitters are depleted, the increase in synaptic neurotransmitter levels results in an increase in MAO and COMT metabolism (From The National Institute of Drug Abuse).

the uptake of neurotransmitters back into the presynaptic neuron. In doing so, synaptic levels are increased. As synaptic neurotransmitter levels rise, relief of symptoms is observed.

Monoamine Oxidase (MAO) and the Catecholamine O-Methyl Transferase (COMT) enzymes metabolize serotonin, dopamine, norepinephrine, and epinephrine. The monoamine neurotransmitters are relatively stable and are not metabolized until they come in contact with the MAO and COMT enzymes. When neurotransmitters are in the vesicles of the presynaptic neuron, they are not exposed to metabolism by the MAO and COMT enzymes; they are safe and stable. When neurotransmitters are in the synapse between the presynaptic and postsynaptic neuron, they are exposed to enzymatic metabolism, which leads to the depletion of neurotransmitters if proper levels of amino acid precursors are not administered to compensate for this process.[24]

In depressed patients, synaptic neurotransmitter levels are not high enough to prevent disease symptoms, as illustrated in Figure 29.2. Treatment with reuptake inhibitors leads to a decrease in presynaptic neurotransmitter levels (where they are safe from enzymatic metabolism) and an increase in the number of neurotransmitters in the synapse. The blocking of neurotransmitter reuptake increases synaptic levels and the probability that neurotransmitters will experience enzymatic metabolism.

With regards to Figure 29.2, the net effect of enzymatic metabolism is the depletion of neurotransmitter levels in the central nervous system. Neurotransmitters do not cross the blood-brain barrier. Therefore, the only way to increase central nervous system levels or to prevent the overall depletion of neurotransmitters when administering prescription drugs that block reuptake is to provide amino acid precursors, which are then synthesized into neurotransmitters. Administering L-tyrosine (not phenylalanine or n-acetyl-tyrosine) or L-dopa is the only way to predictably raise dopamine, norepinephrine, and epinephrine. Administering tryptophan or 5-hydroxytryptophan (5-HTP) is the only way to predictably raise serotonin levels in the central nervous system. It is noted that 5-HTP, L-dopa, and tyrosine are available in the United States without a prescription. The ability of tryptophan to raise serotonin levels is limited because it is a rate-limited reaction.

The effects of neurotransmitter depletion by drugs may have far-ranging implications. It has been found in studies that depletion of serotonin by drugs may also lead to a reduction in the number of serotonin synapses in the hippocampus.[43]

Monoamine Synthesis from Amino Acids

The synthesis of serotonin and the catecholamines is illustrated in Figure 29.3. Peripheral administration of only 5-HTP (serotonin system) or only L-dopa (dopamine system) will decrease the synthesis of the other system (dopamine or serotonin respectively).[57] With administration of only one amino acid precursor, the administered amino acid precursor dominates the enzyme and compromises proper synthesis of the other system's neurotransmitters. This is due to the fact that the same enzyme catalyzes the conversion of 5-HTP to serotonin and L-dopa to dopamine everywhere in the body.

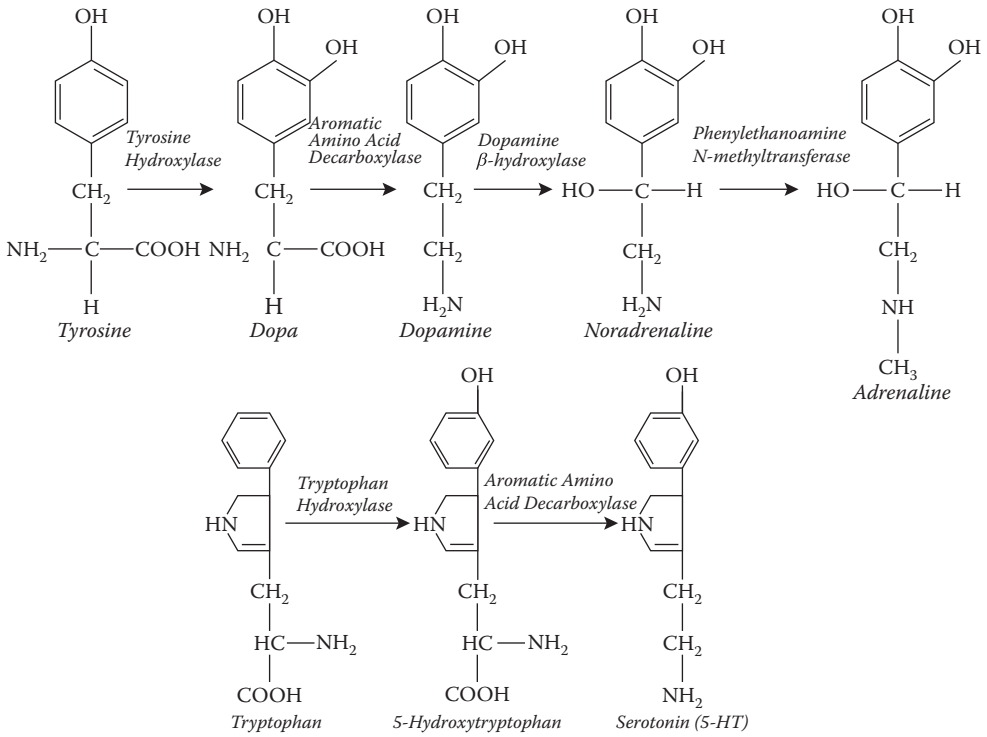

FIGURE 29.3 The synthesis of serotonin, dopamine, norepinephrine, and epinephrine from amino acid precursors.

The aromatic L-amino acid decarboxylase enzyme is also known as 5-HTP decarboxylase enzyme or L-dopa decarboxylase enzyme, as well as the general decarboxylase enzyme, is illustrated in a kidney in Figure 29.4 (bottom right). The implications of this fact are profound.[10] The administration of only 5-HTP or L-dopa will compete with and inhibit the synthesis of the opposite precursor (dopamine and serotonin, respectively) at the enzyme.

In patients with Parkinson's, the long-term administration of L-dopa with insufficient serotonin precursor will result in depression. The literature is very clear that this depression is a serotonin-dependent depression, which responds optimally to the most serotonin specific reuptake inhibitor, citalopram.[11]

Amino Acids and Monoamine Metabolism

The MAO and COMT enzymes metabolize serotonin and the catecholamines, as illustrated in the kidney in Figure 29.4 (bottom left).[12] The implications are that the levels of these two enzyme systems are not static; they fluctuate in response to changing neurotransmitter levels. When neurotransmitter levels are increased, enzymatic activity also increases.[14,23–26]

If you administer L-dopa or 5-HTP, the activity of MAO and COMT increases due to the increase in dopamine or serotonin levels, respectively. The problem occurs when L-dopa is administered without 5-HTP, both dopamine and serotonin will be subjected to increases in metabolism by these two enzyme systems. However, serotonin will not experience an increase in production, which leads to further depletion. The same rule is true of 5-HTP administered without the use of dopamine precursors. The bottom line is that the administration of 5-HTP or L-dopa that is unopposed or improperly balanced with the amino acid precursors of the other system will deplete the other system as a result of the increased metabolism of MAO and COMT, decreased synthesis, and uptake competition (as covered in the next section).

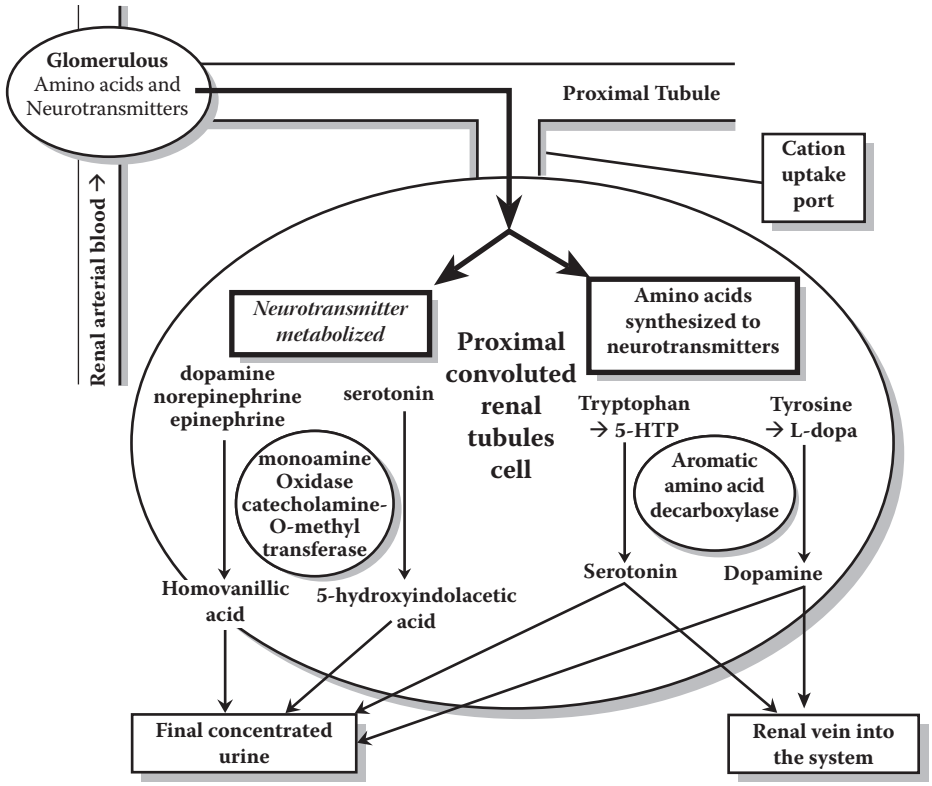

FIGURE 29.4 The neurotransmitters and amino acids are filtered as the glomerulous are uptaked in the proximal renal tubules by the cation ports of the proximal convoluted renal tubule cells. The proximal convoluted renal tubule cells then further filter the neurotransmitters and amino acids into separate areas where the neurotransmitters are metabolized and the amino acids are synthesized into new neurotransmitters that are then either excreted into the urine or secreted into the system via the renal veins.

Amino Acid Uptake

In order for the synthesis of monoamine neurotransmitters to occur, the amino acid precursors must undergo uptake into the cells performing synthesis. This process occurs in numerous places throughout the body including the central nervous system, kidneys, liver, gastrointestinal tract, mesentery, lungs, and peripheral nerves. The "cation uptake ports" found in the proximal convoluted renal tubule cells are a prototype for amino acid uptake (see Figure 29.4 at the top center).[16]

Neurotransmitters synthesized by the kidneys are the source of urinary serotonin and catecholamines.[16–19] Serotonin and the catecholamines are synthesized by the kidneys, then excreted into the urine or secreted into the system via the renal veins.[20] Uptake is affected by administration of a single amino acid precursor or improperly balanced amino acid precursors as may overwhelm and compete with uptake of the other amino acids. Administration of only L-dopa inhibits uptake of 5-HTP.[44] Administration of only 5-HTP has the same effect on L-dopa uptake.

V. TREATMENT

It is not possible to design a diet where the patient can obtain enough amino acids to affect even level 1 amino acid dosing (see Table 29.1), since the amino acid dosing requirement is higher than can be achieved with diet alone. Amino acid precursors of serotonin and dopamine have two primary applications. First, proper use of amino acid precursors will keep drugs that work with neurotransmitters

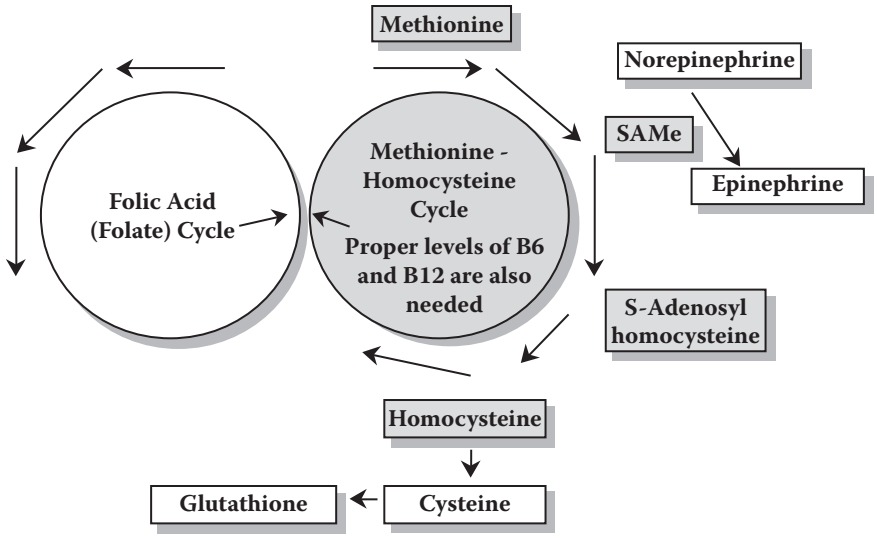

FIGURE 29.5 The methionine–homocysteine cycle, the heart of the sulfur amino acids.

into the central nervous system.[46] Selenium binds irreversibly to methylmercury in the central nervous system rendering the methylmercury biologically inactive and nontoxic.[47]

Folic acid is required in order to provide optimal function of the folic acid cycle, which in turn prevents hyperhomocysteinemia from preventing the methionine-homocysteine cycle from functioning properly. As noted previously, without proper administration of amino acids of the methionine-homocysteine cycle there will be depletion of epinephrine. It would appear the second factor driving epinephrine levels beyond methionine-homocysteine cycle depletion is hyperhomocysteinemia. It can take 3 to 6 months for hyperhomocysteinemia to return to normal when proper levels of folate, vitamin B6, and vitamin B12 are provided for. It appears to be no coincidence that it can take 3 to 6 months for epinephrine levels to return to normal—a fact that appears to parallel homocysteine improvement.

When the goal of treatment is to prevent depletion of neurotransmitters by prescription drugs or in associated situations where prescription drugs are no longer working effectively during treatment due to the neurotransmitter levels falling too low from depletion due to circumstance set up by the drug,[45] the patient should be placed on the level 1 amino acid dosing (see Table 29.1) along with the prescription drug, cysteine, selenium, and folate. While amino acid precursors when used alone and properly are highly effective, a drug/amino acid combination may be desirable with severe disease, such as the suicidal patient, the catatonic patient, or the patient unable to take part in normal day-to-day functions such as work. Supplementing with amino acid precursors allows reuptake inhibitors to continue to function optimally without tachyphylaxis.

When amino acids are used as the initial therapy, start all patients on the level 1 dosing protocol of Table 29.1 along with cofactors and proper methionine-homocysteine cycle support at the first visit. Patients should return in 1 week, at which time focus on how the patient's symptoms were the previous day. Asking about the previous day's symptoms is more indicative of changes in the system brought about by amino acid therapy since it takes 3 to 5 days for the full effects of starting or changing an amino acid dosing to be displayed.

If symptoms are not fully under control in 1 week, increase to the level 2 dosing along with cofactors and proper sulfur amino acid support and instruct the patient to return in 1 week. At the 3rd visit, if symptoms are not under control, increase to the level 3 dosing along with cofactors and proper sulfur amino acid support and have the patient return to the clinic in 1 week. If in 1 week symptoms are not under control, continue the level 3 dosing and obtain a urinary neurotransmitter test of the caliber

provided by a laboratory under the direction of a hospital-based laboratory pathologist.[40] Follow the amino acid dosing recommendations generated after review of testing preformed under the supervision of a board-certified laboratory pathologist. Patients should return in 1 week to discuss results and amino acid dosing changes that may be needed. Any time an amino acid dosing change occurs, patients should return in 1 week to evaluate the results. Over 60% of patients tested needed only one neurotransmitter test. This is consistent with complete resolution of symptoms after adjusting the amino acid dosing in accordance with the consultant recommendations on the test.

When treating depression, if amino acid dosing changes establish both the serotonin and dopamine in the phase 3 therapeutic range (see urinary neurotransmitter testing in the following) and no relief of symptoms is achieved, consider the possibility of depressive bipolar disorder. Under treatment with the amino acid protocol approximately 2% of patients are found to suffer from depressive bipolar disorder that has not been previously diagnosed. The primary care physician at this point should continue the amino acids and initiate a psychiatric referral in order to affect starting of a mood-stabilizing bipolar drug. It is noted that as long as the amino acids are continued, over 99% of patients started on mood-stabilizing drugs such as lithium, Depakote, or Lamictil find complete resolution of depression on the standard starting dose.

VI. SAFETY

The following is a side effect profile developed from approximately 50 patient-years of databased treatment in hand at NeuroResearch Clinics, Inc. The following results were obtained from patients taking only amino acids with no prescription drugs:

Dry mouth	34 (2.1%)
Insomnia	14 (0.9%)
Headache	12 (0.7%)
Nausea	10 (0.6%)
Dizziness	6 (0.4%)
Constipation	6 (0.4%)

All other side effects were reported at a rate of less than 1 in 500 visits (0.02%). No irreversible side effects were noted.

Amino acid precursors are safe to administer with any prescription drug, but amino acid precursors can also cause the side effects of the prescription drugs to be displayed. Any side effect associated with the drug can be triggered. For example, a patient was taking an SSRI with the side effect of malignant neuroleptic syndrome listed. As the amino acids were started, the patient developed new onset malignant neuroleptic syndrome. When drug side effects occur, it is necessary to manage the situation as you would with any other prescription drug side effect, which in general means decreasing or stopping the drug not the amino acid.

With regards to pregnancy there is nothing in the literature indicating that the amino acid precursors are a problem. Nor is there anything in the literature indicating studies have been performed indicating they are safe. In this light it is recommended that amino acid precursors not be used in the first trimester of pregnancy.

VII. SYSTEMS PRIORITY

The serotonin and/or catecholamine system has a role, either directly or indirectly, in controlling most of the other systems and functions in the body. For example, cortisol synthesis is controlled in part by norepinephrine. Hormone synthesis is dependent on norepinephrine. The sympathetic nervous system is controlled by norepinephrine. Other neurotransmitter systems are partially controlled by the serotonin and/or catecholamine systems. For example, the GABA neurotransmitter

system is associated with control of anxiety and panic attacks. Yet when the serotonin and/or catecholamine neurotransmitter levels are brought to proper levels, as confirmed by lab testing, these diseases may be fully under control. This would indicate control of GABA by the serotonin/catecholamine system even though at this time we have been unable to identify a chemical pathway for such in the literature.

VII. PATIENT EVALUATION: URINARY NEUROTRANSMITTER TESTING MONOAMINES IN THE KIDNEYS

Urinary neurotransmitter testing prior to amino acid therapy is of no value. There is no correlation between baseline testing and urinary neurotransmitter phases once the patient is taking amino acid precursors. It is not necessary or even useful to measure baseline urinary neurotransmitters in treatment.[40]

Urinary monoamine neurotransmitters do not cross the blood-brain barrier.[2–5] Urinary monoamine neurotransmitters are not neurotransmitters filtered by the glomerulous of the kidneys and excreted into the urine. They are neurotransmitters that are synthesized by the kidneys and excreted into the urine or secreted into the system via the renal veins.[20] With simultaneous administration of serotonin and dopamine amino acid precursors, three phases of urinary neurotransmitter response have been identified on laboratory assay of the urine (see Figures 29.6 and 29.7). The three phases of response apply to both serotonin and dopamine. In all the life forms tested that have kidneys along with serotonin and catecholamine systems, the three phases of urinary neurotransmitter response exist.[40] In reviewing the literature it would appear that the three phases of urinary response to neurotransmitters were present in previous writings but were not identified as such. For example, a 1999 article notes that administration of L-dopa can increase urinary dopamine levels (phase 3) and decrease urinary serotonin levels (phase 1).[42]

The goal of treatment is to establish both urinary serotonin and dopamine levels in the phase 3 therapeutic range. To determine the phase of serotonin and dopamine with certainty requires two urinary neurotransmitter tests to be performed with the patient simultaneously taking a different amino acid dosing of dopamine and serotonin amino acid precursors on each test and comparing the results. Not all patients will need to have the urinary serotonin and dopamine levels in the phase 3 therapeutic range for relief of symptoms. In many cases, adjusting the amino acids so that the patient moves closer to the phase 3 therapeutic range of urinary serotonin and dopamine induces relief of symptoms. Then, no further amino acid adjustments or testing are needed unless disease symptoms return. If the patient misses one or more amino acid doses in the week prior to testing, wait until 1 week has passed with the patient properly taking all of their amino acids.

In phase 1, neurotransmitters synthesized by the kidneys are inappropriately excreted into the urine instead of being secreted into the system via the renal vein where they are needed (see Figures 29.6 and 29.7). Increasing the amino acid dose in phase 1 will correct the problem of inappropriate neurotransmitter excretion. The amino acid precursor dosing of serotonin and dopamine, where the individual patient is in phase 1 varies widely in the population. The level at which the urinary serotonin is no longer in phase 1 ranges from 37.5 mg of 5-HTP per day to 3000 mg of 5-HTP per day. The level at which the urinary dopamine is no longer in phase 1 ranges from no L-dopa (with the use of L-tyrosine only in some patients) to 540 mg of L-dopa per day in the patients not under treatment for Parkinsonism or Restless Leg Syndrome.

Administration of proper levels of tyrosine with L-dopa is known as a "tyrosine base." Proper use of the tyrosine base greatly reduces wild fluctuations in dopamine levels found with administration of L-dopa alone and greatly decreases the need for L-dopa. It is postulated that the tyrosine hydroxylase enzyme is not completely shut down with the administration of L-dopa, leading to fluctuations in the L-dopa produced from tyrosine synthesized to L-dopa then dopamine, which ultimately causes fluctuations of dopamine. By providing ample tyrosine with administration of L-dopa, these fluctuations of dopamine cease and the overall dosing needs of L-dopa decrease.

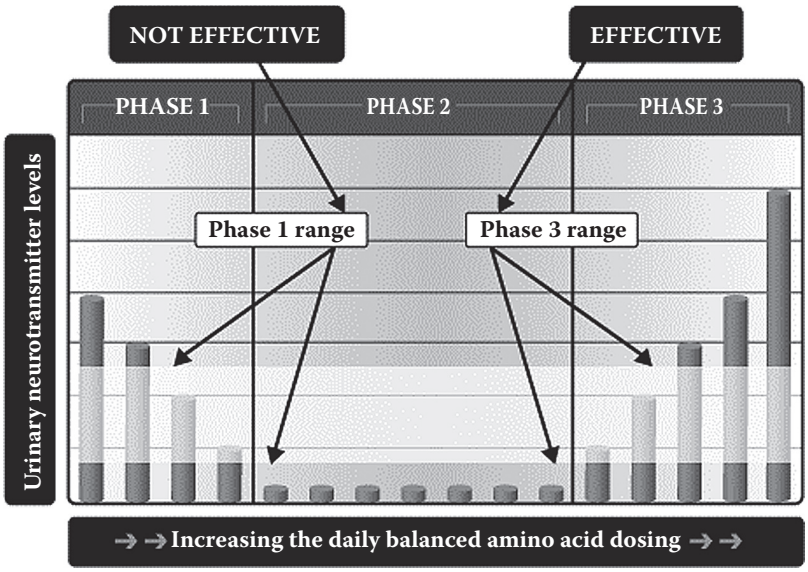

FIGURE 29.6 The three phases of urinary neurotransmitter excretion in response to amino acid dosing. The horizontal axis is not labeled with specific amounts; it reflects the general trend seen in the population. Amino acid dosing needs are highly individualized. The dosing level needed to inflect into the next level varies greatly throughout the general population. For example, some patients inflect into phase 3 on 37.5 mg of 5-HTP per day, while others need as high as 3000 mgday (From DBS Labs database).

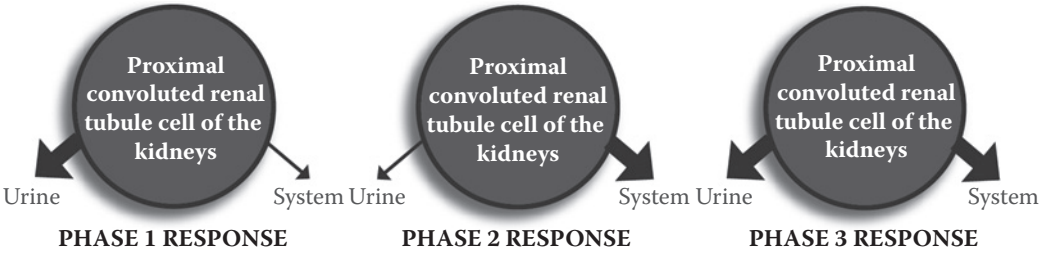

FIGURE 29.7 The three phases of urinary response to amino acid dosing (Two urinary neurotransmitter tests are required to determine the phase with certainty). PHASE 1: In phase 1, as the amino acid dosing increases or decreases the urinary serotonin or dopamine decreases or increases respectively. In phase 1, there is inappropriate excretion of neurotransmitters into the urine instead of the system where they are needed. PHASE 2: In phase 2, as the amino acid dosing increases or decreases the urinary serotonin or dopamine is low (<800 µgr/gr creatinine for serotonin or <300 µgr/gr creatinine for dopamine). In phase 2, there is no inappropriate excretion of neurotransmitters into the urine. The neurotransmitters are being excreted appropriately into the system and the urine. PHASE 3: In phase 3, as the amino acid dosing increases or decreases the urinary serotonin or dopamine increases or decreases respectively. In phase 3, there are adequate systemic serotonin and dopamine levels. The excess serotonin and dopamine are appropriately excreted into the urine.

By increasing the amino acid dosing of serotonin and dopamine precursors above the dosing of phase 1, the phase 2 response is observed (see Figures 29.6 and 29.7). In Phase 2, urinary neurotransmitter levels are low (<300 micrograms dopamine per gram of creatinine or <800 micrograms serotonin per gram of creatinine, the neurotransmitter-creatinine ratio compensates for dilution of the urine) and the inappropriate excretion of neurotransmitters into the urine has ceased. When in phase 2, neurotransmitters are being appropriately secreted into the system and not into the urine.

The model used to explain phase 2 is, "inappropriate excretion of neurotransmitters has now ceased as the amino acid precursor dosing is increased and the system is now filling up appropriately."

As serotonin and dopamine amino acid precursors are increased above the phase 1 and the phase 2 levels, all patients enter the phase 3 response (see Figures 29.6 and 29.7). Further increases in the amino acid dosing lead to increases in urinary dopamine and serotonin neurotransmitter levels if they are in phase 3. Phase 3 represents appropriate secretion into the system and appropriate excretion of excess neurotransmitters synthesized by the kidneys into the urine.

In the case of chronic depression, research has shown neurotransmitter levels need to be established at levels that are in phase 3 and higher than the reference range reported by the laboratory in order to achieve optimal relief of group symptoms.[40] In the case of serotonin, the reference range reported by the research lab is 48.9 to 194.9 micrograms of serotonin per gram of creatinine. The therapeutic range of urinary serotonin for the treatment of chronic depression is defined as 800 to 2400 micrograms of serotonin per gram of creatinine in phase 3. The reference range reported by the research lab of urinary dopamine reported by the laboratory is 40 to 390 micrograms of dopamine per gram of creatinine. The therapeutic range of urinary dopamine for the treatment of chronic depression is defined as 300 to 600 micrograms of dopamine per gram of creatinine in phase 3.

It would appear that in depression, the same mechanism of action may be at work as is found in Parkinson's disease. There is damage to dopamine and/or serotonin neuron bundles controlling affect, which can be compensated for by increasing serotonin and dopamine neurotransmitter levels higher than is normally found in the system. Just as with Parkinson's disease, the bundle damage in chronic depression is permanent. In most patients simply returning neurotransmitter levels to normal or the reference range reported by the lab, as suggested by the monoamine theory, will not lead to relief of symptoms. As with Parkinsonism, treatment of depression may require long-term use of amino acids to control symptoms. After symptoms associated with monoamine neurotransmitter diseases are controlled with the proper administration of amino acid precursors, the need for ongoing amino acid therapy may present if symptoms have not been addressed fully under the monoamine theory.

Urinary monoamine neurotransmitter testing is used only when the patient has not responded to the levels 1 through 3 of the dosing protocol. Over 80% of patients will achieve relief of depression symptoms without laboratory testing.

Generalizability

Laboratory-guided supplementation with amino acid precursors is also associated with clinically favorable outcomes in RLS and peroxismal limb movement disorder, where dopamine agonists are also the first line of therapy and clinical response is readily observable by patients and documented with sleep studies. The dosing level of L-dopa at which dopamine is no longer in phase 1, in patients not suffering from RLS, ranges from 0 milligrams of L-dopa per day to 6000 mg of L-dopa per day. With a proper "tyrosine base" in place, L-dopa dosing in these patients range from 10 to 1040 mg/day.

VIII. CONCLUSIONS

The bundle damage theory creates a framework by which to offer patients new treatments for clinical depression. The theory underscores the importance of minimizing toxic exposures, through avoidance where possible, through diminished uptake, and through adequate nutrients. Similarly patients who have inadequate substrate for neurotransmitter synthesis may need cofactors, nutrients involved in sulfur pathways, and amino acid precursors. Patients may also receive benefit from amino acid precursors beyond what can be obtained from diet alone.

There are three primary considerations in the use of amino acids for treating depression. First, proper levels of amino acids should be administered with the drugs to prevent depletion of neurotransmitters. Second, proper use of amino acids will keep the drug functioning properly,

avoiding tachyphylaxis. Third, the use of amino acids may cause a drug side effect to become active. In summary, amino acids hold more therapeutic potential and less potential for harm when administration is physician-guided.

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