How addiction hijacks the brain

Desire initiates the process, but learning sustains it.

The word “addiction” is derived from a Latin term for “enslaved by” or “bound to.” Anyone who has struggled to overcome an addiction—or has tried to help someone else to do so—understands why.

Addiction exerts a long and powerful influence on the brain that manifests in three distinct ways: craving for the object of addiction, loss of control over its use, and continuing involvement with it despite adverse consequences. While overcoming addiction is possible, the process is often long, slow, and complicated. It took years for researchers and policymakers to arrive at this understanding.

In the 1930s, when researchers first began to investigate what caused addictive behavior, they believed that people who developed addictions were somehow morally flawed or lacking in willpower. Overcoming addiction, they thought, involved punishing miscreants or, alternately, encouraging them to muster the will to break a habit.

The scientific consensus has changed since then. Today we recognize addiction as a chronic disease that changes both brain structure and function. Just as cardiovascular disease damages the heart and diabetes impairs the pancreas, addiction hijacks the brain. Recovery from addiction involves willpower, certainly, but it is not enough to “just say no”—as the 1980s slogan suggested. Instead, people typically use multiple strategies—including psychotherapy, medication, and self-care—as they try to break the grip of an addiction.

Another shift in thinking about addiction has occurred as well. For many years, experts believed that only alcohol and powerful drugs could cause addiction. Neuroimaging technologies and more recent research, however, have shown that certain pleasurable activities, such as gambling, shopping, and sex, can also co-opt the brain. Although the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) describes multiple addictions, each tied to a specific substance or activity, consensus is emerging that these may represent multiple expressions of a common underlying brain process.

From liking to wanting
Nobody starts out intending to develop an addiction, but many people get caught in its snare. According to the latest government statistics, nearly 23 million Americans—almost one in 10—are addicted to alcohol or other drugs. More than two-thirds of people with addiction abuse alcohol. The top three drugs causing addiction are marijuana, opioid (narcotic) pain relievers, and cocaine.

Genetic vulnerability contributes to the risk of developing an addiction. Twin and adoption studies show that about 40% to 60% of susceptibility to addiction is hereditary. But behavior plays a key role, especially when it comes to reinforcing a habit.

Pleasure principle. The brain registers all pleasures in the same way, whether they originate with a psychoactive drug, a monetary reward, a sexual encounter, or a satisfying meal. In the brain, pleasure has a distinct signature: the release of the neurotransmitter dopamine in the nucleus accumbens, a cluster of nerve cells lying underneath the cerebral cortex (see illustration, page 3). Dopamine release in the nucleus accumbens is so consistently tied with pleasure that neuroscientists refer to the region as the brain’s pleasure center.

All drugs of abuse, from nicotine to heroin, cause a particularly powerful surge.
Addiction continued

of dopamine in the nucleus accumbens. The likelihood that the use of a drug or participation in a rewarding activity will lead to addiction is directly linked to the speed with which it promotes dopamine release, the intensity of that release, and the reliability of that release. Even taking the same drug through different methods of administration can influence how likely it is to lead to addiction. Smoking a drug or injecting it intravenously, as opposed to swallowing it as a pill, for example, generally produces a faster, stronger dopamine signal and is more likely to lead to drug misuse.

Learning process. Scientists once believed that the experience of pleasure alone was enough to prompt people to continue seeking an addictive substance or activity. But more recent research suggests that the situation is more complicated. Dopamine not only contributes to the experience of pleasure, but also plays a role in learning and memory—two key elements in the transition from liking something to becoming addicted to it.

According to the current theory about addiction, dopamine interacts with another neurotransmitter, glutamate, to take over the brain’s system of reward-related learning. This system has an important role in sustaining life because it links activities needed for human survival (such as eating and sex) with pleasure and reward. The reward circuit in the brain includes areas involved with motivation and memory as well as with pleasure. Addictive substances and behaviors stimulate the same circuit—and then overload it.

Repeated exposure to an addictive substance or behavior causes nerve cells in the nucleus accumbens and the prefrontal cortex (the area of the brain involved in planning and executing tasks) to communicate in a way that couples liking something with wanting it, in turn driving us to go after it. That is, this process motivates us to take action to seek out the source of pleasure.

Tolerance and compulsion. Over time, the brain adapts in a way that actually makes the sought-after substance or activity less pleasurable.

In nature, rewards usually come only with time and effort. Addictive drugs and behaviors provide a shortcut, flooding the brain with dopamine and other neurotransmitters. Our brains do not have an easy way to withstand the onslaught.

Addictive drugs, for example, can release two to 10 times the amount of dopamine that natural rewards do, and they do it more quickly and more reliably. In a person who becomes addicted, brain receptors become overwhelmed. The brain responds by producing less dopamine or eliminating dopamine receptors—an adaptation similar to turning the volume down on a loudspeaker when noise becomes too loud.

As a result of these adaptations, dopamine has less impact on the brain’s reward center. People who develop an addiction typically find that, in time, the desired substance no longer gives them as much pleasure. They have to take more of it to obtain the same dopamine “high” because their brains have adapted—an effect known as tolerance.

At this point, compulsion takes over. The pleasure associated with an addic-
tive drug or behavior subsides—and yet the memory of the desired effect and the need to recreate it (the wanting) persists. It’s as though the normal machinery of motivation is no longer functioning.

The learning process mentioned earlier also comes into play. The hippocampus and the amygdala store information about environmental cues associated with the desired substance, so that it can be located again. These memories help create a conditioned response—intense craving—whenever the person encounters those environmental cues.

Cravings contribute not only to addiction but to relapse after a hard-won sobriety. A person addicted to heroin may be in danger of relapse when he sees a hypodermic needle, for example, while another person might start to drink again after seeing a bottle of whiskey. Conditioned learning helps explain why people who develop an addiction risk relapse even after years of abstinence.

The long road to recovery

Because addiction is learned and stored in the brain as memory, recovery is a slow and hesitant process in which the influence of those memories diminishes.

About 40% to 60% of people with a drug addiction experience at least one relapse after an initial recovery. While this may seem discouraging, the relapse rate is similar to that in other chronic diseases, such as high blood pressure and asthma, where 50% to 70% of people each year experience a recurrence of symptoms significant enough to require medical intervention.

Fortunately a number of effective treatments exist for addiction, usually combining self-help strategies, psychotherapy, and rehabilitation. For some types of addictions, medication may also help. (We’ve covered specific addictions in detail in previous articles. See Harvard Mental Health Letter, March 2009, January 2010, and April 2011.)

The precise plan varies based on the nature of the addiction, but all treatments are aimed at helping people to unlearn their addictions while adopting healthier coping strategies—truly a brain-based recovery program. ♥

* Harvard Mental Health Letter subscribers can obtain a special discounted subscription to the Harvard Review of Psychiatry by visiting the Web site http://informaworld.com/hrp or by calling 212-520-2763.

For more references, please see www.health.harvard.edu/mentalextra.
When depression starts in the neck
Treating an underactive thyroid gland may improve mood.

When someone develops depression, the brain usually becomes the focus of attention. But other organs can be the source of the problem. A common example is when the thyroid gland produces too little hormone—a condition known as hypothyroidism.

Nearly 10 million Americans suffer from hypothyroidism. The condition is much more common in women than in men, and becomes more prevalent with age. As many as one in five women will develop hypothyroidism by age 60.

Although researchers aren't entirely sure why there is a link between hypothyroidism and depression, it is likely that some people are taking antidepressants when they should really be taking thyroid medication. Here is a brief review of when clinicians and patients should consider hypothyroidism as a possible cause of low mood—and what to do next.

The mighty thyroid
The thyroid gland is a small butterfly-shaped structure that sits low in the neck, below the Adam’s apple (a protrusion made of cartilage that both women and men have). Although it weighs less than an ounce, the thyroid exerts a powerful influence throughout the body. It does so by secreting hormones that affect metabolism, a chemical activity that controls how fast and efficiently cells convert nutrients into energy. By regulating metabolism, the thyroid indirectly affects every cell, tissue, and organ in the body—from muscles, bones, and skin to the digestive tract, heart, and brain.

The thyroid, in turn, is regulated by the pituitary or “master” gland. The pituitary gland (a pea-sized gland that sits beneath the brain) constantly monitors blood levels of hormones, including those produced by the thyroid. When blood levels of thyroid hormones fall, the pituitary gland uses a chemical signal known as thyroid-stimulating hormone (TSH) to prompt the thyroid to pump up production. In response, the thyroid uses iodine from food to produce two hormones. Triiodothyronine, known as T3, contains three iodine atoms, while thyroxine, or T4, contains four. A normally functioning thyroid gland, working in conjunction with the pituitary gland, secretes T3 and T4 into the bloodstream at a steady pace.

In a person with hypothyroidism, however, the thyroid gland does not fully respond to TSH, so blood levels of T3 and T4 remain low. Assuming the pituitary is functioning normally, TSH levels rise; physicians often use the TSH level to help make a diagnosis of hypothyroidism.

When thyroid hormone levels are low, many organs and internal systems slow down, creating a wide range of symptoms—including depression. People over 60 may have only one symptom—such as mood impairment or difficulty concentrating.

Causes of hypothyroidism
Hypothyroidism often develops because of some underlying disease or because a medical treatment impairs thyroid function.

Autoimmune disorders. The most common cause of hypothyroidism is Hashimoto’s thyroiditis, a chronic autoimmune disorder in which white blood cells make antibodies that attack and gradually disable the thyroid gland. Another autoimmune condition, atrophic thyroiditis, shrinks the thyroid. Either of these conditions sig-

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<tr>
<th>Distinguishing depression from hypothyroidism*</th>
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<td><strong>Shared symptoms</strong></td>
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<td>• Depressed mood</td>
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<td>• Fatigue</td>
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<td>• Weight gain</td>
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<td>• Trouble concentrating</td>
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<td><strong>More typical of depression</strong></td>
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<tr>
<td>• Insomnia</td>
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<td>• Restlessness and inability to sit still</td>
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<td>• Feelings of worthlessness</td>
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<td>• Inappropriate guilt</td>
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<td>• Thoughts of death or suicide</td>
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<td>• Planning or attempting suicide</td>
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<td><strong>More likely hypothyroidism</strong></td>
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<td>• Feeling chilled or overly sensitive to cold temperatures</td>
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<td>• Constipation</td>
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<td>• Muscle cramps or stiffness</td>
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<td>• Hair loss</td>
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<tr>
<td>• Hoarseness</td>
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<td>• Slowed heart rate</td>
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*Blood tests measuring thyroid function are necessary to confirm a diagnosis of hypothyroidism.
nificantly reduces thyroid hormone production.

**Surgery.** Partial or complete removal of the thyroid gland—whether for the treatment of thyroid cancer, an overactive thyroid (hyperthyroidism, the opposite of hypothyroidism), or some other problem—permanently decreases or eliminates thyroid hormone production, depending on how much of the gland is removed.

**Radiation.** Another treatment for an overactive thyroid, radioactive iodine, may disable the gland, causing permanent hypothyroidism. Likewise, radiation treatment for Hodgkin’s disease, lymphoma, or cancers of the head and neck may have the same effect.

**Damage to the pituitary gland.** A tumor, radiation, or surgery may damage the pituitary gland, thus impairing its ability to produce and release TSH. Without this chemical signal, hormone production in the thyroid may fall.

**Medications.** Some medications—including the mood stabilizer lithium—can suppress thyroid hormone production.

**Other causes.** An infection, pregnancy, or other conditions may cause a temporary inflammation of the thyroid gland (thyroiditis). This may trigger a brief period of hyperthyroidism, followed by hypothyroidism. In some cases, the thyroid never fully recovers and hypothyroidism becomes permanent.

**Diagnosing and treating hypothyroidism**

Unless the pituitary gland is malfunctioning, a simple blood test to measure TSH provides a definitive test for hypothyroidism. Typically a clinician also feels a patient’s neck to assess the size of the thyroid gland and checks for other physical signs of hypothyroidism, such as brittle nails and dry skin.

Treatment usually involves taking a medication once a day to restore thyroid hormone levels to normal. Several options exist.

**Levothyroxine.** The most commonly prescribed drug is a purified form of synthetic T4, levothyroxine (Levothyroid, Synthroid, others). Levothyroxine works in the same way natural thyroid hormone does, provides stable levels of hormone, and is well absorbed.

All brands are equally effective, but each brand or generic formulation contains slight variations of ingredients that may affect the amount of drug in the blood. The issue is not one of quality, because generic drugs undergo the same potency tests that brand-name drugs do. Instead, the problem is that pharmacies may substitute one generic for another. Therefore it’s important to consult with your doctor if, for any reason, you receive a new brand.

Clinicians determine the initial dose of levothyroxine based on a patient’s weight, age, severity of hypothyroidism, and other medical conditions or medications. In older people, for example, raising thyroid hormone levels too quickly may place stress on the heart—so clinicians usually begin with a low dose and increase it gradually. All people metabolize drugs in different ways, making the same dose more effective in one person than another. Certain medications—such as the mood stabilizer carbamazepine (Tegretol) and the antidepressant sertraline (Zoloft)—may reduce the effectiveness of levothyroxine. Given all these factors, clinicians order periodic blood tests to monitor how effective a thyroid medication is for each individual, and make adjustments based on the results.

**Other options.** Liothyronine (Cytomel), a synthetic version of T3, is eliminated from the system faster than T4, so levels fluctuate more. Another option is liotrix (Thyrolar), which combines both T3 and T4 in one pill. Both of these drugs may require more careful dosing to avoid raising thyroid hormone levels too far. Yet some people respond better to these medications.

**Chances of recovery**

Most people with hypothyroidism respond positively to treatment and find that depression and other bothersome symptoms subside with time. How long that takes is an individual matter, ranging from weeks to months. Elderly people may take longer to respond, since doses of thyroid medications need to be increased slowly to avoid putting any strain on the heart.


For more references, please see www.health.harvard.edu/mentalextra.

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**Combining antidepressants and thyroid medications**

Thyroid medications are sometimes added to antidepressant treatment to improve mood—even when thyroid function is normal. Clinicians usually recommend liothyronine (T3 hormone) to augment antidepressant therapy, but in some cases they recommend levothyroxine (T4). One theory is that thyroid drugs act in concert with antidepressants in the brain. Another idea is that thyroid pills boost chemical activity in the brain, improving mood and concentration.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study evaluated the combination of T3 thyroid hormone and antidepressants in people who had not improved after two previous treatments. About 25% of those taking T3 thyroid hormone saw additional improvement in their symptoms.
Expressive writing—a technique that involves writing about thoughts and feelings that arise from a traumatic or stressful life experience—may help some people cope with the emotional fallout of such events. But it’s not a cure-all, and it won’t work for everyone.

Expressive writing appears to be more effective for healthy people who have sustained an emotional blow than it is for people struggling with ongoing or severe mental health challenges, such as major depression or PTSD.

A flexible approach

Dr. James W. Pennebaker, currently chair of the psychology department at the University of Texas, Austin, has conducted much of the research on the health benefits of expressive writing. In one early study, Dr. Pennebaker asked 46 healthy college students to write about either personally traumatic life events or trivial topics for 15 minutes on four consecutive days. For six months following the experiment, students who wrote about traumatic events visited the campus health center less often, and used a pain reliever less frequently, than those who wrote about inconsequential matters.

In the years since then, expressive writing has evolved and its use expanded. Studies have involved all sorts of permutations: for example, participants writing for 10 to 30 minutes at a time, for one to five days—or weekly for four weeks.

The standard format involves writing for a specified period each day about a particularly stressful or traumatic experience. Participants usually write non-stop while exploring their innermost thoughts and feelings without inhibition (and the writing samples remain confidential for that reason). They may also use the exercise to understand how the traumatic event may revive memories of other stressful events.

Most studies have evaluated the impact of expressive writing on people with physical health conditions such as sleep apnea, asthma, migraine headaches, rheumatoid arthritis, HIV, and cancer. Likewise, most of the outcomes measured are physical, and the findings—such as blood pressure and heart rate—suggest that expressive writing initially may upset people but eventually helps them to relax.

More recently, researchers have evaluated whether expressive writing helps reduce stress and anxiety. One study found that this technique reduced stigma-related stress in gay men. Another found that it benefited chronically stressed caregivers of older adults. And a study by researchers at the University of Chicago found that anxious test takers who wrote briefly about their thoughts and feelings before taking an important exam earned better grades than those who did not.

Why writing may help

When Dr. Pennebaker and other researchers first started studying expressive writing, the prevailing theory was that it might help people overcome emotional inhibition. According to this theory, people who had suppressed a traumatic memory might learn to move beyond the experience once they expressed their emotions about it. But it’s not quite that simple. Instead, multiple mechanisms may underlie the benefits of expressive writing.

The act of thinking about an experience, as well as expressing emotions, seems to be important. In this way, writing helps people to organize thoughts and give meaning to a traumatic experience. Or the process of writing may enable them to learn to better regulate their emotions. It’s also possible that writing about something fosters an intellectual process—the act of constructing a story about a traumatic event—that helps someone break free of the endless mental cycling more typical of brooding or rumination. Finally, when people open up privately about a traumatic event, they are more likely to talk with others about it—suggesting that writing leads indirectly to reaching out for social support that can aid healing.

Timing also matters. A few studies have found that people who write about a traumatic event immediately after it occurs may actually feel worse after expressive writing, possibly because they are not yet ready to face it. As such, Dr. Pennebaker advises clinicians and patients to wait at least one or two months after a traumatic event before trying this technique.

Even with these caveats, however, expressive writing is such an easy, low-cost technique—much like taking a good brisk walk—that it may be worth trying to see if it helps.


For more references, please see www.health.harvard.edu/mentalextra.
**Long-term results of deep brain stimulation for depression**

The longest follow-up study of people who underwent deep brain stimulation for treatment-resistant major depression has concluded that this technique provides progressive and lasting improvements for some of them. But the investigators caution that many challenges remain before this still-experimental modality is ready for use beyond research studies.

Although it is sometimes likened to a pacemaker for the brain, deep brain stimulation is not quite that simple. In deep brain stimulation, a surgeon implants electrodes in the brain and connects them to a small electrical generator in the chest. Electricity transmitted through the electrodes modulates the transmission of signals in particular areas of the brain—although exactly how this occurs remains unclear.

Investigators at the University of Toronto and Emory University recently reported outcomes for 20 people who first received deep brain stimulators between 2003 and 2006 and agreed to be followed over time. By the third year of follow-up, six participants had dropped out of the study (three of them because they were not benefiting from deep brain stimulation). The remaining 14 participants were followed for three to six years, depending on when they first received their implant.

Some of the outcomes were encouraging. At the three-year mark, 60% of the original 20 participants—or 12 of the 14 who remained—had experienced a significant degree of symptom relief from deep brain stimulation, and 35% of the total—or seven of the 14 who remained—had achieved complete relief (remission). This is particularly noteworthy since participants gained entrance into the study because they had not been able to find relief from multiple antidepressants or other treatments.

Still, not everyone benefited. Eight participants entered the hospital during follow-up, half of them for psychiatric reasons such as worsening depressive symptoms. Two patients died by suicide during the follow-up period.

The investigators note that a major challenge remains: identifying the optimal brain targets for deep brain stimulation. Complicating matters, it is likely that the exact targets will vary from one person to the next. Thus it may take years to fully understand the potential and risk of deep brain stimulation.


**More evidence that exercise aids the brain**

Some memory loss is normal as people age (as any middle-aged person who has spent an hour looking for misplaced car keys can attest). But by age 65, more than half of adults say they are concerned about memory problems. Although it is still impossible to prevent neurological disorders that contribute to memory loss, such as Alzheimer’s disease and most other dementias, a new study adds to the evidence that engaging in regular physical exercise protects against normal age-related memory decline.

Researchers at the University of Pittsburgh recruited 120 adults, ages 55 to 80, and randomly assigned them to one of two groups. One group walked briskly for 40 minutes per day, three times a week, while the other performed stretching exercises for the same amount of time.

One year later, participants in both groups were more physically fit than they were when the study began, but the walkers improved significantly more than those who did stretching exercises. Likewise, while scores on a memory test improved in both groups, the walking group improved more than the other group.

Moreover, test scores correlated closely to findings of magnetic resonance imaging (MRI) scans taken at the start of the study and one year later. The MRI scans revealed that the hippocampus—a structure in the brain involved in the processing and storage of memories—increased by 2% in the walkers but decreased by 1.4% in the people who did stretching exercises. The larger the hippocampus—whether the participant was assigned to walking or stretching—the better his or her score on the memory test.

In older adults, the hippocampus tends to shrink by 1% to 2% per year—which likely contributes to age-related memory loss. This study provides evidence that hippocampal shrinkage—and memory loss—may not be inevitable. Keeping physically fit, and especially engaging in aerobic activities like brisk walking, apparently not only exercises physical muscle but also boosts brain power.

Parents, advocacy groups, and some scientists have long worried about a possible link between artificial food colorings and hyperactivity in children. In March, an FDA panel concluded that there isn’t enough evidence to prove that artificial food colorings contribute to hyperactivity, distractibility, and other behavior problems in most children. They did not find evidence that the substances are inherently toxic to the nervous system. Rather, the panel wrote that certain children with attention deficit hyperactivity disorder (ADHD) may be uniquely vulnerable, not just to food colorings, but to any number of food additives. On that theme (see Harvard Mental Health Letter, June 2009), only a small minority of children are vulnerable to the effects of artificial additives and it’s difficult—and in practical terms, almost impossible—to determine who they are.

The FDA convened the Food Advisory Committee to review the scientific evidence on artificial dyes and hyperactivity after receiving a 2008 petition submitted by the Center for Science in the Public Interest (CSPI). The CSPI asked the FDA to ban food dyes used in commercially prepared food.

For more than 30 years, researchers have been examining whether synthetic dyes and other chemicals might contribute to behavioral changes in children. Teasing out whether food coloring causes ADHD or if the two are merely associated is a tall order. By no means do the experts have it sorted out yet. The FDA committee’s vote was in line with the consensus view among scientists, that diet alone is probably not the driving force behind ADHD symptoms such as inattention, hyperactivity, or impulsive behavior.

Yet the FDA’s ruling—and several recent studies—suggested that food additives could contribute to symptoms in some children. In 2007, for example, a well-designed study in Britain found that preschoolers and elementary school students became slightly more hyperactive when they consumed drinks containing artificial colors. Using a complex calculation of “effect size,” the investigators estimated that the additives might explain about 10% of the behavioral difference between a child with ADHD and one without the disorder.

This was similar to the effect size reported in an earlier review by researchers at Columbia University and Harvard University, who estimated that removing artificial food colorings from the diets of children with ADHD would be about one-third to one-half as effective as treatment with methylphenidate (Ritalin).

Here is some advice for those who are worried about the impact of artificial colorings in food:

Avoid a radical approach. For most children with ADHD, there is no evidence that radical diets that eliminate nearly all processed foods and many fruits and vegetables—such as the Feingold diet—do any good. And there is no easy way to identify the few children who might benefit from diets that ban particular foods.

Try eliminating some foods. If you are concerned about behavior changes in your child, or yourself, experiment a bit. Try removing the major dietary sources of artificial colors and additives and see if symptoms improve. The major sources are candy, junk food, brightly colored cereals, fruit drinks, and soda.

Follow a sensible diet. The best advice for anyone with ADHD is to follow a sensible diet. Emphasize fruits and vegetables, whole grains, healthful unsaturated fats, and good proteins. Go easy on unhealthy saturated fats and trans fats, typically found in fast food or prepared meals.

Start moving. Physical activity is great for the brain as well as the body. Children (and adults) benefit when they have time to participate in sports, take dance classes, or just play—outdoors or inside.

You’ll notice that these recommendations are healthy recommendations for anyone. Minimizing candy and sugared drinks, eating a truly balanced diet, adding physical activity to the menu—these habits will have any number of health benefits (both for the body and the brain). I don’t make these suggestions lightly. I know how difficult it is to get your child (especially a child with behavioral difficulties) to eat his or her vegetables. But I also believe it is wise not to let concern over food additives distract parents from established guidelines for healthy eating.