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The Serotonin Connection

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Abstract

Serotonin metabolism is disordered in a variety of clinical states. These include addictions, attention deficit disorder, chronic pain, depression, dysthymia, eating disorders, headache, obsessive-compulsive disorders, panic, poor impulse control, post-traumatic stress disorders, premenstrual syndrome, sleep disorders, stress disorders, sudden cardiac death and violence. A decreased serotonin state has also been implicated in sleep disorders which may then progress into dysthymia and depression. Serotonin can be altered by a variety of means, including acupuncture, body work, cranial electrical stimulation, diet, electromagnetic fields, exercise, light, sound, and the highly effective Serotonin Selective Reuptake Inhibitors (SSRI). An individual's genetically determined stable set point for serotonin may be disordered by environmentally induced events, leading to altered sleep, dysthymia and depression. This imbalanced neurochemistry cascades into an autonomic nervous system hyperactivity causing symptoms. The neurochemical biophysiological basis of much mental as well as much multifactorial illness in becoming clearer. It is hypothesized that potentially treatable low serotonin states are the final common pathway in many medical disorders.

Introduction

We are in the midst of a paradigm shift. Most extant institutions are foundering. Medicine is no exception. The explosion of new information during the past two decades is now being reviewed and integrated into our knowledge and data bases.[1] This has led to a realization that we have much to learn. This was emphasized by Professor David Eddy of Duke University who pointed out that despite the 30,000 biomedical journals in the world, only 15 percent of medical interventions are supported by solid scientific evidence. This is because only 1 percent of the articles are scientifically sound.[2] Would you be satisfied with the above when we are spending approximately 14 percent of the total gross national product (GNP) for health care?

Many people are not satisfied. David Eisenberg's article, "Unconventional Medicine in the United States"[3] reveals that approximately 1/3 of those surveyed used alternative modalities. In 1990 some 425 million visited alternative therapists, while only 388 million visited all primary care physicians. They were willing to spend $10.3 billion out of pocket for alternative treatments. This is impressive since the out of pocket expense, the same year, for all hospital care was $12.8 billion and for all physician services, $23.5 billion.

The following clinical applications article will draw from my multiple disciplinary interests, two decades of clinical experience and the expanding knowledge base. It may challenge some of your early medical training. It will require an open mind, a re-evaluation of certain knowledge and a willingness to learn. The article will present a different perspective of multiple diseases and an underlying commonality of disordered serotonin metabolism. A useful 13 question Serotonin Index, copyrighted in 1995 by Robert A. Nash, will be discussed. This has helped me select the proper medication the first time for the vast majority of my patients.

Some of society's pressing problems are viewed from an altered serotonergic perspective which would bring them into

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the realm of medicine and medical treatment. Prompt treatment with serotonergic agents and/or alternatives which raise serotonin, coupled with patient education may very well decrease the overall illness of the nation and increase its general health at a reduced bottom line.

Myofascial Pain Syndrome

I first became interested in the myofascial pain syndrome (MPS) in 1977. MPS is a chronic, wide spread musculoskeletal pain associated with trigger points and non-restorative sleep.[4–9] Chronic is defined as greater than six months or longer than the normal healing time. Fibrositis, fibromyalgia, chronic sprain, post laminectomy syndrome and multiple other names are often used as pseudonyms for MPS. The purists may argue each is different. However, I perceive them as being similar in mechanism.

The mechanism is not fully elucidated, although continuing research is documenting its probable mechanism. An alpha-delta sleep disturbance has been well documented in MPS.[7–11] This appears to be serotonergically mediated. The pathophysiology of MPS is complex but breaks down to a neuromusculoskeletal problem and sleep problems. The injured soft tissue (muscles, ligaments and nerves which subserve them) are sensitized to circulating catecholamines, particularly norepinephrine, bradykinins and substance P.[7] Any time the circulating catecholamines increase, such as from pain, lack of sleep, fear, anger, or frustration, the pain increases and the sleep disturbance is exacerbated.

The neurological pain pathways are well summarized in Howard Field's excellent book, PAIN,[12] A peripheral and a central mechanism is theorized. The peripheral mechanism appears to be nociceptive, catecholaminergic sensitization of the soft tissue.[7,13] Serotonin and other neurotransmitters are implicated at the dorsal root entry zone (DREZ) of the spinal cord where the afferents connect. Endorphins, serotonin, substance P and norepinephrine are the major neurotransmitter modulators identified in the endorphin mediated activating system (EMAS) which is the neurological pain pathway.[7,12] A presently unknown central mechanism is involved in disordered sleep.[7–11]

Through the efforts of the American Pain Society and the American Academy of Pain Medicine, a new specialty of pain medicine has evolved. Their respective journals, the *APS Journal* and the *Clinical Journal of Pain* have provided leadership in the understanding and treatment of pain. The multi-specialty and multi-disciplinary interests in chronic, myofascial pain and more recently, fibromyalgia, have spawned two additional journals, *The Journal of Musculoskeletal Pain* and *The Journal of Myofascial Therapies.*

Multiple alternative therapies are used in the treatment of MPS and its first cousin, fibromyalgia. I began to treat the sleep disturbance component in the late 1970s. The use of tricyclic tertiary amines (amitriptyline, imipramine and doxepine) as well as the tricyclic secondary amines (desipramine and nortriptyline) were less than satisfactory because of patient noncompliance usually from the anticholinergic side effects. With the triazolopyridine derivative, trazodone, compliance was better. With the development of fluoxetine and its subsequent serotonin selective reuptake inhibitors (SSRI) and the norepinephrine serotonin reuptake inhibitors (NSRI) compliance improved even more. My patients began to sleep better, although some never realized they had a sleep disturbance. Their energies increased, their moods increased and their pain decreased. It should be noted that there is a subtle change in the name of medications that alter neurotransmitters. SSRI is preferred to anti-depressants.

I have observed two clinically significant trends in treating MPS patients. Increasing serotonin increases stage IV sleep

which allows maximum endorphin production. This leads to marked improvement of the chronic pain patient. Patients ingesting alcohol or any potentially addicting medications, barbiturates, benzodiazepines or narcotics did not improve. Their sleep may have improved on the serotonergic medications, but their pain did not. This implied there may be a requirement to stop all addicting substances before the brain can maximally release endorphins

Serotonin, endorphins and gamma amino butyric acid (GABA) became of increasing interest to me. The GABA gate of the neuron has been implicated in increasing chloride ion transfer which hyper polarizes the cell membrane. This causes a decreased activity of the emotional stress of the brain. The hippocampus and medulla respond with decreased arousal and anxiety.[14] These observations aroused my curiosity about addiction.

Addiction

In 1988, the National Science Foundation Symposium had a presentation about altered metabolism of cyclic-AMP in genetically produced alcoholic rats. This prompted me to inquire about addiction or addictive tendencies in families of MPS patients. I only asked about parents and grandparents. It became readily apparent that the vast majority of MPS patients came from an addictive family background. The addiction could be work, religion, television, food, shopping, alcohol, sex, gambling or other drugs. I asked myself if these patients could have a neurochemical imbalance predisposing them to develop MPS or chronic pain?

I then explored any previous depressive episode in my patients' lives. Most had none before the trauma that had precipitated the MPS. This made me think about a familial or genetic predisposition to altered brain chemistry as a possible central mechanism to explain the sleep disturbance in MPS patients. Many of these patients had tendencies toward obsessive-compulsive behaviors. This led me to think that a variety of addictive behaviors may have an obsessive-compulsive basis. This led to more questions that might explain our society's continuing sojourn with substance abuse. Concerns about the association of substance abuse, AIDS and tuberculosis were noted by former Secretary of HEW, Joseph A. Califano, Jr.[15] This author was quoted from a November, 1992 meeting dealing with the "Medicalization of Drug Addiction." There is increasing evidence that much addiction is genetic or familial. Dr. Nash believes that addiction and obsessive-compulsive behaviors are on a medical continuum that reflects an underlying "continuity of electro-chemistry" in the brain.[16]

The controversy of familial or genetic alcoholism continues in medicine.[17-19] However, the mechanism of alcohol at the neuron is known.[20] It works at the GABA gate via the hyper polarization mechanism previously stated.[21] The GABA gate of the neuron is the site of action of ethyl alcohol,[20] benzodiazepines,[22] and barbiturates.[20] I hypothesized that narcotics may be in part metabolized or controlled by this same GABA gate based upon my patient observations.[23]

Recently a new class of neurotransmitters have been hypothesized to bind to the benzodiazepine receptor at the GABA gate. These neuroactive steroids, allotetrahydro DOC, and allopregnanediol are secreted by the adrenal glands in response to stress and may be excreted by the brain. These steroids appear to increase GABA which inhibits the brain's production of ACTH which in turn lowers the stress response.[24] Neuroscientists are investigating the GABA gate for anti-epileptic drugs (AED). Valproate sodium, an AED which acts in part at the GABA gate, is used in the treatment of acute mania,[25] and affective disorders.[26,27] Gabapentin, a new AED, is structurally related to GABA. It does not interfere with the GABA receptor and its mechanism of action is currently unknown. Beta endorphins have

been well mapped out in the neuraxis and modulate the Endorphin Mediated Activating System (EMAS) previously referred to.[12] Endorphins and serotonin are present at the DREZ of the spinal cord as pain modulators, according to the modified gate theory.[12,28] Endorphins and serotonin are increased by acupuncture,[29] meditation, vigorous physical exercise and stage IV sleep.

I have already alluded to an ill-defined relationship between maximum endorphin production and the possible effects of addicting medications at the GABA gate. This implies a probable cross addiction at the GABA gate of the neuron. This might help explain why some post operative patients don't receive adequate pain relief from normal doses of narcotics. They may be genetically predisposed to metabolize narcotics like the alcoholic rats metabolized alcohol. In the case of the latter, large amounts of alcohol were needed before any untoward effect was noted. This was presumptively on the basis of altered cyclic-AMP metabolism. Could such a metabolic abnormality be present in the percentage of post operative patients who often require two or three times the analgesic dose before pain control is achieved?

The use of serotonergic medications in my patients who were on no addicting substances, including medications, was dramatic. Their sleep was re-regulated, their pain lessened and often previous addictive tendencies and obsessive-compulsive tendencies lessened. This serotonergic connection appeared to correct many disparate problems and led me to learn more about serotonin.

Serotonin

Our knowledge of the brain and its neurochemistry is evolving. The complexity is challenging as thousands of neurotransmitters may be present. We are in the process of understanding several hundred. Our pharmacopoeia is limited and we have approved medications to treat about a dozen. What follows is therefore incomplete and is acknowledged as such. However, the importance of these clinical observations is such that they beg for further investigation and research.

It is known that melatonin, produced by the pineal gland, is important in the regulation of other neurotransmitters. It is inversely proportional to serotonin. Melatonin can be altered by exogenous electromagnetic fields (EMF).[30-32] Serotonin has also been altered by cranial electrical stimulation (CES).[23,33,34] Michael Smith and others,[35-38] have used acupuncture for detoxification of opiates, alcohol and other substances. Acupuncture is known to increase endorphins and serotonin.[29] Robert Elliott, a cardiologist, has studied "hot responders" and Type-A personalities and has concluded stress contributes significantly to sudden cardiac death (SCD). This has been known to neurologists as well as cardiologists in the form of neurogenic cardiomyopathy and sudden death.[39] Could these "hot responders" and Type-A personalities come from the same familial or genetic obsessive-compulsive/addictive backgrounds as my MPS patients and just have a different target organ? This has gained recent support by articles by Kawachi, et al, in the journal, Circulation. In his most recent article,[40] coronary heart disease (CHD) was increased from 2.45 to 3.77 times due to anxiety. "When fatal CHD was further categorized into sudden cardiac death and non-sudden cardiac death, the excess risk was confined to sudden and was 6.08 times with a 95% confidence interval (CI). His earlier article stresses anxiety and panic disorders and an increased risk of CHD. Panic disorder effects between 2 and 5 percent of the general population and 10 to 14 percent of the patients in cardiology practice. A recent report suggested an increased risk of fatal myocardial infarction (MI) among women using benzodiazepines, tricyclic antidepressants and barbiturates.[41] The observed increase in violent deaths due to suicide and homi-

cide following serum cholesterol lowering therapy is then discussed, and is hypothesized to caused by low serotonin. The analysis of studies lowering cholesterol with diets and drugs were reviewed.[42,43] The probable mechanism is due to low serotonin from converging lines of evidence.[44] This paper goes on to show that low serotonin is associated with poor impulse control and most likely leads to violence to self and others in susceptible individuals.

The role of serotonin has been noted in an expanded number of conditions traditionally in the psychiatric realm.[45] This article orders affective disorders from more impulsive to more compulsive: mania, pathological gambling, intermittent explosive disorder, pryomania, attention-deficit hyperactivity disorder, bipolar disorder, major depression, trichitillomania, anorexia nervosa, obsessive-compulsive disorders, and body dysmorphic disorders. SSRI are effective in depression, obsessive-compulsive disorder, anxiety, eating disorders, premenstrual syndrome, chronic pain, self destructive behavior, poor impulse control and addictions. An entire new literature of serotonin, sumatriptan and headache has evolved over the past decade. A nice summary of the various serotonin, (also known as 5-hydroxytryptamine), receptors and functional responses is presented in Putt's article.[46] A variety of receptors are also noted for endorphins and other neurotransmitters but are beyond the scope of this article and will not be further mentioned in this article.

Since the first in-depth coverage of the first SSRI, fluoxetine, as a new option,[47] the literature has exploded. Only a few citations will be given for each condition. A serotonergic basis, along with the disordering of other neurotransmitters, has been shown to be associated with anorexia nervosa and bulimia nervosa.[48-50]

Chronic pain studies have shown the serotonin modulation of pain in animals and humans. Morphine analgesia is potentiated by simultaneous treatment with fluoxetine.[51,52] Phantom limb pain,[53] chronic pain and headaches,[54] and diabetic neuropathies have all been successfully treated with SSRI.

Obsessive-compulsive disorder may contribute to addictive behaviors due to poor impulse control. Low steady-state serotonin levels can be further decreased by alcohol and addicting substances as well as decreased cholesterol.[40,41] This could lead to compulsive drinking, compulsive eating, compulsive gambling, compulsive sex and other addictive behaviors. SSRI have been shown to be effective in the treatment of obesity,[55] panic,[56] alcohol and smoking cessation,[57] premenstrual syndrome,[58] attention deficit disorder,[59] post traumatic stress disorder,[60] alcohol, nicotine, morphine, amphetamine and cocaine abuse,[61] postpartum depression,[62] and obsessive-compulsive disorder.[63]

Serotonin and endorphins have been increased by acupuncture as previously noted.[29] CES[33] and its subset, neuroelectric therapy (NET)[34] as well as a variety of EMF gadgets and techniques also effect these neurotransmitters.[1,64-69] Of course, EMF can also be hazardous to your health, having been implicated, at least epidemiologically, in childhood leukemia and lymphoma and brain tumors.[70]

This has led to the espousal of a freer hand in treating many problems. The Megabrain Report[68] calls it, "The Biopolitics of Serotonin: From Prozac to Brain Tech", in which we replace cosmetic psychopharmacology with "meta-cosmic neurotechnology." Contributors to the Megabrain Report include Eugene Peniston, Nancy White, Thomas Budzynski, Julian Isaacs and others.[68] Each has a special interest, expertise and knowledge to share. Michael Hutchison reports on "Listening to the Brain."[68] He describes a serotonergic basis for many problems and claims neurotechnology can increase appropriate neurotransmitters. He describes the one dominant male, or alpha male in primates, who has far higher levels of se-

rotonin. "When a dominant male is removed from his position of dominance, his levels of serotonin plummet by some 50 percent and his former unshakable confidence and self assurance turn into insecurity and anxiety. When former non-dominant monkeys are placed into positions of dominance, their serotonin levels soar by 40 to 60 percent."

In summary, low serotonin states appear to be the biophysiologic basis of many mental problems, addictions, poor impulse control (which may contribute to unplanned pregnances, violence and other social problems), sleep disturbances (which may contribute to dysthymia and the low serotonin state previously known as depression), and even sudden cardiac death. Although the serotonin connection and its complex mechanism is not fully elucidated, treatments with SSRI and a variety of Alternative Therapies can increase serotonin and make for healthier individuals and a healthier nation.

The Serotonin Index

Three years ago I developed a serotonin index to assist me in the selection of the appropriate medication for my patients.

Figure 1

Nash Serotonin Index c.1995.

		YES	NO
1.	Do you usually skip breakfast?	___	___
2.	Are you refreshed upon awakening from sleep in the morning?	___	___
3.	Do you have outbursts of anger for no apparent reason?	___	___
4.	Were your parents or grandparents heavy or daily users of alcohol or cigarettes?	___	___
5.	Do you have difficulty sleeping?	___	___
6.	Are you or your parents workaholics?	___	___
7.	Do you prefer to be in control of most situations?	___	___
8.	Do you have morning stiffness if you don't sleep under more than one blanket at night?	___	___
9.	Does noise bother you?	___	___
10.	Do you feel really good about doing well in school, sports or your job?	___	___
11.	Do you eat before going to bed?	___	___
12.	Do you bite your fingernails?	___	___
13.	Are you a long distance runner?	___	___

The index consists of 13 questions which I have found to be very useful clinically. I actually started with only 12 but added question 13 a year ago. The Nash Serotonin Index is shown in Figure 1. The index was copyrighted in 1995 by the author. It has not been tested anywhere but in my office with approximately 1200 patients. It is offered as a practitioner's aid in assisting with the selection of the first neurotransmitter-enhancing medication.

I devised the questions and answers to quickly determine if serotonin (S) or norepinephrine (NE) is deficient. I view these two neurotransmitters as being on opposite sides of a see-saw. When someone is balanced, in good health and feeling well, the yes and no answers are fairly balanced.

When someone is deficient in NE, they will answer only one or two questions with yes and the remaining questions with a no. Some of these patients have true anxiety with or without true panic. There is a subset of the elderly who also answer as above who usually have a sleep disturbance and vague headache or other complaints like dizziness. The patients, whom I clinically treated as having low NE states, do remarkable well with desipramine and other mostly NE-enhancing medications.

The S-deficient patients answer two or three questions no and the rest yes. The patients have many common traits. They are often hard-working, obsessive compulsive, addictive-prone patients with little or no previous mental illness. I often see these patients for headache or pain, including chronic forms of these problems. Most do have a sleep disorder. If they answer yes to the fingernail biting question (# 12), I tend to treat them for obsessive-compulsive disorder with fluvoxamine maleate. Any of the SSRI and/or trazodone benefit these patients. Question # 13 was added after two distance runners answered the index as though they were NE deficient. Desipramine made these patients' sleep disturbance worse and they were helped with SSRI or trazodone. Therefore, if question # 13 is a yes, it's all you need to know that these patients have the typical low S states seen in obsessive-compulsive disorder and they can be treated with fluvoxamine maleate or the SSRI of your choice. I have hypothesized that daily distance runners have already raised their own serotonin and endorphin levels to the point that they respond to the index with a false positive to a low NE state. They are usually unable to run when I see them and the benefit from the exogenous enhancement of serotonin.

When the patient is mixed, say four to five yes or no answers, your clinical acumen is needed. A sleep disturbance can be manifested by awakening with headache or neck or back pain, or a feeling of fatigue during the day. These normally respond well to trazodone or the SSRI of your choice. If five or six questions are yes or no and you have a clinical index of suspicion (AKA intuition) of OCD, the SSRI may be helpful.

With experience the index is very helpful in selecting the proper medication the first time. Permission is granted for all readers to reproduce 10 copies to gain experience with the utility of the index. Additional copies can be obtained from the author.

Conclusions

The above has begun to form the basis of a common serotonergic etiology for many mental, physical and social ills. Treatment of the low serotonin state has given marked relief of symptoms and a return to normality to many people. There has also been a marked decrease in the expenditure for their overall medical care. Alternative therapies may work, in part, by raising the patient's serotonin levels. This may lead to the research to further the mechanistic understanding of many alternative treatments.

Individual useful observations include:

a) Myofascial pain (including fibrositis and fibromyalgia) and its associated sleep disturbance are biophysiologic and medi-

ated by serotonin.
b) A cross-addiction potential may exist at the GABA gate of the neuron for alcohol, barbiturates, benzodiazepines and possibly narcotics. These substances may inhibit the brain's maximal production of endorphins and encephalins during Stage IV sleep.
c) Serotonergic agents facilitate achieving Stage IV sleep which maximizes muscle relaxation and endorphin production.
d) CES, acupuncture and other serotonergic treatments for addicts yield a recidivism rate of only approximately 20 percent. Many traditional addiction treatments have recidivism rates as high as 80 percent. Most addictions are secondary to low serotonin.
e) Many of our violent behaviors, which often lead to crime and incarceration may be due to low serotonin.
f) The vast majority of incarcerated persons are there for violent crimes while under the influence of addicting substances.
g) New evidence suggests low serotonin may be implicated in sudden cardiac death. The underlying serotonergic deficiency becomes more manifest in disease states as our knowledge of the "integrated energy being" called Homo Sapiens increases.

Individual clinical practitioners can use the index and become aware of altered brain neurochemistry. Low serotonin states may explain many clinically difficult patients who have been labeled by a variety of names to mask our ignorance. Becoming aware and treating these low serotonin states are most gratifying to the patients and the practitioners. It may help decrease the 602 percent increase in sudden cardiac death associated with low serotonin. It may even prove less expensive than coronary artery bypass grafts. Treatment of low serotonin states may decrease myocardial infarction and stroke by reducing the brain's hyperactive autonomic nervous systems with lowering of high blood pressure and a reduction of other symptoms.

Individual researchers and policy makers, including the editors of this journal, have an opportunity to bridge alternative therapies and traditional therapies via the serotonin connection. A re-evaluation of the underlying etiology of disease is needed. The Mind-Body-Spirit triad has marshaled evidence that our thoughts, beliefs and attitudes effect our well-being. The evidence builds that serotonin may be one of the keys in understanding the increase in diseases of our modern society, cancer, cardiovascular disease, addictions, AIDS , chronic diseases and pain. A new, open and vital research effort is needed. We need to shift our traditional investigatory biases and begin to integrate what is known. This has been my attempt to do so and it is hoped other researchers will rise to the challenge to learn more about the serotonin connection.

The policy makers, politicians and criminal justice systems need to rethink our present approaches. The War on Crime, The War on Drugs and most traditional detoxification systems and incarceration systems could be improved. The evidence that the recidivism rate can be markedly reduced as demonstrated in the Dade County, Florida drug court needs to be studied. First time drug offenders are given a choice. They may get acupuncture and counseling with urine drug screens for one year, or be incarcerated for one year. Of the over 3,500 who have elected acupuncture, the recidivism rate is only approximately 25 percent, not only with substance abuse but also with the criminal justice system. The yearly cost is approximately $1,000 for acupuncture and counseling, versus approximately $20,000 for incarceration. The difference appears to be raising the serotonin and endorphins by acupuncture.

What if a medical approach was taken to poor impulse control, violence and addiction? Increasing the serotonin levels early in life, despite economic circumstances, might result in marked decreases in the rates of addiction, crime, school drop-outs, teenage pregnancies and violence. This could lead to a happier and

saner society who could then concentrate on the true American dream of brotherhood, peace and prosperity.

The real reasons for selective low serotonin states in individuals is not yet known. It appears familial or genetic but may require an environmental trigger such as physical or emotional trauma. While the underlying serotonin connection mechanisms are being discovered, we as health care professionals, can be aware of the possibilities. Think sleep disturbance; think serotonin; and be a clinician and treat your entire patient. The reality of the serotonin connection will give you and your patients great satisfaction. It will put the fun back into your practice.

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