Nutritional Implications for Patients Taking Stimulant Medication: Treating Unintended Weight Loss

(Chapel Hill, North Carolina)

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Introduction

Many Americans take stimulant medications daily to manage conditions such as Attention Deficit Hyperactivity Disorder, depression, and narcolepsy. One common side effect is weight loss. Studies have shown reductions in patient body weight by as much as 10% in the first six months of stimulant treatment (Goldfield). Though many studies have observed this pattern, few have evaluated interventions to prevent it. This may be in part because in the United States, weight loss is almost always regarded as a positive outcome. Unfortunately, the reality is that some patients rely on stimulant medication to function, yet can become malnourished as a result. This paper will investigate the literature for mechanisms of that weight loss and strategies to prevent it.

Stimulant Medications

Central nervous system (CNS) stimulant medications, commonly called stimulants, are prescribed widely in the United States, despite their reputation for causing significant weight loss. They are composed of amphetamines, dextroamphetamine mixtures, and methylphenidate. Common brands include Dexedrine, Adderall and Ritalin, respectively. For ADHD especially, these drugs remain first line treatment options, as they work to correct symptoms for more than 70% of patients (Mayo). Increasingly, stimulants are also being prescribed for weight loss in obese patients, and to improve impulse control for people with binge-eating disorder. However, there are not yet proven recommendations to manage the unintended (except for in obese patients seeking it) weight loss side effects.

Much of this type of available data is about children, because kids used to be the main group diagnosed with ADHD, and it was expected to resolve prior to adulthood. In reality, adults are increasingly being diagnosed and medicated as well. According to the

2016 National Survey on Drug Use and Health, 6.6% of adults reported taking stimulants, and 2018 National Institute of Mental Health data estimates a 4.4% prevalence of ADHD among adults. Treatment can be lifelong- and so can side effects (Heal).

Percent of Children (ages 4-7) Taking Stimulant Medication by State (2011 Data)

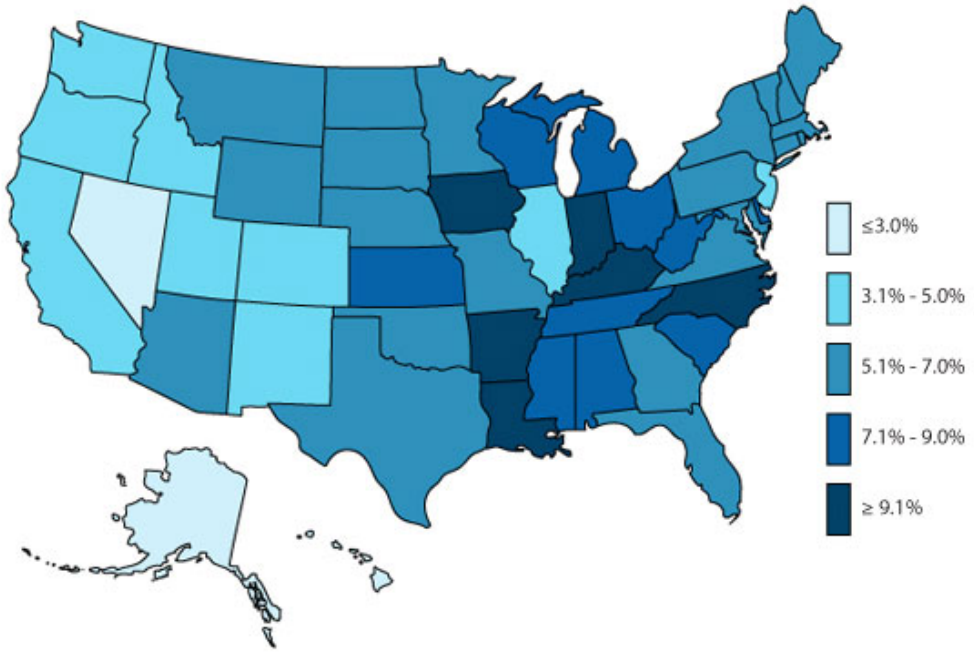

Figure 1: (Key Findings)

National Survey of Children's Health data from 2011 showed that in six states, greater than 9% of children were currently taking these medications, and that in the majority of others, greater than 5% of children were (Key Findings). The states with the highest rates are all in the eastern part of the country, and many are poorer states like Louisiana. Medicaid spends more money on ADHD management than for conditions like anxiety and depression combined, and lower income Americans are the fastest growing group of patients taking these drugs. Researchers also note that states with the lowest rates of people taking stimulants are more likely to have high Hispanic populations, which is in line with lower rates of stimulant use in Hispanic versus white Americans, per Medicaid

data. As of 2016, one in 20 Hispanic adolescents were treated for ADHD, versus one in six non-Hispanic white adolescents (Piper).

Trends in Stimulant Prescription between 2006 and 2016

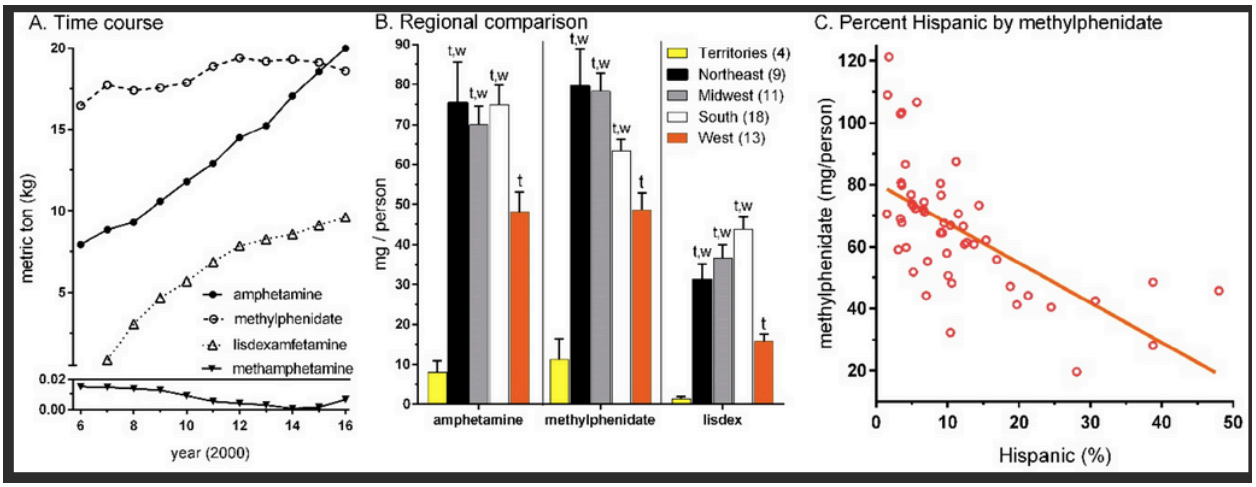

Figure 2 (Piper)

A History of Stimulant Medications

Amphetamines were first synthesized in the late 1800s. They became commercially available as an inhaled decongestant in 1934, sold under the name Benzedrine. In a 1935 study of the medication, researchers observed euphoria and decreased tiredness among patients. Then, in 1937, the American Medical Association approved Benzedrine to treat conditions such as depression and narcolepsy (Rasmussen).

Worldwide, consumption of amphetamines increased. During World War II, Germany manufactured 35 million doses of Pervitin (a form of methamphetamine) for its soldiers. Pervitin became colloquially know as "tank chocolates;' such was its ubiquity. The allied forces used stimulants as well, to stay awake and keep up morale *(*Grinspoon*).*

Meanwhile, the public began to use amphetamines as party drugs, and so the United States Department of Agriculture banned Benzedrine and required prescriptions to obtain other amphetamines. Then the other main stimulant ingredient, Methylphenidate, was created in 1954 and was licensed in 1955 as a treatment for hyperactivity. In 1971, the United States passed the Controlled Substances Act, designating stimulants as C-2 Controlled Substances (Rasmussen).

Stimulants were identified as a treatment for ADHD in 1972 and have been used as such since (Heal). In 1997, the FDA ruled that controlled substances could be marketed directly to consumers, in contrast to most other countries (Piper). Stimulants are still classified as C-2 controlled substances, requiring additional steps for providers to write and pharmacies to fill the prescriptions, such as proof of medical condition, limitations on amounts given, 30 day supply restrictions and registries requiring identification at pharmacies to try to curb drug abuse (Key Facts).

Specific regulations still vary between states, though, and stimulants are still widely used, including by the United States-Air Force. In fact, as recently as 2003, the Air Force defended the practice of giving the pills to servicemen, claiming they always took them voluntarily. The then-Chief of the US Air Force Surgeon General's science and technology division referred to stimulants as the "gold standard for anti-fatigue" (Air). The DEA refers to the effects of amphetamines as "similar to cocaine, but with a slower onset and longer duration." The United States consumes over 83% of the global volume of stimulants, mostly to treat ADHD (Piper).

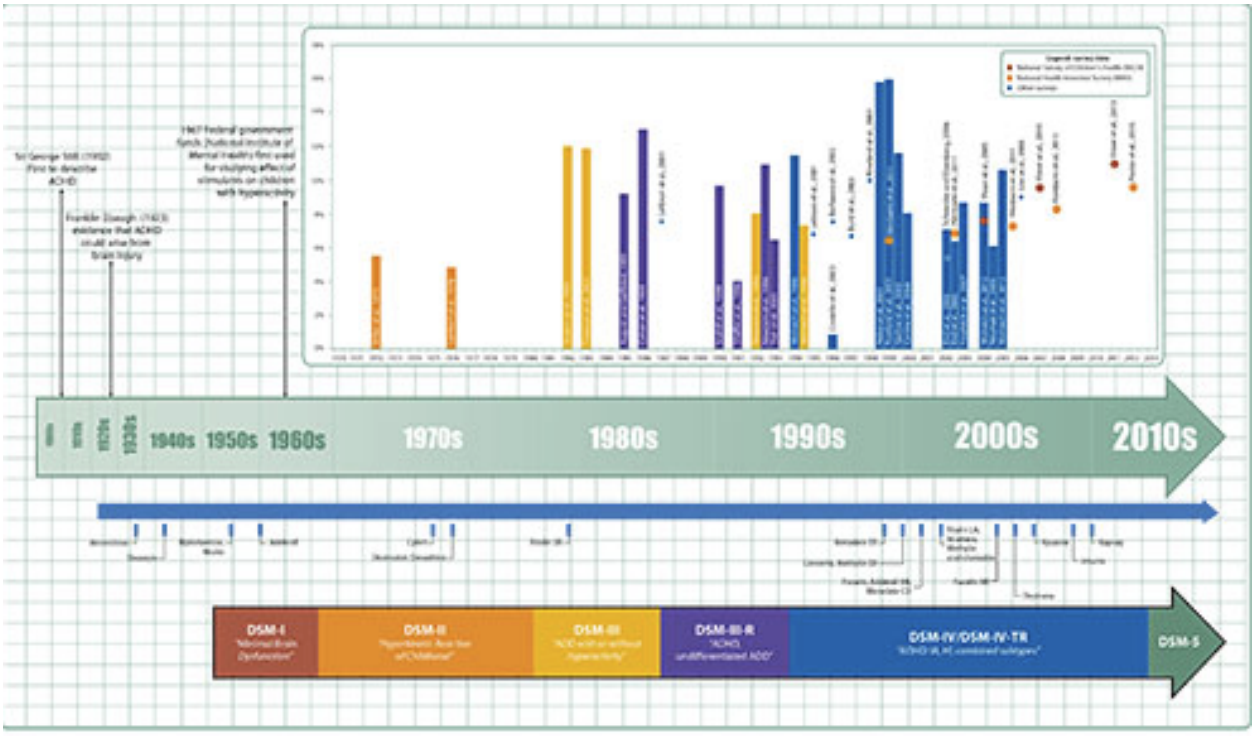

Figure 3 (Key Facts)

Therapeutic treatment for ADHD

When ADHD was first identified, development of symptoms before age 12 was part of its categorization, and distractability and hyperactivity were the main symptoms (Spencer). Currently, ADHD is classified as a neurodevelopmental disorder that can have symptoms present throughout life, and is associated with (as diagnostic criteria changes) difficulty focusing, poor impulse control, disorganization, forgetfulness, excessive speaking, difficulty working with others, and distractibility and hyperactivity, as before. These symptoms may be related to impaired dopamine and norepinephrine signaling in the brain (Heal). Sufferers often also have other signs of abnormal brain function, such as weak reflexes or neurological structural irregularities, particularly in the frontal lobe, which

could explain the deficits in executive functioning. People with ADHD are more likely to have poor grades, be incarcerated, be unemployed, abuse alcohol and take unnecessary risks (Key Findings).

Patients also often have co-morbidities such as depression, anxiety, bipolar disorder, and oppositional defiant disorder. Some estimates demonstrate that 90% of people with ADHD have a co-morbid disorder, which may also require treatment (Key Findings). One longitudinal study over a ten-year period found that girls and women with ADHD were significantly more likely than controls to have eating disorders, mood disorders, and addiction disorders. This is in line with studies of men. However, patients being treated with stimulants did not share this association, which implies that the drugs are protective (Biederman). The true cause of ADHD has yet to be identified, but possibilities include alcohol use during pregnancy, environmental exposure to hazardous materials, (such as lead), low birth weight, and genetics.

Stimulant Medication Mechanism of Action

Stimulants are taken orally, and come in instant-release and extended-release forms. Instant release forms typically begin to work 15 to 30 minutes after ingestion, and effects last for four to six hours. Extended release forms typically begin to work about 45 minutes after ingestion, and last for about eight to twelve hours. Many factors influence duration, such as type of stimulant chosen and rate of metabolism (Heal).

Types of pills vary. Instant release pills are often capsules. Upon entering the stomach, gastric juices quickly dissolve the pill shell and release beads of the active drug form, which are then absorbed through gastrointestinal mucosa and enter the blood stream. Longer release forms may have harder, waxed shells, with release control

membranes and multiple compartments of beads to yield a slower release of medication. The active ingredient again enters the blood stream, where is it transported to the brain. Abusers of the medications may snort or inject pill contents to absorb the contents more quickly, yielding a "high" (Miller).

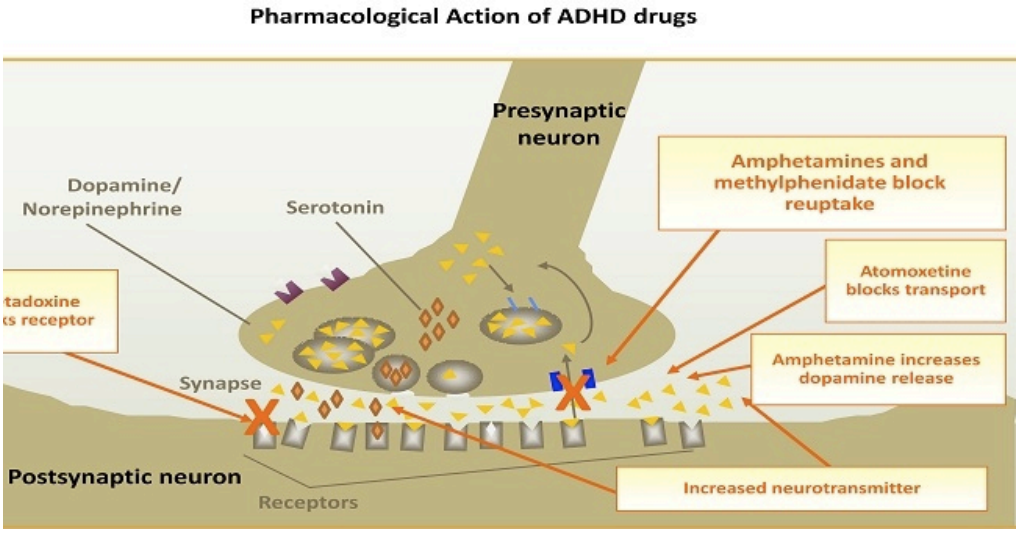

Figure 4 (Goldfield)

Stimulants act in the brain on the neurotransmitter dopamine. By limiting dopamine re-uptake via competitive inhibition, stimulants give it more time to circulate and exert effects; this is similar to how many anti-depressants are serotonin reuptake inhibitors. In fact, serotonin and dopamine are both neurotransmitters associated with positive feelings, although dopamine is also implicated in improving concentration and decreasing distractibility, and serotonin also regulates appetite (Heal). These medications improve a patient's both working and long-term memory, and improve inhibition, helping them to be less impulsive. Also, studies have shown long-term improvements in brain function for patients: a "normalizing" of structural abnormalities (Spencer).

Stimulants also target and increase norepinephrine concentrations (of which dopamine is a precursor), and so in addition to stimulating the central nervous system,

they act indirectly on the sympathetic nervous system (Jones). In fact, norepinephrine is part of why stimulants can improve physical performance (Spencer). As part of the "fight or flight" response, norepinephrine secretion results in brain responsiveness that helps with the neurological issues related to ADHD, such as poor memory. It also leads to increased glucose uptake in muscle, increased glucagon secretion, and increased lipolysis in adipose tissue. In short, the body prepares for battle by making sure glucose and energy are readily available (Pinter). This mobilizing of fat likely contributes to weight loss, especially since it is coupled with a slowing of the digestive system, potentially causing patients to feel full even if they haven't eaten recently (Spencer).

Interestingly, blood tests show a decrease in the hormone leptin in these subjects after a few months of the medication. Leptin is a satiety hormone produced by fatty tissue that indicates fullness. Decreased leptin is consistent with a normal bodily response to weight loss- the reduction in satiety hormone should increase hunger so that a person will regain the weight. However, with these stimulants, those cues are being superseded, and the person is not hungry, and is likely to feel full sooner if they do eat. (Poulton). Other studies have also shown increased ghrelin (the "hunger hormone" produced those stomach) among those taking stimulants, which should also contribute to hunger, yet somehow evidently doesn't (Sahin).

Nutrition Related Side Effects

Indeed, among patients taking these medications, decreased hunger and weight loss are key side effects. One study found that patients consumed 11% fewer calories when taking Ritalin, a popular stimulant (Davis). Patients usually also feel more alert and awake and may not sleep as much as they used to (Goldfield).

Daily Caloric Intake by Patients Taking Methylphenidate (Stimulant) vs. Placebo

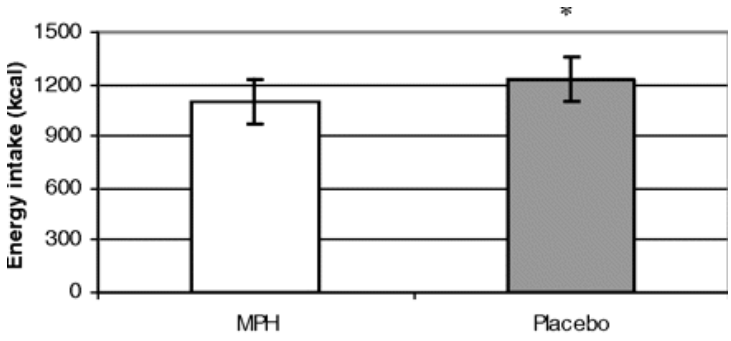

Figure 5 (Goldfield)

Studies of children have shown that typically stimulants cause weight loss and reduced height velocity (decreased growth) of, on average, 1cm per year (Cowell). This is in tandem with a weight loss of up to 10kg (22lbs) in the first six months of treatment (Poulton). This effect is especially pronounced in the first year, suggesting that the body may adjust and weight loss will plateau. In the past, researchers suggested that a child would rebound for any height losses if they stopped taking the medication, but that has not been proven to be true (Biederman). Additionally, it may not be relevant if the treatment is life-long. Increasingly, patients take these medications for decades, and can develop a tolerance, necessitating an increase in dose for the same effect, and an adult is likely to need a higher dose than a child to begin this. This increase heightens the risks of potential weight-related side effects.

Potential Physical Effects of CNS Stimulant Use

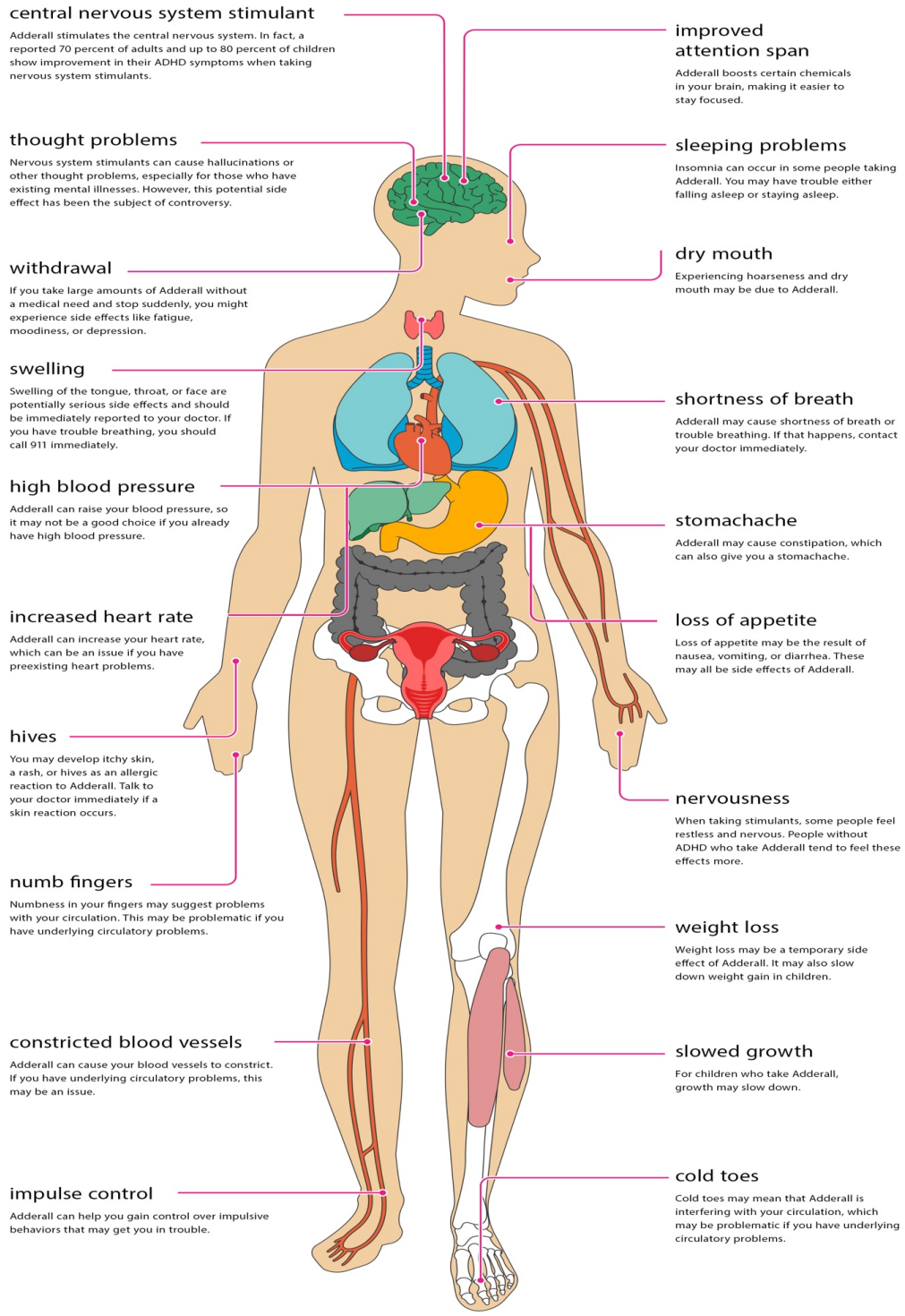

Figure 6 Pietrangelo

When people who do not have ADHD (or other neurological issues necessitating this treatment) abuse these drugs, they may find that their already adequate focus and memory get even better, and that they experience euphoria- but this unnecessary neurotransmitter manipulation can result in too much stimulation for the brain's amygdala, lowering a person's appetite even more than in an ADHD patient, increasing anxiety and

depression, and even causing mania and hallucinations (Brown).

By promoting the release of catecholamines, stimulants sometimes deplete dopamine and serotonin stores, leading to an unpleasant withdrawal feeling. This is more likely for patients abusing stimulants by taking too much, or for people using crystal meth. After all, meth is also made of amphetamines, albeit generally in a much higher amount than a legitimate prescription would contain (Calipari). In theory, a patient's appetite would return during a withdrawal, but so could serious symptoms such as psychosis, depression, aggression, and paranoia.

Norepinephrine contributes to side effects such as sweating, shaking hands, dry-mouth, and headaches, but it improves physical performance as well (to the point that stimulants are banned in major sporting events). Stimulants also cause an increase in plasma free fatty acids, which may be a factor in weight loss effects; there are clearly several contributing mechanisms, and researchers acknowledge that there is still a lot to learn (Pinter). Patients taking stimulants often experience increases in blood pressure, pulse, and body temperature, suggestive of increases in metabolic rate. Usually, a person would burn fewer calories after losing weight, but not these patients. Providers are encouraged to see these patients regularly, to monitor changes, especially in weight and blood pressure.

In addition to lowered appetite, people taking stimulants also may have increased stamina and endurance for exercise, and therefore may be more physically active (Poulton). This increase in calories burned can contribute to weight loss too. Interestingly, for those taking the medication for severe ADHD, the net caloric intake may not be significantly less than before, as prior to taking medication some are very active (or

hyperactive, as the name ADHD implies), and are unable to focus on eating at mealtimes without the aid of medication (Lickteig). However, for most, some decrease in size still occurs.

The weight loss happens to abusers of the medication, too, of which there are many. One study found that 3.4% of participants reported using medications such as Adderall without a prescription (Sweeney). Another found that 11% of medical students were taking stimulants, fewer than a quarter of who had a prescription (Fallah). Furthermore, these numbers may be artificially low, as participants might not want to admit to doing something illegal. It also may include people who have a legitimate prescription but may not actually have ADHD; recently the medical community has tried to tighten diagnostic criteria so that people cannot erroneously claim to be distracted in order to obtain the pills (Heal).

Literature Review of Weight Loss

Since amphetamines both increase both satiety and basal metabolic rate, a person taking them can both be less hungry and burn more calories, compounding weight loss (Jones). Prescribing providers are encouraged to monitor patients for weight loss but may not do so.

Additionally, some patients seek out these medications specifically to enable a disordered pattern of eating and to lose weight. The people primarily prescribed stimulants, people with ADHD, are 16 times more likely than the general population to have eating disorders. Therefore, someone may be taking a drug for legitimate reasons, but still be trying to maximize weight loss side effects (Biederman)). One lifetime prevalence study of 731 women with eating disorders found that about 7% reported abusing

stimulants, but that in the sub-group of women who had both anorexia and bulimia, that number more than tripled, to 23% (Root). Observing and curtailing this use may be especially relevant for dietitians working in eating disorder treatment.

Patients may regain some weight if they cease treatment with this type of drug. In one study of dexamphetamine specifically targeting weight loss (where patients were encouraged to also incorporate a good diet and exercise as well), adult patients lost an average of 10.6kg (23lbs) over six months of treatment. After going off the dexamphetamine, participants gained back an average of 4.5 kg (10lbs), thus resulting in an overall loss of 7 kg (15lbs- note, this math is slightly off, written as reported in the study). However, the study consisted of a sample size of only twelve people, which is too small to draw large conclusions.

The study also found a significant association in a subgroup in which the women who lost the most weight while taking dexamphetamine also regained the least amount of weight. This is different from outcomes observed in many other weight loss methods, such as a low carbohydrate diet, in which people who lose the most may also gain the most back. However, this study was small, studying only 14 people for six months of treatment and an additional six months of follow-up. Additionally, researchers encouraged healthy diet and exercise, which may have contributed (Poulton). Still, it does imply that for patients whose weight loss cannot be curtailed, terminating the medication should allow for some weight regain.

Indeed, one option to manage weight loss is to work with the prescribing provider so that they might experiment with different medications and administrations. There are several stimulant brands available, with slightly differing compositions. One might have

less of an impact on a patient's weight than another. One study suggests shorter versus extended release capsules might allow for more hunger as the medication wears off. Additionally, studies show a dose-response curve in weight loss, meaning that taking greater amounts was correlated with greater weight loss, so giving the patient the lowest possible therapeutic dose (for them) might curtail excess weight loss (Davis).

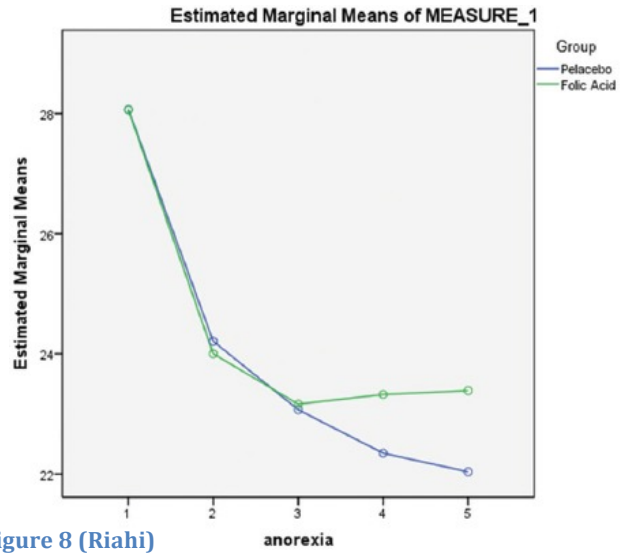

Figure 8 (Riahi)

One promising double-blind study done in Iran found that folic acid supplementation significantly increased hunger among children taking methylphenidate. The study had 70 participants and only lasted for eight weeks, but it suggests that micronutrient deficiency may contribute to poor appetite. Researchers did rely on parent report of child hunger, which may not be wholly accurate. There were also greater increases in weight among the group supplemented, but they were modest and not statistically significant. However, a previous study, on 20 younger children, showed the same improvements in hunger among those given folic acid supplements. Performing blood tests to measure micronutrient levels, and studying adults too, could help illuminate this relationship. It may be useful for children taking stimulants to also take vitamins, or else choose a diet that emphasizes nutrient dense food.

Another study found greater growth in children taking stimulants who also took melatonin, a natural supplement that helps with sleep. This suggests that normalizing circadian rhythms and sleeping well may reduce the hunger and weight loss effects. It is

also possible that the melatonin itself somehow stimulated appetite- but this was one 8-week study, of 60 children, so this has yet to be determined, and more research is needed. Whether using melatonin or not, patients should be encouraged to try to get substantial, restful sleep to prevent weight loss (Mostafavi).

Patient Macronutrient Intake Following Methylphenidate or Placebo Administration

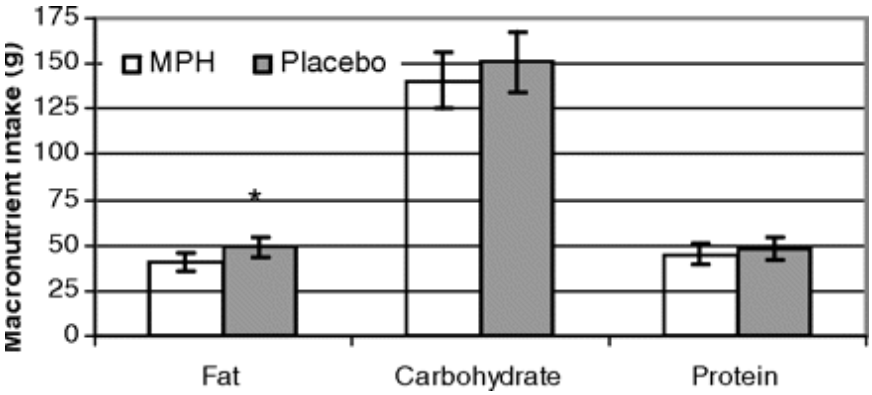

Figure 9 (Goldfield)

In another study focused on understanding reasons for stimulant-induced weight loss, researchers saw that after stimulant administration normal weight participants ate 11% fewer calories (a more recent study of obese men showed a 23% percent reduction!) and had decreased intake of all three macronutrients, including a 17% reduction in fat intake (Goldfield). Urging patients to increase or at least maintain fat intake (since fats are the most calorie-dense macronutrient) by means of choosing full-fat dairy or consuming more butter and oils in cooking could help them avoid weight loss, but this has not yet been proven.

Furthermore, eating a high fat breakfast has been shown to increase bioavailability of the stimulant Methylphenidate (Brand name Ritalin). Food quickens absorption of the medication in the stomach, causing a greater concentration of stimulant in the blood at peak levels, compared to those in a fasted state. The medication would also

peak slightly sooner, at about four hours, versus so eating it on an empty stomach with a peak concentration at closer to six hours. It's unclear if this pattern is beneficial or not, and another study found that for people taking amphetamines rather than methylphenidate, they actually had better bioavailability in the fasted state. Both studies were small, though, (Sallee).

Methylphenidate Plasma Concentration for Fed and Fasted Patients

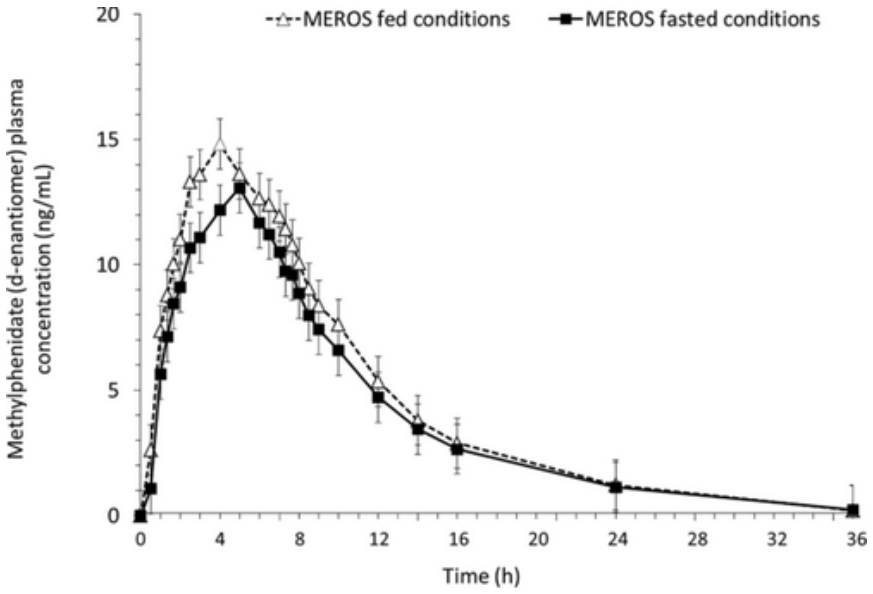

Figure 10 (Sallee)

Several studies observed that two months into treatment, patients have altered nutrition-related lab values, such as increased adiponectin and decreased leptin levels in their blood. This is similar to lab value changes evident in cancer-induced caxechia, (though stimulant patients may see more fat-based weight loss,) so methods to prevent weight loss used in cancer treatment may be effective for stimulant patients as well (Sahin). These techniques include eating smaller meals more often, trying to eat more later in the day as the medication wears off, using supplementary calorie drinks such as Ensure, and scheduling times to eat regardless of appetite, (as recommended by the American Society

of Pediatrics). These strategies are recommended, but have not been studied in this context, or proven to be effective. One key difference is that people taking stimulants are more likely to maintain muscle than cancer patients.

Appetite stimulants, such as Megestrol, may be helpful, but have not yet been studied as a treatment for weight loss from stimulant medications. They have their own unpleasant side effects, which may be one reason they have not been studied. Additionally, since ADHD has so many co-morbities, polypharmacy is a common issue. Increasingly, there are new options that are cannibinoids, such as Cannibigerol, that may offer appetite increases with fewer risks. Hopefully they will be studied for use with CNS stimulant drugs soon.

Aromatherapy may be a tool to prevent weight loss. A study of 13 pregnant women found that after smelling linalool for 5 minutes, their pulse rates decreased, suggesting a decrease in norepinephrine signaling (Irigashi). Another study found increases in calm behavior among rats that smelled lavender. Though there have been several studies of specifically of aromatherapy and appetite, most are aiming for a decreased appetite response. In one study that was evaluating appetite stimulation, researchers found that patients who consumed a fragrant drink before being offered food ate less than those who had a plain beverage. This could mean that trying to supplement meals with nutrition drinks could backfire, with patients potentially eating less of their meal because of the strongly scented accompanying beverage. This needs more research in order for the mechanism to be clear.

Discussion

There are few studies specifically about preventing weight loss for people taking stimulants; there are many interventions specifically seeking weight loss as an outcome, or else merely observing it. Some studies suggest a flattening of weight loss trajectory after six months, but they are largely small and short. Indeed, there are not enough studies of long-term use of these medications, especially concerning adults. Most studies available are of small groups (often fewer than forty participants) and are of children.

Additionally, as in a lot of research, studies are mostly of boys and men, even as at least one study suggests that women may be more responsive to appetite suppressive effects of stimulants, possibly due to the influence of female sex hormones, causing greater weight loss (Davis). Since prescribed stimulants haven't been studied during pregnancy, recommendations for pregnancy are based on clear adverse effects for infants born of women recreationally using amphetamines, such as Crystal Meth. For women prescribed these medications, it would be prudent to know whether they would be able to gain weight effectively and birth children of appropriate weight without having to stop taking the medication (Oei).

There have only been two meta-analyses of the long-term MRI data, one of which focused solely on children (Spencer). The adult study did find improvements in structural abnormalities for the patients taking stimulants, such as resolving issues in the basal ganglia and anterior cingulated cortex, but this research only provided structural MRI data, rather than functional. A functional MRI could look for changes in how the brain is used, specifically looking at how the brain responses to food stimuli, such as sight or smell of food, or to fasting, to more fully understand the lack of appetite. For a class of medications

so widely prescribed, more information would be useful and could help to identify tools to curtail the reduction in appetite (Spencer).

Additionally, studies have shown that stimulants can help the ADHD brain to restructure but actually can hurt the non-ADHD brain through overstimulation, (or any brain in mega doses) (Lakhan). It would be advantageous to know more about why that is, and what the long-term effects of that restructuring might be on hunger or on basal metabolic rate. This is especially prudent because some physicians recommend that ADHD patients take medication "holidays" periodically, such as every weekend, to avoid developing a tolerance for stimulants (Pietrangelo). Is this protective, or could lack of consistency be harmful? This has not yet been established, though one long-term study, The Multimodal Treatment Study of Children with ADHD, suggests that medication breaks may help improve growth outcomes in children (Murray). If these holidays are beneficial, or are least not detrimental to symptom management, they might be used as a strategic tool to prevent excess weight loss. However, more information is needed.

One retrospective naturalistic study evaluated adults who had been diagnosed with ADHD an average of six years ago to see if they still took stimulant medication. Of the half who still did, more than 25% reported decreased appetite as a side effect. This is of the group that continued taking the medication- the number for the patients who stopped entirely would likely be much higher, as many cited side effects as the reason they did not continue with the stimulants. Unfortunately, that group was not asked about appetite, so that is speculation (Edvinnson).

Conclusions:

Much of the research on these medications is still being done with the presumption that children are the sole consumers- this is no longer accurate. Weight loss and lack of appetite could potentially be lifelong issues for aging patients. Therefore, as dietitians, it is important to know if a client is taking stimulants, whether by a prescription or illegal means, as it could help explain a patient's unusual weight or weight trends.

Of course, some patients may be prescribed these medications or similar for weight loss- they should of course still be monitored for safety, and patients and prescribers should have healthy weight loss goals. Because loss may be rapid, patients experiencing decreased appetite and weight loss should be given malnutrition focused physical exams when possible, even if they are not yet underweight. Patients may be reticent to discuss these medications, so techniques such as motivational interviewing and good listening skills may help build rapport with patients so that they might feel comfortable discussing their medications, even if they are being obtained illegally. In a hospitalized setting, drug screening can show recent amphetamine use, whether by legal or other means.

Doubling in total weight (metric tons) of amphetamine, methylphenidate, lisdexamfetamine, and methamphetamine as reported to the Drug Enforcement Administration for the United States and Territories from 2006 to 2016.

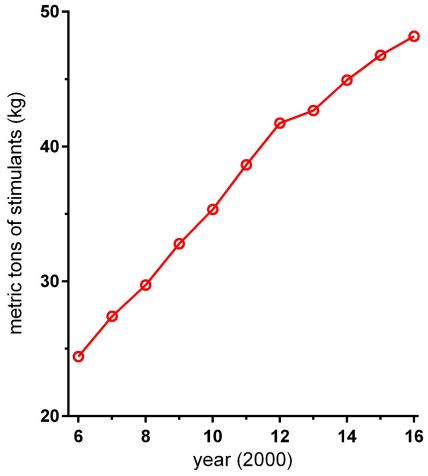

Figure 11 Piper

Prescription of CNS stimulants continues to rise, probably due in part to increased awareness of and screening for ADHD (Olfson). To best serve patients' nutritional needs without disregarding the importance of psychiatric care, it is crucial for these medicines to continue to be researched, with studies of specific interventions to slow and/or prevent weight loss. With more information, dietitians will be able to make recommendations based on proven techniques and thus can help patients more effectively.

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