

NEUROLOGY NEWSLETTER

College of Medicine
California Northstate University

Lou Gherig- "Isn't he a baseball player?"



February,
2016

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In This Issue... we discuss the neurodegenerative movement disorder, Parkinson's disease; the degenerative muscle disease, Duchenne's Muscular Dystrophy; the demyelinating neurodegenerative disease Amyotrophic Lateral Sclerosis; and the autoimmune encephalopathy, Multiple Sclerosis. Additionally, our very own Steven Nemcek has contributed a whimsical poem about our favorite organ. I hope you enjoy this February 2016 issue.

THE BRAIN

-By Steven Nemcek

They say man's soul resides within the heart,
We feel it change tempo near those we love,
But a puppet does not in fact impart,
Nebulous Consciousness. That's from above.

In gyri, sulci, and electric grooves,
The breadth of human experience hums,
Though pure dopamine sitting in a tube,
Is not pleasure without its human drum.

Stirner says the only Good here resides,
Ego, self, spirit soaring thru blue sky,
Are virtues, She eloquently replies,
"To say 'I love you' one must first know how to say the 'I.'"

Knowest thou the true color of a brain?
Knowest thou the true color of a life?
Hatred, rage, lust, love, under sunset's wane,
Crimson, crimson, and crimson burn so bright.

Though sometimes individuality is lonely;
I wish I could share the pleasure I derive from finishing a poem with metalanguage.

UNDERSTANDING PARKINSON'S DISEASE

In 2011, Michael J. Fox, a longtime actor who was diagnosed with Parkinson's Disease in 1991, stated, "With Parkinson's Disease (PD), it's like you're in the middle of the street and you're stuck there in cement shoes and you know a bus is coming at you, but you don't know when. You think you can hear it rumbling, but you have a lot of time to think. And so you just don't live that moment of the bus hitting you until it happens. There's all kinds of room in that space." The challenges that Mr. Fox endures are similar to the trials that 500,000 other Americans living with PD experience on a daily basis.

PD is a chronic, neurodegenerative movement disease of the central nervous system characterized by tremor (trembling of the limbs and face), rigidity (resistance to movement), bradykinesia (slowness of movement), and postural instability (impaired balance). Usually, the symptoms become progressively worse over time, and

patients find it harder to complete simple tasks, such as walking and talking. Researchers have found that the primary cause of PD is the destruction or impairment of dopamine-producing neurons in the substantia nigra, which is a part of the basal ganglia near the base of the brain. Dopamine is a vital neurotransmitter that is synthesized

in the substantia nigra and sent to the corpus striatum to produce smooth, purposeful movement. Without dopamine, abnormal nerve firing patterns are seen resulting in impaired movement. Additionally, a decrease in dopamine levels also contributes to depression, which is another common symptom seen in PD patients.

Current PD researchers hypothesize that various genes and environmental agents may play a role in the death of these dopamine-producing neurons. However, the disease is mostly sporadic as it doesn't always appear to run in families. It has been discovered that abnormal deposits of the protein alpha-synuclein, also known as Lewy bodies, are found in many PD patients. Therefore, there may likely be a link between alpha-synuclein gene mutations on chromosome 4 and PD. Other genes that have been implicated in PD include parkin, DJ-1, PINK1, and LRRK2. "The parkin gene is translated into a protein that normally helps cells break down and recycle proteins. DJ-1 normally helps regulate gene activity and protect cells from oxidative stress. PINK1 codes for a protein active in mitochondria, and mutations in this gene appear to increase susceptibility to cellular stress."

Every year in the United States, approximately 50,000 people are diagnosed with PD, and for unknown reasons, PD appears to affect men 50 percent more than women. The average age of onset is around 60 years of age, although there is a rare form of early-onset PD that exists where individuals may be

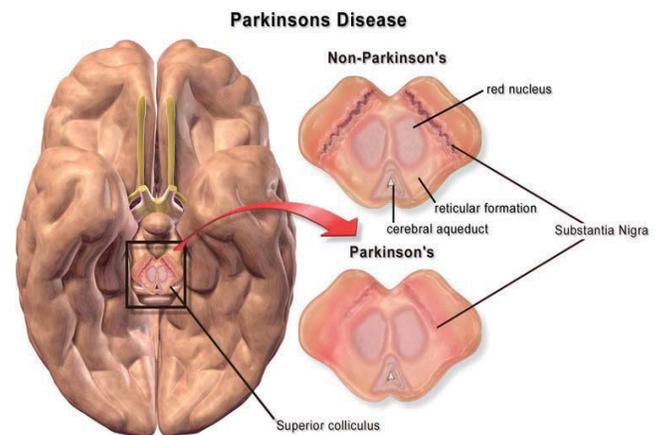


Figure 1. Substantia Nigra in Parkinson's vs Normal

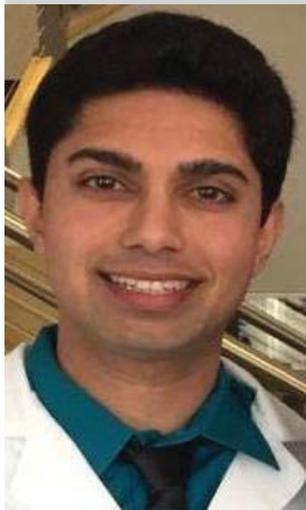
"it's like you're in the middle of the street and you're stuck there in cement shoes and you know a bus is coming at you, but you don't know when"

"PD is a chronic, neurodegenerative movement disease of the central nervous system characterized by tremor (trembling of the limbs and face), rigidity (resistance to movement), bradykinesia (slowness of movement), and postural instability (impaired balance)."

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"For everything this disease has taken, something with greater value has been given--sometimes just a marker that points me in a new direction that I might not otherwise have traveled."

"So, sure, it may be one step forward and two steps back, but after a time with Parkinson's, I've learned that what is important is making that one step count; always looking up."



-Salil Babbar
MS1, CNUCOM

diagnosed before the age of 50. There are currently no blood or laboratory tests available for testing sporadic PD. Additionally, CT and MRI brain scans of people with PD appear normal. Thus, the best way to obtain an accurate diagnosis is through a medical history and neurological examination. However, it is usually hard to predict how PD will affect a particular individual, since there is a wide spectrum for symptom progression and severity from person to person.

There are two main categories of PD drugs that patients can take to improve their motor functions. The first group of drugs increases the levels of dopamine in the brain, mimics dopamine, or slows its breakdown. A common example is levodopa/carbidopa, which increases the levels of L-DOPA in the brain for conversion to dopamine. Other critical drugs include bromocriptine (a dopamine agonist), amantadine (increases dopamine release and decreases dopamine reuptake), and selegiline (blocks dopamine breakdown). The second group of drugs relieves symptoms by affecting other important neurotransmitters in the body. A well-known example is the anticholinergic drug benztropine, which relieves symptoms like tremor and rigidity. If drug therapy is ineffective, PD patients can also choose to undergo "deep brain stimulation, where an electrode is surgically implanted into a part of the brain, typically the subthalamic nucleus or the globus pallidus." This procedure helps stimulate the brain, which blocks the nerve signals that cause the abnormal motor symptoms. Additionally, particular lifestyle choices can help improve the quality of life for PD patients. Eating a well-balanced diet and exercising regularly may help improve mobility and flexibility and prevent symptoms from becoming worse.

The biggest challenge that faces PD researchers today is finding a cure. However, researchers remain optimistic because of the great strides that have been made in producing effective medications to treat PD symptoms. Organizations like the National Institute of Neurological Disorders and Stroke (NINDS), which is a component of the National Institutes of Health (NIH), are currently focused on discovering a single biomarker that all PD patients might share. Testing for this biomarker would allow doctors to find out who is at risk for PD and develop new treatments for early stage PD. Additionally, there are numerous national organizations with local support groups available to PD patients and their family members. Michael J. Fox remains hopeful about the quality of the remaining years of his life. He says, "For everything this disease has taken, something with greater value has been given--sometimes just a marker that points me in a new direction that I might not otherwise have traveled. So, sure, it may be one step forward and two steps back, but after a time with Parkinson's, I've learned that what is important is making that one step count; always looking up."

- Salil Babbar

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-Letitia Pirau
MS1, CNUCOM

"nearly half (45%) of the oldest males in each family affected with Duchenne/Becker Muscular Dystrophy had at least one of three mental health concerns: behavior concerns, depressed mood, or attention-deficit/hyperactivity disorder"

DMD: MORE THAN JUST MUSCULAR DEGENERATION

Duchenne's Muscular Dystrophy (DMD) is a debilitating childhood disorder associated with rapid muscle degeneration due to a decrease in muscular mass. DMD is usually identified as an X-linked recessive inherited disorder, but more often than not is a spontaneous mutation, thus prevention other than genetic counseling is sparse. While certain symptoms may appear at birth, many parents only realize something is wrong when their boys fall a lot and usually child's play such as running, jumping, and hopping are severely impaired, according to the CDC. Microscopically, fat infiltrates the muscular tissue giving rise to the hallmark "pseudo hypertrophic calves" appearance. However, the hallmark of DMD is the Gower sign, in which boys must use their hands and arms to "walk up" from a squatting position. By age 8-19 boys will require leg braces, and by 16-18, most boys succumb to fatal pulmonary infections. Very few boys diagnosed with DMD live beyond the age of 30. According to CDC guidelines, the treatment for DMD consists of corticosteroids, specifically prednisone, to improve strength and pulmonary function, but it only alleviates symptoms until the inevitable -- death.

New research points to significant cognitive and behavioral problems that arise within patients who have DMD. Working with the CDC, researchers from the Muscular Dystrophy Surveillance and Research Network published a surveillance study in The Journal of Developmental and Behavioral Pediatrics, which showed that "...nearly half (45%) of the oldest males in each family affected with DBMD [Duchenne/Becker Muscular Dystrophy] had at least one of three mental health concerns: behavior concerns, depressed mood, or attention-deficit/hyperactivity disorder (ADHD)". Dr. James Poysky addresses some of these behavioral and cognitive deficits associated with DMD through a workshop report of four articles. First, Dr. Poysky discusses Dr. Sue Cotton's meta-analysis on two neurodevelopmental points associated within DMD patients: IQ and verbal span. In 32 studies examining patients with DMD, the average IQ of DMD patients was one SD below the population, while 35% had an IQ in the mental retardation range. However, she concluded that the variability in results was of limited value. In terms of verbal span, DMD boys were generally weaker, specifically on sentence recall or following verbal directions. Second, according to Dr. Jos Hendriksen's research one of the more important problems associated with DMD are learning disabilities, such as dyslexia, dyscalculia

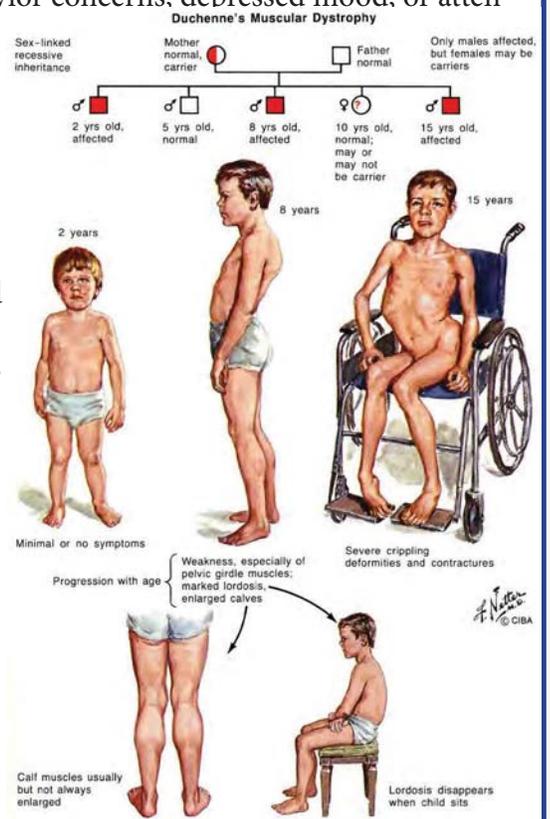


Figure 2. Progression of Duchenne Muscular Dystrophy

"DMD patients have problems with "theory of mind" – the ability to understand another person's perspective, and the connection between external factors on emotional states"

The most recent hypothesis is that...the absence of dystrophin distorts neural function... causing disruption in cognition, behavioral functioning, sleeping patterns, and response to medications.

(difficulty in arithmetical calculations), and dysgraphia (inability to write coherently). Third, according to Dr. Veronica Hinton, many seem to display autistic traits as well, such as being more withdrawn, having a poor attention span, and poor socialization skills. Dr. Hinton incorporated two principles into her study: developmental perspective due to life's normal stressors (i.e. getting a bad grade) and illness stressors (becoming wheelchair dependent). The younger the boy is the worse the adjustment is at that age. With time, the boys become better adjusted to the stressors, yet peer relations become worse. In particular, DMD patients have problems with "theory of mind" – the ability to understand another person's perspective, and the connection between external factors on emotional states .

Dr. Poyosky then refers to the work done by Dr. John Morley's lab and other meta-analyses to better understand the connection behind the physiology and the behavioral/cognitive problems found in DMD. Dr. Morley found that dystrophin loss, the hallmark of DMD, was related to cognitive and neurobehavioral disorders. In the central nervous system of non-DMD participants, clusters of dystrophin are most abundant on the soma and proximal dendrites of pyramidal cells in the cerebral cortex, hippocampus, and of Purkinje cells in the cerebellum. Dystrophin is especially found in the postsynaptic densities of GABAergic inhibitory synapses and is also colocalized with dystrobrevins in Purkinje fibers of the cerebellum. Testing on an mdx mouse, which lacks a full length sized dystrophin gene, led to the disruption in the targeting or stabilization of receptors at the post-synaptic membrane, thereby diminishing the number of GABA-A receptor clusters. The most recent hypothesis is that while the role of dystrophin in the CNS is ambiguous, the absence of dystrophin distorts neural function by stopping ion channel localization. This in turn, changes the electrical environment of neurons downstream of the axon and alters calcium homeostasis as well as synaptic plasticity. These changes will then cause disruption in cognition, behavioral functioning, sleep patterns, and response to medications. Moreover, the most recent hypothesis is that the cerebellum and its association with dystrophin clusters within Purkinje fibers might explain dyslexia. This data corroborates a 1998 research trial led by Dr. Marie-Pierre Moizard, in which different dystrophin isoforms (Dp71 and Dp140) were found to have caused significant cognitive impairment in DMD patients.

Dr. Poyosky's analysis of Dr. Morley's, Hinton's, Cotton's, and Hendrikson's research comes to a close with his emphasis on one point -- to utilize behavioral and cognitive testing early on DMD patients. The question still remains what exactly is the cause of these cognitive challenges faced by DMD boys. Some potential causes could stem from the psychological trauma of being wheelchair bound at a young age or the physiological effects due to a lack of dystrophin. Nevertheless, the fact remains that patients can better cope with such challenges through cognitive behavioral therapy. Thus, it is essential for behavioral and cognitive testing to be done soon after a patient has been diagnosed with DMD.

for reducing drug use in the United States through treatment and prevention programs, receiving bipartisan support. Along with supply reduction funding (National Prescription Drug Take-Back Day), this totals to \$27.6 billion. The resources are there, and now it is up to the healthcare system, alongside humanity, to develop strategies to reduce opioid related deaths while still effectively

treating seriously debilitating symptoms like chronic/acute pain.

-Letitia Pirau

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WHAT HAPPENED WITH THE ICE BUCKET CHALLENGE?

In July and August of 2014, an unusual spectacle pervaded social media. During just two months of summer, countless videos of people pouring ice water over their heads – on purpose – spread throughout the internet. This strange phenomenon was the Ice Bucket Challenge: an event intended to raise money and awareness for amyotrophic lateral sclerosis, also known as ALS or Lou Gehrig's disease. Ordinary individuals and celebrities alike took part in the challenge and passed it along to others: endure a bucket of icy water or donate money for ALS research, often both. The widespread popularity of the ice bucket challenge successfully raised money and awareness, but it also raised many criticisms. As the trend died down, many questioned what the money had actually accomplished.



Figure 3. Where the Money Went

The ALS Association (ALSA) reports that the ice bucket challenge donations added up to \$115 million, out of which they have used \$47.1 million, primarily for funding research. The ALSA intends to allocate the remaining funds over several years, primarily towards research but also to community services and ALS education. A complete breakdown of their funding, including specific projects that the money has funded, is available on their website: <http://www.alsa.org/fight-als/ice-bucket-challenge-spending.html>



-Flynn Kaida-Yip
MS1, CNUCOM

"The Ice Bucket Challenge donations added up to \$115 Million"

-Flynn Kaida-Yip



-Matthew Zabel
MS1, CNUCOM

Zika virus...manifests with a constellation of seemingly benign symptoms in adults...However, the severest symptoms are currently manifesting in newborn babies, the most prominent... microcephaly

"We now must prepare our healthcare system for the Zika virus, again prompting the question of whether or not we are ready."

THE DEADLY NEUROLOGICAL CONSEQUENCES OF A BENIGN VIRUS

It has not yet been a year since the last viral outbreak affecting a large developing population left the twenty-four-hour news cycle—that was the Ebola virus outbreak in West Africa, which only began to wind down last fall. With that infection, many concerns were raised if the U.S. was prepared to handle such a devastating disease. Now, a new viral outbreak is sweeping through parts of Central and South America and is expected to make a more robust appearance in the U.S. soon. We now must prepare our healthcare system for the Zika virus, again prompting the question of whether or not we are ready.

Unlike the Ebola virus, the Zika virus is spread by the mosquito *Aedes aegypti* and manifests with a constellation of seemingly benign symptoms in adults including mild headache, fever, joint pain and a skin rash. However, the severest symptoms are currently manifesting in newborn babies, the most prominent of which is microcephaly—a neurodevelopmental disorder where the brain and skull fail to grow resulting in seizures, impaired intellectual development and motor disturbances. Already, Brazil reports 4,000 cases of congenital neurological abnormalities in 2015¹. According to the World Health Organization, an outbreak in the US is very likely to occur.



Figure 4. Child with Microcephaly

This raises special alarm due to the severity of neurological deficits—that is, besides microcephaly, many victims are also manifesting a rare autoimmune disease called Guillain-Barre Syndrome (GBS). GBS usually occurs after an influenza-like illness caused by a number of microorganisms resulting in autoimmune destruction of peripheral nerves. The syndrome manifests with ascending paralysis and loss of reflexes, which can become life-threatening when the disease reaches the nerves supplying the diaphragm. Although the occurrence of GBS in the context of Zika virus is correlational (not causal), the increase in the number of cases has many doctors and scientists concerned and the US Centers for Disease Control and Prevention (CDC) is helping Brazil run a study to determine if the link exists.

The CDC has already issued guidelines in collaboration with the American Academy of Pediatrics on how to evaluate infants suspected of being infected². Additionally, the WHO has planned a \$56 million tour-de-force to study the virus and how it spreads and push quicker vaccine development and diagnostics³. Already, several companies and the US National Institutes of Health are predicting a developmental timeline to human trials of a Zika virus vaccine by the end of the 2016⁴. In the short term, North and South American governments are trying to contain the virus by controlling its vector, the mosquito. It is hoped that more knowledge can be gleaned about the virus and potential vaccine options in the meantime. For now, it does seem that we are taking the necessary steps to respond to this potentially fatal epidemic.

-Matthew Zabel



-Steven Nemcek
MS1, CNUCOM

"I saw firsthand the resilience and determination in many of those affected by the disease and was inspired by their perseverance – the same perseverance I saw in my grandfather."

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A PERSONAL LOOK AT MULTIPLE SCLEROSIS: THE STORY OF MY GRANDFATHER

During our first morning of the neuroscience block, Dr. For-Shing Lui noted that many patients would rather die than be diagnosed with a progressive, debilitating neurological disorder. I would presume that there are few things in life more emotionally trying than knowing one's body will progressively degenerate such that it is no longer under one's own control. This is why one of my personal heroes is my grandfather, who was diagnosed with Multiple Sclerosis many years ago but has faced his condition with an intense defiance throughout.

Multiple Sclerosis is the most common autoimmune disorder affecting the Central Nervous System¹. It is a demyelinating disorder and usually takes on one of two forms: it can be episodic, in which the patient suffers bouts of symptoms, or it can be progressive in which the patient's symptoms gradually worsen over time². The cause is unknown, but a variety of papers have purported to show a link between the illness and commensal bacterial flora (akin to the cross-reactivity seen in seronegative arthropathies) or a link between the illness and one's exposure to sunlight through biological levels of Vitamin D. I had an undergraduate professor in Biochemistry who was studying the latter of these two hypotheses and whose work can be sampled below³. Symptoms, as one would expect, include a wide variety of neurological issues which include, but are not limited to, motor, coordination, speech, swallowing, incontinence, and psychiatric problems⁴. There is currently no cure for the disease.

I grew up with the reality of my grandfather's condition. My first realization that something was wrong was when I was five years old, and I saw him trip down a flight of stairs into a church basement. At the time, I didn't understand what exactly was going on, I just knew that grandpa was "sick."

As I matured I began to learn more about the condition through conversations with family and through local fundraisers. The National Multiple Sclerosis Society hosts a series of fundraising events throughout the country each year, including "MS Walks" (our students are invited to attend the Sacramento event in April). My family would always either participate or volunteer. I saw firsthand the resilience and determination in many of those affected by the disease and was inspired by their perseverance – the same perseverance I saw in my grandfather.

My grandfather is a good man. He served in the United States Air Force, paid his own way through dental school, successfully raised five children and put them through college, has had a successful marriage for many decades, and ran his own dental practice into his seventies. He is the kind of man who

"even with so many of the neurological diagnoses that can be life-altering and can shake patients to their core, the fire of hope can always exist for those who choose to bear their burden head-on"

Drowning In Student Loans?

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E-mail your answers to CNUSIGN@gmail.com

refused to let his disease define or beat him.

He maintains a daily routine of waking up at dawn to perform hours of physical exercise. He refused the use of an electric wheelchair until walking became a literal impossibility. He kept his dental practice open until he couldn't physically manipulate his hands in the way he needed, and retired that very same day. He is otherwise in relatively good health - in his eighties.

My grandfather is a hero in my eyes; he embodies all of those human values that so many of us try to emulate. When I think about his fierce pride and fortitude, I am reminded that even with so many of the neurological diagnoses that can be life-altering and can shake patients to their core, the fire of hope can always exist for those who choose to bear their burden head-on. Thank you, grandpa, for giving me the courage to try to live a life like yours.

-Steven Nemcek

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CLINICAL PEARLS OF PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder, characterized by the progressive loss of dopamine neurons and the consequent decrease in the neurotransmitter dopamine. The areas on the brain involved is most significant with substantia nigra pars compacta which explains the motor symptoms of PD. However, there are other dopaminergic neurons in the brain and even the gastrointestinal tract that also degenerate and result in non-motor symptoms of PD. These non-motor symptoms may predate the motor symptoms and diagnosis of PD for years.

I will list some as follows:

1. Impairment of smell. This often predates the diagnosis of PD for years even up to decades. Smell testing is actually a very sensitive test for early PD when the clinical diagnosis is unclear. It is good to ask this question when you suspect PD.

2. Sleep related disorders: restless leg syndrome is a very common association. It is explained at least in part by the loss of iron (depigmentation) in the substantia nigra. REM sleep behavioral disorder is also very common predating the diagnosis of PD. Their bed partners most often complained that the patients "acted out" in their dreams.

3. Constipation: part of early non-motor symptom with onset before the actual diagnosis.

4. Variety of neuropsychiatric and sleep disorders due to involvement of the meso-limbic dopaminergic pathway and brainstem serotonergic/norepinephrinergetic involvement. These tend to occur late in the course of illness.

It is interesting to note that a couple of rare but relatively serious side effects of dopaminergic treatment especially with the newer dopamine agonists



-Trevor Tsay
MS1, CNUCOM

"We have a defining moment before us—the kind of moment that we will look back on in years to come as one in which we as a profession rose to the challenge to save our patients, our families and our communities during a time of crisis."

Neurology Newsletter, a monthly newsletter published by students in the Student Interest Group in Neurology (SIGN) at California Northstate University, College of Medicine (CNUCOM) is meant to bring abreast information in the ever changing field of neuroscience to ultimately provide our patients with excellent medical care and top-notch patient education. Our website can be found at <http://cnu-comorgs.wix.com/student-groups>. All correspondence should be e-mailed to CNUSIGN@gmail.com.
Chief Editor: Trevor Joel Tsay
Assistant Editor: Rainy Dae Zhang
Faculty Advisor: For-Shing Lui, MD, MRCP(UK), FRCP(Edinburg)

Published: Friday, February 19th, 2016

such as pramipexole and rospinozole are obsessive compulsive behaviors and sleep attacks. Patients taking these medications may present with "sleep attacks" such as falling asleep behind the wheel. I have personally seen patients who became obsessed with gambling and sex. It was interesting and embarrassing when one of my patient's spouse asked me to talk to her 87-year-old husband not to ask for sex on a daily basis. These problems resolved quickly once the dopaminergic culprit was removed.

-Dr. For-Shing Lui

A CALL TO ACTION- ENDING OUR OPIOID EPIDEMIC

In our inaugural issue from last month we raised the question of whether or not America has an opioid epidemic. The answer is clear: we do. Just this week a nine year old boy in Wisconsin died from yet another opioid overdose. While the Center of Disease Control (CDC) sits on the verge of releasing their guidelines for prescribing opioid based pain killers, the president of the American Medical Association (AMA), Steven J. Stack, MD, has released a call to action: "Physicians must turn the tide of the opioid epidemic."

Earlier this month a southern Californian physician was convicted of murder for the overdose deaths of three of her patients. She was sentenced to 30 years in prison and marks the very first physician to be convicted of murder for recklessly prescribing medication. This makes the public's as well as our judicial system's opinion extremely transparent: the results of prescription opioids are the responsibility of physicians. This proves the point that is best stated by Dr. Steven Stack, "We have a defining moment before us—the kind of moment that we will look back on in years to come as one in which we as a profession rose to the challenge to save our patients, our families and our communities during a time of crisis."

The AMA is asking for all of us to just take five specific steps:

1. We should register for and use our state's prescription drug monitoring program (PDMP).
2. We may need to enhance our education and training about safe prescribing. We should ask ourselves two simple questions: When was the last time we looked at the research on opioid alternatives? And when was the last time we took education to ensure we are prescribing safely and appropriately?
3. We should co-prescribe naloxone to patients at risk of overdose. The AMA Task Force to Reduce Prescription Opioid Abuse offers concrete recommendations for when you should consider co-prescribing naloxone to your patients.
4. We should get training to provide medication-assisted treatment (MAT) for substance use disorders.
5. We need to speak out against stigma and stand up for what we know is right. Patients in pain deserve care and compassion, not judgment.

-Trevor Tsay

9-Year-Old Wisconsin Boy Dies After Having Tonsils Removed - <http://www.nbcnewyork.com/news/national-international/Milwaukee-Wisconsin-Boy-Child-Dies-Tonsillectomy-Oxycodone-368953781.html>

A call to action: Physicians must turn the tide of the opioid epidemic - http://www.ama-assn.org/ama/ama-wire/post/call-action-physicians-must-turn-tide-of-opioid-epidemic?utm_source=Lyris&utm_medium=email&utm_term=021716&utm_content=opioids&utm_campaign=marketing_campaign-wire_alert

Southern California doctor sentenced in overdose deaths of 3 patients- <http://www.cnn.com/2016/02/05/health/california-overdose-doctor-murder-sentencing/>