Sackler Journal of MEDICINE

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MISSION STATEMENT

What's emerging in medicine today? The Sackler Journal of Medicine – a forum where trends in medicine including translational research, the economics and policy of healthcare, and clinical experiences are explored, analyzed and discussed. SJM is a peer-reviewed journal for medical students to discuss and learn about the latest medical breakthroughs and the fundamentals of medicine.

We encourage student and physician collaboration to bring you literature reviews, case reports, original research, reflective pieces, and short commentaries on published papers. Take the opportunity to contribute your work, experiences and voice to the conversation.

SUBMISSIONS INFORMATION

Submissions from students, faculty, and individuals are welcomed. For more information please visit the "Submissions" page on the Sackler Journal of Medicine website at sacklerjom.org

COVER IMAGE

The cover image was provided by Tziporah Thompson.

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Table of Contents

Letter From the Editor

Brian Wolf
editor-in-chief

Welcome to the Sackler Journal of Medicine (SJM), a peer-review medical journal written by and for the medical student body. Beginning with our inaugural issue— imagined and implemented in the span of less than nine months —we will learn from one another what a medical student-run journal is, and what it can inspire in our constantly evolving world.

Since we announced the launch of SJM with our website, www.sacklerjom.org, in April 2016, I've been trying to answer a question that seems crucial for a so-called medical student journal. Namely: What can this journal add to the ever growing field of medicine? At this point, this medical student journal is a forum in which we can shape and mold the conversation. What we are all really after—and what SJM is all about—is the "charged-up" feeling that comes with reading a blog post or an original paper, learning something new, and then applying this knowledge. It's about planting a seed; as we progress not just our schooling but in our medical careers, we are constantly learning, growing, and adapting our medical methods to best serve patients and the greater community.

Whether you are reading this journal as a print copy or a PDF, on your laptop or your cell-phone, this issue was a work put together by an editorial team for a discerning audience- a striking package that a group of medical students prepares for its readers. Finally, a journal is about context: how ideas and images (in this case, graphics and figures) are juxtaposed and presented to one another.

But enough theorizing- let me tell you about this inaugural issue of SJM. So the essential question is, what can we learn about medicine from our peers? We went looking for it in our news briefs (found on our website under SJM Commentary), consisting of commentaries from students who read some fascinating papers and wanted to share their thoughts/comments/ideas. Want to know what goes into a peer-tutoring histology session? Jonathan Shayo (MS4) brings to you a reflection piece on what goes on inside the mind of a peer-tutor, and what may seem like riffs and fills are part of his deliberate steps to teach students and get them interested. One of our advisory board members and recent Sacker graduate, Dr. Maxine Stachel, reports about her recent experience with the residency match, something that we, as medical students, will undertake. Our inaugural issue profiles pieces ranging from current events in medical marijuana, the biochemistry of drug addiction, and treatment of multiple sclerosis, as well as the implications of the tau protein in Alzheimer's disease. These review papers, written by both inquisitive and research-oriented medical students on the latest breakthroughs and understandings in medicine, are integral to the journal's mission to broaden medical students' knowledge outside the confines of a lecture hall. To equipoise these substantive review pieces, a feature of this issue from Melissa Schechter (MS2) explores a specific topic (HIV/AIDS diagnosis and disease timeline) with narrative that applies archetypal information to a realistic scenario. Michael Burke and Amira Beeber (MS4) detail their proposed analysis for congenital heart disease follow-up. Lastly, dispersed throughout the issue are "key points" to help clarify medical terminology or expand on topics discussed in the pieces.

So here's our modus operandi: Let's have great success. Let's discover the wide-ranging corners of medicine, really examining the crooks and crevices. Let's explore our own interests, tailored to what we want to better understand and also gets us excited. Let's make our academic lives more creative and, in turn, help us to become kickass future physicians. Let's learn. Let's enjoy. If any that speaks to you, then this is the journal for you.

Stay with us—and expect more.

Brian Wolf

Letter from Dr. Allen

Aaron Allen M.D.
Faculty Adviser- SJM
Deputy Director
Sackler School of Medicine
New York State / American Program
Tel Aviv University
Israel

Dear Readers of SJM,

It is with great pleasure that I write to you on the occasion of the inaugural issue of the Sackler Journal of Medicine. Less than one year ago, Brian Wolf and his group of bright eyed editorial staff came to me with the idea for SJM. At first, I was a little skeptical but nonetheless overjoyed. The idea that a student-run medical journal could come out of Sackler seemed not only appropriate but long overdue. Since the school's inception, we are committed to providing the finest in clinical and basic science education anywhere. This mission, combined with a drive to excel in all fields of medicine including research, has guided our efforts since then and is evident in our outstanding graduates and alumni who today lead in both clinical and research fields throughout North America. It seemed fitting therefore that Sackler take its place along other first-rate North American medical schools in having its own student medical journal.

The goal of the journal is not only to provide a platform for academic research but also to educate the student reader with timely pieces summarizing literature or topics germane to students such as the residency match. On behalf of the administration of the New York State/American Program, I would like to encourage all the readers to take an active role in writing and editing SJM. Indeed, it is up to you, the students, who make this journal the finest student publication anywhere in keeping with the fabulous Sackler tradition of outstripping everyone's expectation of you at every juncture.

Hospital and clinics are a fertile ground waiting for Sackler students to research, discover and grow. We hope that with each paper and discovery SJM will be by your side to serve as a platform for your discoveries and for you to share your experiences with your fellow students and colleagues worldwide.

Again, congratulations, and we are here to root you on at every step of the journey!

Mazal Tov!

Aaron Allen M.D.

SJM Commentary

007 meets The Lancet

Joshua Fein, BS
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Ten years after becoming international news as the KGB-cum-British spy, taken out by shady Russian operatives using new radioactive poisonings, Alexander Litvinenko has made it back into the (medical) news in a recent case study in the Lancet. His doctors are free to describe his case, now that any state secrets involved have been exposed in the court of law. Thus, The Lancet brings us the closest thing I've seen in a medical journal to a spy thriller. Alright, perhaps not quite so suspenseful, since we know the tragic outcome from the get-go. Still, a fascinating toxicology tale describing the natural history of Po-210 poisoning. There are interesting parallels to be drawn to the effects of chemotherapy: first nausea and vomiting (though possibly attributed to a potential concomitant *C. difficile* infection), then alopecia, then bone marrow failure, and finally multiple organ failure and death (Figure 1). The treating physicians note that, at the dosage with which he was poisoned, there was never any hope of his recovery, though they raise the possibility of treatment of lower Po-210 doses and raise interesting questions about hospitals' ability to recognize cases of this poisoning. A worthy read, both for the sake of geopolitics and for a good primer in radiotoxicology.

Nathwani A. C., Down J. F., Goldstone J., et al. (2016). Polonium-210 poisoning: a first-hand account. Lancet, 388(10049), 1075-80.

Karen Arane: *No Comment*

Mindfulness in Medicine – Helping Community and Physician Health

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Mindfulness is a form of meditation that focuses on nonjudgmental present moment awareness. The study by David S. Ludwig MD, PhD, and Jon Kabat-Zinn, PhD, titled "Mindfulness in Medicine" suggests that the practice of mindfulness is not only beneficial for patients who may experience chronic illness, pain and substance abuse, but also to the physician's ability to be more compassionate and make better clinical decisions that may prevent medical error. Medical students selected at random to participate in mindfulness-based, stress reduction training showed decreased stress levels and increased empathy compared to those that did not participate in the study. The study analyzed cases where patients with cancer, type 2 diabetes, psoriasis, sleeping disorders, ADHD, obesity and other conditions showed a positive increase in mood, perception and acceptance of pain, overall stress reduction, better physical functioning, increased overall well-being, and ability

to cope better with everyday life.

Another study titled "The Neuroscience of Mindfulness" aimed to analyze the effects of mindfulness on the brain and reveal specific neural pathways involved during mindfulness meditation. MRI data suggests that mindfulness meditation might lead to increased cortical thickness and increased activity within the white matter. Eight different brain regions were shown to be involved in mindfulness meditation: the frontopolar cortex, involved in meta-awareness; the sensory cortices and insula, involved in body awareness; the hippocampus, involved in memory; the anterior cingulate cortex, mid-cingulate cortex and orbitofrontal cortex, areas involved in emotion; and the superior longitudinal fasciculus and corpus callosum, areas involved in communication within and between cerebral hemispheres.

Both of these studies suggest that cultivating present moment awareness through the practice of mindfulness can have major positive benefits with regards to the quality of life of patients and physicians alike.

Ludwig D. S., & Kabat-Zinn J. (2008). Mindfulness in medicine. JAMA, 300(11), 1350-2.

Tang Y. Y., Hölzel B. K., & Posner M. I. (2015). The neuroscience of mindfulness meditation. Nat Rev Neurosci, 16(4), 213-25.

Zika Virus: Looking Back and Forward

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The authors of a recent publication in The Lancet examined whether or not a correlation exists between infection with Zika virus, an emerging arbovirus, in pregnant mothers, and microcephaly in the developing fetus. After gathering data from an epidemic that took place in French Polynesia prior to the outbreak that occurred in the Americas, the authors found an increased risk for microcephaly, and resultant brain/mental damage, in infants born to mothers infected with Zika virus during the first trimester. This risk was estimated to be about 1%. The statistical significance of their findings should be taken into account by health professionals worldwide. Although further prospective studies need to be done to establish stronger connections between maternal infection and microcephaly, these data indicate that significant correlation likely exists. Emerging viruses present the potential to cause devastating epidemics, and thus should be tackled with full force in order to prevent morbidity and/or mortality. Zika virus, being an emerging virus, thus has direct effects on healthcare personnel, who need to be aware of the potential risks associated with maternal infection, and to ensure that their patients are adequately informed. By doing so, medical professionals can limit the number of diagnosed cases of congenital microcephaly. Medical students and young doctors need to be made aware of the variety of emerging viruses, as well as their potential treatments and methods of containment, as they will be the ones that will treat those patients who are unlucky enough to become infected.

Cauchemez S., Besnard, M., Bompard P., et al. (2016). Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. Lancet, 837(10033), 2125-2132.

PD-1 Blockade in Melanoma

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The authors examine the use of pembroluzimab, a monoclonal antibody designed to block the PD-1 pathway in metastatic melanoma. PD-1 ligand has been found to be expressed on several cancer cells, including metastatic melanoma, and when bound to the PD-1 cell-surface receptor on T-cells, functions to reduce immune mediated destruction of those cancerous cells. Blockade of this pathway has the potential to promote T-cell mediated cytotoxicity and reduce tumor burden. The authors note that further studies need to be done to establish which patients should receive treatment with pembroluzimab and

whether this treatment should be started after initial therapy with other monoclonal antibodies directed against differing cell surface receptors (i.e. BRAF/MEK). The use of monoclonal antibodies shows great promise as a future treatment option for a wide variety of diseases, and thus medical students, and all medical professionals, should be made aware of the amount of potential of such therapy.

Bhatia S., & Thompson J. A. (2016). PD-1 blockade in melanoma: a promising start, but a long way to go. JAMA, 315(15), 1573-5.

What is Precision Medicine?

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The emerging and rapidly progressing field of precision medicine, in which treatment is tailored to patients on an individual basis, is examined by the authors. Advances in the fields of genetics, proteomics, diagnostic imaging, and several others have allowed physicians to establish treatment options for patients that show greater efficacy and fewer unwanted side effects in comparison to administration of broad-spectrum therapy. The authors note that it will likely be difficult for the desires of patients, physicians, insurance companies, and pharmaceutical industries to align. More than likely, there will have to be a joint effort carried out so that precision medicine can become the norm in patient care. As an emerging field, medical students and other training physicians need to stay well informed as any changes in regards to precision based medical approaches will likely affect how they practice medicine in the future

Jameson J. L., & Longo D. L. (2015). Precision medicine–personalized, problematic, and promising. N Engl J Med, 372(23), 2229-34.

E-Cigarette Policy

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This paper examines the ever-increasing use of electronic cigarettes as a possible alternative to the use of combustible tobacco products. The authors note that many anti-tobacco advocacy groups tend to focus on the adverse effects of electronic cigarette use, rather than noting the potential benefits of these nicotine delivery systems. The authors argue that electronic cigarettes can provide an excellent outlet for smokers who are unable or unwilling to quit smoking. With the use of electronic cigarettes, smokers are able to intake the desired nicotine, whilst avoiding the harmful tar and other byproducts introduced into the body with combustible tobacco products. Due to the major side effects and deaths associated with combustible tobacco products, the possibility of appeasing smokers' addictions using a less harmful delivery system can dramatically reduce medically related symptoms, including morbidity and mortality. This has an incredible amount of potential, with the possibility of greatly reducing healthcare costs associated with tobacco use. Young physicians should take note of the potential benefits of using e-cigarettes as they may be employed to appease addictions while avoiding the toxic effects of inhaling combustible products.

Green S. H., Bayer R., & Fairchild A. L. (2016). Evidence, policy and e-cigarettes — will England reframe the debate? N Engl J Med, 374, 1301-1303.

NEJM: Betamethasone for Late Preterm Births

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This April 2016 article in the New England Journal of Medicine raises lots of new and interesting questions as it answers some existing and important ones! The authors, on behalf of the NICHD, present results of an RCT giving antenatal betamethasone to women at high risk of late-preterm delivery (W34-W36) to see if this would lessen adverse respiratory events among these preterm newborns. Steroids are regularly given when early pre-term birth is expected, but the data has been unclear about what to do with the late pre-term pregnancies.

And it continues to be unclear! I love this study for its classic methodological elegance. Double-blind, randomized controlled trial; relatively large sample sizes (~1400 in each group); beautiful symmetry between groups; immediate and relevant primary and secondary outcomes.

And the results? I confess I'm not sure what to make of them. For mitigating the primary outcome (respiratory distress of a variety of different flavors, within 72 hours), the Number Needed to Treat (NNT) represents the predicted number of patients treated for one patient to see benefit. For example, if the NNT is 100, then–on average–out of one hundred patients treated, one is expected to receive the benefits of the therapy described in the trial. The NNT for this study was 35, with a 95% confidence interval from 19 to 259. Various secondary outcomes had more clearly meaningful margins, and, as the authors (and Crowther & Harding's commentary) point out, the best test will be in late follow up, several years from now. The authors point out one particularly interesting subgroup: there was a significantly meaningful reduction in risk in those patients for whom a cesarean delivery was planned. It would be interesting to see how the NNT played out in that group.

Overall, given a relatively mild adverse reaction profile (the authors note a need to follow the newborns for hypoglycemia), I am curious to see how this plays out in terms of recommended practice. Perhaps we'll have to wait to see the long-term follow-up before we know, though I wouldn't be surprised if this starts to become common practice in the c-section group sooner, at very least.

Gyamfi-Bannerman C., Thom E. A., Blackwell S. C., et al. (2016). Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med, 374, 1311-1320.

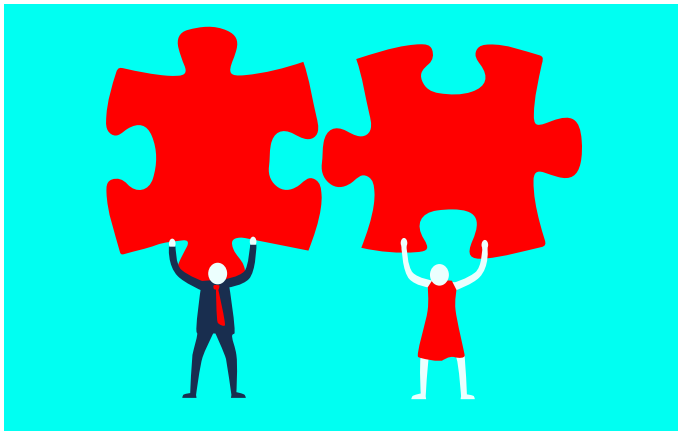
Reflecting on the Residency Match

Maxine Stachel, MD Sackler Alumni '16
New York University (Physician-Scientist Pathway Residency)

Earlier this year, when deciding my residency, I matched into my first choice: the "Physician-Scientist" residency at New York University (NYU), a seven-year commitment that allows me to complete internal medicine residency in two years (instead of three), cardiology fellowship in two years (instead of three), and then pursue 3 years of "protected" research (meaning guaranteed funding, with only 15-20% of my time in the clinic). As I transition from the bedside to the bench, I will have the opportunity to take advanced coursework in applicable fields to refresh and refine my research acumen. The faculty will provide advising and grant-writing support, and if I'm productive, may fund a technician or two to assist me. In my 7th year, I will become NYU faculty. Most applicants have an MD/PhD (I didn't), but you do need to have a strong research record in order to be competitive.

When pursuing a career in academic medicine, there are a number of options you might consider. The research track I outlined (also called the "ABIM research pathway" or, confoundingly, "fast-track") can be adapted to any internal medicine fellowship path (Heme/Onc, GI, etc.); in all cases, it takes one year off of the usual fellowship length. Knowing the exact area of interest may not be absolutely necessary, but it will help definitely frame your prior research experience and plans into a coherent narrative. Most major universities offer this track; in NYC, Columbia, Cornell, NYU & Mt. Sinai each takes approximately 2 people per year. The research pathway also exists for pediatrics and its fellowship tracks with additional information found through the American Board of Pediatrics. Lastly, if a 7-year commitment may sound overwhelming, the clinical investigator tracks, which are less intensive and less selective, are offered at some institutions and involve taking part in research electives during an otherwise traditional residency.

When interested in a specific institution, I'd recommend looking up their program leadership and email them directly for more information. Also, consider emailing prospective PIs with your CV and statement of intent. Regardless of your intended path, the third year of medical school is the time to start thinking about what you want from a program and what those programs will want from you—and then decide how to tell them you have those qualities/credentials.



Micah Belzberg: *Match Up*

Key Point: Match Statistics

Of the 27,860 first-year positions, 13,744 (49.3%) were in primary care specialties.

Internal Medicine has gained positions every year in the past five years, from 5,277 in 2012 to 7,024 in 2016, an increase of 33.1%.

NRMP enables two applicants to participate in the Match as a couple by linking their preference lists. A record-high of 1,046 couples participated (11 more than last year) and 95.7% matched to first-year positions.

National Resident Matching Program. (2016). Results and Data 2016 Main Residency Match.

Addiction: A Literature Review of Biological Factors Leading to Addictive Tendencies and Potential Treatments

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Abstract

Addiction is an epidemic; the consequences of an addiction can tear apart families and cause immeasurable damage to many lives. Based on medical literature from the past twenty years, this paper focuses on common biological changes present in addiction and medical treatments available and being researched. Specifically, critical changes observed in the levels of dopamine receptors, transcription factors, and stress hormones, are analyzed. In addition, by assessing the treatments, including vaccines that block the entry of substances through the blood brain barrier and surgical interventions that act directly on the area of the brain that controls addiction, the biological changes are better understood. Overall, this paper provides a review of past research and medical breakthroughs in the field of addiction, as well as the burgeoning directions in this field.

Micah Belzberg: *Prescription*

Introduction

Addiction is characterized by a loss of control, or a dramatic behavioral change "from impulsivity to compulsivity" (1). Behaviors, which had once been engaging for pleasure, become painfully forced and addicts are unable to cease their behavior. Substance dependence specifically is defined by the American Psychiatric Association as "a maladaptive pattern of substance use that subsequently leads to clinical impairment or distress" (2). It is diagnosed by the appearance of specific symptoms when three or more occur within 12 months. These symptoms include, but are not limited to, increased substance tolerance, withdrawal, increased intake, recurrent desire to reduce substance use, frequent drug-seeking behaviors, reduction in social, occupational or recreational activities, and continual substance use despite deleterious physical or psychological consequences (2). Or as summarized by Dr. George Koob in three major symptoms: "compulsion to seek, loss of control in limiting intake, negative emotional state with withdrawal" (1). Signals that the addict associates with addiction (such as friends, locations, drug equipment) can remind him of his previous behaviors and thereby cause a relapse. Like substance addictions, non-drug addictions appear in similar psychological and behavioral patterns including craving, impaired control over the behavior, tolerance, withdrawal, and high rates of relapse (3).

The modelling of addiction as a brain disease is controversial, as is the equation of behavioral abuses with addiction (4-6). In spite of this, this paper attempts to present some of the ongoing research into changes that the brain undergoes under pathological activity. Although every substance and behavior that is abused has a variety of different effects on the brain, this paper will attempt to focus on the common factors seen in behavioral abuses and substance abuses.

Materials and Methods

A Google Scholar search was performed using keywords, such as: addiction, compulsion, behavioral addiction, biology of addiction, neurobiology of addiction, ablative surgery, and deep brain stimulation.

Results

Biological Basis of Addiction

Associated Brain Regions

The reward regions of the brain seem to have evolved long ago. The basis for the complex reward pathways present in mammals has existed for nearly 2 billion years, when flies and worms evolved. They evolved to regulate a creature's responses to natural rewards, like food, sex, and social interaction, and are therefore critical for survival. The areas implicated in addiction are grouped together and referred to as the mesocorticolimbic projection. This consists of dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain and their targets in the limbic forebrain, especially the nucleus accumbens (NAc), and the prefrontal cortex. Every drug of abuse regardless of its distinct method of action converges on this pathway with common acute effects. Several other brain areas that network with the VTA and NAc are essential for the chronic changes associated with addiction. Specific portions of the limbic system (namely, the amygdala, hippocampus, and hypothalamus) are associated with addiction. The amygdala is important to help to assess whether an experience is pleasurable or aversive and whether it should be repeated or avoided and to create connections between an experience and associated cues. The hypothalamus is crucial for the stress activation system. The hippocampus functions to record the memories of an experience. Additionally, the cingulum, which allows for communication between areas of the limbic system, is a central structure in learning to correct mistakes. These regions are the traditional areas of memory formation and their association implies that addiction involves emotional memory (7). The orbitofrontal cortex, a sub-region of the prefrontal cortex, contributes to the impulsivity and compulsivity that characterizes an addicted state (8).

Key Point: Dopaminergic Areas and Associated Pathways in the Brain

Ventral tegmental area of midbrain:

- Mesocortical pathway: Blockage leads to increased negative symptoms of schizophrenia
- Mesolimbic pathway: Blockage relieves positive symptoms of schizophrenia

Substantia nigra pars compacta of midbrain:

- Nigrostriatal pathway: Damage may lead to Parkinson's disease

Arcuate nucleus of hypothalamus:

- Tuberoinfundibular pathway: Blockage leads to increased prolactin release

Fitzgerald, P., & Dinan, T. G. (2008). Prolactin and dopamine: What is the connection? A review article. J Psychopharmacol, 22(2 suppl), 12–19.

Nestler E. J., Hyman S. E., & Malenka, R. C. (2009). Molecular Neuropharmacology: A Foundation for Clinical Neuroscience, 2nd Ed., McGraw-Hill, New York.

Plasticity

Every cell contains some 20,000 to 25,000 protein-coding genes; cells differ from each other based on which of these genes are expressed. Cells retain

the capability to change which specific genes are expressed to adapt to changes. In the nervous system this capacity is especially important because neurons do not generally undergo mitosis. Therefore, the changes in the brain, including newly created synapses and extended dendrites, are the method in which the nervous system adapts to external stimuli. The repeated stimulation, caused by drugs of abuse and abusing natural rewards, repeatedly activates the body's natural reward system and creates changes in the brain not seen through natural activation of this system. By consistently activating this system, these drugs and behaviors change the nerve cells in the reward pathways. The cells change in terms of the neurotransmitters released, and consequently morphological changes occur. These changes severely affect a person and in some extreme cases addicts cannot respond normally to natural rewards, and instead depend on drug and their addictive behaviors for the sense of reward. The effects of addiction are long lasting and addicts remain susceptible to relapse long after they have ceased their behavior. This implies that a dramatic, lasting change has occurred in their neuro-circuitry caused by changes in gene expression.

Receptors

Receptor Activation

Dopamine is the primary neurotransmitter involved in the reward pathway. It is released in response to all natural rewards. There are two families of dopamine receptors on postsynaptic neurons, D1 type receptors and D2 type receptors. The D1 family includes D1 and D5 receptors; the D2 family includes D2, D3 and D4 receptors. The D1 family consists of two G-protein coupled receptors (GPCR) and when activated, they stimulate adenylate cyclase to convert adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) within the cell. The D2 family receptors consist of three GCPRs and when activated they stimulate Gi alpha to inhibit ATP from being converted to cAMP. When induced, cAMP activates cAMP-dependent protein kinase A (PKA) which subsequently activates transcription factors that allow genes to be read and produce mRNA and eventually be translated to protein.

D2 Receptor Levels

It appears that in a brain in an addicted state there are a lower proportion of D2 receptors expressed in the cell membrane. Low levels of dopamine D2 receptors have been seen in individuals addicted to cocaine, alcohol, opiates, as well as in people with obesity. This is true to the extent that in obese individuals the D2 receptor levels were inversely correlated with their BMI. It is possible that the decrements in dopamine D2 receptors in obese individuals represent a down regulation to compensate for dopamine increases caused by chronic dopamine release. It is also possible that individuals that previously expressed low numbers of D2 receptors may be more vulnerable to addiction (9).

Transcription Factors

Transcription factors are proteins that control gene expression. Transcription factors are essential proteins in the process of addiction.

CREB

An important transcription factor implicated in addiction is the cAMP response-element binding protein (CREB). It leads to the production of many proteins associated with addiction and appears to promote tolerance. Overexpression of CREB in the NAc inhibits the rewarding effects of drugs of abuse and natural rewards. One protein that CREB upregulates, dynorphin, inhibits the activity of dopamine cells and reduces the release of dopamine from presynaptic neurons. This reduces the sense of reward produced by drugs and natural rewards, thereby promoting tolerance (10).

ΔFosB

The transcription factor ΔFosB is a common pathway for addictive tendencies. The family of Fos transcription factors heterodimerize with the family of Jun proteins. The heterodimers form activator protein-1 (AP-1) complexes, causing gene expression or repression. Most Fos family proteins are induced after acute exposure to drugs and natural rewards; the spliced ΔFosB however accumulates after chronic exposure (7). This is due to its very stable structure (8). The high molecular stability of ΔFosB means it

is retained in neurons for several weeks after abusive behaviors have ceased, before returning to normal levels. However, the behavioral changes caused by these addictions may reoccur years after ceasing these behaviors. Therefore, ΔFosB must affect other molecules in order to cause the long-term behavioral effects. Consequently, it seems as though ΔFosB acts as a "molecular switch" which begins the genesis of addiction (11).

Overexpression of ΔFosB increases behavioral responses to drugs and natural rewards. Silencing ΔFosB's transcription activity reduced behavioral responses to drugs of abuse and natural rewards. Conversely, when ΔFosB is expressed even without drug use or natural reward stimulation, then the behaviors and changes associated with addiction do occur. This implies that ΔFosB is both necessary and sufficient for the behavioral features associated with addiction (8). Interestingly, when cocaine is self-administered it induces several times more ΔFosB than when it is researcher-administered. This volitional aspect of addiction implicates the prefrontal cortex (which controls conscious decision-making) in addiction pathogenesis (12).

Downstream Proteins Induced by ΔFosB (Table 1)

ΔFosB also increases the sense of reward. It increases the expression of glutamate receptor 2 (GluR2), an AMPA glutamate receptor subunit that significantly reduces the conductivity of AMPA receptors and makes the channel impermeable to Ca2+. This has been seen to increase the rewarding effects of cocaine (7).

ΔFosB increases the expression of cyclin dependent kinase 5 (Cdk5), a protein kinase required for neuronal development, survival and synaptic signaling. It has been directly linked to increases in dendritic spine density. Another protein upregulated by ΔFosB is nuclear factor kappa B (NF-κB). It has previously been implicated in the plasticity of learning and memory, in addiction it has been seen to be necessary for increased dendritic spine density and for the rewarding effects of drug use. Increased dendritic spine density may create new neural connections that solidify a behavioral propensity towards reward (8).

ΔFosB may also cause an increase in brain derived neurotrophic factor (BDNF). BDNF, a growth factor, increases the neuronal dendritic density in the NAc and the prefrontal cortex. Animals chronically exposed to stimulants (such as cocaine) show increased levels of BDNF in VTA of the brain, and exogenous BDNF causes animals to act as if they are dependent on drugs. On the other hand, mice that did not express BDNF (through a gene knockout) display less drug seeking behavior (13).

Table 1. Proteins induced by ΔFosB and their effects.

Upregulated Protein	Neural effects	Behavioral effects
GluR2	Reduces AMPA conductivity	Increased drug reward
Cdk5	Increased dendritic density	Addictive tendencies
NF-κB	Increased dendritic density	Increased drug reward Addictive tendencies
BDNF	Increased dendritic density	Addictive tendencies

Stress and Addiction

Corticotropin releasing factor (CRF) is recognized to play a key role in relapse. CRF is a 41 amino acid polypeptide present throughout the brain with particularly high concentrations in the amygdala. CRF increases the levels of adrenocorticotropic hormone, which, in turn, increases cortisol levels. Cortisol has global effects in the body and stimulates the fight or flight response. This pathway is activated during withdrawal from all drugs of abuse. Competitive CRF receptor antagonists have been found to reduce stress as well as drug seeking behavior (1).

Environmental Enrichment and Exercise

Enriched environments (EE) containing novel objects, exercise equipment and social partners, provides reinforcement to animals; it is shown to activate the mesolimbic dopaminergic system. Significant neural plasticity is observed when animals are housed in an enriched environment. This includes

drastic changes in brain weight, angiogenesis, neurogenesis, gliogenesis, and dendritic structure in response to environmental enrichment. The plasticity caused by EE appears to reduce the sensitivity to drugs of abuse and seems to cause a "protective phenotype" against drug use. For example, following psychostimulant treatment, EE caused reduced sensitivity to nicotine, as well as reduced cocaine self-administration and drug-seeking behavior. EE did not lead to differences in NAc dopamine synthesis in the mesolimbic projection; in the prefrontal cortex, EE reduced dopamine transport capacity. Due to the connection between the prefrontal cortex and the mesolimbic projection, this could impact mesolimbic activity, impulsivity, and consequently drug self-administration. EE significantly reduced the activity of CREB and reduced BDNF in the NAc following 30 days EE. This "protective" effect is so significant that it has potential for protecting and improving recovery from neurological diseases including schizophrenia, Huntington's and Parkinson's diseases (3).

Treatments

Vaccines

A critical mechanism of substance addiction is the capability of the substance to reach the brain, the target of its effects. If the substance can be prevented from crossing the blood-brain-barrier, then the addictive effects of the substance will be eliminated. To this end, vaccines for morphine, nicotine, methamphetamine, and cocaine have been developed. It is most effective to prevent relapse in cocaine users who are motivated to cease their use, since enough cocaine will overwhelm the antibodies produced by the vaccine. The theory is that the vaccine may be able to prevent limited use from turning into a full-scale binge and complete relapse (14-15). However, this therapy seems to be of little use, as many addictions cause a cross-sensitization, i.e. an addiction to one substance can easily lead to abusing another substance, and therefore immunity to one substance will not solve the problem (16).

Stereotactic Neurosurgical Treatments

Ablative stereotactic neurosurgery creates small lesions in the central nervous system, in order to change a particular form of neural activity. Areas in the frontal cortex, hypothalamus, anterior cingulum, cingulate gyri, and NAc have been targeted with varying success rates. These procedures have been mostly terminated for reasons regarding their efficacy, safety, and ethical implications.

Deep Brain Stimulation (DBS) is a particularly successful treatment for many disorders. It has proven to be helpful for a variety of neurological conditions such as Parkinson's disease, chronic pain, depression, Tourette syndrome and obsessive compulsive disorder. Although it has some possible serious side effects, they are generally reversible. In DBS, electrical current is applied to areas of the brain through stereotactically implanted electrodes; high-frequency stimulation at similar targets as the ablative surgeries produces clinical effects similar to ablation, but unlike ablation, DBS effects are generally reversible once the stimulation ceases (17). Research studies have tested DBS for alcohol, cocaine, opioid, tobacco, binge eating, morphine, and heroin abuse. The most promising region for implantation is the NAc. The mechanism of DBS is unknown, but one hypothesis is that it normalizes the firing of neurons and thereby eventually rectifies the changes due to addiction (18). As of yet, there have been no double-blind studies published on DBS' efficacy for addiction.

Medication

Some medications function by blocking the effects of drugs. One example of this method is naltrexone. Naltrexone is effective in treating alcohol, nicotine and behavioral addictions. It blocks the receptors in the brain for endorphins and opiates, and thereby blocks opiates' capacity to amplify dopamine release (19). That is to say, if rewarding behaviors are no longer rewarding, because naltrexone is blocking the sense of reward, then addiction can be ameliorated. Morning use of naltrexone blocks the euphoria that accompanies the behaviors and substances, and thereby makes drug relapse less likely. Over time, this treatment may cease the association these behaviors with positive reinforcement. However, the clinical use of naltrexone is limited because it is associated with low rates of compliance, apparently due to the fact that naltrexone induces dysphoria (10).

Some substance addictions can be treated with substitution therapy, that is, to stimulate the body in a similar fashion as the substance would. The idea is to provide similar stimulation in a more controlled manner to wean the body off its dependence. For example, an addiction to cigarettes can be treated with nicotine prepared in a safer mechanism of delivery, such as nicotine patches or nicotine chewing gum. For opiate addictions, administration of a long-acting oral, such as levo-α-acetylmethadol (LAAM) or methadone is administered. They have a much shorter half-life; and must be slowly tapered. This treatment suppresses craving and drug-seeking behavior. Similarly, buprenorphine, a partial μ-opioid-receptor agonist, is used. It blocks the effects of heroin by binding to the μ-receptor and only partially activating the receptor. These drugs are usually administered in the context of highly structured psychosocial interventions, as they themselves have potential for abuse and addiction. However, unlike naltrexone, buprenorphine does not produce dysphoria. Suboxone, a combination of buprenorphine and naloxone, is a promising therapy in the long-term treatment of opiate addiction. By smoothing out the highs and lows that often characterize heroin use, this treatment facilitates rehabilitation and increases an individual's ability to sustain employment and stabilize social relationships (17).

Discussion and Future Steps

Dynorphin, mentioned earlier as being stimulated by CREB, produces dysphoria by acting on κ-opioid receptors. This raises the possibility that κ-opioid antagonists may be useful in the treatment of withdrawal; this has been supported by animal models. A goal of current research is to identify other CREB-regulated genes and define their influence on drug tolerance and dependence. CRF, the hormone that induces stress, has been also been a major area of research. CRF antagonists have reversed the negative effects of cocaine, ethanol, and opiate withdrawal in animal models and have reduced drug-seeking behavior (20).

The current pharmacological treatments for addiction either imitate the manner in which drugs activate receptors or they block the drugs action on receptors.

Key Point: Roles of Dopamine Outside of Reward/Addiction pathway

Dopamine produced in the pars compacta promotes movement via activation of the direct excitatory pathway (D1 Receptor)

Dopamine produced in the hypothalamus inhibits prolactin secretion from the anterior pituitary gland

Dopamine works in the prefrontal cortex to promote a tightly regulated working memory

Dopamine works in the frontal lobes to promote cognition

Cools, R. (2008). Role of Dopamine in the Motivational and cognitive control of behavior. The Neuroscientist, 14(4), 381–395.

Wise, R. A. (2004) Dopamine, learning and motivation. Nature Reviews Neuroscience 5, 483-494.

They don't focus on the changes in the brain that determine the addiction process. An appreciation of the changes at the molecular level taking into account all the changes previously discussed can hopefully lead to the development of new types of medications that target these changes.

An interesting possibility that may arise from the studies performed on ΔFosB is the possibility of using ΔFosB as a marker for addiction. Or in the words of Dr. Eric Nestler, ΔFosB can be a "biomarker to assess the state of activation of an individual's reward circuitry, as well as the degree to which an individual is 'addicted', both during the development of an addiction and its gradual waning during extended withdrawal or treatment" (8).

More research is necessary to identify the connection between the manner in which addiction is expressed and the actual biological changes that take place. This research will be very closely related to the research into learning, depression, and stress activation. All of these areas are inextricably intertwined and will all shed light on one another. Many of the same

pathways are affected in all of these conditions, and treatment of one will probably produce possibilities for the others.

This highlights the necessity to have a structured form of healthy living and social sphere. The research into EE indicates that a healthier environment produces important neurological changes that assist in recovering from addiction. Therefore, a primary component of addiction therapy should be psychosocial assistance in the form of cognitive–behavioral interventions, community reinforcement and 12-step facilitation (the various anonymous groups). These rehabilitation methods will help repair and rebuild the addict's life. The medications prescribed and being researched will make rehabilitation more effective by overcoming the neuro-circuitry that became disposed to addiction.

Conclusion

Addiction is a complex disease that poses enormous challenges to healthcare and society. The concomitant processes of learning, memory, and reward complicate and inform this disease. Continuing research that identifies its pathogenesis will lead to better understanding and treatment. Current research has identified key biological markers that are promising targets for the development of drugs.

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Reflecting on Peer Tutoring

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The empty seats seemed more intimidating than usual as I entered the lecture hall. We were 20 minutes early and no one had arrived yet. I turned to Nati, "Are you ready to roll?" He gives me a nod of approval. Nati and I put together an interactive review program to help the first year students by providing the tools, tricks and tips needed to study the fundamentals of histology. It was one of the more challenging courses at our school and, as a second year, I felt that I could make it easier for other students to learn.

I pulled out my markers as my partner prepared the PowerPoint presentation: red, green, blue, black--they were all there. Our teaching methodology was (1) put a simple but concise presentation on the projector and (2) draw pictures on the dry erase board. Histology lectures were daunting at times, especially the professors' PowerPoint presentations that included a multitude of microscope slides accompanied by quite descriptive characterizations. A quandary arises as to what to include in the presentation.

Simplify, that's what we needed to do. Accordingly, Nati and I created worksheets in order for each student to transcribe exactly what I drew (e.g., flattened "pancakes" as stratified squamous cells) on the dry erase board onto their pages. The titles of each subject and the information from the Powerpoint slides were already on the paper. This took the attention off the projected slides and put it directly on us: the peer tutors. No time for laptops and no time for spacing out; just active learning.

Looking around the lecture hall, I spotted an auxiliary cable. I plugged it into my phone, picked a song, and pressed play. The room was injected with my upbeat tunes; as the music flowed in, students did as well, bobbing their heads excited for the lecture to follow. With this relaxed environment, there was a better chance that the students would be able to focus and understand the material.

As the room started to fill up, I could feel a pit growing in my stomach. I remind myself about all of my preparation. "You've done this before, Jon," I reminded myself. My drawings were polished after numerous attempts and my lines were rehearsed. Nati and I honed our teaching skills in our living room, with our little white board and the Sheetrock as our audience. "Maybe we should start passing out those worksheets," my partner said as he woke me up out of my reverie. All eyes were all on me and it was game time.

Fast forward one year and I am standing in the same lecture hall. "Look who's here! What's up Jonny?" Josh, a second-year student who was in the audience during the previous year's lesson and now teaching a peer tutoring session, called out from the front of the room.

Upon reflection, that day ended up being a hit; it led to more teaching and mentorship opportunities to apply our methods to other courses, as well to teach other students this model. We were able to apply our peer-tutoring course into research due to the students' great testing performances. We also presented our model at the Association for Medical Education in Europe (AMEE) conference.

You see, the benefits of peer tutoring are two-fold. For the younger students, it gives them an opportunity to earn from colleagues who can simplify the subject matter as opposed to professors who can sometimes present material in a more complex way. For the upperclassmen, along with acquiring a deeper understanding of the material, we have found that it is extremely rewarding. "Good luck today," I tell Josh as I look at the crowd. A chill goes down my spine as that same pit develops in my stomach.

REVIEW

Mini Case for Lab Diagnostics and HIV Review

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Case Description:

A 26-year-old woman presents in your clinic. She has recently immigrated to the US from Uganda. She is sexually active but has not been practicing safe sex. Upon examination, you find vaginal candidiasis. You are highly suspicious of HIV and send a test for ELISA of HIV-1 and HIV-2. These tests come back positive. Confirmation by western blot is received. PCR for HIV RNA and flow cytometry for CD4 are ordered to assess progression of disease.

CD4 Count

CD4 T cells are T-helper cells which are preferentially attacked by HIV infection. One factor in determining the severity of disease, especially risk for infection, is the CD4 T cell count. In order to determine this the clinical laboratory uses fluorescence-activated cell sorting, commonly known as FACS or flow-cytometry to measure the amount of CD4 T cells/μL of blood (Figure 1). This process is represented in Figure 1.

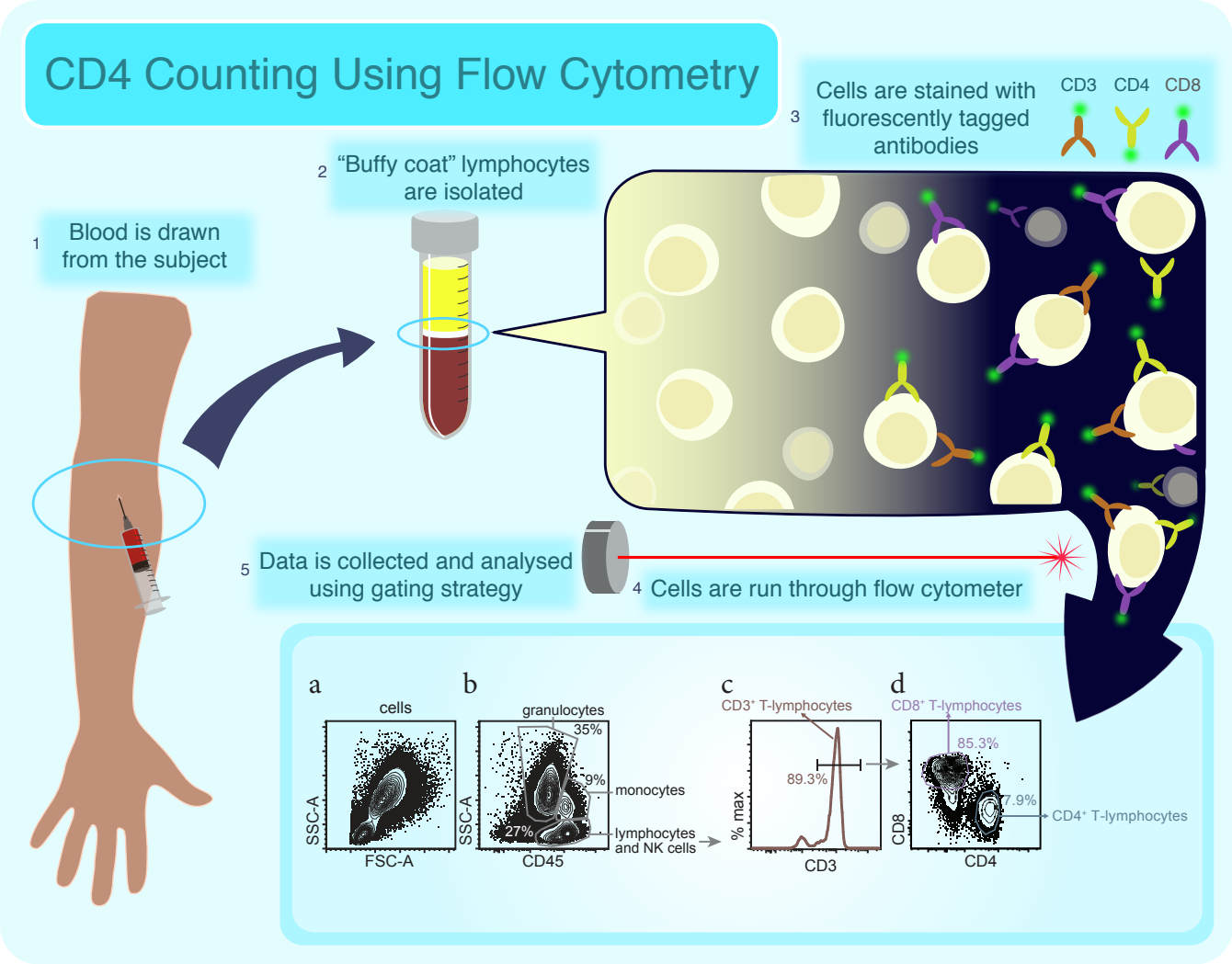

Figure 1. Flow cytometry for CD4 counting. *Image by* **Tziporah Thompson**.

First, white blood cells are isolated from blood by performing a FICOLL, otherwise known as ficoll plaque (Fig 1.2). This process will gradate blood and separate the serum, white blood cells, and RBCs. Next, the cells are stained with antibodies raised against cellular markers that are conjugated to immunoflouresent dyes (Figure 1.3). These antibodies will identify T cells, and more specifically CD4 T cells. Once cells are stained, their fluorescence (and thus, cell type) along with the cell size and granularity are measured by the flow cytometer's laser, producing a diagram of cells which are separable based on size and granularity (Fig1a) as well as by cell markers (Fig1b-c). Once lymphocytes are gated on (Fig1b), CD3 positive lymphocytes are selected (Fig1c). Of CD3 positive cells, we can now identify CD4 and CD8 positive T cells (Fig1d). Here only 7.9% of CD3 positive lymphocytes are also CD4 positive-indicating lymphopenia in this patient.

HIV Progression

We aim here to provide students with an overview of the timeline of HIV infection (Figure 2). Note that not all patients follow this timeline.

ACUTE/EARLY
CD4 ~1000 cells/μL[1]
Presentation: Fever, lymphadenopathy, sore throat, rash, myalgia.

Note on prevention of HIV infection: In order to prevent infection, aside from barrier protection such as condoms, pre-exposure prophylaxis (referred to as "PrEP") was approved in July 2012. PrEP is the pill truvada (a combination therapy containing tenofivir and emtricitabine) and is commonly used to treat HIV. When PrEP is taken consistently by those with risk of getting HIV, is has been shown to reduce risk by up to 92%. See guidelines for providers for more information.[2]

SEROCONVERSION/ VIRAL SET POINT
CD4 ~780 cells/μL[1]
Definition: Development of detectable antibody against HIV, stable viral load.
Presentation: In a study of 7,500 HIV-infected individuals with CD4 counts between 200-499 cells/μL symptoms were[3] : 21.3% thrush (Candida albicans), 9.2% oral hairy leukoplakia, 6.7% herpes zoster, 3.7% paripheral neuropathy.

AIDS
CD4 <200 cells/μL[1] or AIDS-defining illness.
Presentation: Prior to highly-active antiretrovial therapy (HAART): most common presentations (US, 1992-1997)[4]: 36% pneumocystis pneumonia (PCP), 12.4% esophageal candidiasis (Candida albicans), 11.6% Kaposi Sarcoma (HHV-8), 7.8% wasting syndrome, 6.4% Mycobacterium avium.

In the HAART era, AIDS defining opportunistic infections used to be the most common cause of morbidity and mortality. Now, in ART treated patients, non-AIDS mortality has increased compared to opportunistic infections.[5,6]

ADVANCED HIV INFECTION
CD4 <50 cells/μL[1]
Presentation: Varies; most common presentations are cytomegalovirus (CMV) and Mycobacterium avium.

Figure 2. Timeline of HIV infection.

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Proposed Analysis of the Transition Process from Pediatric to Adult Care for Patients with Congenital Heart Disease in Israel

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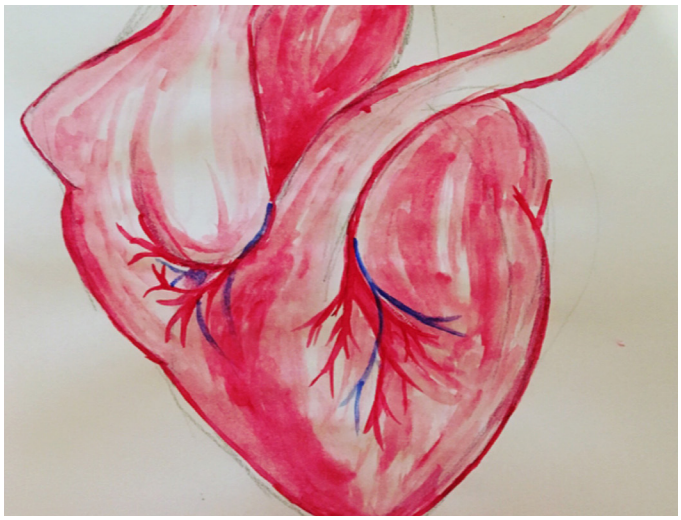
The global prevalence for congenital heart disease is 9 per 1000 live births, making it the most common congenital anomaly in the world (1). Due to medical advances, individuals with CHD are living longer than ever, with over 90% reaching adulthood. It is estimated that within the next decade, nearly 1 in 150 young adults will have some form of CHD. More than 50% of these individuals will be vulnerable to complicated co-morbidities later in life stemming from their CHD, such as hypertension, pulmonary, renal, and myocardial disease, and coronary artery disease, and therefore need to be seen regularly and followed for life by cardiologists (2).

However, despite a clear need for follow-up among a large portion of the population, patients suffering from CHD often go without it, having been lost during the transition from pediatric to adult care. This phenomenon of loss to follow-up during transition has been noted in several countries, though the results differ. In Belgium, one study found the percentage of patients with CHD lost to follow-up to be 7.3% (3), while a study concerning American patients with CHD found that 18% had no cardiology visit within 2 years (3-4). The percentage of patients lost to follow-up in Canada was explored in two studies, which recorded that 27% and 61% of patients over the age of 18 had no cardiac follow-up (5-6). Even when the transition occurs within a single institution, nearly half of these patients will be lost to follow-up (7).

This issue has been difficult to address, in part, because of the non-standardized definition of "loss to follow-up" among different studies. Heery, et al., makes note of some these definitions, including no cardiac consultation after leaving pediatric care, no cardiac consultation since 18th birthday, and



Karen Arane: *He***art**

no cardiac follow-up within two years of interview (1). That paper concludes that this area of research requires for a large, multicenter, international study with standardized definitions in order to be properly researched.

The topic of the 32nd annual meeting of the American College of Cardiology in 2000 was the needs of adults with congenital heart disease. Task Force 2, a steering committee of pediatric cardiologists, concluded that "managing the transition to adulthood begins in childhood" and that an effective transition program would include the following six elements: a set time for transition to adult care, a preparation period and education program for patient and family, a coordinated transfer process (including a written plan, pre-transfer visits, introduction to the adult provider, and a designated coordinator), an adult center of equal quality to the one the patient is leaving, administrative support, and primary care

involvement (8). However, a study conducted in 2008 examining pediatric cardiology programs in the United States and Europe found that among centers that reported transferring patients into adult care, of which three-quarters of the centers in the study claimed to do, only one-third provided structured preparation for patients and family (9). While more than half of the centers had plans to develop formal transition programs, there is still a concerning lack of programs in place and a lack of data concerning which programs are the most effective.

Further complicating the issue is the fact that young patients with stable CHD rarely seek medical follow-up because they tend not to experience symptoms (10). Yet it has been shown that a lapse in care among patients with CHD was associated with a 3.1-fold increase in urgent cardiac intervention (11). One can argue the importance of successful transfer and follow-up among this population is not only crucial to the patient, but to the economics of the health care system as well, because the cost of these urgent interventions may exceed the cost of secondary prevention (12).

Currently, there is no published data concerning the rates of successful transitioning from pediatric to adult cardiology among patients with CHD in Israel. In 2012, the prevalence of CHD in Israel was 5.6 per 1,000 live births, making it by far the most common malformation present among live births (13). Given that there were 170,940 live births in Israel in 2012, there would be nearly 1,000 children born with CHD that year alone. According to Schneider Children's Medical Center, about 70% of Israeli children with CHD are treated in their cardiac intensive care unit, the largest of its kind in Israel (14). The unit performs more than 500 cardiothoracic surgeries annually on patients until age 18. While half of the patients in the unit are under one year of age, 8% of the patient population consists of adults with CHD. Because of the volume of CHD patients treated at Schneider, it seemed logical to explore the phenomenon of transition from pediatric to adult care by examining a cohort from this hospital.

A study should be done to deduce whether or not there is a problem with transition from pediatrics to adult cardiology among patients with CHD in Israel.

Key Point: Types of Congenital Heart Defects

Congenital Heart Defects: Most Common Congenital Disorder in Newborns

Septal Defects (or "Holes in the Heart"): defect allows blood to mix between the two sides of the heart through either atrial or ventricular septal defects, ASD and VSD, respectively

Patent Ductus Arteriosus: abnormal blood flow occurs between the aorta and the pulmonary artery

- Heart murmur may be the only sign of a PDA

Narrowed Valves (control flow of blood between atria & ventricles and ventricles & pulmonary artery/aorta)

- Stenosis: occurs when the flaps of a valve thicken, stiffen, or fuse together -> valve cannot fully open
- Atresia: valve doesn't form correctly -> lacks hole for blood to pass
- Regurgitation: valve doesn't close tightly -> blood leaks back through valve

Tetralogy of Fallot (A Complex Congenital Heart Defect)

- Combination of
(1) pulmonary valve stenosis
(2) large VSD
(3) overriding aorta
(4) right ventricular hypertrophy

U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. (2011). Congenital Heart Diseases. Available from http://www.nhlbi.nih.gov/health/health-topics/topics/chd

The cohort should be stratified based on severity of defect, according to the ACC Task Force 1 report, to keep the data standardized with current practices. Examining variables such as socioeconomic status, geographic distance from institution, and living arrangements upon leaving home, would allow for the identification of associations that could predict patients who are high risk for failure to follow-up. This will help to demonstrate the need for follow-up and provide quantitative evidence of the consequences when the process fails.

This research would be the beginning of Israel's contribution to the ongoing research concerning the transition to adult care among the CHD population. Immediately, the conclusions of this research would allow reasons for transition failure to be addressed, potentially helping thousands of children and adults. There is the hope that because Israel is a small nation, it can establish a formal transition program quickly. Once in place, we can gain more understanding of what aspects make a program most effective, and whether these structured transitions have true benefit. On an international scale, once the data collected in our study becomes available, Israel will be able to participate in future large, multinational studies that are needed in the field, further diversifying the cohort and allowing for more generalized conclusions.

Key Point: Pulse Oximetry for CHD Detection

Pulse oximetry screening (in all newborns after 24 hours of life or as late as possible if early discharge is planned) targets defects that require intervention in the first year of life and may present with hypoxemia, or low level of oxygen in blood.

Screening with pulse oximetry was better at identifying infants with critical CHD than with just physical examinations.

Oster M. Newborn screening for critical congenital heart disease using pulse oximetry. Available from http://www.uptodate.com/contents/newborn-screening-for-critical-congenital-heart-disease-using-pulse-oximetry.

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Clearing Away the Smoke: An Analysis of Current Affairs in Medicinal Marijuana

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Introduction

With regard to patients with Parkinson's, Alzheimer's, lupus, rheumatoid arthritis, and various cancers, a growing number of physicians have become in favor of the use of marijuana as an analgesic. Marijuana (cannabis) is a plant that is often used as a psychoactive drug that acts on the CNS; particularly the brain. Marijuana also gives the user a sense of bliss and relaxation.

In 1970, marijuana was categorized as a Schedule I drug under the Controlled Substances Act; such drugs have potential for abuse and have no accepted medical use in the USA. However, marijuana has been considered for medicinal usage as an analgesic for patients in excruciating, unavoidable chronic pain as well as for other medical purposes. Advocates of medicinal marijuana have targeted cancer patients as particular beneficiaries of the drug. As of 2016, 23 states and the District of Columbia have legalized medicinal marijuana (1). The states of Washington, Colorado, Oregon, and Alaska, as well as the District of Columbia, have gone as far as to legalize recreational usage of the drug. Under federal law, these state legislatures have defied the Controlled Substances Act, as marijuana is still considered a Schedule I drug. Even though a physician can prescribe marijuana to a patient under state law, he or she is violating a federal act. In this paper, the use of marijuana as medicine is analyzed and explored, as well as the challenges being faced with studying marijuana in research laboratories.

Synopsis of "Medicinal Use of Medicinal Marijuana"

In the New England Journal of Medicine (NEJM), Drs. Michael Bostwick, Gary Reisfield, and Robert DuPont provided an interactive article entitled "Medicinal Use of Marijuana" to objectively bring to light the ethical question of medicinal marijuana (2). In a selected case, a 68-year old patient named Marilyn suffers from breast cancer that has metastasized to

Micah Belzberg: *Rx*

Key Point: Antiemetic Medications

Ondansetron: a 5-HT3 antagonist that targets a certain serotonin receptor found in the vagus nerve and the brain in order to treat nausea and vomiting mainly for cancer treatment and off-label for morning sickness in pregnancy

Prochlorperazine: a dopamine D2 receptor antagonist used as an antiemetic for chemotherapy, radiaiton therpay and pre/post operative setting

Longstreth, G. F., & Hesketh, P. J. (2016). Characteristics of antiemetic drugs. Retrieved from: https://www.uptodate.com/contents/characteristics-of-antiemetic-drugs

the lungs and spine. She is undergoing chemotherapy and complains of fatigue, minimal appetite, and spinal pain. To alleviate her symptoms, Marilyn is taking antiemetic medication (ondansetron and prochlorperazine) for nausea, along with acetaminophen and oxycodone for her pain. So far, her medications have had minimal success. Marilyn asks her primary care physician about the possibility of using marijuana to help alleviate the pain, nausea, and fatigue. This article presents two physicians' opinions: to use or disuse medicinal marijuana.

Psychiatrist Dr. J. Michael Bostwick recommends the use of medicinal marijuana. He argues that, despite limited research on cannabis, there is growing literature on its efficacy, though mostly anecdotal. A dearth of research is mainly attributed to the federal ban on the production, buying, and selling of marijuana. "Federal policy has failed to keep pace with recent scientific advances," he argues.

Dr. Bostwick sheds light on the most abundant cannabinoids in the marijuana plant: THC, or Δ^9-tetrahydrocannabinol, and cannbidiol (CBD). These cannabinoids are structurally similar to the trace cannabinoids in our brains, called endocannabinoids. These endocannabinoids bind to these respective receptors on the presynaptic cell after neurotransmitters bind to the postsynaptic cell. Cannabinoids thus regulate the amount of neurotransmitter released and its duration. When THC is inhaled into the lungs, it quickly flows through the blood-brain barrier, where it binds to cannabinoid-1 (CB_1) receptors and prevents the neurons from resting in between action potentials. Neurotransmitters continuously flow from the presynaptic cell to the postsynaptic cell. This alters one's mood, cognition, and sense of reality.

Under the auspices of the FDA, no trials "have compared medicinal marijuana with traditional analgesics." The federal law limits research on marijuana and its components. Studies are seldom done on its psychiatric and neurological side effects due to its national ban. While some say that marijuana has no business being used in a clinical setting, many Schedule I drugs, such as heroin, morphine, codeine and ecstasy have legal medicinal derivatives. The structures of THC and CBD, for instance, differ only by an esterification of a hydroxyl group. Furthermore, no vaporized inhalants are currently available in the United States as an alternative to marijuana, and oral cannabinoids are "ill suited to relieving Marilyn's acute distress." It is with this in mind that Dr. Bostwick would recommend the medicinal use of marijuana only after conservative options have failed and the patients are fully informed.

In opposition to medicinal use of marijuana are anesthesiologist Dr. Gary M. Reisfield and psychiatrist Dr. Robert L. DuPont. It is interesting to note these two doctors' areas of expertise: Dr. Reisfield has had fellowships in pain medicine and addiction medicine; Dr. DuPont served as the second White House Drug Czar (1973-1977) and has been on the forefront of marijuana prohibition. In their segment of the article, Drs. Reisfield and DuPont argue two main points. Firstly, there is not enough evidence to support the use of smoked marijuana for nociceptive pain. There has not been a meaningful amount of research done on the analgesic effects of smoked marijuana, as opposed to the high-quality research supporting medicinal use of specific cannabinoids. Additionally, the cannabis plant contains hundreds of pharmacologically active compounds, most of which have not been properly examined. Perhaps the use of smoked marijuana following chemotherapy would cause more harm than good to the patient. Could these unknown active compounds destroy the already weak brain cells, immune cells, or lymphatic cells? Too much is left uncertain with regard to the use of smoked marijuana.

Secondly, prescriptions of specific cannabinoids are available, including dronabinol and nabilone. Both of these compounds are quite similar to THC and are FDA-approved for the treatment of chemotherapy-related nausea. These drugs have shown to be effective, but are orally administrated and demonstrate slower onset. Nonetheless, dronabinol and nabilone are chemically pure and have precise dosages.

After the article was published, 1,446 readers participated in a poll about recommending the use of medicinal marijuana. Interestingly, this prompted a subsequent article explaining the results with 76% in favor of the use of marijuana for medicinal purpose and that most of the votes came from countries in

which this use is illegal. However, this poll was concluded as skewed; over 1,000 (73.5%) of the votes polled were from North America. Given that North America represents a minority of the NEJM readers, the surveyors concluded that the topic (namely, use of medicinal marijuana) "stirs more passion among readers from North America than among those residing elsewhere" (3).

Discussion

After reading these two positions, it seems the most crucial factor to this ethical question is the lack of research. Because of the federal ban on marijuana, there is minimal literature and study on the topic. Drs. Reisfield and DuPont express a fear of the unknown. There is tremendous uncertainty regarding the hundreds of compounds in the cannabis plant. Yet, scientists cannot determine these compounds, their effects when smoked, and their impact on cancer patients. Furthermore, physicians in states that have legalized prescription marijuana face, as Dr. Bostwick puts it, a catch-22: "Although 18 states have legalized medicinal marijuana, physicians in those states who write prescriptions violate the law of the land." If prosecuted enough times, these doctors could face significant time in prison. Although US government is preventing further abuse of marijuana, it is also causing distress to medical patients.

Then again, the enforcement of marijuana laws has not been especially successful. While marijuana law enforcement costs hover over the billion-dollar mark, the drug is still the most consumed illicit substance in the United States, with about 6% of the population having tried marijuana in their lifetime (4). Indeed people can abuse marijuana and become addicted to it. However, this abuse should not result in a total outlaw of the drug. Many drugs are addictive that are still legal, including alcohol, nicotine, and oxycodone. Legalization and regulation would allow for further research on the cannabis plant. This would solve many of Drs. Reisfield and DuPont's concerns.

Drs. Reisfield and DuPont mention that cannabinoid medications already exist that have been studied and purified. These medications are orally administered, not inhaled. They argue that the option of cannabis inhalants is not necessary. It is only fair that a fully informed patient should decide if he or she wants to administer a fast-acting inhalant to relieve pain.

The literature regarding adverse effects of marijuana use is quite fuzzy. Some research has shown associations between marijuana use and negative consequences. A 2014 publication from NEJM titled "Adverse Health Effects of Marijuana Use" states that long-term marijuana use can lead to addiction, especially when starting in adolescence when the developing brain is still vulnerable to environmental insults (5). One particular finding shows that frequent use of marijuana can lead to IQ decline (6). However, the 2014 article explains that causality has not been established. The associations of marijuana as a gateway drug have not been confirmed, as there are numerous factors as to how further drug addictions may occur. Furthermore, the relationship "between cannabis use by young people and psychosocial harm is likely to be multifaceted, which may explain the inconsistencies among studies" (5).

Other studies, including a 2009 publication from The Lancet, suggest the importance of other factors to the potential issues with frequent marijuana use. This publication refers to data pertaining to the THC content in cannabis in the United States, which has greatly increased from less than 2% in 1980 to 4.5% in 1997 and 8.5% in 2006 (7). This Lancet paper, in particular, also presents potential, but mild, adverse effects on neonates when cannabis is given to pregnant mothers, including decreased birth weight and developmental abnormalities in the first couple months of life. However, "no effects were seen at 1 month, or on ability tests at 6 and 12 months." At 12 years of age, children who were exposed to cannabis prenatally did not differ on full-scale IQ scores from children who were not exposed (8). Additionally, drivers intoxicated with THC have shown impaired reaction time, information processing, attention, and motor performance (9). Many other studies, as presented in a 2004 publication from Multiple Sclerosis, have shown favorable results when cannabis is administered to patients with glaucoma, nausea, AIDS-associated anorexia, chronic pain, epilepsy, and multiple sclerosis (10). These are among many other factors that must be taken into account when assessing the usefulness and possible dangers of cannabis use.

Implementation of medicinal marijuana laws may also show economic benefits, especially with regard to federal spending. In a 2016 study from Health Affairs, it is suggested that increased prescription of medicinal marijuana in states that have executed its legality have decreased prescriptions of more traditional FDA-approved drugs for various conditions (i.e., pain, depression, anxiety, seizures). Overall, this led to a reduction of $165.2 million in federal spending in 2013 for Medicare Part D (11).

Although federal law in the United States of America restricts cannabis research, it is more liberally studied in other countries such as Israel, where THC was first isolated in 1964 (12). A recent study at Sheba Medical Center evaluated the use of cannabis for cancer patients of which the cannabis treatment was defined by referring physicians mainly for palliative care (13). Overall, the results to this study shows that 70% of patients reported pain control improvement, improved appetite by 60%, and reduced nausea by fifty percent. Eighty-three percent of those surveyed reported high overall efficacy.

Conclusion

Patients should have the option to administer medicinal marijuana only if traditional alternatives for pain or other related symptoms have failed and the patient is fully informed. With the policies recently implemented by the Obama administration to study the marijuana in research laboratories, more research in this field is definitely warranted in order to understand the utilization of marijuana for clinical use. Lastly, patients should not become victims of bureaucratic dictums during their time of struggle and pain and the recent actions to study marijuana as medicine indicate that progress is being made.

Key Point: What is Medicare?

Medicare: a public health insurance program available to patients ≥ 65 years old, < 65 with certain disabilities, and with four distinct parts:

- Part A (hospital insurance)
- Part B (basic medical bills; diagnostic tests)
- Part C (additional care from HMOs/PPOs)
- Part D (prescription drug coverage)

Kaiser Family Foundation. (2016). An Overview of Medicare. Retrieved from: http://kff.org/medicare/issue-brief/an-overview-of-medicare/

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The Biochemical Foundations of Alzheimer's Disease and Potential for Immune Therapies

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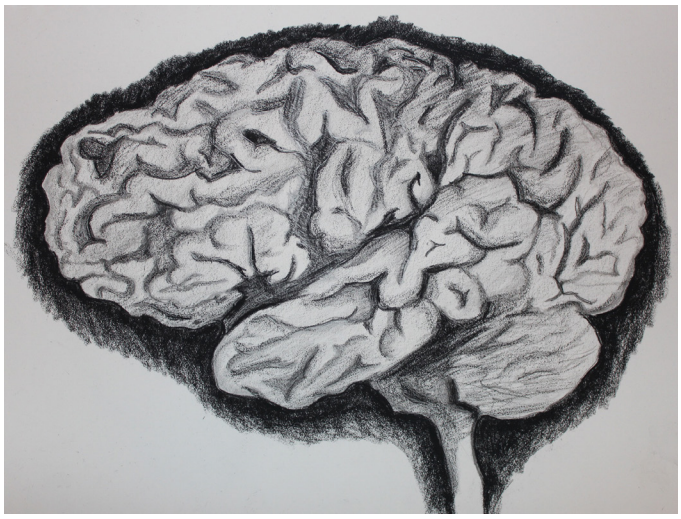
Alzheimer's Disease

Alzheimer's disease (AD) is characterized by progressive neurocognitive decline associated with widespread propagation of amyloid-beta and tau protein fibrils. Early stages are asymptomatic though the onset of cognitive debility and subsequent dementia emerges with the prion-like propagation of amyloid deposits and tau neurofibrillary tangles, resulting in pervasive neuronal death and white matter atrophy.

The Biochemical Foundations of Alzheimer's Disease

Multiple theories have been established to explain the physiological cascade involved in the onset of AD. Oldest among these theories is the cholinergic hypothesis, which arose during a particularly research-intensive era in the field of neurochemistry and anatomy (1). Findings from this two-decade period from the mid-1960s to the mid-1980s established a foundation upon which the molecular basis of neurodegenerative diseases could be closely examined. Chief among these neurophysiological mediators are cholinergic receptors, which play an important role in a wide spectrum of homeostatic functions. Consequently, the manifold nature of these receptors gives way too broad a range of neurological disease states upon their dysfunction (2-4), including those found in AD (5). Amyloid beta deposits have been found to form extracellular amyloid clumps known as plaques, leading to neuromodulating effects that can occur at picomolar concentrations, irrespective of the neurotoxic state of amyloid beta (6).

The role of acetylcholine in memory recall was demonstrated by the use of receptor antagonists in monkeys and rats. Subjects receiving infusions in the peripheral cortex showed marked decline in the ability to recognize stimuli (7, 8). Subsequent studies demonstrated that various degrees of cognitive impairment arise from region-specific application of receptor antagonists (9, 10). Post-mortem examinations of AD brains revealed depleted levels of cholinergic activity, particularly choline acetyltransferase, a transferase responsible for acetylcholine synthesis, and acetylcholinesterase, a hydrolase that breaks down acetylcholine, in the neuromuscular junction and neural synapses located within the cerebral cortex (11). In Alzheimer's patients, frontal and temporal regions of the brain responsible for memory and cognition were especially depleted with respect to cholinergic receptors (12, 13).



Elana Cohn: *Sagittal*

Much of the criticism levied against this hypothesis stems from confounding factors that show a natural decline of cholinergic activity in healthy

rat brains (14, 15), as well as a broad spectrum of neurodegenerative disease (16). These revelations point to the more general phenomenon of cholinergic decline as a symptom, rather than the impetus of neurodegeneration.

Amyloid-Beta

The pivotal role of amyloid-beta in the progression of AD pins the peptide as the central tenet of the amyloid cascade hypothesis. Upon observation of Auguste Deter's brain (who would later become the first patient to be formally diagnosed with AD) Alois Alzheimer, the physician credited with the first published clinical observation of AD dementia, noted "numerous small miliary foci are found in the superior layers...[that] are determined by the storage of a peculiar material in the cortex". Indeed, Alzheimer would go on to conflate these plaques with "the most serious form of dementia", adding that "the plaques were excessively numerous and almost one-third of the [patient's] cortical cells had died off" (16). These extracellular plaques would eventually come to be known as abnormal accumulations of peptide amyloid-beta. The description of amyloid-beta pathology as a "cascade" implies its central role as a vanguard of AD progression, postulating the formation of amyloid plaques as the prerequisite for neurofibrillary tangle formations of tau protein.

Amyloid-beta's precursor, amyloid precursor protein (APP), is a transmembrane protein which has been found to influence synaptogenesis and, most recently, protein synthesis in dividing human cells (17), among other processes. Its abundance in interneuronal ER and Golgi (18) membranes contributes to its involvement in AD pathogenesis, whereby the sequential cleavage of APP by either α or β (BACE-1) and γ-secretase enzymes, respectively, produces plaque forming and non-plaque forming variants of free-floating amyloid-beta peptide in the neuronal interstitium. In the event of primary cleavage by α-secretase, soluble APP (sAPPα) is secreted, leaving behind an 83- residue membrane-bound fragment (CTFα) (19). Conversely, initial cleavage with β-secretase produces a 99 amino-acid transmembrane peptide (CTFβ). In both instances, the membrane bound peptides are next cleaved by γ-secretase to yield amyloid-beta from CTFβ and a small protein (P3) from CTFα. The amyloidogenic potential of cleavage products is determined by the location of γ-secretase proteolysis; in the event of cleavage of amyloid-beta valine-40, Ab-40, a 40 amino-

Key Point: Alzheimer's Symptoms

Generally symptoms first appear in patients in their mid-60s. Three stages : (1) early, preclinical stage with no symptoms (2.) Mild Cognitive Impairment (MCI) and (3) Alzheimer's Disease.

- Early symptoms most often include memory problems, but may also include other forms of cognitive difficulties including difficulty finding words, visual or spatial problems, or impaired reasoning and judgment.

- Mild AD is the stage at which AD is most commonly diagnosed. Patients may wander or get lost, lose the ability to handle money or pay bills, repeat questions, spend longer to complete normal daily tasks, or misplace items. Behavior and personality changes may also be seen.

- Moderate AD advances memory loss and confusion. Patients may have problems recognizing familiar faces, difficulty carrying out multistep tasks, hallucinations, delusions, and paranoia. They may have an inability to learn new things, problems coping with new situations, and impulsive behavior.

- Severe AD is the stage at which patients lose the ability to communicate and take care of themselves. They may experience weight loss, seizures, skin infections, and difficulty swallowing. They may sleep more, groan, moan, or grunt, and lose control of bowel and bladder.

Retrieved from https://www.nia.nih.gov/alzheimers/topics/symptoms.

acid variant, is secreted. In the event of cleavage at alanine-42, ab 42, the 42 amino-acid variant, is secreted. While Ab-40 has been determined to be a natural component of cerebrospinal fluid and plasma (20), even potentially possessing neuroprotective properties, it's counterpart, Ab-42 has been implicated as the pathological trigger of plaque formation (21).

The Tau Hypothesis

In post-mortem examination of AD patients, Alois Alzheimer's also described "peculiar, deeply stained bundles of neurofibrils" colocalized with dead cortical cells. Unbeknownst to the physician, he was describing one of the two neuropathological findings consistent with AD — tau neurofibrillary tangles. Distinguished in its ubiquity across a spectrum of neurodegenerative disorders, tauopathies are not unique to AD, however tau fibrillation subsequent to amyloidosis is a hallmark sign.

As a major microtubule stabilizing protein in the central nervous system (CNS), tau maintains cytoskeletal stability through polymerizing and depolymerization of tubulin subunits (22). It's affinity for tubulin is modulated by kinases and phosphatases (23). In the event of hyperphosphorylation, tau dissociates from its cytoskeletal origin in the form of free-floating tau monomers. Consequently, these monomers self-assemble to form oligomeric structures which serve as scaffolds for the development of larger, pathogenic neurofibrillary tangles capable of propagating interneuronally, whereupon exogenous tau fibrils can induce tauopathies in neighboring cells in a prion-like manner known as seeding (24).

The duality of amyloid plaques and tau fibrils in the pathophysiology of AD lend credence to two of the later aforementioned theories. AD-associated tauopathies can seldom form without the presence of amyloid plaques (25), however extracellular amyloid deposition is not sufficient to elicit neurodegeneration (26, 27). The tau hypothesis is therefore the most concise understanding of the biochemical underpinnings of AD (28).

The molecular intersect between the two processes remains unclear; however, recent studies have shown that oxidative stress stemming from the presence of toxic amyloid-beta upregulates a regulator (RCAN1) of calcineurine, a phosphatase of tau, and glycogen-synthase kinase-3β (GSK3β), a tau kinase. Concomitantly, the imbalance between an increase in phosphorylation activity and a decrease in dephosphorylation of tau results in the formation of tau fibrils, thus providing a coherent link between amyloidosis and fibrillation (29). This link implies that the mitochondria invariably plays a part in AD etiology, giving birth to a relatively novel theory in which the cellular powerhouse forms the crux of the disease. The mitochondrial cascade hypothesis posits the formation of amyloid plaques on the genetic resiliency of the mitochondrial electron transport chain. Over time, the propensity of the mitochondria to regulate damage via reactive oxygen intermediates, along with its ability to generate ATP via oxidative phosphorylation, declines (30). Age-related physiological changes in mitochondrial function result in compensatory responses, among them the secretion of amyloid-beta. Indeed, studies have found an association between mitochondrial amyloid-beta levels and the degree of cognitive impairment in transgenic mice (31). Moreover, rat neurons treated with electron transport chain inhibitors have been found to enhance tau pathology (32, 33) while cytochrome oxidase inhibitors, which function to impede the reduction potential of the final link in the ETC, cause substantial alterations in the cleavage of APP towards its toxic amyloid-beta descendant (34). This theory helps bridge the discrepancy between genetics and sporadic onset of AD otherwise not explained by allelic variants that induce amyloidosis.

Structural Characteristics of Tau Protein

Microtubule associated protein tau is a seminal component in the maintenance of structural integrity of neurons. Located on the 17th chromosome, tau transcripts in the CNS are composed of 16 exons, three of which (2, 3, and 10) are alternatively spliced to produce six potential isoforms expressed differentially throughout development. These isoforms are characterized by the presence of three or four repeat tubulin binding regions at the C- terminus and the presence, or lack thereof, of additional inserts at the N-terminus. The presence and absence of exon 10 in the modified tau transcript gives rise to four and three repeat regions, respectively. Irrespective of the

presence of exon 10, the repeat regions 3R (R1-R3) or 4R (R1-R4) are also encoded by exons 9,11, and 12 (35). The largest of these isoforms contains exon 4A (an intermediate region between exon 4 and 5) and is unique in its localization to regions of the peripheral nervous system such as the spinal cord and the retina.

The importance of the N-terminus as a projection domain is maintained by a highly acidic character capable of interacting with cellular components such as the plasma membrane (36), mitochondria and serving as a key intermediate in the maintenance of structural rigidity (37), axonal growth (38) and diameter (39). Conversely, the C-terminus is characterized as a positively charged, basic region connected to the N-terminus via a proline-rich mediator (39). This region is directly bound to cytoskeletal tubulin and facilitates polymerization events conducive to cytoskeletal alterations. It is important to note that while 4R and 3R variants of tau bind microtubules, additional repeat regions have been shown to enhance binding affinity while simultaneously contributing to nucleation rates among dissociated tau (39).

Post-Translational Modification of Tau

Post-translational modifications of tau have been proposed as key drivers of Alzheimer's pathology, among them glycosylation (40), acetylation (41) and phosphorylation (42).

The hyperphosphorylation of tau protein is a common factor among all aforementioned scenarios (42). As such, the phosphorylation state of tau has thus far been the main determinant of tau pathology and the balance between kinase/phosphatase activity takes center stage. Full length tau (441 aa) has been found to have a total of 80 serine/threonine, along with 5 threonine phosphorylation sites (46), each corresponding to various severities of cytopathology in AD (47). Most of these phosphorylation sites lie in the proline-rich region connecting the projecting N-terminus with the microtubule binding C-terminal region (39). Similarly, tau serves as an intermediary between phosphatases, enzymes that dephosphorylate targeted substrates, and microtubule stability (48).

Structural and Mechanistic Features of Tau Fibril Formation

Dissociation of protein tau from microtubule binding sites is the neuropathogenic foundation of tauopathy in AD. Subsequent to detachment, monomeric tau assumes an unstructured configuration, which can be attributed to its positive charge low hydrophobic character at physiological pH levels and (49). The lack of hydrophobic residues precludes sufficient hydrophobic forces to sustain a secondary structure, and phosphorylation events contribute to a change in electrostatic character, disassociation and self-assembly (50). These amyloid regions, narrowed down to hexapeptide sequences ^{275}(VQIINK)^{280} and ^{306}(VQIVYK)^{311} are sufficient for the growth and propagation of tau fibrils, among other amyloid derivatives (51,52). While a significant portion of tau retains its random-coil structure even within fibrils, constituent regions of the amyloid core retaining the beta-sheet rich motifs remain (53). This is also demonstrated by the aggregation of tau in the presence of anionic compounds such as heparin (53) and arachidonic acid (54). Spectroscopic studies using FRET and hydrogen/deuterium mass spec examinations have proposed an 'S' shaped model for monomeric tau, whereby contact is maintained between the N-terminus and the proline-rich region and the C-terminus and amylodigenic regions of tau (55). Interactions between tau hydrophobic regions or polyanionic substances results in a conformational change from unstructured random-coils to beta-sheets, a pervasive feature of amyloids (51).

Tau monomer interactions result in the formation of parallel "stacks" of tau beta-strands connected via intermolecular hydrogen bonds, similar to structures of amyloid-beta (56) and alpha-synuclein deposits (57) in Parkinson's disease. Outer regions of tau filaments exhibit exposed hydrogen bond donors and acceptors (58), features that promote further aggregation and are absent in natural beta-sheet proteins to avoid aggregation (59). In this way, tau dimers are able to attract proximal monomers and grow in an unimpeded stacking fashion.

Key Point: Taupathies

Tau protein's normal function: microtubule assembly and stabilization

Progressive supranuclear palsy (PSP): onset over 40 years of age, falls within first 12 months of disease, vertical supranuclear gaze palsy, pseudobulbar palsy, axial dystonia, and dementia

Pick's disease (PiD): aphasia, behavioral changes (apathy, disinhibition, alteration in food preference, poor self care), and dementia (poor planning, reasoning and organization)

Frontotemporal dementia with parkinsonism (FTDP-17): familial syndromes in which there are personality and behavioral changes early or motor difficulties often mistaken for Parkinson's or PSP

Corticobasal degeneration (CBD): movement disorder and dementia (non-fluent aphasia, behavioral changes, apraxia)

Parkinson's disease complex of Guam (PDC Guam): Parkinsonism and dementia found in the fifth and six decades of life in the Chamorro people of Guam

Dementia associated with Down's syndrome: similar presentation to Alzheimer's but occurring 10-20 years earlier

Williams, D. R. (2006). Tauopathies: classification and clinical update on neurodegenerative diseases associated with microtubule-associated protein tau. Intern Med J, 36(10), 652-60.

Seeding and Intercellular Propagation of Tau

The presence of preformed tau aggregates potentiates fibrillation of endogenous tau by recruiting of dissociated monomers and oligomers (60). This facet of tauopathies allows tau fibrils to propagate in a pathogenic, prion-like fashion whereby exogenous fibrils or oligomers serve as "seeds", or molecular scaffolds, for monomeric tau in adjacent cells. Indeed, transgenic mice expressing P301L human mutant tau localized to the entorhinal cortex demonstrated propagation of fibrils to adjacent regions (61). Cultured cell experiments demonstrate cellular ability to uptake tau oligomers, but not monomers, via endocytosis (62). This seeding potential is determined by its structural conformation. In these instances, deletion of motifs ^{275}(VQIINK)^{280} and ^{306}(VQIVYK)^{311} eliminates the capacity of full-length tau to seed (63). Currently, there are two potential models to explain seeding, the oligomer-nucleated conformation induction and template-assisted growth (64). The major difference between these two models is the structural component(s) of tau that influence fibril formation. Oligomer-nucleated conformational induction establishes a high-energy scaffold which attracts monomeric tau that binds in succession to lower energy and form oligomers (65). Unlike the template- assisted growth model, fibrils do not integrate dissociated monomers, but are rather formed only after the formation of oligomers (66). Dimeric, trimeric and oligomeric intermediates between monomer and fibril formation have been established in aggregation studies involving other fibrillation prone agents (67) and AD peptide amyloid-beta (68). Toxicology comparisons between neurofibrillary tangles and tau oligomers injected into mouse brains found that oligomer-infused brains showed diffuse tau pathology into neighboring brain regions, whereas NFT-treated cells displayed localized deposits, implicating oligomers as the component most responsible for intercellular tauopathies (69).

Braak Staging and the Prion-like Propagation of Tau

The entorhinal region receives input from the neocortex and is involved in higher cognitive functions and the limbic system, as well as in the

formation of memories and emotions. Intracellular tau deposits first appear in an area adjacent to the entorhinal region called the transentorhinal region, which functions as a relay between the neocortex and the entorhinal region. The manner of neurofibrillary tangle propagation is closely associated with the degree of cognitive decline (70). The limbic stages consist of minimal NFT presence in the neocortex, with the fibrils concentration localized to the entorhinal and transentorhinal regions, concomitant with noticeable cognitive impairment. End stage AD presents with widespread damage to the neocortical areas, resulting in extensive cognitive impairment and advanced dementia.

Origins of Immunotherapy Against Alzheimer's

As one of the hallmark pathologies of AD, aggregates of amyloid beta have been one of the primary immune targets of AD therapies for quite some time. Mice immunization with $A\beta_{1-42}$, an alloform associated with toxic oligomers, showed reduced plaque burdens and retained cognitive functions relative to their non-immunized counterparts (71). Subsequent human trials were halted after a subset of patients developed encephalitis post-immunization, likely due to the extensive activation of CD8+ cytotoxicity (72, 73). Nevertheless, post-mortem autopsies indicated clearance of amyloid but retention of Tau pathology (74). This efficacy of this active vaccine, known as AN-1792, was undermined by a dearth of clinical effectiveness in rescuing cognitive decline (75). In another study on animal models, the clearance of extracellular amyloid plaques was accompanied by the reduction of early tau pathology but retention of hyperphosphorylated neurofibrillary tangles (76, 77). Conversely, tau antibody treatment did not affect amyloid load, indicating that amyloid deposits serve as a precursor to tauopathy, though analysis of normal brained individuals has shown tangle formation in the temporal lobe without the presence of amyloid plaques.

Passive immunizations with monoclonal antibodies against Aβ epitopes have proven effective in phase II and III clinical trials. CSF analysis in patients immunized with bapineuzumab showed a significant decline in phosphorylated tau (78). Nevertheless, phase III trials where discontinued when 6% of subjects developed aseptic meningitis.

Passive and active immunization of targeting Tau fibrils have also become a mainstay in AD immune-therapy. Studies exhibiting clearance after antibody treatment were either targeted at tau phosphor-epitopes or fibril specific conformations. In these cases, phosphorylation of tau was reduced and fibril load significantly decreased (79), establishing a correlation between tau antibody titer count, fibril load and cognitive performance (80). In other cases, passive immunization of phosphorylated tau was found to have significantly decreased NFT burden while increasing microglial activity (81).

Mechanism of Antibody Mediated Therapy

Although the efficacy of tau antibodies against pathogenic aggregates has been well documented, the mechanism by which this phenomenon occurs is obscure. Chief among several theories is that antibodies directly inhibit the fibrillation or even work to reverse the process altogether (82). This theory is corroborated by the clearance amyloid-beta aggregates in in-vitro studies. Indeed, studies have found that, similar to their amyloid-beta counterparts, tau antibodies cross the neuronal membranes via clathrin-mediated endocytosis and co-localize with intercellular fibrils (83). Additionally, antibodies have been found to interfere with the prion-like interneuronal propagation of tau by directly interacting with extracellular tau seeds (84).

Due to the neuroinflammatory nature of tauopathies, microglial clearance has been found to be a major form of fibril clearance (85). However, studies using mouse models for anti- amyloid-beta antibodies have also shown that clearance can occur in a non-Fc-mediated fashion with the use of antibodies lacking fragment crystallizable regions essential for the interaction of immune system components, such as microglia, with pathogens (86).

The Blood-Brain Barrier, An Obstinate Foe

One of the major obstacles to immunotherapy against neurodegenerative disorders is the human blood-brain barrier (BBB), a restrictive vasculature

of endothelial cells exhibiting high electrical resistance. In healthy individuals, the BBB functions as a selective safeguard against potential antigens and neurotoxins, impeding the entry of large or hydrophilic molecules, while facilitating transport of metabolically essential nutrients and molecules. The innate bulkiness of immunoglobulins poses a major obstacle to developing effective therapeutic measures for combating neurodegenerative disorders. Indeed, radioimmunoassays have found that approximately 0.1% of circulating IgGs, the most common of the 5 immunoglobulin classes (A,G,M,E, and D), can be detected in the CNS (87). However, the efficacy of the BBB can be severely compromised during neurological disorders such as multiple sclerosis, viral meningitis and tumors (88). Inflammatory events in AD have also contributed to increased BBB permeability and the pathological spread of amyloid plaques. Given the rapid turnover of cerebrospinal fluid (CSF) into the bloodstream, intrathecal injections directly into the CSF are equivalent to prolonged intravenous injections, amounting to limited therapeutic efficacy (89). Moreover, a logarithmic decrease in drug distribution throughout the brain has been shown in bulk-flow delivery of drugs directly into brain tissue (90). As such, antibody delivery for neuro- immune therapy is a popular research topic. Three major approaches to this problem include the application of lipid-mediator molecules, which can passively diffuse through the BBB; carrier mediated transport (CMT) of small water-soluble molecules; and the exploitation of receptor-mediated transport (RMT). Theranostics, the use of molecular platforms for drug delivery and diagnostics, relies on lipid or water-based carriers to transport antibodies across the membrane (91). These platforms have been used in the delivery of AB-antibody fragments via synthetic liposomal elements such as polyethylene glycol polymer chains (PEG) (92). Advances in RMT take advantage of metabolic receptors mediating BBB access to transport bound antibodies into the brain parenchyma. Insulin and transferrin receptor ligand-bound AB-antibodies have been shown to effectively cross the BBB through receptor-mediated transcytosis, enhancing brain exposure 55-fold in some instances (93, 94).

Additional Obstacles in Immunotherapy

Differences in the neurophysiology of animal models and human patients is an obstacle. Trangenic animal studies utilizing exogenous tau may find considerable discrepancies in phosphorylation patterns and epitope sites in patient counterparts. The lingering possibility of cytotoxicity from T-cell mediated responses has been a repetitive theme in human studies, all of which have been failed due to recurrent instances of neuroinflammation. In animal studies, the use of Freund adjuvant to stimulate cell-mediated immunity actually exacerbated tau pathology and neuroinflammation (95, 96). Subsequent commentary on these outcomes suggests that adjuvants eliciting a Th2 response, which triggers humoral immunity and the production of antibodies, could potentially help mitigate these outcomes (97).

The Future of Immunological Therapy

Immunological therapy was the paragon of medical discoveries in the 20th century. Priming the host immune system against external pathogens has been a mainstay of western medicine for centuries and continues to be at the forefront of preventative medicine. However, physiological diversity in disease states such as Alzheimer's make this task more challenging as epitopes, adverse reactions and physiological barriers represent barriers to developing clinically effective therapies.

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The Elusive "Most Effective Treatment:" A Review of Pharmaceutical and Physical Therapies to Treat Multiple Sclerosis

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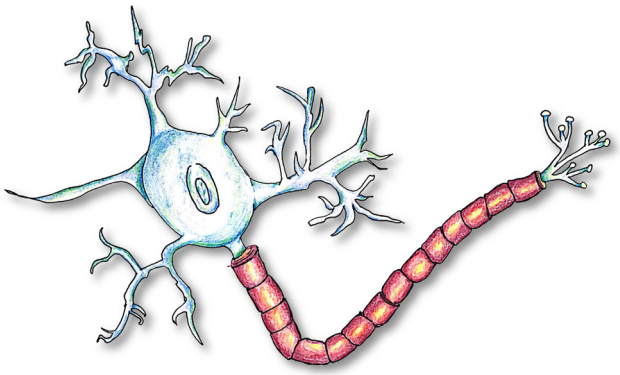
Abstract

Substantial developments in the treatment of the debilitating disease of multiple sclerosis (MS) have arisen with a greater understanding of its involvement with inflammation, demyelination, and neurodegeneration. Yet, despite advancements in clinical efforts, many current treatments produce terrible side effects that cause patients to discontinue their use.

The objective of this review is to discuss the current therapies and the best approach for future treatment. This review utilizes articles published from 1990-2016 to accomplish this task and to cumulatively suggest a future course of treatment. The review suggests that the most effective treatment of MS can be achieved by use of low dosage neuro-protective and anti-inflammatory pharmaceuticals, combined with various different types of physical therapy (PT) to keep muscle mass, coordination, balance and cognitive function at a high level.

Introduction

Multiple sclerosis (MS) is a degenerative autoimmune disorder that affects the central nervous system (CNS) due to the demyelination of neurons within the CNS (1). Demyelination of axons causes neurons to become permeable and makes it difficult for an action potential to propagate down the axon to the connecting cell. In essence, the demyelination of the axons interrupts the inter-web of communication



Tamar Yacoel: *Neuron with Myelin*

within the CNS, causing a disruption of information flow.

Though the cause of MS is not well known, recent studies suggest that deficiencies in the blood-brain barrier allow lymphocytes to infiltrate the CNS where they accumulate and attack the neurons at the myelin sheaths that surround the axons (2). As a result of the over-permeability of the blood-brain barrier in the CNS, an inflammatory response occurs and foreign cells (T-cell and B-cell lymphocytes) invade the brain and/or spinal cord. As a result of this infiltration, the T and B cells cause significant damage and demyelination. Promising results already show that medications that are effective in limiting B-cell proliferation and migration to the CNS help to reduce lesion formation and relapse rate (3).

The incidence of MS in the United States is an alarming 30+ cases per 100,000 people and affects more women than men (4). The first symptoms occur between the ages of 20-40 and often involve visual

or balance problems. Over time, symptoms worsen to severe motor and sensory disability; cognitive functional ability may be affected and muscle atrophy may occur due to the disruption of the connection between the CNS and the muscles. Muscle atrophy will then lead to the number one reported symptom of MS: fatigue (5). General fatigue and feelings of malaise are reported in more than 75% of all MS patients with over half stating that it is one of their worst symptoms (5). Several studies suggest that MS-related fatigue was associated with anxiety, depression, and decreased socialization (6).

It is important to study and address different approaches to treat and control MS due to the devastating and debilitating effects of the disease. Current treatment consists of pharmaceutical and physical therapies (PTs). However, neither is perfect and both have their advantages and disadvantages. The aim of this review is to discuss the treatments available for multiple sclerosis and to better understand the synergistic effect of immunomodulatory and cytoprotective medications with rehabilitation.

Treatments for Multiple Sclerosis: From the Pharmaceutical to the PT Approach

Immunomodulatory & Cytoprotective Medications: Natalizumab and Fingolimod

Various medications, ranging from immunomodulatory and immunosuppressive therapeutic agents to monoclonal antibodies are readily available to lessen the occurrence of symptoms and to try to slow the degeneration of the CNS (7). The mechanisms by which these medications work involve either the permeability of the blood-brain barrier, the way that cells can attach to their targets or the regulation of lymphocyte expression.

For the subset of relapsing-remitting MS, based on their profile, interferon-beta (IFNβs), naturally occurring anti-inflammatory cytokines, are given as a first-line treatment through subcutaneous or intramuscular injection with skin reactions as a possible side effect. IFNβ appears to directly increase expression and concentration of anti-inflammatory agents while also downregulating the expression of pro-inflammatory cytokines. As a result, interferon beta increases suppressor activity and inhibits T cell proliferation (8). Another widely used first-line agent and injectable medication is glatiramer acetate, a synthetic protein that is physically similar to a component of myelin and stimulates the immune system to generate anti-inflammatory responses (9).

Key Point: MS Symptoms

Scanning Speech: broken speech with frequent pauses between syllable pronunciation

Intention Tremor: slow meandering voluntary movements when extending towards an object

Nystagmus: involuntary eye movement due to brainstem and/or cerebellar lesion

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Over the past two decades, new treatments have arisen for MS. One such treatment is natalizumab, a monoclonal antibody targeting the VLA-4 receptor that is expressed on activated T cells and other mononuclear white blood cells. This drug binds to specific points on lymphocytes and controls their migration through the blood brain barrier (10). Since the lymphocytes cannot attach strongly to the endothelial cells to travel into the CNS, the demyelination rate is drastically reduced and axons are spared. This preventative means of treatment slows scarring and the growth of lesions and can subsequently slow down the symptoms of MS.

There has been evidence that natalizumab is still effective even with reduced doses. One study showed that the normal 6 mg administration of natalizumab gave negligible benefits versus a reduced dosage of 3 mg daily (11). Interestingly, the amount of new lesion formation was less among the 3 mg group than the 6 mg group, indicating that 3 mg may even be better at reducing lesion formation. Furthermore, it was seen that the increased dosage augmented the occurrence

of side effects, which included headaches and certain infections such as the John Cunningham virus (JCV) (12). Concurrent with reduced side effects and lesion formation, there was a reduced relapse rate of 68% among patients taking a reduced dosage compared to the placebo.

A particularly severe adverse effect of natalizumab has been noted for patients prescribed natalizumab in any dosage: an increase in contraction of Progressive Multifocal Leukoencephalopathy (PML) due to the drug's immunosuppressive effects (13). PML is also a demyelinating disease of the CNS. However, PML is caused by the JCV. Active infection with the virus allows lymphocytes to infiltrate the brain at a higher rate than in MS alone. Furthermore, JCV attacks and kills oligodendrocytes, which are already sorely lacking in a MS inflicted brain; ultimately, this leads to the inability to repair axons by means of re-myelination. PML is very similar to MS, but progresses much more rapidly; over the course of months versus years. Although the drug has shown beneficial results, the adverse consequences of contracting PML, may not justify the use or implementation. Patients that are seropositive for Anti-JCV antibodies are 44 times more likely to contract PML than those who are antibody negative. Therefore, current regulations stipulate that MS patients should be tested for JCV before being given natalizumab.

There are many limitations with medications that control lymphocytes, infiltrate the CNS, and adhere to target cells. It is very difficult to create a drug that can pass the non-permeable blood-brain barrier efficiently. Effects are transient and medications must be taken consistently to maintain efficacy (15). One study followed patients that had been taking natalizumab for more than 12 months after which they were told to cease treatment for a 6-month period (16). Results showed a disturbing 67% increase in clinical symptoms after this 'holiday' period. This suggested that cessation of these medications led to recurrence of MS symptoms. This suggests that the drug is successful in combating MS symptoms even though it has serious side effects.

Through another mechanism, the cytoprotective drug, fingolimod, acts as a protecting agent to change lipid markers on oligodendrocytes to prevent destruction by T-cells from the immune system. Since the oligodendrocytes are protected, they can continue producing the axon-protecting myelin (17). However, fingolimod decreases oligodendrocyte differentiation when given on its own (18). In order to overcome this barrier, researchers found that when fingolimod was given with the growth factor NT3, pathways promoting oligodendrocyte progenitor survival increased (18). Thus, this suggests that when given with NT3, fingolimod protects progenitors that may lead to oligodendrocyte proliferation and re-myelination in patients with MS. Nonetheless, a study done in 2006 showed that patients taking fingolimod showed a staggering 53% drop in relapse rate when compared to the placebo group, indicating very positive results (18). An interesting and important note is that the same study noticed similar, if not better, efficacy of fingolimod at 0.5 mg dosage than 1.5 mg. Additionally, another finding showed fewer adverse effects in this reduced dosing when compared to the 1.5 mg dose (18). This lower dosage was not only more beneficial in treating MS, but also significantly reduced the potential for severe side effects.

Pharmaceuticals are extremely valuable in mitigating

Key Point: MS Diagnostic Tests and Clinical Findings

Lumbar puncture reveals elevated IgG levels in CSF

MRI exam is hallmark of MS diagnosis often revealing plaques (axon destruction and/or loss of oligodendrocytes) around the lateral ventricles

CNS damage due to MS leads to subsequent reactive gliosis wherein hypertrophy of glial cells (microglia, oligodendrocyte and astrocytes) occurs leading to glial scar formation

Olek, M. J. (2016). Epidemiology, risk factors and clinical features of multiple sclerosis in adults. Retrieved from www.uptodate.com/contents/epidemiology-and-clinical-features-of-multiple-sclerosis-in-adults

negative effects of MS. However, these medications pose serious risks, especially at high dosages. Taken in lower doses, these drugs can allow an MS patient to live a better quality of life with fewer symptoms, relapses, and, most importantly, with fewer side effects. Despite the effectiveness of these medications, they do not counteract muscle atrophy, fatigue, and balance issues that are caused by MS. Another approach is needed to combat these problems; an approach that has close to no side effects.

Treatments: The Physical Therapy Approach

Pharmaceutical approaches are effective but can have dangerous side effect profiles and are somewhat limited in their performance. They can prevent additional degeneration from occurring, but they cannot reverse previous degeneration. In addition to the pharmaceutical approach, PT should also be used to combat MS issues related to motor processes, body/muscular control, etc. Various types of PT have been developed for MS patients with the goal of slowing down the effects of neuromuscular degeneration. Depending on the severity of the disease, patients can experience issues in balance and control of their bodies and muscles. This is due to the effects of MS on the neurons that control the muscles that deal with gait and also those within the cerebellum, which controls balance and fine motor control (19). In addition, the cerebellum and other motor areas of the brain cannot relay messages to the other parts of the body due to interruption of neuronal pathways. The aberration of signals sent to the peripheral nervous systems inhibits proper action from occurring and muscle atrophy can, and likely will, occur. Patients gradually lose control of their muscles and they are unable to maintain posture and balance. Since medication cannot reverse the prior degeneration of the CNS, physical therapy can be utilized to stimulate trained brain pathways that are used in balance, coordination, gait and muscular control without any serious side effects (19). Therefore, there is a need for MS patients to exercise with an emphasis on posture, balance, and torso control. The different exercises allow the muscles to maintain their mass and also helps to keep the CNS-muscle pathways open via consistent use (19). Among the multiple possibilities to implement PT rehabilitation to help with muscle atrophy and loss of neuronal pathways is whole body vibration (WBV).

Key Point: MS Immunosuppressant Therapy and Multiple Sclerosis

Natalizumab is administered to MS patients who show poorer response to previously administered immunotherapy drugs.Dimethyl fumarate is administered to treat flare-ups or relapsing MS and is shown to reduce the risk of relapse by 50 percent

Patients should receive a blood test to rule out JCV before treatment regimen with natalizumab or dimethyl fumarate and during their treatment phase to ensure that JCV has not be contracted

Chen Y., Bord E., Tompkins T., et al. (2009). Asymptomatic Reactivation of JCV in Patients Treated with Natalizumab. N Engl J Med, 361:1067-1074.

Rosenkranz T., Novas M., & Terborg C. (2015). PML in a patient with lymphocytopenia treated with dimethyl fumarate. N Engl J Med, 372: 1476–1478.

WBV therapy is a technique that is still undergoing trials to truly determine its efficacy pertaining to patients with MS. The therapy utilizes a mat that vibrates at two specific frequencies and amplitudes, while a subject is performing different types of exercises such as squats, stands, and lunges. The exact way that WBV benefits the muscle is not well known, but studies have shown that WBV stimulates muscle spindles and alpha motor neurons that cause contraction of the muscles (20). This could lead to increased muscular force generation and increased overall motor-muscle functionality (21).

Studies have suggested that WBV reduced mean time for the Timed Up and Go Test (TUGT), a test where a subject must lift himself out of a chair, walk 9 feet, turn around, walk back to the chair and sit down (22). The WBV exercise improved a patient's TUGT results by an average of 9 seconds (22). This can be attributed to WBV strengthening the muscles so that they do not become easily fatigued. Other studies have shown the benefits of WBV when performed for

as little as 7-12 minutes, 3 times a week (22). It was found that it improved muscle force output in specific walking muscles and also showed that the therapy can actually increase walking distance and endurance after a short training period (23). Furthermore, it was demonstrated that WBV can increase sensory organization (24). In the hardest part of the Sensory Organization Test, which measures the ability to coordinate visual, vestibular and proprioceptive input, WBV treated patients fell less often compared with those that were not treated (25). This can lead to increased ability to perform daily tasks such as walking and sitting up. These actions are important because most activities of daily living, whether they be personal, social, or work related, involve these motions. These results suggest that WBV can be beneficial in improving muscle functionality in walking and other areas and also improve muscular force output.

Strenuous exercise is typically burdensome to people with MS as it can be painful and they fatigue easily. As a result, WBV seems like a good alternative to standard PT. When done for durations longer than seven minutes, it can be helpful in muscle force generation, endurance, functional capacity and improved walking speed among patients with MS (26, 27). It can lead a person to being able to walk and lift himself out of bed autonomously. A limitation of PT is that it will never allow a person to completely regain balance control and coordination but only help slow the processes already in place as they are in a constant state of degeneration. As such, we can conclude that WBV may be well suited for those with extreme muscle fatigue because it requires less exertion of effort than other types of PT.

Another type of PT that is beneficial for MS patients is resistance training. Resistance training utilizes resistance bands to strengthen muscles within the legs, arms, and core. Resistance bands are placed on the feet of an individual or on the arms, and patients must counteract the resistance with their own force. The resulting increased muscle mass is beneficial to MS patient by increasing their strength and their ability to accomplish day to day tasks (28, 29). Those who did resistance training programs over 8 weeks also had a 24% decrease in self reporting fatigue according to the modified fatigue impact scale (29). This data is valuable since it shows a negative correlation between exercise and muscle strengthening versus fatigue levels specifically in MS patients. Even more interesting is that studies have also demonstrated that physical activity and exercise improve cognitive function in people with MS (30). Resistance training is beneficial but has its limitations. First, many MS patients have suffered the debilitating effects of the disease for too long and their muscles have atrophied to a point where they can no longer efficiently counteract the resistance. As a result, resistance training is best utilized for patients who have recently been diagnosed with MS. Additionally, to achieve continued control of symptoms, it is imperative that physical rehabilitation programs such as resistance training are frequent and continuous. Studies have shown that improvement of symptoms from small bouts of physical activity over a limited amount of time are fairly temporary (26, 27).

Resistance training and physical activity will have a positive effect on symptom control and cognitive function when done regularly and sustained over a period of time. However, if not continuous, then a patient will only see negligible benefits. Furthermore, many late stage MS patients suffer from severe fatigue and muscle atrophy and cannot perform such strenuous exercise. Thus, this therapy is most beneficial in early stage treatment. If done consistently, resistance training can help maintain muscle mass and functional capacity and thus counteract any atrophy caused by MS.

A third and very important type of PT is vestibular rehabilitation (VR), "consisting of upright postural control and eye movement exercises" (31). VR is done by a physical or occupational therapist and is accomplished by repeatedly habituating the brain to the offending stimuli thus retraining the brain to recognize that the movements should not be causing dizziness (32). Since MS degenerates the pathways that are attributed to balance, posture, control, and gait. VR aims to retrain the CNS to compensate for vestibular deficiencies and truly hone in on the patients' balance and coordination. Furthermore, balance exercises have been seen to help upright posture control, which can help with walking (32).

VR has many positive benefits that affect a variety

of different systems. Walking distance can be effected drastically so that MS patients can perform routine activities. One study showed that a 14-week intervention program that consisted of vestibular rehabilitation led to a significant increase in walking distance measure by the Six-minute Walk Test (31). Further evidence showed that VR also can improve fatigue levels, balance, and feelings of depression (31). Thus, VR not only improves coordination, balance, control, and posture, but it may also combat the depression and fatigue which are among the most debilitating symptoms associated with MS (31).

Although VR is therapeutic for MS patients, it has its challenges as well. For instance, it is very difficult for many people with MS to get out of bed, let alone get to a physical therapist. As a result, the accessibility of this type of rehab is extremely limited. It has also been suggested that symptoms of vestibular deficiencies, such as nausea, often get worse when first starting VR (31). Consequently, many patients cease the therapy regimen before positive benefits can be attained. Although this is not considered a side effect, it is a limitation of VR. MS patients are already suffering from their debilitating symptoms and making them temporarily worse can result in many individuals distancing themselves from this type of therapy.

However, VR has also seen positive results in reducing fatigue levels and depression (31). VR would seem to be most beneficial when combined with other physical therapies. If VR was performed with PT, the symptoms of muscle atrophy, functionality, fatigue, muscle coordination, gait control, balance and posture could all be addressed.

In conclusion, every PT technique has its pros and cons. WBV only improves muscle functionality, force exertion, and muscle mass so an individual with gait or balance control problems may not benefit from this PT regimen. Resistance training has similar benefits but is considered more effective in increasing muscle mass in the early stages of MS. As stated previously, the increased muscle mass benefits the strength and functional capacity in MS patients. However, resistance band therapy is not a viable therapy for those in a more progressive stage of MS as they would be too weak to perform the exercises properly. Lastly, VR is an important rehab technique that can be done by anyone diagnosed with MS. Since MS effects balance, gait, and fine motor movement, it is important to maintain and improve these skills constantly. However, some people may get worse before they get better and it must be done by a PT so many people do not continue their therapeutic regimen. Since all of the rehabilitations affect different processes and symptoms of MS, a combination of the PTs would be most beneficial to combat the muscular, vestibular, and cognitive deficiencies caused by the disease.

All of the PTs discussed have positive effects on symptoms of MS such as cognitive defects, fatigue and depression while also fighting muscle atrophy, loss of neuronal control and loss of balance/gait. A combination of different PTs will allow a patient to maintain as much control of their body as possible,

Key Point: MS & Depression

Depression may be associated with 50% of MS patients

MS patients without depression compared to a healthy control group shows over activity of the ventrolateral prefrontal cortex and its lack of association with the amydgla region of brain (Both areas of the brain crucial in mood regulation)

Over activity of the ventrolateral prefrontal cortex in MS patients may signal a compensatory mechanism to maintain a non-depressed state due to lack of proper connectivity with the amygdala region

A subsequent conclusion can be drawn that an MS ridden brain has to exert more effort to maintain a normal mood state than a healthy brain and thus has less cognitive reserve to counter stressful events that may lead to a mood disorder such as depression

Feinstein, A. (2011). Multiple sclerosis and depression. Multiple Sclerosis, 17(11), 1276–1281.

with minimal side effects. However, PT is only therapeutic and not a cure because it cannot stop the degenerative process of the disease. This is why low dosage medication, in conjunction with many different PTs would seem to be the best mode of treatment. The combination decreases the possibility of adverse effects associated with pharmaceuticals, the occurrence and severity of symptoms and relapses, and allows a patient to gain muscle mass and coordination so that they can perform daily tasks and have an improved quality of life.

Conclusion

Multiple sclerosis demyelinates axons in the CNS leading to scarring in the brain and/or spinal cord, which impedes the ability of the CNS to transmit and receive messages, and causes the loss of muscle mass, coordination, and the loss of sensory functionality. Though adverse secondary effects can be observed, many cytoprotective and immunomodulatory medications reduce brain lesions and lessen the occurrence of relapses in patients. Furthermore, physical therapy such as WBV therapy and resistance training are beneficial in maintaining muscle mass and reducing the symptoms of MS. By avoiding new lesion formation and preventing attacks of the CNS by lymphocytes, and through following a PT program to increase muscle mass and reduce symptoms, MS progression may be significantly reduced and symptoms may be kept to a minimum. With treatment, axons that otherwise would have degenerated, will be able to continue to convey messages throughout the entire body leading to a relatively normal life without fatigue or relapses. Cytoprotective and immunomodulatory pharmaceuticals, combined with postural/balance therapy and resistance training to strengthen muscles and reduce fatigue, offer the best possible results for controlling MS and reducing the negative symptoms associated with it.

A reduction in pharmaceutical dosage will permit continuous efficacy of the drug, and will also tremendously reduce potential serious side effects. As discussed earlier, many drugs have been seen to be effective at lower doses while also limiting adverse events. A lower dosage will allow patients to worry less about the adverse side effects of their medications while still receiving the necessary dosage for prevention of further axonal degeneration. Since balance and coordination are a common problem in MS patients, vestibular therapy can help one to maintain proper balance and gait so they can continue walking and perform activities of daily living. Furthermore, postural/balance therapy and resistance training allow a patient to combat muscle atrophy and strengthen muscle mass, coordination, and neuro-muscular communication. In conclusion, lower dosage of pharmaceuticals, combined with extensive and continuous PT, may help achieve the best possible outcome for controlling MS and combating the symptoms associated with the disease, while limiting potential harmful side effects. This ultimately allows an individual with MS to have encouragement about their future health and most importantly, their quality of life.

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