Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org March/April 2015

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Implications for the Modern Clinician



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Missouri Medicine

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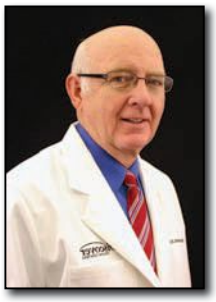
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"Is it possible for the mind to transcend the physical boundaries of the brain? The cumulative experimental database strongly indicates that it can. It is not clear that this implies the mind is separate from the brain but it does suggest that a comprehensive explanation for NDEs will require revisions to present scientific assumptions about the brain-mind relationship."

-Dean Radin, PhD

WITH THIS ISSUE *Missouri Medicine* is concluding the most comprehensive, in-depth presentation and examination of near-death experiences (NDE) in the world's literature. The contributing authors are world famous and range from Raymond Moody, MD, who in 1975 introduced the new term 'near-death experience' for an event known for millennia to Eben Alexander III, MD, whose own NDE is arguably the most familiar in the world to the general public.



John C. Hagan, III, MD, FACS, is a Kansas City ophthalmologist and *Missouri Medicine* Editor since 2000. He is a multi-year Super Diamond Contributor to MMPAC.
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My own interest in NDE began several years ago when at a party I asked a friend and college fraternity brother what he was reading. "Evidence of the Afterlife: The Science of Near-Death Experiences by Dr. Jeffrey Long," he said, "You should read it when I'm done. It's very thought provoking. I think they are for real." After reading more than a dozen books on the subject, I concluded a multi-article scientific review of NDE by physicians and other scientists would be a tremendous precedent-setting achievement for *Missouri Medicine*. Of course questions and contemplation of death, the mystery of the terminal process of dying and fear/faith/fatalism about the nature or existence of an after-life are hard-wired in our DNA since the beginning of sentience.

In September/October 2013, Raymond Moody, MD, PhD - the Father of NDE and the author of books that have sold over 20 million copies - described how historical records dating to ancient Greece contain descriptions congruous with the

modern concept of a NDE. Moody's book "Life After Life" (1975, HarperOne) presented an initial collection of over 150 contemporary NDEs. The NDE typically includes many of the following: the mind leaving the body and travelling upward; passing from dark to a brilliant light often within a tunnel. The light which is often interpreted to be God or the Supreme Being is ineffable and transmits joy, peace, love, comfort. They meet with deceased loved ones, friends, relatives that welcome them. They have a life review in which they understand the meaning of their life and how they have lived it and how it affected others. They never wish to leave this unity with the light source of love. They return to our mortal life they say reluctantly to help those needing them on earth or sometimes involuntarily because "your time has not yet come." Upon returning to their earthly body most live a more purposeful, love-filled life. Thereafter the fear of death is largely absent.

Bruce Greyson, MD, Professor at the University of Virginia School of Medicine and a Co-Founder of the International Association of Near-Death Studies (IANDS) in November/December 2013 reviewed postulated scientific explanations of NDE including: expectancy, birth memories, altered blood gasses, REM intrusion, toxic and/or metabolic hallucinations, neurochemistry and neuroanatomy phenomena without finding a definitive explanation for NDE. In addition to the positive aspects during and after a NDE he was the first to point out "distressing NDEs" which are disturbing, even terrifying to those that experience them. He also noted that most people that have NDEs are mentally healthy and that NDEs must not be confused or equated with depersonalization, dissociation, post-traumatic stress disorder or pathologic conditions such as Charles-Bonnet Syndrome.

Dean Radin, PhD, one of the foremost experts in using evidence and laboratory based science to study NDE, reported these conclusions in January/February 2014, "With one exception, NDEs may be interpreted as unusual forms of hallucinations associated with the injured or dying brain. The exception involves perceptions described from vantage points outside the body that are later confirmed to be correct and could not have been inferred. Over a century of laboratory studies have investigated whether it is possible in principle for the mind to transcend the physical boundaries of the brain. The cumulative experimental database strongly indicates that it can. It is not clear that this implies the mind is separate from the brain but it does suggest that a comprehensive explanation for NDEs will require revisions to present scientific assumptions about the brain-mind relationship."

Pim van Lommel, MD, an eminent Dutch cardiologist has conducted prospective studies on patients having cardiac arrests during hospitalizations. In 18% of 344 successfully resuscitated patients they report typical NDEs. He also reports four other similarly designed prospective studies that found between 10 and 20% of 562 patients report NDEs. Greyson states over nine million people in the U.S. have reported NDEs. Van Lommel is the first in our series to raise the subject of nonlocal consciousness as a necessity to scientifically explain many of the

"My understanding of near-death experiences has made me a better doctor.

I face life with more courage and confidence. I believe near-death experiencers really do bring back a piece of the afterlife.

When they share their remarkable experiences, I believe a piece of the afterlife, in some mysterious way, becomes available to us all."

-Jeffrey Long, MD, Radiation Oncologist & Founder NDEF

"A central tenet of neuroscience holds that all human experience arises from the brain, akin to the Germ Theory of Disease and the Theory of Evolution in other branches of science. So far, the narratives of NDE fit securely within the framework of conventional neuroscience. "

-Kevin Nelson, MD Professor of Neurology, University of Kentucky

presently puzzling phenomena of NDE. Non-local consciousness is thought-provoking and the subject of his book "Consciousness Beyond Life." (2001, HarperOne).

Jean Hausheer, MD, is a widely respected ophthalmologist who previously taught at University of Missouri - Kansas City and now is Clinical Professor at the University of Oklahoma School of Medicine. In May/June 2014 she describes for the first time her own NDE at Independence Regional Hospital. In July/August 2014 Tony Cicoria, MD, Assistant Professor SUNY Upstate School of Medicine, wrote about his much publicized NDE that occurred in 1994 when he was struck by lightning. Post-NDE he had an obsession with learning to play the piano and write original music. He succeeded in both. View the video at https://www.youtube.com/watch?v=tDtYkxSCV18. Both physicians describe their NDE as a positive, life-changing event that is enriching their lives, re-affirming their belief in God and that removed any fear of death.

Jeffrey Long, MD, a Louisiana radiation oncologist, established the nonprofit Near Death Experience Research Foundation for collection, international reporting, and study from NDE people worldwide. Please visit their website www.nderf.org to understand how universal and cross-cultural the NDE experience is. In the September/October 2014 issue Long elaborates on nine lines of evidence that converge on the explanation that NDE cannot be scientifically explained at this time. Among the most impressive of these nine are factual reports of events that have occurred in the past, or did happen in the future, or that transpired during the person's NDE that were physically remote and otherwise unknowable by the person. Other unaccountable events: totally blind individuals describing accurately vivid visual events during their resuscitation and also precise accounts from individuals that were having hypothermic surgery in which they had no pulse, no heart activity, no blood pressure and a flat EEG. Ninety-six percent of NDE reporting patients to NDERF, many highly educated and scientifically trained, call their experience "definitely real."

Nancy Evans Bush, MA, Previous President of IANDS and Bruce Greyson, MD, Director of the Division of Perceptual Studies University of Virginia, in November/December 2014 skillfully present the little discussed "distressing near-death experience (DNDE)." Their review of over 30 years of NDE

Questions and contemplation of death, the mystery of the terminal process of dying and fear/faith/fatalism about the nature or existence of an after-life are hard-wired in our DNA since the beginning of sentience.

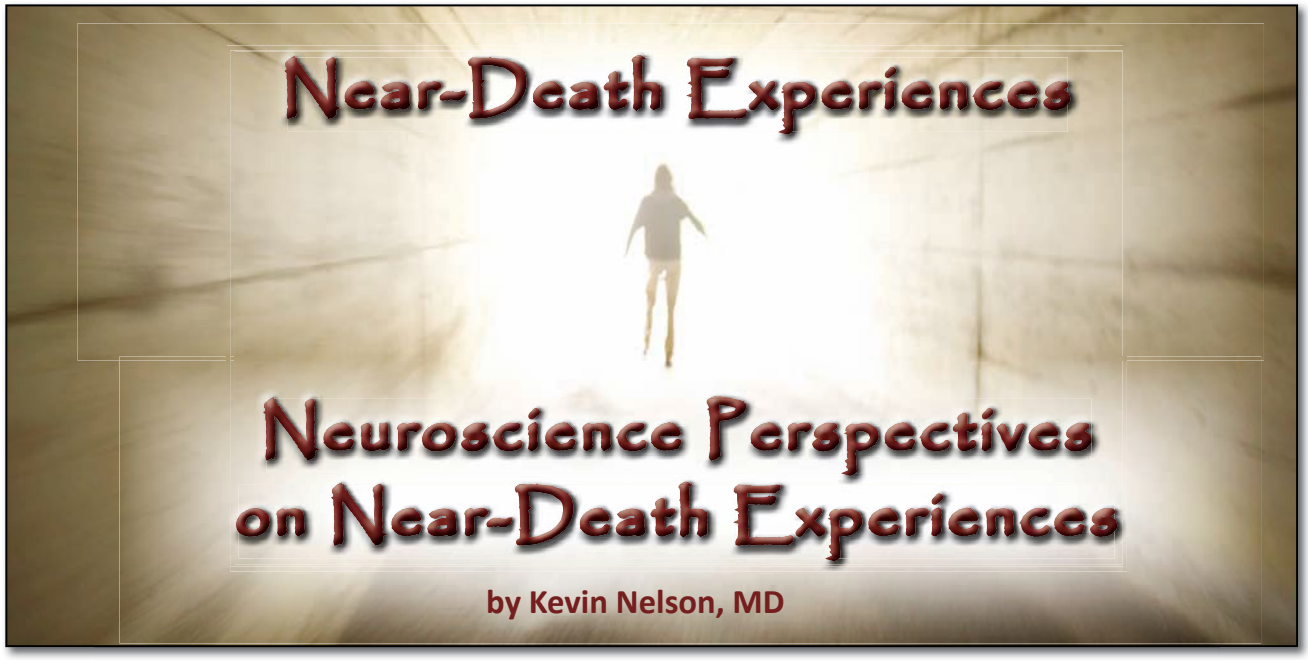
literature concludes that DNDE may occur as often as one in five cases and that there are both external and internal barriers to reporting them that make them under-reported. The DNDE has negative connotations to hallmark events of the positive NDE. The context of the DNDE is a "void" with feelings of aloneness, isolation, emptiness, even a sense of annihilation. Lastly the 'heavenly and redemption' theme of most NDEs is replaced by a 'hellish and damnation' experience. Much time and effort is required by these individuals to work through the debilitation and negative residua of the DNDE. Three mechanisms often employed include: "I needed that" in which the individual seeks to make amends in their life and become a better person. Movement to a dogmatic religious group is common. A second methodology is reductionism in which the DNDE is explained away or repudiated as a hallucination or adverse drug reaction. A third group struggle for years trying to comprehend why the DNDE happened to them and why they cannot shake off its negative aftereffects. They often commit to long-term psychotherapy which is usually ineffective. Neither NDE nor DNDE are pre-conditioned by the conduct of an individual's life - a saintly person may still have a DNDE while felons and misanthropes may experience pleasant, redemption-giving NDEs.



Eben Alexander, III, MD, former Harvard neurosurgeon, is the best-selling author of "Proof of Heaven: A Neurosurgeons Journal into the Afterlife" (2012) and a comprehensive sequel "The Map of Heaven: How Science, Religion and Ordinary People are Proving the Afterlife." (2014, Simon & Schuster both) In the January/February 2015 issue he recounts his own miraculous full recovery from a virtually always fatal case of *E. Coli* meningo-encephalitis and the complex NDE he experienced while in a septic coma. Drs. Radin, Van Lommel, Alexander, and pioneering neurosurgeon Wilder Penfield, MD, all deny that the complexity of the brain can account for the existence of consciousness. Alexander writes, "The truth is that the more we come to understand the physical workings of the brain, the more we realize it does not create consciousness at all. We are conscious in spite of our brain! The brain serves more as a reducing valve or filter, limiting pre-existing consciousness down to the trickle of the illusory 'here-now' in which we find ourselves in this physical realm." He continues, "The NDE community, as well as related spiritually-transformative experiences of all stripes, provides compelling evidence that consciousness is fundamental in the universe."

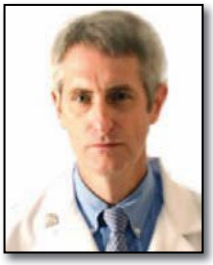
In this March/April 2015 issue Kevin Nelson, MD, Professor of Neurology, University of Kentucky School of Medicine and author of several books including "The Spiritual Doorway in the Brain" (Plume, 2012), provides what he feels is a 'brain-based' explanation for near-death experiences emphasizing rapid eye movement intrusion and altered neuro-physiology. Whether you believe in some, all or none of the interpretations and explanations of NDE offered by previous NDE authors as physicians believing in the scientific method it is mandatory to read Nelson's theory of their causation.

This NDE theme has been one of the most commented on series of articles in my 15 year tenure as Editor. During the recent White Coat Tort Reform Day in Jefferson City a physician sought me out and told me of his NDE (which I hope he will share in a Letter to the Editor). As I have become more knowledgeable and comfortable with NDE, I have asked patients that have had cardiac arrests or who were unconscious and almost died about what it was like. Several have described typical NDE without prompting. No question but some of our patients and a few of our colleagues experience what is currently called near-death experiences. It is a clinical syndrome you need to recognize and be able to appropriately respond to. **MM**



Dr. Nelson explores near-death experiences through the lens of science and discovers that near-death fits within the conventional neuroscience framework as securely as the Germ Theory of Disease and Evolution stand in other branches of science.

In our time, near-death experiences (NDE) dominates the discussion of spiritual experience. The drama of going through a tunnel, being enveloped by "the light," floating above one's body, and sometimes meeting deceased loved ones or spiritual beings constitutes a narrative thoroughly portrayed by the media. In the early 20th century, American physician, philosopher and psychologist William James makes little mention of NDE in his seminal work, *The Varieties of Religious Experience*. Yet, NDE fulfills his expectation of a spiritual experience whereby "feelings, acts and experiences" touch "whatever they may consider the divine."[1]



Kevin Nelson, MD, is Professor of Neurology at the University of Kentucky engaged in the clinical practice of neurophysiology for thirty years, as well as Director of Medical Affairs for nearly twenty. He is author of the book *The Spiritual Doorway in the Brain*.
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Today's early 21st century view of these NDE starts by first training our gaze on near-death's many overlooked scientific truths; some facts deliberately ignored and others simply neglected. So far, inundating the public with near-death topics has most served to reinforce media stereotypes rather than rooting out mistaken ideas.

'Near-Death' Is Often a Misnomer

For half of the instances of "near-death" the term is a misnomer because the person does not face imminent death. An excellent but seldom cited study examined the medical records of 58 people who experience near-death.[2] Twenty-eight of those had a true medical crisis, while the other 30 were not medically endangered at the time. Surprisingly, the results showed almost identical experiences in both groups. Regardless of danger, people went through a tunnel, and had similar thoughts and emotions. Sixty-eight percent of all subjects had an out-of-body experience (OBE) whether they were medically near-death or not. The only physiologically interesting difference between their experiences intriguingly focused on "enhanced light" appearing to those truly endangered.These findings resonate with what else we know about the origins of near-death. Many things can cause near-death including fear alone.[3, 4]

Cardiac arrest stands among the most sensational triggers for near-death, occurring in approximately 10 percent of survivors that recover with sufficient memory to recall the experience in some form.[5-7] (See Figure 1.) Although this scenario features prominently in the public mind, it is not likely to top the list of causes for NDE. We have yet to see a well-designed study in the general population, however, in a self-selected series of 55 subjects, syncope edged out cardiac events (10 versus 8).[8]

The role of syncope is crucial in NDE. Syncope alone in the safely controlled environs of the neurophysiology laboratory produces features indistinguishable from NDE.[9,10] This includes out-of-body experiences about ten percent of the time. Upwards of one-third of people faint within their lifetime, often while feeling endangered, making syncope fertile ground for a spiritual experience. This may also explain why it was said that upwards of 18 million Americans may have had a near-death experience by a 1997 issue of *U.S. News & World Report*.

Out-of-Body Experience

Out-of-body experience (OBE), often a feature of near-death, is also an astoundingly frequent and normal experience separate from NDE. In a survey of over 13,000 individuals in the general population, 5.8 percent reported at least one OBE.[11] It is sobering to look upon a large crowd knowing that one in twenty have had an out-of-body experience. And like near-death, many physiologic factors lead to OBE. The common experience of syncope helps us understand the high incidence of OBE, but another physiologic state, a normal one, surely contributes as we shall soon see.

OBE accompanies near-death experience 76 percent of the time.[12] Do OBE experiences always embody the qualities of spiritual experience? No! I have many subjects who regard their out-of-body experiences as a curiosity. One night drifting off to sleep, my psychiatric colleague floated a few feet above her bed and turned to see herself and husband beneath the quilt she crafted as a newlywed. She considered the intoxicating illusion "odd" but not profound. Many who have experienced OBE agree with the philosopher Descartes, not in his division of mind and brain, but when he said: "Whatever I have up till now accepted as most true I have acquired either from the senses or through the senses. But from time to time I have found that the senses deceive, and it is prudent never to trust completely those who have deceived us even once."[13] The OBE illusion is one of these sensory deceptions, and arises in the brain's temporoparietal region. Directly stimulating the temporoparietal cortex with a small electrical current evokes OBE,[14, 15] arguably by disturbing the integration of visual, proprioceptive and motion senses into the coherent self. In the laboratory or operating room, the neurophysiologist can bring a patient in and out-of-body, back and forth with the flip of a switch. (See Figure 2.)

Figure 1

Cardiac arrest stands among the most sensational triggers for near-death experiences, occurring in approximately 10 percent of survivors that recover with sufficient memory to recall the details in some form.



As important as NDE has now become, another variety of spiritual experience reigns supreme by the fact that it is always and exclusively spiritual, and consequently the most historically influential variety serving as the "root and center" for organized religions of nearly every sort. James identified this experience as the 'mystical sense of Oneness.' Some of the many words use to describe the mystical Oneness include: boundless, ceaseless, bottomless, nothingness, fathomless, infinite, empty void, barren, abyss, abysmal, and absolute.

The philosopher W.T. Stace elaborated on the mystical nature brought out by James, noting that the core feeling of Oneness could be expressed in two forms.[16] The extrovertive mystical experience looks outward to the world through the physical senses and finds unity. On the other hand, the introvertive mystical experience turns inward, shuttering out the senses and transcending into a "pure" consciousness.

Both James and Stace believed the core nature of mystical experience was universal to humans. NDE also appears universal but the narratives vary widely between persons and cultures, and are not always viewed in a spiritual perspective. Little thought has tied NDE and mystical Oneness together until recently. A sizable

42 percent of near-death experience subjects feel "united, one with the world."[8] Although not as thorough a measure as other tools provide,[17] this finding suggests that mystical Oneness may play an unsuspected role in making NDE spiritual. This is important because much of the neuroscience behind mystical Oneness experience is understood.

Figure 2

Directly stimulating the temporoparietal cortex with a small electrical current evokes out-of-body experience. In the laboratory the neurophysiologist can bring a patient in and out-of-body, back and forth with the flip of a switch. In young healthy adults, out-of-body experience accompanies the sleep paralysis of REM intruding into waking consciousness.



Mystical Feelings of Oneness

Mystical feelings of Oneness are expressed through a special quality of serotonin neurochemistry, specifically the serotonin-2a receptors. Much like a molecular scalpel, if serotonin-2a is pharmacologically blocked or parts of the limbic system containing serotonin-2a surgically removed, then the mystical expression is blocked too.

In retrospect the connection between NDE and the mystical Oneness should not come as a shock since fear, the primal emotion of the limbic system and survival, often accompanies mystical experience. Which brings up another point. When exploring brain function during spiritually transforming experience it is not just the fervor over the drama of near-death that blinds some to the importance of the brain. The grandeur of the brain's accomplishments leads many to overlook the brain's prime biologic and evolutionary purpose lying at the heart of many spiritual experiences. First, last and foremost the brain needs to keep itself alive through the crisis of near-death.

One extensively studied physiological crisis concerns cerebral blood flow. Crucial to its prime purpose, the brain governs its blood flow each second of life. Brain activity relies upon aerobic metabolism that demands a constant supply of oxygen and glucose at rest, in exercise, and during physiological and emotional stress. Controlling cerebral blood flow depends principally upon the arterial baroreflex that in turn pivots on the yoked opposition of cholinergic and adrenergic neurons in the peripheral and central nervous systems. Fading cerebral blood flow with looming unconsciousness, often the proximate circumstance leading to NDE, signals a crisis to the brain that then orchestrates a cascade of survival responses, including the familiar fight-or-flight guiding our ancestors survival for millions of years. In the initial seconds of failing cerebral blood flow and dimming consciousness, there is no reason to expect the brain reacts differently between uncomplicated syncope and cardiac dysrhythmia.

When the brain becomes ischemic, many times the border between consciousness and unconsciousness is indistinct, and between these two borders exists a borderland of consciousness then entered. Consciousness is lost if blood flow drops below a threshold, and consciousness can come and go if cerebral blood flow rises and falls across this threshold, which routinely happens in clinical settings. It remains a scantly appreciated observation that the eyes remain open at syncope's onset[18] and beyond. So as consciousness waxes and wanes, a person may be far more aware of surrounding events than appreciated by others tending to medical urgencies. And those stricken may later recall the episode in startling detail. Simply because one does not respond while in shock or peri-syncopal does not mean the person is unconscious or dead (for example see the case of Ms. Martin[19]). Adding to this caution, evidence suggests that the brain electrical activity may persist even during deep coma and apparent isoelectric electroencephalogram.[20]

Although a misnomer a good part of the time, in one way the term "near-death experiences" aptly describes these experiences. They are not "return-from-death" experiences. Regrettably, some investigators use the term "clinical death" to "signify a period of unconsciousness caused by insufficient brain blood supply because of inadequate circulation, breathing, or both."[5] By this definition even harmless syncope is "clinical death" and we have already seen how this ambiguity can seriously mislead the unwary. Linking NDE to "clinical death" erroneously implies NDE happen when the brain has died and the neurons lysed, a hallmark of neurologic brain death. Confusing cardiac dysrhythmia and "clinical death" has gone to extremes, leading one author to claim that these experiences are direct scientific evidence for "consciousness beyond life."[21]

Table 1
Near-Death Features and Neuroscience Considerations Summarized

Near-Death Feature	Neuroscience Considerations
Tunnel	Retinal ischemia (common with systemic hypotension)
Light	Robust link with visual system (e.g. REM)
Appearing Dead	Atonia while alert
Out-of-Body	Temporoparietal association
Life Review	Activating memory in the face of danger
Bliss	Dopamine reward system
Narrative Quality	Left hemisphere, limbic and other brain regions
Paranormal Impressions	Limbic system
Mystical Oneness	Serotonergic-2a receptors and limbic system

One near-death experience has commanded so much media attention that it deserves some of ours; that of Eben Alexander, III, MD, a neurosurgeon versed in neuroscience principles. [Editor's note: See *Missouri Medicine* January/February 2015;112:17-21.] In the midst of severe delirium from *E. coli* meningitis he describes a fantastic NDE sojourn. Later believing his brain had completely ceased functioning during his NDE, he titled his book, *Proof of Heaven*.[22] However, a simple question seemingly dismisses his contention: When in his delirium did the NDE arise? Since he provides no answer to that question, I believe there is no scientific basis to his assertion that his experience happened with his brain completely shut down.

Dr. Alexander's delirious memories do demonstrate one thing. The influence of near-death experience can be powerful enough to conflate faith and science even in the mind of a neurosurgeon. They also show Descartes is once again correct, that our senses and the mental images derived from them can fool us about what we think we know.

The claims of Alexander, characterized by the eminent neurologist Oliver Sacks as anti-science, clash[23] with the sage words of a brilliant Canadian neurosurgeon from the mid 20th century. Wilder Penfield dedicated his career to electrically stimulating the brain and his observations unveiled important new insights into the mysteries of mind and brain. He concluded that as scientists "we can only set out the data about the brain, and present the physiological hypotheses that are relevant to what the mind does." But as a human, he believed that "it is not unreasonable for him to *hope* (italics added) that after death the mind may waken to another source of energy."[24] Hope springs from faith, and there is room in the brain for faith.

A central tenet of neuroscience holds that all human experience arises from the brain,[25] akin to the Germ Theory of Disease and the Theory of Evolution in other branches of science. So far, the narratives of NDE fit securely within the framework of conventional neuroscience. Sometimes I hear that neuroscience fails to explain a part of someone's recollection of their NDE; after allowing for selective, suggestible, reconstructed and imperfect memory as well as the difficulty of knowing when in the crisis an experience occurred, nothing about NDE, including OBE, offers objective evidence that consciousness can exist without a living brain. Extraordinary claims require extraordinary evidence and here not even the most ordinary objective data supports the bold assertion of human consciousness outside the brain. When more facts become known in "unexplained" cases, a plausible neuroscience explanation has always been found. Belief in consciousness beyond the brain lies in the realm of faith beyond science. Faith has its place separate from science, in part because science has its limits imposed by the requirements of verification and reproducibility. Still, keep in mind that although not every scientific fact has been uncovered about black holes that still does not make black holes a supernatural force.

Alexander's book and others like *Heaven is Real* fall into a slick and clever literary genre works taking the interpretation of near-death experiences as absolute and literal truth.[26] The literalist's success in the marketplace fails to substitute for evidence challenging the foundation of neuroscience.

Although science looks askance at the literalist take on NDE, they do raise a valid question. Do near-death experiences provide a glimpse of "The undiscover'd country, from whose bourn no traveller returns?" (Hamlet, act 3, scene 1). Of course we have no way of

scientifically verifying if those having a NDE were on road, off road, made it part way, or almost all the way to that undiscover'd country (absolute death). The distance, direction and destination of absolute death will never be proven scientifically.

Certainly if one posits the brain unnecessary for the sublime near-death experience, one can gloss over the arcane details of brain anatomy, chemistry, and physiology necessary to understand the brain's role. At the same time, for good reasons not everyone wants to know how the brain functions in spiritual experience. In an example from a different physiologic venue, I personally give little thought to my pancreatic juices as I dine on an excellent meal. My sister-in-law made clear to me why knowing how the brain works may not matter for a more important reason. Her father sustained a series of heart attacks and during one he left his body and calmly moved toward a warm glowing light. Afterwards he lost his fear of death and gained a new purpose in life, giving witness to the real, positive value of some NDEs. "I don't care what the brain is doing" she said, "I'm just happy with the comfort it gave dad."

But something deeper, something driving the neurologist within has set me on the quest for understanding NDE. Split-brain studies from the 1970s unveiled the left cerebral hemisphere as the curious side, the one dominant for speech and symbolic understanding that also compels us to seek explanations for our experiences. There have been a host of offerings on what takes place in the brain during NDE. Most flounder because of their simplicity by failing to recognize that the diversely rich experience of near-death surely draws upon more than a single physiological or biochemical system, or anatomical structure. (See Table 1.)

Any neuroscience basis for NDE must not only explain NDE features but provide a testable hypothesis and one that explains the relationship with syncope and the multitude of other triggers.

Many other factors must also be taken into account, factors which have received only the slightest attention. Since consciousness is central in many near-death experiences, explanations must address mechanisms regulating consciousness. In crisis, survival demands an awake and attentive brain to meet the threat head on. This expectation seems so intuitively obvious that it typically escapes scrutiny. However, to survive the brain cannot take for granted being in the right conscious state at the right time. In waking consciousness attention suddenly orients to whatever survival requires. Therefore, consciousness and its altered states are bound to fight-or-flight action coordinated by the brainstem arousal and limbic systems. Essential to an effective survival response is the arousal system's locus coeruleus, the brain's nearly exclusive source of norepinephrine. The locus coeruleus is a minuscule cluster of pontine neurons key to regulating consciousness as well as survival behavior. This nucleus sends adrenergic neural projections throughout most of the entire brain.

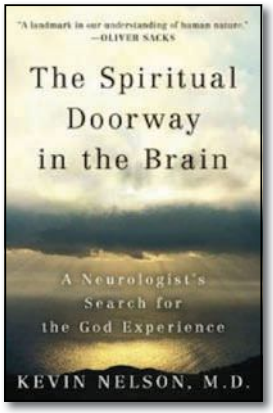
Rapid Eye Movement Consciousness and NDE

The strongest case for the neurophysiologic contribution to NDE can be made for a borderland of consciousness. A borderland when the conscious states of waking and rapid eye movement (REM) blend, forming a hybrid conscious state. REM consciousness is named for the saccadic eye movements that accompany the robust visual system activation characterizing this conscious state. Cortical activation similar to wakefulness and the atonia of non-respiratory muscles also distinguish the REM state. The most complex dreaming takes place during REM sleep in cortical regions far removed from the pontine brainstem switch triggering REM. Importantly, these different elements of REM consciousness commonly fragment, and can individually intrude into the waking state. Most often the REM intrusion occurs in the transitions between REM and waking, happening in up to a quarter of people at least once in their life.[8] The blending of REM and waking consciousness takes the form of complex visual and auditory hallucinations, dream narratives, as well as

Table 2
Summary of Evidence that REM Consciousness Contributes to Near-Death*

- Those with a near-death experience are strongly predisposed to life-long REM intrusion
- Arousal electroencephalogram recorded after cardiac arrest
- REM switch components linked to survival behavior that includes during systemic hypotension
- Many clinical conditions provoke REM intrusion into waking consciousness
- REM switch is part of the brainstem instrumental to the cardiovascular response to crisis (e.g. syncope/cardiac event)
- Vagal nerve electrical stimulation briskly provokes REM intrusion
- REM consciousness in situational context leads to many near-death features (e.g. out-of-body, paralysis, visual hallucinations, narrative, paralysis)

**A fuller discussion is found elsewhere [27,28]*



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The Spiritual Doorway in the Brain: A Neurologist's Search for the God Experience

BOOK REVIEW

by Kevin Nelson, MD

"Kevin Nelson has made a lifelong study, from a neurological viewpoint, of the remarkable phenomena of near-death and out-of-body experiences. Combining patient accounts and the latest neuroscience, he shows that what was once regarded as a purely spiritual or religious experience is rooted in biologic processes. In no sense does he diminish the remarkableness of these experiences, or the spiritual impactthey may have-but he gives us a sense of how evolutionarily based mechanisms in the brain can serve the highest religious functions. This book is an eloquent and compassionate landmark in our understanding of human nature."

-Oliver Sacks, M.D., author of The Man who Mistook His Wife for a Hat

the atonia of sleep paralysis or cataplexy. This borderland is unstable, lasting seconds or minutes before reverting to a more stable conscious state.

The REM intrusion hypothesis of near-death was first investigated by discovering that those with a near-death experience have a 2.8 times greater incidence of lifetime REM intrusion than age and gender matched controls.[8] Near-death subjects possess a pontine REM switch so astoundingly predisposed to REM intrusion that the incidence of sleep paralysis does not differ between near-death and the sleep disorder of narcolepsy. Furthermore, for those who have been near death, REM intrusion happened with the same frequency before as after their near-death experience, telling us that near-death is but a single episode in a lifetime of REM intrusion.

To understand how conscious states interplay during a crisis like near-death, it is necessary to understand how the brainstem regulates consciousness and how the REM switch reacts in crisis to blend waking and REM consciousness bringing about effective survival behaviors. These details are beyond the scope of this review and chronicled more fully elsewhere.[27, 28] Table 2 summarizes the evidence that REM intrusion contributes to the near-death experience.

Another frequently overlooked fact is the long established relationship between out-of-body and REM consciousness. Narcolepsy is a boundary of consciousness disorder whereby the afflicted suffer from REM frequently intruding into waking consciousness. Narcoleptics are very prone to out-of-body experience,[27, 29, 30] especially during sleep paralysis. The frequency of out-of-body wanes as the narcolepsy is treated. Out-of-body also appears in lucid dreams[31] – a special expression of dreaming wherein the dreamer maintains insight while dreaming. In young healthy adults, OBE accompanies the sleep paralysis of REM intruding into waking consciousness.[32] (See Table 2.) The selective temporoparietal activity that normally takes place during REM[33] neatly explains the strong link between REM consciousness and OBE. REM intrusion further explains the gripping feature of out-of-body often central to the NDE narrative and common in syncope. Further evidence of the bond between REM consciousness and NDE comes from the observation that persons with a near-death experience are as likely to have OBE transitioning between waking and REM consciousness as they are to have it during NDE itself.[12] Their OBE often accompanies sleep paralysis.

Is REM intrusion the last word in NDE? Of course not! However, a notion sometimes expressed by those unfamiliar with the physiology of REM consciousness contends that near-death experiences do not engage REM mechanisms because NDE "doesn't feel like a dream." This assertion seems straightforward on the surface. After all, the memory of many near-death experiences feels "realer than real" is at striking odds with the oftentimes outlandish, unreal and faint impressions left by dreams upon awakening. Somehow this contention dismisses a crucial physiologic fact. Actually, we should expect different experiences from the same REM mechanism expressed under the very different conditions of routine sleep and NDE. Context means much to experience. For example, temporoparietal brain stimulation in the laboratory evokes an OBE unlike an OBE while piloting a fighter jet. So, too, the crisis of NDE brings its own context to influence an experience based upon the same brain physiologic mechanisms as REM sleep. One of my subjects, a severe narcoleptic with near daily REM intrusion, commonly has out-of-body experiences and nightly visions that feel every bit as real to him in the

night as they do in the morning. Only through repeated occurrence does the true nature of REM intrusion reveal itself to him. He possesses no motivation, psychological or otherwise, to consider his illusions and hallucinations real. So the notion that NDEs are unrelated to REM because they do not feel like dreams carries little neuroscience weight. As a reminder, the feelings of deja vu cause by mesotemporal seizures leave an intensely real but false impression both during the seizure and afterwards.

In spite of the differences between near-death and dream narratives, near-death can be almost identical to lucid dreams, whereby the dreamer retains self-insight. This normal manifestation of dreaming conceivably arises when dorsolateral prefrontal cortical activity, instrumental to logical executive cognition and normally shut down during REM, persists during REM consciousness. Why some experiences seem real and others do not endures as a compelling question that applies to more experiences than just near-death. Persisting dorsolateral prefrontal brain activity while REM blends with wakefulness in a moment when impaired cerebral metabolism struggles to sustain consciousness, may deeply touch someone's impression of reality.

What Can We Conclude About Near-Death Experiences?

Clinicians must welcome near-death accounts with non-judgmental reassurance, providing safe harbor for patients with experiences that often bring overwhelming passions and memories. Medical professionals who tout spiritual shortcuts by forsaking science seriously risk debasing near-death experiences in the minds of many who hold science in esteem. We must not allow unsubstantiated literalists claims playing upon popular sentiments too tarnish the sincere near-death narrative.

In the end, the neuroscience of how the brain participates in near-death experiences does not demean their why or spiritual interpretation; these lie in the province of personal faith. Clinicians have an ethical responsibility to clearly differentiate the domains of science and faith. And with respect to the power of near-death experiences to steadfastly transform personal meaning and spirituality, I urge heeding the advice of James when he drew upon biblical inspiration to counsel on spiritual experience: "by their fruits ye shall know them, not by their roots."[1]

References

1. James W. The Varieties of Religious Experience: Longmans, Green, and Co., 1902.
2. Owens JE, Cook EW, Stevenson I. Features of "near-death experience" in relation to whether or not patients were near death. Lancet 1990;336:1175-1177.
3. Dostoyevsky F, Garnett C. The Idiot. New York: Dell, 1959.
4.Frank J. Dostoevsky, the years of ordeal, 1850-1859. Princeton, N.J.: Princeton University Press, 1983.
5. van Lommel P, van Wees R, Meyers V, Elfferich I. Near-death experience in survivors of cardiac arrest: a prospective study in the Netherlands. Lancet 2001;358:2039-2045.
6. Parnia S, Waller DG, Yeates R, Fenwick P. A qualitative and quantitative study of the incidence, features and aetiology of near death experiences in cardiac arrest survivors. Resuscitation 2001;48:149-156.
7. Greyson B. Incidence and correlates of near-death experiences in a cardiac care unit. Gen Hosp Psychiatry 2003;25:269-276.
8. Nelson KR, Mattingly M, Lee SA, Schmitt FA. Does the arousal system contribute to near death experience? Neurology 2006;66:1003-1009.
9. Lempert T, Bauer M, Schmidt D. Syncope and near-death experience. Lancet 1994;344:829-830.
10. Lempert T, Bauer M, Schmidt D. Syncope: a videometric analysis of 56 episodes of transient cerebral hypoxia. AnnNeurol 1994;36:233-237.
11. Ohayon MM. Prevalence of hallucinations and their pathological associations in the general population. Psychiatry Res 2000;97:153-164.
12. Nelson KR, Mattingly M, Schmitt FA. Out-of-body experience and arousal. Neurology 2007;68:794-795.
13. Descartes R, Cottingham J, Williams BAO. Meditations on first philosophy : with selections from the Objections and replies, Rev. ed. New York: Cambridge University Press, 1996.
14. Blanke O, Ortigue S, Landis T, Seeck M. Stimulating illusory own-body perceptions. Nature 2002;419:269-270.
15. Blanke O, Landis T, Spinelli L, Seeck M. Out-of-body experience and autoscopy of neurological origin. Brain 2004;127:243-258.
16. Stace WT. Mysticism and philosophy. London: Macmillan, 1960.
17. Hood RW, Ghorbani N, Watson PJ, et al. Dimensions of the Mysticsm Scale: Confirming the Three-Factor Structure in the United States and Iran. Journal for the Scientific Study of Religion 2001;40:691-705.
18. Lempert T, von Brevern M. The eye movements of syncope. Neurology 1996;46:1086-1088.
19. Moody R. Life after life. Covington, GA: Mockingbird Books, 1975.
20. Kroeger D, Florea B, Amzica F. Human brain activity patterns beyond the isoelectric line of extreme deep coma. PLoS ONE 2013;8:e75257.
21. van Lommel P. Consciousness beyond life : the science of the near-death experience, 1st ed. New York: HarperOne, 2010.
22. Alexander E. Proof of heaven : a neurosurgeon's journey into the afterlife, First Simon & Schuster hardcover edition. ed2012.
23. Sacks OW. Seeing God in the Third Millennium. The Atlantic 2012 12/12/12.
24. Penfield W. The mystery of the mind : a critical study of consciousness and the human brain. Princeton, N.J.: Princeton University Press, 1975.
25. Kandel ER. A new intellectual framework for psychiatry. AmJPsychiatry 1998;155:457-469.
26. Gottlieb R. Back from Heaven-The Science. The New York Review of Books 2014 11/6/2014.
27. Nelson KR. The Spiritual Doorway in the Brain: A Neurologist's Search for the God Experience. New York, NY: Penguin Group, 2011.
28. Nelson KR. Near-death experience: arising from the borderlands of consciousness in crisis. Annals of the New York Academy of Sciences 2014;1330:111-119.
29. Mahowald MW, Schenck CH. Dissociated states of wakefulness and sleep. Neurology 1992;42:44-51.
30. Overeem S, Mignot E, van Dijk JG, Lammers GJ. Narcolepsy: clinical features, new pathophysiologic insights, and future perspectives. J Clin Neurophysiol 2001;18:78-105.
31. LaBerge S, Levitan L, Brylowski A, Dement W. "Out-of-body" experiences occurring in REM sleep. Sleep Res 1988;17:115.
32. Cheyne JA, Girard TA. The body unbound: vestibular-motor hallucinations and out-of-body experiences. Cortex; a journal devoted to the study of the nervous system and behavior 2009;45:201-215.
33. Maquet P, Ruby P, Maudoux A, et al. Human cognition during REM sleep and the activity profile within frontal and parietal cortices: a reappraisal of functional neuroimaging data. Prog Brain Res 2005;150:219-227.

Disclosure

None reported.

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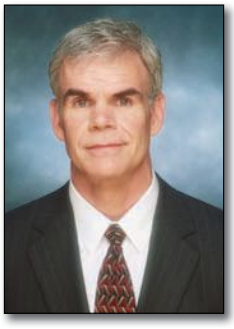
THE DOCTORS COMPANY

UNCOMPROMISING PROTECTION

Talk to Me

by Jeffrey G. Copeland, MD

Talk to me, and to colleagues, patients, officials and decision-makers of all stripes about all those things that matter to you. Tell your story. It will pay you back for your effort.



Jeffrey G. Copeland, MD, MSMA member since 1988, is a plastic surgeon in St. Charles, Missouri, and President of the MSMA.
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It is hard for me to believe that my year at the presidency of MSMA is almost over. I have come to understand that while the president has a significant role as the face of the Association, most of the workings occur in other locations and by other people (MSMA Staff, I am talking to you). One of the most important lessons I have learned is that communication between physicians, and communication between physicians and decision-makers is of highest priority. As a group we are, by tradition and through selection, highly educated and literate people. One cannot easily navigate medical training without that quality, but I believe it is easy for us to be ineffective in our communication for a wide variety of reasons, mostly not of our choosing.

Loss of Focus

My practice is plastic surgery, and as such I know that I am in a different situation than those who are delivering primary care to patients on a daily basis. I have tried to keep that understanding dead center as I go around representing MSMA to members and non-members alike. I think about that daily when I am spending 45 minutes or an hour talking with a patient about a procedure and occasionally just visiting. It is one of the joys of my practice that I can (or at least have convinced myself that I can) afford to spend that time for the sake of clear understanding and a high level of preparedness of my patients for various interventions that they may undergo.

I am certain that a primary care physician does not have that luxury. In the face of caring for a high volume of patients during a busy flu season or even during a less hectic day, it must be daunting to have to go from one room to another four or five times an hour and keep track of lab, orders, follow-up and think about compliance and risks. There is the ever-present love/hate relationship with the Electronic Health Record that puts up a wall between physician and patient. Much like the trite saying about men and women, we "can't live with them but can't live without them." Inherent in such a practice environment is the need for focus and attention to a million details. Not to mention the need to remain current and, recently, continuously "certified." It is easy to imagine that there would be a tendency to want some relaxation after a day like that. With that, there is the risk of losing focus on larger issues out of sheer fatigue. That risk is not unique to primary care; we all have different things we attend to and think about. But I know it is a high risk for many of us who carry a large patient population.

Challenges

While distractions and impediments to synthetic thinking abound, there is a matching plethora of challenges to practice that physicians face. The list is

familiar, but it is hard, if not impossible, to keep track of the status of all the issues in play at a given moment. At a recent AMA Advocacy conference, the main issues were SGR repeal and replacement with a well-reasoned and adequately-funded alternative and diminution of the regulatory burdens and potential penalties that are rapidly becoming real threats, specifically penalties for Meaningful Use non-compliance, Physicians Quality Reporting System (PQRS) requirements and the Value-Based Payment modifier, on top of the automatic 2% sequester. Then there is ICD-10 and the IPAB which, while it hasn't yet posed problems, has huge potential to do so.

These are all payment issues, but make a big difference in the solvency of a practice. Consciously or unconsciously, we prioritize our concerns. Physicians worry first about their ability to continue to practice. This drives many physicians to the decision to join a health care system and become employees so they can turn over the responsibilities of managing the business issues to a business entity. Along with that can come a sense that their employer will protect them from the complexity of modern medical practice. It is at least tempting to think that, but I would posit that the priorities of a health care system which seeks to survive and prosper, and physicians, employed or not, are not necessarily aligned.

Meanwhile, we have the "interesting" activities of the federal and state legislatures and the Supreme Court.

Every legislative season brings new twists on old themes and completely new initiatives to watch and manage. In Missouri, examples of current legislative issues include Tort Reform, Scope of Practice for Advanced Practice Nurses, Maintenance of Certification issues, and whether the Missouri State Board of Healing Arts and other state boards can give practical advice to applicants and licensees without going through a major formal rule promulgation process.

Recent examples of important court actions include the SCOTUS's decision about the dental board in North Carolina, which was told that they cannot regulate tooth whitening by non-dentists for anti-trust reasons because while their state had set up the board, it was populated with members of the marketplace (dentists, i.e., those trained in the delivery of dental care) who might have a financial interest in keeping non-dentists out of the marketplace, and the state was not "actively supervising" the regulatory activity. This is a specific situation, but it is of concern because of the potential breadth of application of this decision. Dissenting opinion held that the board was a designated state entity and thus was appropriate in its actions without an outside state supervision component. But that argument did not carry the day. It seems ironic that we have decisions like this, which threaten licensing boards' authority to determine who are appropriately trained individuals occurring simultaneously in an environment where there is an ever-increasing emphasis on protecting the public through such measures as "maintenance of certification."



Telling stories also makes us more memorable to other people (legislators, colleagues and patients alike) and, in my experience, increases my enjoyment of interacting with people.

There is another interesting pending case in the SCOTUS, *KBR v. United States of America Ex Relator Benjamin Carter* which would open the door for continued, non-time-limited suits and heavy fines against physicians for infractions committed at any time in the past related to provision of services under Medicare and other federal health care programs. One would essentially never be free from the threat of a suit or large fine. This case was heard in the Court in January. The decision is pending at the time of this writing.

Telling Stories

I have sought to have substantive conversations with as many physicians as possible in the places I have been privileged to go this year in my official capacity, including MSMA Council meetings, Missouri component medical societies, annual meetings of Iowa, Kentucky, Texas and Florida and AMA functions, including two general AMA meetings, a candidate training function and the National Advocacy Conference. That has given me a lot of opportunity. It has been possibly the best part of the job, because so many of us have great personal stories to pass on, patient experiences, new approaches to problems, and empathy with each other for circumstances that we all face together.

During the AMPAC Candidate Training session (note: I am not planning on running for anything) it became clear that telling a compelling story is critical to getting the attention of people in the position to make decisions. Politicians/legislators know this and seem to greatly enjoy real life examples that they can use to explain their decisions and give legislative actions a personal touch. I think it also provides them with a framework with which to consider otherwise nebulous ideas. This makes laws that are hard to understand a little less inscrutable and (maybe) easier to tolerate. Telling stories also makes us more memorable to other people (legislators, colleagues and patients alike) and, in my experience, increases my enjoyment of interacting with people.

As individuals and as groups, this storytelling is a skill, which physicians should cultivate. Some people have a gift for telling a story, excellent timing, the ability to read the audience and a sensitivity to how the telling is going. Some of that is natural, but some of it is a skill which we all can benefit from practicing.

We have true, great, interesting stories, which we derive from our routine activities with a tremendous source of human experience: our patient visits. Despite time pressures here, a little extra inquiry can yield big returns. We need to hone our collective ear to be sensitive to when these stories are of a character, which can explain our needs relative to patient care and the system in which we deliver that.

I believe that there is a significant place for this activity as we negotiate the complex regulatory and political world in which medicine as a profession now exists.

Other Applications

Another benefit to good storytelling is that we can use it clinically. Patients, like everyone else, sometimes understand things better if they have a memorable example to which they may refer, e.g., relating the positive experience of a previously obese patient who has been able to lose substantial weight provides real reinforcement and a sense of possibility to someone in a similar situation.

My plea then, is for us to put direct energy into our stories, to learn how to identify them from all possible sources and then to use their power to make a difference, to make the practice of medicine more reasonable, manageable and human.

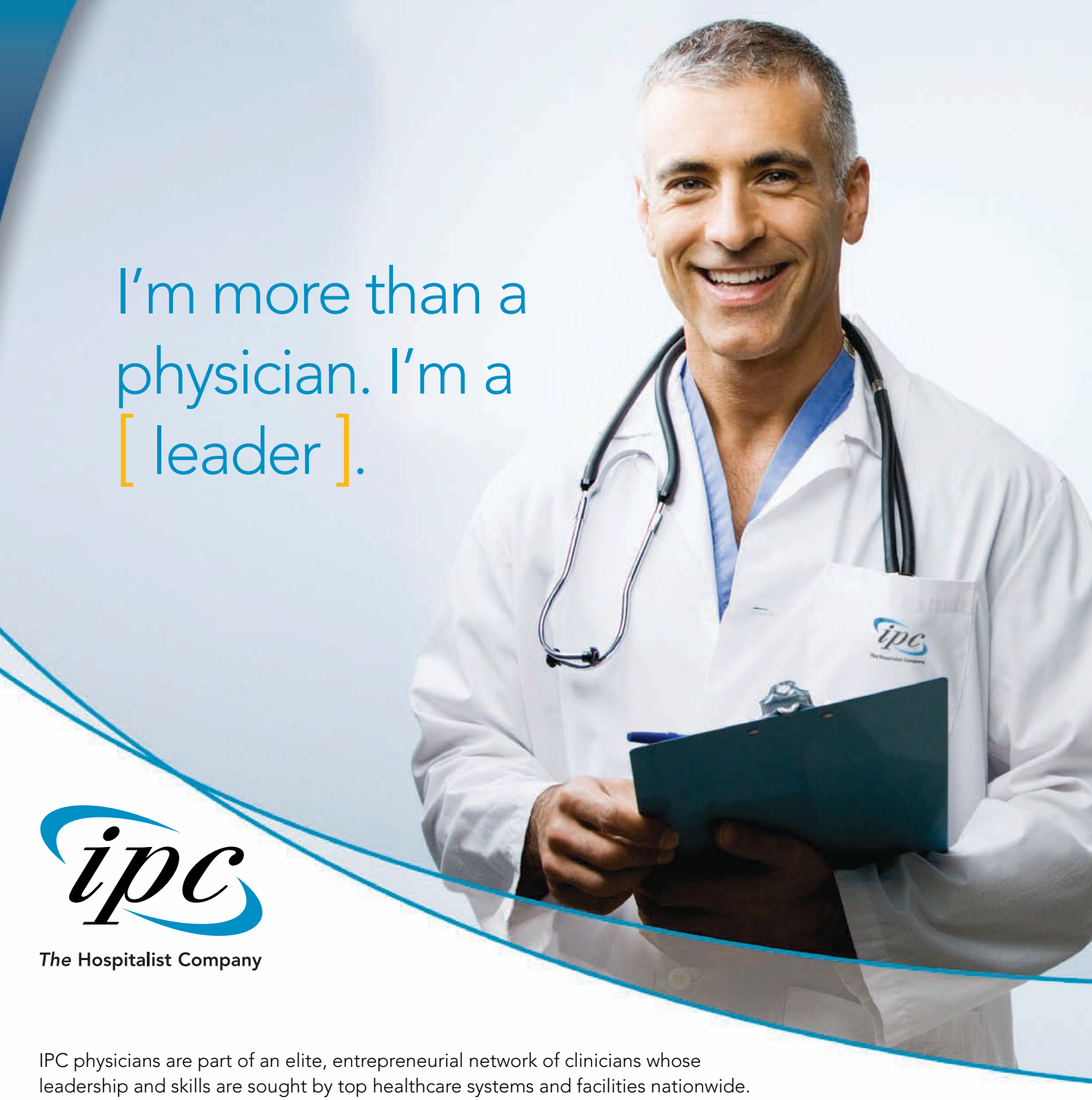
It has been an unexpected pleasure to write some thoughts in a regular column as the president of MSMA this year, and to talk to a lot of people. Please, talk to me, and to colleagues, patients, officials and decision makers of all stripes about all those things that matter to you. Tell your story. It will pay you back for your effort.

One Last Thing

It is impossible for me to count the number of times some expert has talked to participants at a meeting about "process improvement." I get the idea. For most of us, it is not easy to adopt that kind of thinking. Still, I like the idea. The trick is to spend some time regularly looking at the bigger picture. Changes that are occurring in our health care system as it moves from "volume" to "value" make it doubly important to stop and think about things like process and to do long-range planning.

Physicians who are successfully making that transition are not doing anything that is foreign to the prime directive of trying to deliver the best health care to their patients. They are just using a different approach and some different tools. This may be staffing to maintain contact with patients after office visits and hospital discharges to make sure they know what they need to do and that they are complying with plans and taking their medications. It may mean changes to information systems (please, please, please).

But if it isn't part of our routine to sit back and look at what we just did all day and how we could make it better, we really are missing some great opportunities to invent better things. **MM**



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The Measles Outbreak Coming Near You

by Haider Javed Warraich, MD

Parents who won't vaccinate their children are reviving once-dead diseases. Will a vaccine mandate be needed?

I was working on the hospital infectious-disease service when our team was asked to see a young girl with a mysterious illness that no one had been able to diagnose. She had come to the emergency room with a fever and runny nose and had a rash spreading across her body. She had developed a cough so harsh that "whooping cough" had been added to the long list of possible infirmities. But when the senior doctor on our team, Frank Berkowitz, an expert in pediatric infections—arrived at her room, he knew the diagnosis immediately: She had measles.*

Many developing countries continue to suffer from measles, an extremely contagious respiratory disease, but the U.S. in 2000 was declared "measles-free" by the Centers for Disease Control and Prevention. The news of a confirmed case set our hospital abuzz, and uniformed CDC officers soon swooped in.

How did the young girl get the disease? Her parents had refused to vaccinate her.

Hers is far from the only case. Measles is making a terrifying comeback in the U.S., with some 600 cases reported this year, more than in any year in the past two decades. There are two reasons: the ease of international travel, and an increasing number of people refusing vaccinations, usually on behalf of their children.

Because parents seeking exemptions tend to be geographically clustered, these communities can become outbreak hotbeds. For example, the exemption rate in Orchard Prairie in Washington state is 24%, five times higher than the state's median exemption rate and 13 times higher than the national average.

Forty-eight states offer nonmedical waivers for parents to exempt their children from vaccination, and the states where exemptions are the easiest to get are also home to the highest rates of unvaccinated children. States such as Colorado and Oregon, which only require parental signatures for exemptions, have exemption rates close to 6%, among the highest in the country, according to CDC data.

These refusals have directly resulted in an increase in the incidence of almost forgotten diseases like whooping cough and measles. After the introduction of the whooping cough vaccine in the 1940s, cases dwindled to about 1,000 cases annually. Yet the CDC reported nearly 77,000 cases of whooping cough in 2012 and 2013.

These exemptions raise serious ethical concerns. Human beings, at the start and end of their lives, are often unable to make informed decisions. While the elderly designate others as proxies, children rely on their parents. But when parents don't allow their children to get vaccinated, they are willfully putting their child at risk of catching easily preventable—and sometimes deadly—diseases.



Haider Javed Warraich, MD, (above) is a physician at the Beth Israel Deaconess Medical Center in Boston and an instructor at Harvard Medical School. Dr. Gohar Javed, a research associate at the Aga Khan University in Karachi, Pakistan, contributed to this op-ed.

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**Editor's Note: Dr. Warraich presciently wrote this article December 3, 2014 prior to the late December outbreak of measles in California. This validates the concern of public health officials and physicians about the other dangers from the growing number of unvaccinated children.*

Refusing vaccinations also puts other children at risk. Vaccines work when given to individuals, but they are most effective when administered to an entire population. That's because vaccines confer "herd immunity" that disrupts the chain of infections, but only if enough people get the immunization. For a highly infectious disease like measles, that threshold is about 92% of the population. At less than 92%, outbreaks can start to pop up, as is happening now.



Measles in Appalachia, 1964
Source: The LIFE Picture Collection/Getty Images

Some people—such as chemotherapy patients—cannot be vaccinated. Parents who refuse to vaccinate their children are conferred protection from other children who get the vaccine and maintain a prepared herd—but when refusals reach a tipping point, they put everyone at risk, especially the most vulnerable.

We don't let people do most things, such as drunken driving, that endanger themselves or others. So why do we allow people to prevent their children from receiving the most effective public-health intervention known to our species?

West Virginia and Mississippi have the strongest position against vaccine exemptions: Neither allows religious or personal exemptions, and neither has had an outbreak in more than 20 years.

When I asked Dr. Walter Orenstein, the former director of the CDC's National Immunization Program, whether exemptions should be allowed, he offered caution. "I have some concern about 'forcing' vaccinations and not allowing any exemptions," he said. "It could backfire and enhance antivaccination sentiment." Yet with vaccine exemptions sharply increasing, doctors and public-health experts are running out of options.

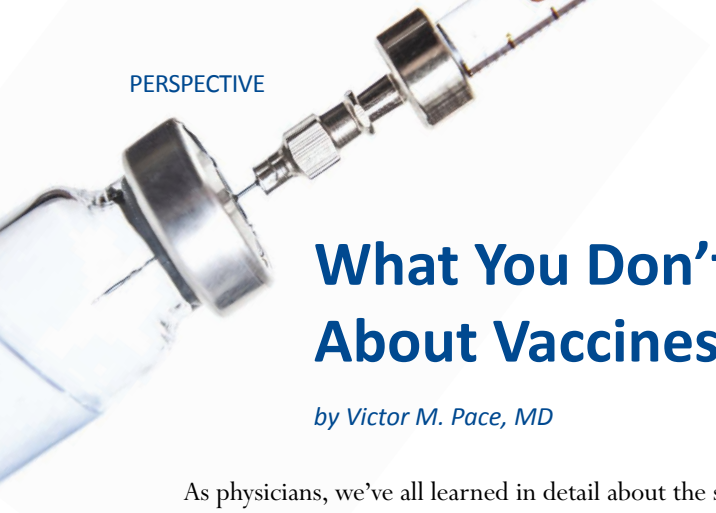
Claims about the dangers of vaccines—such as their purported relationship with autism—have been rigorously studied and debunked. Yet anti-vaccine advocates are becoming more vocal. When scientific proof is overwhelming, and reason fails, they fall back on magical thinking. Lindey Magee, an antivaccine advocate in Mississippi, told *Newsweek* earlier this year, "I saw the Disney movie 'Bears,' and if God gave bears instincts to survive their harsh reality, then human beings certainly have the instincts to protect children." She added, "Mumps, measles and rubella do not scare me."

By wiping out many common and deadly diseases, and thus the fear they induce, vaccination can be its own worst enemy. However, we cannot afford to remain reactive. Seminal work in 2012 by Saad B. Omer, an epidemiologist at Emory University, has demonstrated that making it more difficult to obtain exemptions—say, by requiring physician consultation, education or annual renewals—reduces the rate of exemptions. "The balance of convenience should tip in the favor of vaccinations as opposed to vaccine exemptions," he told me.

Physicians are reimbursed for giving vaccines, but there is no incentive to provide counseling for hesitant parents. "I strongly support a billing code that would allow time for vaccine counseling," Dr. Orenstein added.

The re-emergence of measles may be the harbinger of other infections such as polio returning from the history books. While autonomy needs to be a central value driving medical decision-making, legislators need to protect American children. The young girl at my hospital with measles survived, but others might not be so lucky. **MM**

For the most current updtaes on the CDC's vaccination guidelines visit: www.cdc.gov/vaccines/hcp/acip-recs



What You Don't Know About Vaccines Can Hurt You

by Victor M. Pace, MD

As physicians, we've all learned in detail about the science behind vaccinations, but I suspect few of us have been taught about the history of vaccinations. Sure, we all know that Dr. Jonas Salk developed the poliovirus vaccine, but I wasn't aware that he inoculated himself, his wife, and his three children with his then experimental vaccine.

When our editorial committee decided to focus on vaccinations as our theme for this month's Greene County Medical Society's *Journal*, I perused the internet for interesting topics. I came across a fascinating website, historyofvaccines.org; this website is a project of the College of Physicians of Philadelphia, touted as being the oldest professional medical organization in the United States. I credit the majority of the information in this article to the above website and the rest to the National Institutes of Health (nih.gov) website; I trust that the information is valid and true, based on the agencies behind these websites. Below are some interesting tidbits about vaccine preventable diseases that I found noteworthy to pass on to our readers.

"One in seven of all human beings dies from tuberculosis. If one only considers the productive middle-age groups, tuberculosis carries away one-third, and often more."



Victor M. Pace, MD, FAAFP, is a Family Practice physician in Springfield, Mo., affiliated with Elfindale Family Medicine.
Contact: vmpacemd@aol.com
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Pertussis

Though the causative agent of pertussis was not isolated until the early 1900s by Belgian scientists Jules Bordet and Octave Gengou, the disease was first described during an epidemic outbreak in Paris in 1578 by the French physician Guillaume De Baillou. He referred to the pertussis infection as the common name "quinte," hypothesizing that this name was due to the characteristic whooping sound or the five hour paroxysms of the cough.

Diphtheria

It was thought that a Boston minister and prominent colonist, Cotton Mather, was describing diphtheria when he wrote, "In December 1659 the (until then unknown) Malady of Bladders in the Windpipe, Invaded and removed many Children; by Opening of one of them the Malady and Remedy (too late for very many) were discovered." Reverend Mather was an advocate of variolation and was widely criticized for this view. His second wife and three of his children died of measles in 1713. In 1826, diphtheria received its official name by French physician Pierre Bretonneau.

In 1890, Shibasaburo Kitasato and Emil von Behring developed antitoxin and serum therapy. They showed that the sera of diphtheria immunized guinea pigs contained a protective substance, an antitoxin that prevented the harmful effects when the guinea pigs were reintroduced to lethal doses of diphtheria. Emil von Behring went on to be awarded the first Nobel Prize in Medicine in 1901.

The insurance company, Metropolitan Life, promoted immunizations in New York in 1926 when they donated $15,000 and launched an anti-diphtheria campaign.

Smallpox

As early as the 10th Century, the Chinese were believed to have inoculated themselves with the smallpox virus. It was thought that a Chinese statesman's son had pulverized powdery smallpox scabs, taken from infected individuals, blown into his

nostrils. They may have also scraped smallpox matter onto the skin of healthy individuals. It is also speculated that this inoculation method was first discovered in India and then the practice spread to China.

Smallpox killed several prominent figures in history, including the following: Shunzhi Chinese Emperor Fu-lin; twenty settlers of the Mayflower and their only physician; Queen Mary II of England at thirty-two years of age; and Benjamin Franklin's four-year-old son. Presidents Andrew Jackson, prior to becoming president, and Abraham Lincoln both contracted smallpox but survived. However, President Andrew Jackson's brother and President Abraham Lincoln's valet did not survive their bouts with this disease.

Edward Jenner born in 1749 in Gloucestershire, England, is known as the "Father of Immunology" after his deliberate use of a vaccination to control smallpox. His work was the first scientific attempt to control an infectious disease; this led to the method of vaccination eventually replacing variolation as the method of choice.

The Empress Dowager of Russia was a proponent of vaccinations. In 1801, she gave a young smallpox vaccinated orphan girl a pension for life, and named her Vaccinoff.

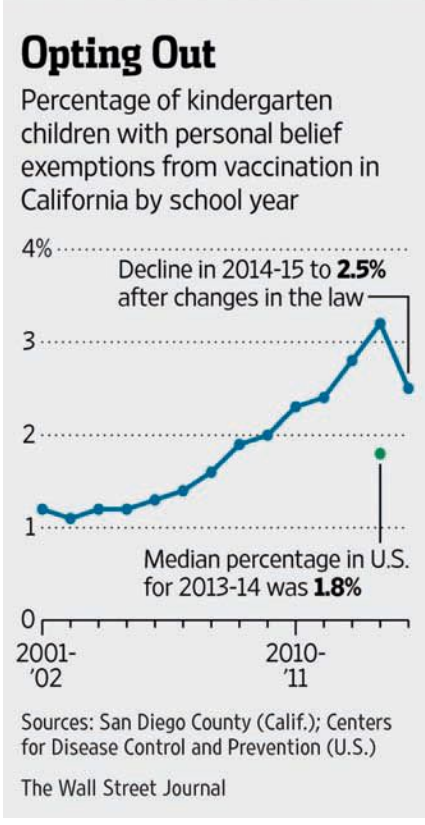
The United States Vaccine Agency was established in 1813, after Congress authorized and President James Madison signed "An Act to Encourage Vaccination." The United States Post Office was required to carry for free any smallpox vaccine material in mail that weighed up to 0.5 ounces.

In 1836, Dr. Edward Ballard, an English physician, advised a better method to increase the potency of cowpox vaccination by using newer rather than older strains of the disease.

As early as 1918, a freeze-dried vacuum packed smallpox vaccination was available and used in tropical climates.

Biological warfare is nearly as old as warfare itself, and smallpox was one of those weapons. Smallpox-infected blankets were distributed to Native Americans by British settlers. Five thousand of the 10,000 Continental Army soldiers contracted smallpox during the Battle of Quebec; a British commander sent recently variolated civilians into the Continental Army's encampments, which may have been a deliberate attempt to spread the disease.

1 Picture = 1,000 Words



Tuberculosis

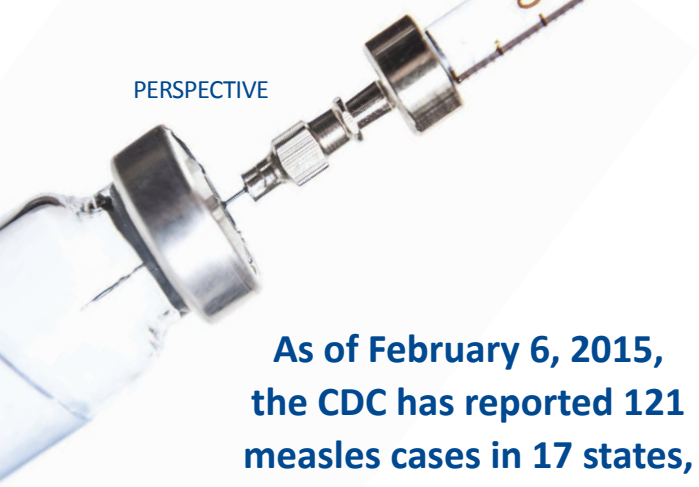
Tuberculosis was such a deadly disease in the 1800s that the German physician Dr. Robert Koch, on March 24, 1882, during his announcement of his discovery of the agent that causes tuberculosis said, "One in seven of all human beings dies from tuberculosis. If one only considers the productive middle-age groups, tuberculosis carries away one-third, and often more." He went on to win a Nobel Prize in 1905 "for his investigations and discoveries in relation to tuberculosis."

Typhoid

Mary Mallon, an Irish immigrant, was a cook for wealthy New York families. She was the first identified healthy carrier of typhoid who spread the disease to others. She was detained in hospitals by the New York City Department of Health from 1907-1910 and then released with the agreement, that she would not work as a cook and that she would take measures to prevent the spread of typhoid. However, in 1915, she was caught working as a cook again and found responsible for spreading typhoid to twenty-five people. She is otherwise known as "Typhoid Mary."

Louis Pasteur

Louis Pasteur was born on December 27, 1822 in Dole, France and died on September 28, 1895 at the age of seventy-two. He observed a rabies outbreak firsthand as a schoolboy in 1831. He was a chemist and was the chairman of the chemistry department at the University of Strasbourg. He had two daughters die of typhoid



As of February 6, 2015, the CDC has reported 121 measles cases in 17 states, mostly from an ongoing outbreak linked to an amusement park in Orange County, California. Most cases were unvaccinated (55%) or of unknown vaccination status (31%).

Source CDC

Practice in a health model of the future.

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fever and one daughter die of a liver tumor. Known by most for his pasteurization method to prevent the growth of bacteria in food items, he also developed several veterinary vaccines, was the first scientist to artificially attenuate viruses for vaccination use and developed the rabies vaccine for human use. In 1876, the New York Board of Health established a vaccine farm in New Jersey, where in 1879, Pasteur produced the first laboratory-developed vaccine, the vaccine for chicken cholera. On July 6, 1885, Joseph Meister was the first person to survive a post-rabies exposure vaccination by Pasteur. Joseph was badly bitten by a rapid dog and until then, Pasteur had never successfully used the vaccine on a human. Pasteur felt the nine-year-old child would surely die, so he took a very risky legal chance and succeeded in saving the boy from developing rabies. Mr. Meister went on to be a caretaker of Pasteur's tomb at the Institute Pasteur.

Polio

In 1929, Drs. Drinker and McKhann published a paper describing successful treatment of paralytic polio with the use of an artificial respirator. First called the Drinker respirator, this sealed tube-like electric powered machine later became known as the Iron Lung.

The March of Dimes was born in 1938 when entertainer Eddie Cantor suggested on the radio that people send dimes to President Roosevelt to help fight polio. Within a few weeks, 2,680,000 dimes were mailed to the White House.

Making Vaccinations Mandatory

Vaccination requirements have become a part of the law. The United Kingdom Vaccination Act of 1853 made smallpox vaccinations mandatory for infants in their first three months of life. Germany made smallpox vaccinations mandatory in 1874. In 1902, the United States Congress passed The Biologics Control Act that is the first modern federal legislative measure to control the quality of drugs; this act created the Hygienic Laboratory of the United States Public Health Service, which eventually morphed into the National Institutes of Health. On February 20, 1905, the United States Supreme Court upheld the constitutionality of mandatory smallpox vaccination programs in the case of *Jacobson v Massachusetts*. **MM**

Correspondence

Near-Death Experiences

Thank you so much for your initiative about publishing the articles about Near-Death Experiences in *Missouri Medicine*. It is a huge contribution for physicians to better accept the NDE and its implication for patients and health care. Your editorial was a good summation and conclusion. Whenever the book with these articles is published, I would appreciate receiving a copy.

Pim van Lommel MD
The Netherlands

Reading Missouri Medicine for the Medicine

I sit in my office at the end of a busy day seeing patients. I took the time to peruse through the most recent Missouri Medicine issue entitled "Health Information Technology: Advancing Healthcare Delivery." I was struck by the lack of articles about real medicine. I added up the number of articles that were nonmedical versus true research articles that discuss medicine. There were 13 articles that were nonmedical, five were medical.

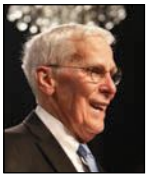
Most of us as physicians are becoming frustrated dealing with increasing mandates by the government, EHRs, electronic records in hospitals, and the nonmedical administrators telling us what to do. At the end of the day, the last thing I want to be told is about more requirements or more nonmedical issues. I went into medicine to study medicine and to care for patients. I did not go into medicine to study computers, EHRs, electronic medical records in hospitals, meaningful use mandates, other miscellaneous requirements, or the dictates that we now live under.

I would hope that Missouri Medicine would remain true to this mandate of discussing Medicine. If this means a thin magazine each month containing articles about Medicine, rather than a thick one with multiple nonmedical articles, I am all for it. Medicine should not take a backseat to the nonmedical aspects of the practice of medicine.

The saddest part of all, I cannot see as many patients on a daily basis because of the new requirements and mandates using EHR's. Where is Medicine going, and what kind of health care will we have available for us as we age?

William E Houck, MD
MSMA Member since 1985
St. Louis, Missouri

News from Missouri Medicine



John Bentley, MD, has been an MSMA member since 1976 and has just been named 2015 Springfieldian at the Springfield Area Chamber of Commerce annual meeting. Dr. Bentley received the Citizenship and Community Service Award in 2003 from MSMA.



Oregon Care Center hosted a meet-and-greet for Amber Brown-Keebler, MD, in early March with free blood pressure tests. She is a new MSMA member from Mound City.

Arthur Center Community Health in Mexico is excited to bring Nancy Bunge, MD, to its organization. Dr. Bunge has been an MSMA member since 1984.



Congratulations to Katarzyna Derlukiewicz, MD, of Hannibal for being awarded fellow status by the American Psychiatric Association. MSMA is honored to have her as a new member in 2015.



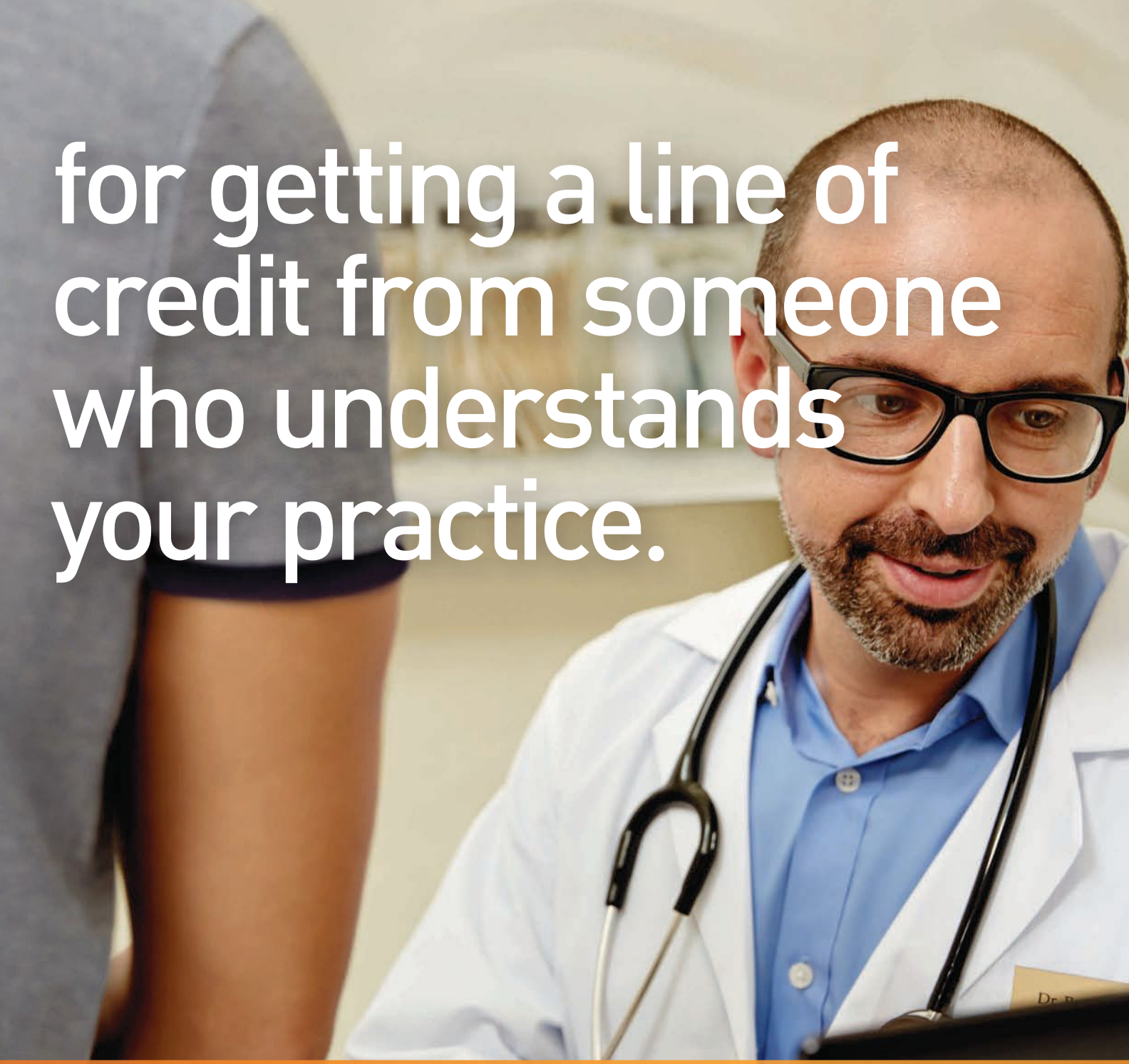
With increased outpatient surgeries, Harrison County Community Hospital has added Jason Gault, DO, to its staff. Dr. Gault is a newer member of MSMA who joined in 2014 from Chillicothe.



MSMA is excited to announce the addition of new member, Grant Hammons, MD, to MSMA and to Bothwell Internal Medicine in Sedalia. Welcome!



Congratulations to Aaron Koonce, DO, from St. Joseph, now providing neurology services at both Mosaic Life Care and Harrison County Community Hospital. MSMA is proud of this member and appreciative of his support since 2008.



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Food, Mood, and Brain Health: Implications for the Modern Clinician

by Laura Lachance, MD & Drew Ramsey, MD

Helping patients to eat a diet that is rich in brain food – fish, seafood, beans and legumes, leafy greens and other vegetables, olive oil (monounsaturated fat), yogurt, nuts – can be an effective and relatively simple way to promote mental health and recovery from mental illness that can easily be integrated into health care.



Laura Lachance, MD, (left) is at the University of Toronto. Drew Ramsey, MD, (right) is Assistant Clinical Professor of Psychiatry at Columbia University College of Physicians and Surgeons in New York, NY.
Contact: laura.lachance@utoronto.ca

Abstract

Improved, innovative strategies are needed for the prevention and promotion of recovery from mental illness as these disorders leading cause of disability worldwide. This article will review the evidence linking dietary pattern to brain-based illnesses and provide an overview of the mechanisms that underlie the association between brain health and the food we eat. Considerations for dietary intervention will be discussed including encouraging a shift towards a traditional or whole foods dietary pattern.

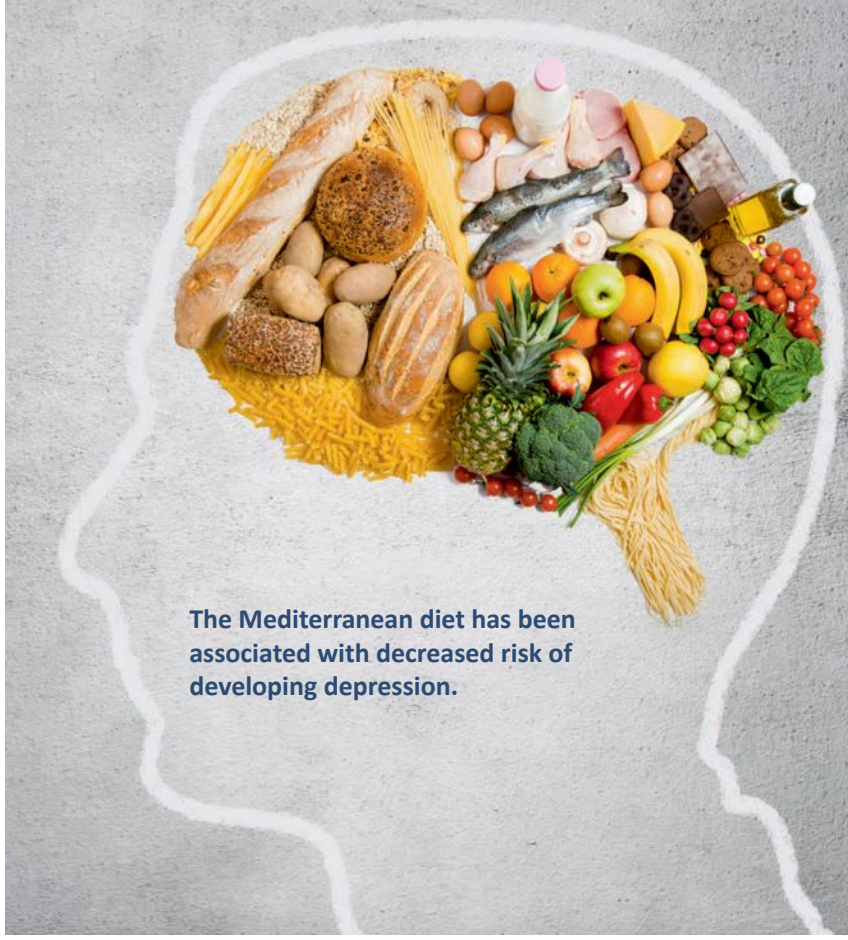
Clinical Vignette

Robert, a 43-year-old married man who presents with irritability and a low mood for two months. He has a history of attention deficit disorder, first diagnosed two years ago, and is currently treated with Vyvanse 70 mg. While his focus and work function are improved, he reports low appetite, fatigue, and difficulty sleeping. He notes that he tends to be quite irritable during mealtimes to the extent that his wife has asked him to stay at work past dinnertime to "stay out of the way." He feels guilty and, concerned about not connecting emotionally to his young children ages 1 and 3. Further history and medical workup reveal no substance use, no active medical issues, and blood work reveals no abnormalities.

The evidence is growing: food choice is strongly implicated in mental health risk. In cases like Robert's, a food history is a vital piece of data, both in assessing low appetite as a possible medication side effect, or as a symptom of depression. Furthermore, a food history is imperative to understand whether targeted dietary recommendations could assist in his recovery.

An approach to consider for patients with mental health symptoms is to offer counseling on lifestyle interventions, such as diet.[1] Physicians often feel ill-equipped to discuss diet due to lack of training, limited time, and a poor reimbursement structure. Physician uncertainty is likely exacerbated by the wide variety of specific dietary recommendations and dietary "tribes" that exist in our society today. Over 2,000 years ago, Hippocrates said, "let thy food be thy medicine and thy medicine be thy food."[2] The evidence base is increasing that we should re-examine his counsel, as the effect of good food has profound implications for brain health.

The global burden of mental illness, both in terms of financial cost and disability, rivals that of all cancers combined.[3,4,5] In addition, unipolar depression is the leading cause of disability in high and middle-income countries. Among individuals aged 15-44, it is the leading cause of disability



The Mediterranean diet has been associated with decreased risk of developing depression.

worldwide.[6] In light of this, it is essential to explore strategies that prevent mental disorders.[7] While several risk factors such as socioeconomic status and trauma are not amenable to simple interventions, nutrition has a simple appeal: all patients eat. Shifting the diet is not only a means to promote mental health; it is also a way to promote recovery from mental illness once it has already taken hold.[8, 9]

Several nutritional deficiencies, such as vitamin B12, B9 (folate), and zinc, can cause symptoms of depression and dementia such as low mood, fatigue, cognitive decline, and irritability.[10, 11] The evidence linking diet to mental illness has evolved from a focus on specific nutrient deficiencies to an emphasis on overall dietary pattern. Dietary patterns high in processed foods, or a "western dietary pattern," are strongly correlated with an increased risk of developing depression, mild cognitive impairment, and ADHD.[12-14] Food insecurity, or inadequate access to sufficient nutritious and culturally appropriate food, is also independently associated with mood and anxiety disorders.[15] On the other hand, a "whole foods," traditional, and a Mediterranean diet have been found to be protective against developing depression among other mental illnesses.[16-18] For instance, a prospective cohort study of over 10,000 university students over 4.4 years of follow up, found that students who most closely adhered to a Mediterranean dietary pattern had a 42% reduced risk of developing depression.[19] This research has taken into account several potential confounders including socioeconomic status. What could underlie this connection between mental illness risk and the food we eat?

This is Your Brain on Food

The brain is an organ with very high metabolic and nutrient demands. On average, the brain consumes 20% of a person's daily caloric intake, approximately 400 calories per day. It is composed of 60% fat, and contains high concentrations of cholesterol and polyunsaturated fatty acids (PUFAs) such as Omega-3s.

Production of monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine, important in the pathophysiology of mental illness, depends on adequate building blocks of amino acids, and mineral dependent co-factors. Folate and other B vitamins are essential for the methylation cycle, which produces a co-factor crucial for monoamine neurotransmitter synthesis, BH-4.[20, 21] Proper function of the methylation cycle also reduces homocystiene elevated levels of which are linked to cardiovascular disease and depression.

Omega-3 fatty acids form an integral part of neuronal cell membranes and influence a number of essential processes in the central nervous system. More specifically, they regulate neurotransmission, influence gene expression, and directly effect neurogenesis and neuronal survival. They also act as anti-oxidants and have anti-inflammatory properties.[22] Along with omega-3 intake, the balance of omega-6 and omega-3 fatty acids also appears to be relevant. Western diets tend to be abundant in omega-6 fatty acids, and quite low in omega-3s, a phenomenon that has occurred with the shift towards industrialized and processed food.[23] Omega-6 fatty acids are the primary fatty acid in many vegetable oils, such a corn oil and soy oil, often the cooking fats of choice in packaged and restaurant food. Long chained omega-3 fatty acids are found in fish, seafood, and grass-fed beef. Typically, these are not foods that come to mind as staples of the standard American diet. Grass fed beef omega-3 content varies greatly, but generally contains 100mg of long-chained omega-3 fatty acids per 100g serving, much less than an equivalent serving of fatty fish.[24] This highlights the importance of educating patients about meat quality and alternatives, such as grass-fed beef, which is generally more nutrient dense than conventionally-raised beef.[25]

Omega-3 fatty acids have been shown to be effective as either stand-alone or adjunctive treatment for ADHD, major depressive disorder, bipolar depression, and PTSD.[26, 27] In addition, an elevated omega-6 to omega-3 fatty acid ratio in the blood has been associated with major depressive disorder

and ADHD.[28, 29] There is some evidence that reducing the omega-6 to omega-3 ratio with omega-3 supplements lead to improvement in symptoms of ADHD.[30] Several possible biological mechanisms underlie these associations, i.e., the same enzymes are required to convert both short chain omega-3 and omega-6 fatty acids to their long chain biologically active versions. Thus, excess omega-6 could interfere with the production of omega-3s by limiting the conversion to the longer chain forms.[23]

As part of the clinical assessment, you decide to engage Robert in a discussion about food and complete a dietary history. Robert admits that he is not generally hungry in the morning and tends to skip breakfast. Lunch is often rushed, and he usually consumes a bowl of cold cereal with skim milk at his desk. Dinner is quite variable and snacks consist of crackers or low-fat granola bars.

These foods are not rich sources of nutrients crucial for brain health. When considering brain health, fish and seafood are among the most nutrient dense foods that one can eat. This food category is rich in all of the nutrients discussed so far namely: omega-3 fatty acids and B vitamins. Is Robert eating any fish or seafood? It may be reasonable to consider asking him this question. Moreover, greens such as kale, beans, and legumes are excellent sources of folate, as are fiber, and B-vitamins. Are these foods part of his diet?

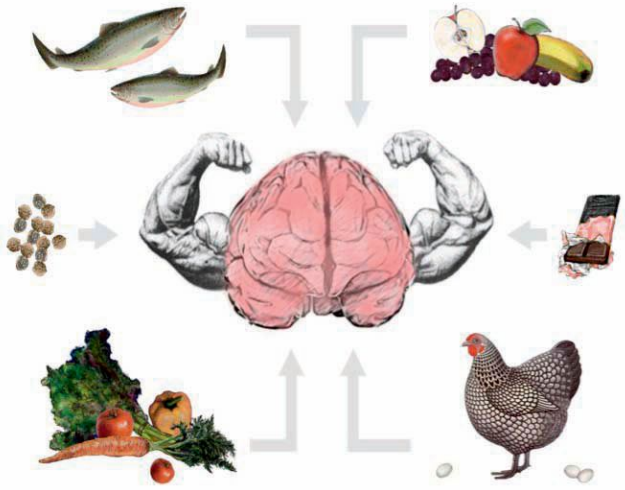


Figure credit Mala Nimalasuriya

Inflammation may play an important role in mediating the link between diet and mental health.[31] Multiple lines of research support the pathogenic role of neuroinflammation in mental illness.[32] Lucas et al. (2014) used several inflammatory biomarkers including CRP, TNF alpha receptor 2, and IL-6 and data from food frequency questionnaires to derive an inflammatory dietary pattern from a sample of over 12,000 participants from the Nurses Health Study. Participants who consumed a diet consistent with the inflammatory dietary pattern had a statistically significant increased risk of developing depression over time after adjusting for multiple confounders.[33] Specifically, over twelve years of follow up, participants with the highest adherence to the inflammatory dietary pattern had a relative risk of 1.41 (1.22-1.63) of developing depression according to the strict definition (physician diagnosis and anti-depressant use). The inflammatory dietary pattern was high in in sugar-sweetened soft drinks, refined grains, red meat, diet soft drinks, and margarine and low in wine, coffee, olive oil, green leafy, and yellow vegetables.

Any mention of olive oil, wine, and vegetables when speaking about nutrition leads to thoughts about the Mediterranean diet. This dietary pattern is based on the traditional cooking style of countries bordering the Mediterranean Sea and is rich in fish, olive oil, legumes, and whole grains. It also contains small, but regular amounts of red wine, cheese, and yogurt. The Mediterranean diet has been associated with decreased incidence and prevalence of depression.[34] In an attempt to explore the potential mechanisms to explain this association, one research group looked at brain derived neurotrophic factor or BDNF.

BDNF is an important neurochemical that is active in many areas of the brain. It plays a role in many crucial functions such as neuroplasticity, neuronal survival, and growth and differentiation of new neurons and synapses.

Low serum levels of BDNF have been found in a number of mental disorders including major depressive disorder, PTSD, Schizophrenia, and Alzheimer's dementia.[35-38] BDNF has also been implicated in the mechanism of action of anti-depressant medications.[39] One prospective study examined the impact of diet on plasma BDNF levels in humans. Participants were randomized to follow one of three diets: the American Heart Association guidelines, a Mediterranean diet augmented with olive oil, and a Mediterranean diet augmented with nuts. After three years of follow up, the Mediterranean diet with nuts group had a relative risk of 0.22 (0.05-0.90) of having a very low plasma BDNF level. What is more, individuals in this group who had depression at baseline had significantly higher mean plasma levels of BDNF at the end of the study.[40]

Another aspect on the frontier of the link between diet and mental health is the microbiome. Fermented foods have been part of the human diet since the Paleolithic period and they remain part of the dietary practices of most known traditional diets today.[41]

These types of foods are commonly referred to as

probiotic since they contain microorganisms that positively influence health. Prebiotics, on the other hand include non-digestible fiber, which stimulates the growth and or activity of these beneficial microorganisms. The impact of the microbiome on mental health is an emerging area of research[42] that is beyond the scope of this article. Suffice it to say that the microbiome provides another link between diet and mental health since short-term dietary changes can induce species level changes to intestinal microbes.[43]

Therefore, it appears that dietary pattern can influence mental health through a number of mechanisms. Basic building blocks of the brain such as monoamine neurotransmitters, myelin, and neuronal membranes depend on adequate nutrient intake. Food choice influences neuroplastic processes via effects on BDNF expression and systemic inflammation via omega-3 to omega-6 ratio. Finally, food is the primary arbiter of the microbiome, an emerging area of research in general and mental health.

Summary

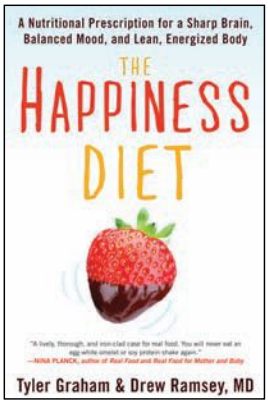
In order to promote mental health and recovery from mental illness, one could consider encouraging patients to eat a diet that is optimal for brain health. Specifically, this diet would include adequate building blocks for monoamine neurotransmitters, be rich in omega-3 fatty acids, be anti-inflammatory, foster BDNF production, and support a healthy microbiome. While this might seem to be very ambitious goal, many traditional diets are based on nutrient dense whole foods and contain all of these nutrients. The Mediterranean diet is an accessible template, but it is only one example.

Robert is provided with education regarding the importance of adequate nutrition for his mental health and encouraged to make some changes to his diet in line with the considerations discussed above. He is glad to hear about steps he can take on his own to improve his mental wellbeing and his self-efficacy increases. You work with Robert to find some nutrient-dense and convenient breakfast options such as scrambled eggs or a nutrient-dense smoothie. He decides to start eating breakfast.

A few weeks later in follow-up, Robert states that despite not feeling hungry when he wakes up, he feels subjectively better ten minutes or so after having breakfast. He also introduces nuts as snacks, instead of crackers and low-fat granola bars, and has started to pack a fruit or vegetable to eat with his lunch. Robert's irritability improves. It is possible that the stimulant medication is suppressing his appetite and his irritability was due to hypoglycemia. Upon further clinical evaluation, Robert endorses some residual depressive symptoms and you recommend a trial of anti-depressant medication. Robert has had one previous depressive episode; however, he did not find medication to be helpful at that time. He is somewhat hesitant but consents to a trial of medication.

After six weeks of treatment with medication and ongoing food intervention, Robert's depressive symptoms have significantly improved. He feels less irritable at mealtimes, is enjoying spending time with his children more, and is having less conflict with his wife. He is feeling positive about the direction his life is heading, and plans to continue to pay attention to his food choices.

Helping patients to eat a diet that is rich in brain food



The Happiness Diet

A Nutritional Prescription for a Sharp Brain, Balanced Mood, and Lean, Energized Body

by Tyler Graham and Drew Ramsey, MD

BOOK REVIEW

Over the past several generations small, seemingly insignificant changes to our diet have stripped it of nutrients—like magnesium, vitamin B12, iron, and vitamin E, as well as some very special fats—that are essential for happy, well-balanced brains. These shifts also explain the overabundance of mood-destroying foods in the average American's diet and why they predispose most of us to excessive weight gain.

"Like the weather everyone talks about diets but no one does anything about them. This comprehensive but easily accessible book guides us to coherent and healthy eating. It will help anyone interested in how the foods we eat can keep us well."
—Philip R. Muskin, MD Professor of Clinical Psychiatry, Columbia University

"Dr. Drew Ramsey has synthesized a compelling body of scientific literature with accessible and lucid conclusions regarding the interface of diet and vulnerability, protection and treatment of mental disorders."
—Roger S. McIntyre, M.D., FRCPC, Associate Professor of Psychiatry and Pharmacology, University of Toronto

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– fish, seafood, beans & legumes, leafy greens and other vegetables, olive oil (monounsaturated fat), yogurt, nuts – can be an effective and relatively simple way to promote mental health and recovery from mental illness that can easily be integrated into health care.Possible side effects and food-medicine interactions, for example leafy greens and wafarin, should be considered. That being said, the side effects in the case of nutritional counseling can include increased self-efficacy and improved physical health. Two more reasons to consider this foundational intervention: talking to our mental health patients about food.

References

1. Sanchez-Villegas A, Martínez-González M. Diet, a new target to prevent depression? Metabolism, Diet, and Disease. 2013;11(3).
2. Graham T, Ramsey D. The Happiness Diet: A Nutritional Prescription for a Sharp Brain, Balanced Mood, and Lean, Energized Body: Rodale; 2011.
3. Murray C, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2010;380(9859):2197-223.
4. Bloom D, Cafiero E, Jané-Llopis E, et al. The global economic burden of noncommunicable diseases. Program on the Global Demography of Aging. 2012;8712.
5. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. The Lancet.349(9064):1498-504.
6. Mathers C, Fat DM, Boerma J. The global burden of disease: 2004 update: World Health Organization; 2008.
7. Author. Changing directions, changing lives: The mental health strategy for Canada. Calgary, AB: Mental Health Commission of Canada; 2012.
8. Sarris J, Logan A, Akbaraly T, et al. Nutritional Medicine as Mainstream in Psychiatry: A Consensus Position Statement from the International Society for Nutritional Psychiatry Research (ISNPR). Consensus Statement ed; 2014.
9. Rucklidge J, Johnstone J, Kaplan B. Single bullet madness–why do we continue to perpetuate this fallacy. Br J Psychiatry. 2013;203:154-5.
10. Sensi S, Paoletti P, Koh J, Aizenman E, Bush A, Hershfinkel M. The Neurophysiology and Pathology of Brain Zinc. The Journal of Neuroscience. 2011;31(45):16076-85.
11. Skarupski K, Tangney C, Li H, Ouyang B, Evans D, Morris M. Longitudinal association of vitamin B-6, folate, and vitamin B-12 with depressive symptoms among older adults over time. The American journal of clinical nutrition. 2010;92(2):330-5.
12. Howard A, Robinson M, Smith G, Ambrosini G, JP P, Oddy W. ADHD is associated with a "Western" dietary pattern in adolescents Journal of attention disorders. 2011;15(5):403-11.
13. Akbaraly T, Brunner E, Ferrie J, Marmot M, Kivimaki M, Singh-Manoux A. Dietary pattern and depressive symptoms in middle age. The British Journal of Psychiatry. 2009;195(5):408-13.
14. Scarmeas N, Luchsinger J, Schupf N, et al. Physical activity, diet, and risk of Alzheimer disease. JAMA. 2009;302(6):627-37.
15. Tarasuk V, Mitchell A, McLaren L, McIntyre L. Chronic Physical and Mental Health Conditions among Adults May Increase Vulnerability to Household Food Insecurity. The Journal of nutrition. 2013;143(11):1785-93.
16. Lai J, Hiles S, Bisquera A. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. American Journal of Clinical Nutrition. 2013;99(1):181-97.
17. Pelsser LM, Frankena K, Toorman J, et al. Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial The Lancet. 2011;377(9764):494-503.
18. FN J, PJ K, M B, AM dS-S, al. e. A Prospective Study of Diet Quality and Mental Health in Adolescents. . PLoS ONE. 2011;6(9):e24805.
19. Sánchez-Villegas A, Delgado-Rodríguez M, Alonso A, et al. Association of the Mediterranean dietary pattern with the incidence of depression: the Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort. Archives of General Psychiatry. 2009;66(10):1090-8.
20. Miller A. The methylation, neurotransmitter, and antioxidant connections between folate and depression. Alternative Medicine Review. 2008;13(3):216-26.
21. Stahl S. L-Methylfolate: A Vitamin for Your Monoamines. Journal of Clinical Psychiatry. 2008;69(9):1352-3.
22. Zeman M, Jirak R, Vecka M, Raboch J, Zak A. N-3 polyunsaturated fatty acids in psychiatric diseases: Mechanisms and clinical data. Neuroendocrinology Letter. 2012;33(8):736-48.
23. Simopoulos A. Evolutionary Aspects of Diet: The Omega-6/Omega-3 Ratio and the Brain. Molecular Neurobiology. 2011;44:203-15.
24. Nuernberg K, Nuernberg G, Ender K, et al. N-3 fatty acids and conjugated linoleic acids of longissimus muscle in beef cattle. European Journal of Lipid Science and Technology. 2002;104(8):463-71.
25. Daley CA, Abbott A, Doyle PS, Nader GA, Larson S. A review of fatty acid profiles and antioxidant content in grass-fed and grain-fed beef. Nutrition journal. 2010;9(1):10.
26. Bloch MH, Qawasmi A. Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: Systematic review and meta-analysis. Journal of the American Academy of Child & Adolescent Psychiatry Vol. 2011 2011;50(10):991-1000.
27. Mischoulon D, Freeman M. Omega-3 fatty acids in psychiatry. Psychiatric Clinics of North America. 2013;36(1):15-23.
28. Adams P, Lawson S, Sanigorski A, Sinclair A. Arachidonic Acid to Eicosapentaenoic Acid Ratio in Blood Correlates Positively with Clinical Symptoms of Depression. Lipids. 1996;31(supplement).
29. Mikirova N, Casciari J, Hunninghake R. The Orthomolecular Correction of Metabolic Imbalances Found in Attention Deficit Hyperactivity Disorder: A Retrospective Analysis in an Outpatient Clinic. 2013;28(2):1-10.
30. Sorgi P, Hallowell E, HL H, Sears B. Effects of an open-label pilot study with high-dose EPA/DHA concentrates on plasma phospholipids and behavior in children with attention deficit hyperactivity disorder. Nutrition Journal. 2007;6(16).
31. Galland L. Diet and Inflammation. Nutrition in Clinical Practice. 2010;25(6):634-40.
32. Najjar S, Pearlman D, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. Journal of Neuroinflammation. 2013;10:43.
33. Lucas M, Chocano-Bedoya P, Shulze M, et al. Inflammatory dietary pattern and risk of depression among women. Brain, behavior, and immunity. 2014;36:46-53.
34. Rienks J, Dobson A, Mishra G. Mediterranean dietary pattern and prevalence and incidence of depressive symptoms in mid-aged women: results from a large community-based prospective study. European journal of clinical nutrition. 2013;67(1):75-82.
35. Bocchio-Chiavetto L, Bagnardi V, Zanardini R, et al. Serum and plasma BDNF levels in major depression: a replication study and meta-analyses. World Journal of Biological Psychiatry. 2010;11(6):763-73.
36. Faria MC, Goncalves G, Rocha N, et al. Increased plasma levels of BDNF and inflammatory markers in Alzheimer's disease. Journal of psychiatric research. 2014;53:166-72.
37. Angelucci F, Ricci V, Gelfo F, et al. BDNF serum levels in subjects developing or not post-traumatic stress disorder after trauma exposure. Brain and cognition. 2014;84(1):118-22.
38. R N, M K, H S. BDNF and schizophrenia: from neurodevelopment to neuronal plasticity, learning, and memory. Frontiers in Psychiatry. 2013;4(45).
39. E C, Rantamaki T. Role of brain-derived neurotrophic factor in the aetiology of depression: implications for antidepressant treatment. CNS Drugs. 2010;24:1-73.
40. Sánchez-Villegas A, Galbete C, Martinez-González M, et al. The effect of the Mediterranean diet on plasma brain-derived neurotrophic factor (BDNF) levels: the PREDIMED-NAVARRA randomized trial. Nutritional Neuroscience. 2011;14(5):195-201.
41. Selhub EM, Alan C. Logan, and Alison C. Bested. Fermented foods, microbiota, and mental health: ancient practice meets nutritional psychiatry. Journal of Physiological Anthropology. 2014;33(1):2.
42. Cryan J, Dinan T. Mind-Altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nature Reviews Neuroscience. 2012.
43. Bested A, Logan A, Selhub E. Intestinal microbiota, probiotics and mental health: from Metchnikoff to modern advances: Part II – contemporary contextual research. Gut Pathogens. 2013;5(3).

Disclosure

None reported.

MM



Childhood Myopia: Epidemiology, Risk Factors, and Prevention

by Matthew Recko, MD & Erin Durrie Stahl, MD

The future of myopia progression therapy is looking brighter and the burden of myopia and its morbidities on the patient and on our society may lighten.



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Abstract

Our understanding of the dynamic interaction between the eye's growth and its ability to adapt to maintain vision has shown that childhood myopia is a significant prediction of progressive myopia and the potentially severe ocular co-morbidities associated with it. It is important for us to better understand this process and its risk factors in order to better develop a prevention and treatment strategy. This article will discuss the epidemiology, risk factors and current therapeutic regimens for reducing myopic progression.

Background

Myopia, or nearsightedness, is a common eye condition in which the image seen by the eye is focused prior to reaching the retina. This produces an unfocused image on the retina and is seen by the patient as a blurred image. In order for an individual to see an object clearly, the image must be projected clearly onto the retina of the eye. Myopia can be optically corrected with glasses to help provide a clear image on the retina. See Figure 1.

Myopia can be divided into two major categories: refractive and axial. Refractive myopia is due to the focusing power of the eye being abnormally strong and focusing the image in front of the retina. Axial myopia, the more common cause, is due to the axial length of the eye being too long, measured from the cornea to the back of the eye. The normally powered cornea and lens focus the light but the retina is further posterior than the focused image. Animal studies show that the eye is dynamic in managing axial length and optical power in order to maintain a clear image during growth and development. If this autoregulation process is poorly controlled, the eye can elongate out of proportion creating axial myopia.[1-3]

The process and progression of myopia follows a typical pattern with normal vision at a young age. Starting around school age a myopic shift and rapid increase in myopia begins which continues until late teenage years.[4,5] High myopia is associated with significant increased risks for retinal degeneration and detachment, open angle glaucoma, and cataracts at a young age. These associated conditions have a significant lifetime risk of severe visual impairment including blindness.[6]

Due to the significant risks associated with the development of high myopia, pediatric ophthalmologists have been very interested in the prevention of myopic progression. Recent studies involving drugs and devices have shown that myopic progression can be modulated.

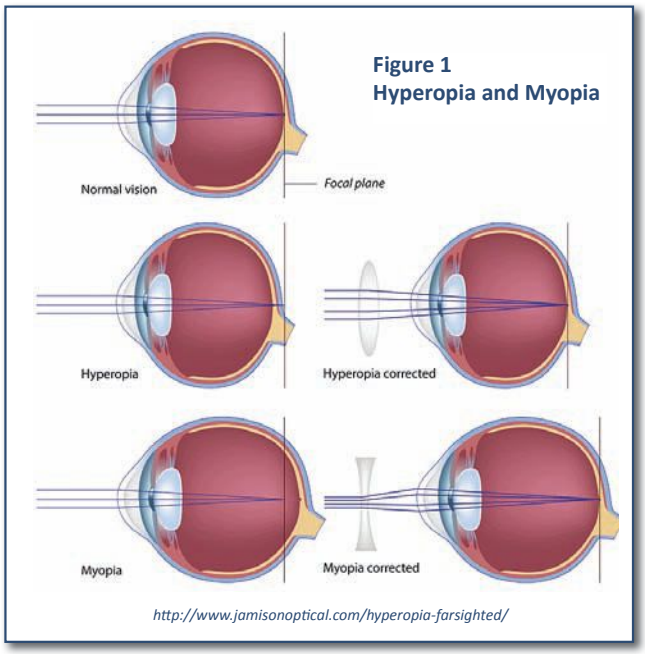


Figure 1
Hyperopia and Myopia

We will discuss published literature on the interventions, their risks and efficacy data.

Epidemiology

Prevalence and Incidence

Myopia is an extremely common ocular condition worldwide. See Figure 2. It has been published that the prevalence in Asian populations approaches the rate of 37-60%.[8,9] The annual incidence in urban Asian communities has been greater than 14%.[10,11] An Australian study found a prevalence of 14.4% and 29.6% in children ages 12 and 17 years, respectively. This same study estimated the annual incidence for the same age groups to be 2.2% and 4.1%, respectively.[12] It is has been estimated that myopia affects approximately 25-33% of adults in the United States and Western Europe.[13,14] Vitale S. et al. found a 66% increase in the prevalence of myopia in the United States over a 30-year period ending in 2004.[15] The Multi-Ethnic Pediatric Eye Disease Study found the prevalence of non-hispanic whites aged 6-72 months in California to be 1.2% while in 3.98% in Asians of the same population.[16] The National Health and Nutrition Examination Survey showed that myopia was more common in non-Hispanic whites (35.2%) than in non-Hispanic blacks (28.6%) or Mexican-Americans (25.1%).[15] The annual incidence rates of myopia in the United States has been reported as 2.6%[17] with children of Euro-Caucasian ethnicity having the lowest odds of incident myopia.[12,18]

Risk Factors

Ethnicity

Ethnicity has been looked into as a risk factor for progression due to the higher prevalences and annual incidence rates among Asian populations. Internationally, the annual rate of myopic progression for Singapore has been reported at -0.80 diopters per year,[11] while European Caucasian ethnicities report progression rates closer to -0.50 diopters per year.[12,19,20] It was shown by Hyman et al. that African-Americans had the least amount of progression after three years compared to Asians, Hispanics, Caucasians, and mixed ethnicities.[7] The COMET Group also found that African-Americans stabilized at a younger age (13.82 years) with less absolute myopia at stabilization (-4.36 D). The same study showed that Caucasians took the longest to stabilize (16.32 years) and Asians had the most amount of absolute myopia at stabilization (-5.45 D).[4]

Age

The most significant predictor of incident myopia is having a less hyperopic refraction at a young baseline age.[18] The strongest independent risk factor for myopia progression is having a myopic refraction of at least -1.25 diopters at a young age, particularly at the myopic shift transition point of 6 to 7 years of age. Not only is the endpoint amount of myopia greater in this group, but the rate of progression and axial length elongation is faster.[7] The fact that the overall amount of myopia would be greater at stabilization in a young patient with myopia makes intuitive sense but the reason for the rate being faster remains unknown. The COMET Group found that the mean age of stabilization of myopia to be 15.61 years with the average amount of myopia at stabilization to be -4.87 diopters. It was also shown that for every year of delayed stabilization, there was an increase in total amount of myopia (overall 0.27 D more myopia per year delayed).[4]

Parental Myopia

Studies have shown us that parental myopia, in even one parent, leads to an increased risk for juvenile myopia. It has even been reported that there is greater than a six-fold increased risk of juvenile-onset myopia if both parents are myopic.[21] In Austrailia, incident myopia in six-year-old children was increased from 7.8% with no parental myopia to 21.4% and 22.0% with one or both parents having myopia, respectively. This same study found that European Caucasian children with parental myopia had increased incidence of myopia.[18]

Parental myopia is not only a risk factor for having myopia, but is also a risk factor for progressive myopia in children.[22] Saw et al. showed children with at least one myopic parent had increased rates of myopic progression compared to children with no myopic parent (0.63 diopter/year vs 0.42 diopters/year, respectively).[23] This was

supported by the COMET group who reported parental myopia was directly related to myopic progression as well as increases in axial length.[22]

Gender

There is conflicting data when assessing sex predilection of myopia. The COMET study showed that there was no difference between males and females.[12,18] The National Health and Nutrition Examination Survey showed that women had a higher prevalence than men for myopia among the 20-40-year-old population (39.9% and 32.6%, respectively, $P < .001$) but that this was not consistent among other age groups.[14]

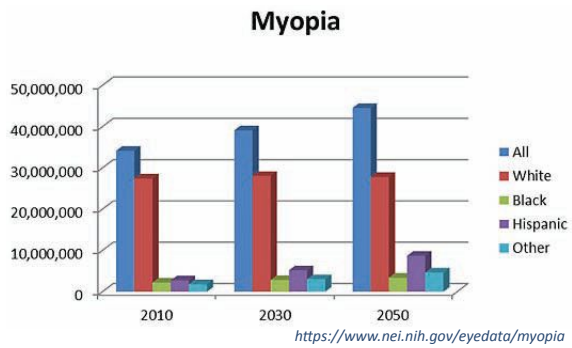
The COMET study's multivariate analysis found that males have a slower progression rate of myopia than females do,[4] which supports the previous conflict of an increased female prevalence of myopia at age 20-39. It is interesting to note that there was no difference in axial length elongation between males and females. The female axial length averaged shorter than males but was compensated by females having steeper, or strong focusing, corneas.

Environmental Factors

Several studies have bern conducted to examine different environmental or non-genetic factors that may factor in the development of myopia. The amount of near work, such as reading or hand-held electronics, a child performs during the day has had weak or no association.[23-26] The CLEERE Study Group showed in their longitudinal study that near work activities in children who became myopic did not differ from emmetropic children before myopia, claiming that nearwork cannot be a causative factor for myopia.[27] One of the most popular and impactful associations is outdoor time. Many studies have found that outdoor time has a negative, or protective, association with myopia.[6, 18, 28] Sherwin et al. performed a meta-analysis to summarize the published reports on the association of outdoor time and myopia in children under 20 years.[6] Their results not only confirmed that increasing time spent outdoors reduces the risk of developing myopia, but the pooled information indicated a 2% reduced odds of myopia for each additional hour of time spent outdoors per week. This offers a practical intervention for myopia prevention with the many other health benefits associated with outdoor activities.

There has been much work and investigation into the genetics and inheritance of refractive errors, including myopia, however, there remains much to be learned. It is agreed that there is a genetic and environmental interaction that is involved and our understanding of myopia inheritance will be better understood as these elements are better investigated.[21,29]

Figure 2
Projections for Myopia (2010-2030-2050) United States



Interventions

The natural progression of myopia and the risk factors associated with it have lead to attempted treatment strategies to not only treat the blurred vision but to prevent the progression of myopia. There are two major therapeutic methods: optical therapy and medication therapy. The following will discuss the more recent and popular researched therapies within each of these categories, but should not be considered a completely inclusive discussion of myopic progression therapy.

Optical Therapies

Bifocals

As discussed previously, the eye can autoregulate its refraction and axial length to attempt a focussed image on the retina. If the eye cannot first adjust its refractive factors, it can elongate to maintain focus.[1-3] Bifocals, lined or progressive, can provide a clear image for images at different points, theoretically reducing the need to elongate. In 2011, Leo and Young performed a review of literature and found that randomized, clinical trials in several countries did not show significant slowing of myopia. Progressive lenses were found in many of the studies reviewed to have little significance or insignificant trends slowing progression.[1] Most recently, Cheng et al. published a three-year randomized trial that progressive lenses had a significant reduction in the rate of myopic progression in children who were progressing at an already accelerated rate.[30] The COMET group did note significant reductions in progression but after further analysis concluded that these reductions were clinically insignificant.[19]

Orthokeratology

Orthokeratology is a corneal refractive therapy in

CMH Pediatric Refractive Surgery Program

The Pediatric Refractive Surgery Program at Children's Mercy Hospitals and Clinics in Kansas City offers advanced surgical treatment for children with debilitating and sight-threatening vision problems. The program serves children with high refractive errors in one or both eyes and who are not developing good vision.

Refractive Surgery Staff

The Pediatric Refractive Surgery Program is one of only a few programs in the U.S. to feature a surgeon who is fellowship trained in both pediatric ophthalmology and refractive surgery. Services are provided by a team of leading pediatric ophthalmologists and optometrists at the forefront of research as well as new techniques and technology to better treat pediatric vision problems.

Department Highlights

Our program is one of only a few in the U.S. with a surgeon who is fellowship trained in both pediatric ophthalmology and refractive surgery. We provided specialized surgical treatment for a full range of pediatric vision problems. Our staff conducts ongoing research to develop new, innovative approaches to treating pediatric vision problems.

Children's Mercy Hospitals and Clinics will offer three types of procedures to correct vision problems in children who meet the clinical research protocols.

Services Offered

Excimer laser procedures, Phakic implantable lenses, Refractive lens exchange, Secondary intraocular lenses

Common Conditions

- Anisometropic Amblyopia
- Aphakia
- Ectopia Lentis
- Bilateral high-refractive error and inability to wear glasses or contact lenses due to:
  - Developmental delay
  - Craniofacial disorders
  - Dermatologic conditions
  - Severe muscle weakness

The main determinant of eligibility for these procedures is documented failure of improvement with standard therapy.

which the cornea is reshaped using a specifically made hard contact lens in an effort to temporarily flatten the curvature of the cornea, thus lessening the optical power of the cornea and focusing the image onto the retina. These lenses are worn at night and removed during the day.[31] Until recently there has been no good long-term data on its effects on myopic progression. Several recent, randomized, clinical trials have shown that orthokeratology can reduce the amount of myopic refractive and axial length progression by 43-63% after two years.[32-34] Sample size is a significant limitation to these studies and may skew these results. The smallest study of 28 subjects completing the study had the highest reduction[32] and the largest study of less than 80 subjects completing the study had the lowest reduction.[33] There is no follow-up data beyond two years or data for the progression rates after cessation of therapy. These studies included children age 6-12 years of age and corrected up to 5 diopters of myopia. The major complications reported by these studies were irregular corneal epithelium, corneal inflammation, and ocular intolerance. A report by the American Academy of Ophthalmology found multiple sight-threatening risks and complications associated with orthokeratology including more than 100 cases of corneal infections.[35]

Medication Therapies

Atropine

Atropine is a non-selective antimuscarinic with a wide range of effects on the eye, most notably reduction of accommodation and causing pupil dilation (mydriasis). The origin for this treatment of myopia started in the 19th century.[1,36] The exact mechanism of atropine for myopia has not been identified, but observations to its effects have been reported through a variety of papers and clinical trials, most of which were limited with short-term data, poor controls, lack of masking, and detailed examinations.[37] The ATOM studies[37-40] were performed in an effort to assess the effects of atropine on myopic progression as well as side effects with two years of atropine therapy. Children aged 6 to 12 years with low to moderate myopia were randomized into placebo, 1%, 0.5%, 0.1%, and 0.01% atropine. After two years of therapy the atropine groups significantly decreased the rate of myopic progression in a concentration related manner: 77%, 75%, 68%, and 59%, respectively. The differences between the concentrations were considered clinically insignificant. Axial length elongation was also compared and found similar findings though not all concentrations were significant: 100% reduction, 28% reduction, 26% reduction, and 8% more, respectively.[37, 39] After the two years, treatment patients stopped therapy and the groups were monitored for progression over the following year. Interestingly, a rebound

in progression was found but inversely to the concentration of atropine used: 0.01% atropine with least amount of rebound myopic progression and 1% atropine with the most amount of rebound myopic progression. The total treatment effect of the atropine groups compared to placebo over the three years (two years treatment plus one year no treatment) showed that all atropine groups had less progression but inversely related to the concentrations: 12.5%, 25%, 37.5% and 56.3%, 1% to 0.01% respectively. Interestingly, the average amount of the axial length change over the three years only had a significant change in the 1% atropine group (reduced elongation) when compared to placebo.[38,40]

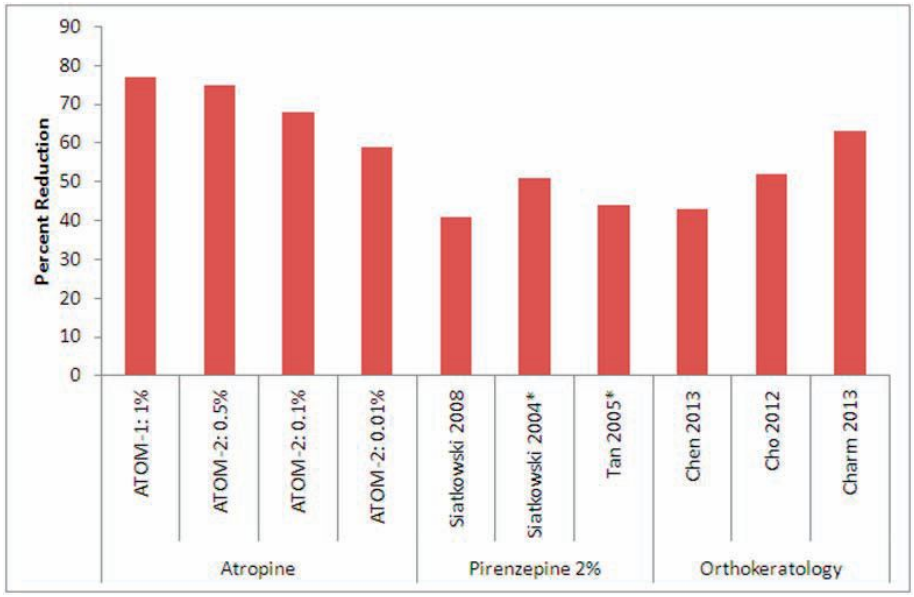


Figure 3
Effect of Treatment Modalities on Myopic Progression.
**Represents one-year results*

Significant visual side effects were mydriasis (pupil dilation), decreased accommodation (ability to adjust focus), and near vision blur from cycloplegia. These were concentration specific with higher concentrations of atropine having more effects and to greater extents than the lower concentrations. In fact, atropine 0.01% had a minimal effect on accommodation and mydriasis and no effect on near vision. All ocular side effects resolved after completion of therapy. The most common side effect was allergic conjunctivitis or dermatitis and again, no cases were found in the 0.01% atropine group.[37-40]

Pirenzepine

In an effort to reduce the side effects of atropine, in particular mydriasis and cycloplegia, pirenzepine 2% gel has been studied.[41-43] Pirenzepine is a selective antimuscarinic with less mydriasis and cycloplegia.[44] The U.S. Pirenzepine Study group found that patients randomized to twice daily pirenzepine slowed the rate of refractive myopia significantly but had no significant effect on axial length elongation. This effect was 51% at one year and then 41% after two years of therapy.[41,42] The Asian Pirenzepine Study group found the same effect (44% at one year) but with significant reduction on the rate of axial length elongation.[43] Significant side effects from the medication included abnormality in accommodation, mydriasis, ocular irritation, reaction, and discomfort, and even some subjective visual acuity decrease.[41-43] Though pirenzepine shows potential clinical therapeutic use to reduce myopic progression, financial and regulatory obstacles has stopped its further development.[1]

Summary

Myopia is a common condition and if severe, has potentially severe ocular debilitating associations. There is much to be learned about its development and progression. Some risk factors have been identified and while gender, parental history, and ethnicity cannot be controlled, the environmental factor of outdoor activities has been shown to help reduce the odds. For those with myopia and in particular the young with actively progressing myopia, there are limited treatment options available.

Discussed in this article were four of the most popular therapeutic regimens. Figure 3 shows the therapeutic myopic progression reduction found in the studies discussed in this article. It is to note that the figure is for the active therapy results and does not include any post-therapy results. Bifocals have not shown to be of any significant benefit. Orthokeratology has shown some benefit while wearing the lenses but is complicated by a number of sight threatening complications including infection. Pirenzepine has shown some benefit but due to expense and the evolving literature of atropine, will likely not be further pursued. Atropine has shown in the past as well as much more recently to be the current therapy of choice. The ATOM studies have shown great therapeutic success with minimal side effects.

Though further study and testing is necessary, the future of myopia progression therapy is looking brighter and the burden of myopia and its morbidities on the patient and on our society may lighten.

References

1. Leo SW, Young TL. An evidence-based update on myopia and interventions to retard its progression. J AAPOS. 2011 Apr;15(2):181-9.
2. Hung LF, Crawford ML, Smith EL. Spectacle lenses alter eye growth and the refractive status of young monkeys. Nat Med. 1995 Aug;1(8):761-5.
3. Wallman J, Winawer J. Homeostasis of eye growth and the question of myopia. Neuron. 2004 Aug 19;43(4):447-68.
4. COMET Group. Myopia stabilization and associated factors among participants in the Correction of Myopia Evaluation Trial (COMET). Invest Ophthalmol Vis Sci. 2013 Dec 3;54(13):7871-84.
5. Thorn F, Gwiazda J, Held R. Myopia progression is specified by a double exponential growth function. Optom Vis Sci. 2005 Apr;82(4):286-97.
6. Sherwin JC, Reacher MH, Keogh RH, Khawaja AP, Mackey DA, Foster PJ. The association between time spent outdoors and myopia in children and adolescents: a systematic review and meta-analysis. Ophthalmology. 2012 Oct;119(10):2141-51.
7. Hyman L, Gwiazda J, Hussein M, Norton TT, Wang Y, Marsh-Tootle W, Everett D. Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial. Arch Ophthalmol. 2005 Jul;123(7):977-87.
8. Saw SM, Goh PP, Cheng A, Shankar A, Tan DT, Ellwein LB. Ethnicity-specific prevalences of refractive errors vary in Asian children in neighbouring Malaysia and Singapore. Br J Ophthalmol. 2006 Oct;90(10):1230-5.
9. Congdon N, Wang Y, Song Y, Choi K, Zhang M, Zhou Z, Xie Z, Li L, Liu X, Sharma A, Wu B, Lam DS. Visual disability, visual function, and myopia among rural chinese secondary school children: the Xichang Pediatric Refractive Error Study (X-PRES)--report 1. Invest Ophthalmol Vis Sci. 2008 Jul;49(7):2888-94.
10.Fan DS, Lam DS, Lam RF, Lau JT, Chong KS, Cheung EY, Lai RY, Chew SJ. Prevalence, incidence, and progression of myopia of school children in Hong Kong. Invest Ophthalmol Vis Sci. 2004 Apr;45(4):1071-5.
11. Saw SM, Tong L, Chua WH, Chia KS, Koh D, Tan DT, Katz J. Incidence and progression of myopia in Singaporean school children. Invest Ophthalmol Vis Sci. 2005 Jan;46(1):51-7.
12. French AN, Morgan IG, Burlutsky G, Mitchell P, Rose KA. Prevalence and 5- to 6-year incidence and progression of myopia and hyperopia in Australian schoolchildren. Ophthalmology. 2013 Jul;120(7):1482-91.
13. Kempen JH, Mitchell P, Lee KE, Tielsch JM, Broman AT, Taylor HR, Ikram MK, Congdon NG, O'Colmain BJ, Eye Diseases Prevalence Research Group. The prevalence of refractive errors among adults in the United States, Western Europe, and Australia. Arch Ophthalmol. 2004 Apr;122(4):495-505.
14. Vitale S, Ellwein L, Cotch MF, Ferris FL 3rd, Sperduto R. Prevalence of refractive error in the United States, 1999-2004. Arch Ophthalmol. 2008 Aug;126(8):1111-9.
15. Vitale S, Sperduto RD, Ferris FL 3rd. Increased prevalence of myopia in the United States between 1971-1972 and 1999-2004. Arch Ophthalmol. 2009 Dec;127(12):1632-9.
16. Wen G, Tarczy-Hornoch K, McKean-Cowdin R, Cotter SA, Borchert M, Lin J, Kim J, Varma R, Multi-Ethnic Pediatric Eye Disease Study Group. Prevalence of myopia, hyperopia, and astigmatism in non-Hispanic white and Asian children: multi-ethnic pediatric eye disease study. Ophthalmology. 2013 Oct;120(10):2109-16.
17. Jones-Jordan LA, Sinnott LT, Manny RE, Cotter SA, Kleinstein RN, Mutti DO, Twelker JD, Zadnik K, Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study Group. Early childhood refractive error and parental history of myopia as predictors of myopia. Invest Ophthalmol Vis Sci. 2010 Jan;51(1):115-21.
18. French AN, Morgan IG, Mitchell P, Rose KA. Risk factors for incident myopia in Australian schoolchildren: the Sydney adolescent vascular and eye study. Ophthalmology. 2013 Oct;120(10):2100-8.
19. Gwiazda J, Hyman L, Hussein M, Everett D, Norton TT, Kurtz D, Leske MC, Manny R, Marsh-Tootle W, Scheiman M. A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. Invest Ophthalmol Vis Sci. 2003 Apr;44(4):1492-500.
20. Donovan L, Sankaridurg P, Ho A, Naduvilath T, Smith EL 3rd, Holden BA. Myopia progression rates in urban children wearing single-vision spectacles. Optom Vis Sci. 2012 Jan;89(1):27-32.
21. Pacella R, McLellan J, Grice K, Del Bono EA, Wiggs JL, Gwiazda JE. Role of genetic factors in the etiology of juvenile-onset myopia based on a longitudinal study of refractive error. Optom Vis Sci. 1999 Jun;76(6):381-6.
22. Kurtz D, Hyman L, Gwiazda JE, Manny R, Dong LM, Wang Y, Scheiman M, COMET Group. Role of parental myopia in the progression of myopia and its interaction with treatment in COMET children. Invest Ophthalmol Vis Sci. 2007 Feb;48(2):562-70.
23. Saw SM, Nieto FJ, Katz J, Schein OD, Levy B, Chew SJ. Familial clustering and myopia progression in Singapore school children. Ophthalmic Epidemiol. 2001 Sep;8(4):227-36.
24. Mutti DO, Mitchell GL, Moeschberger ML, Jones LA, Zadnik K. Parental myopia, near work, school achievement, and children's refractive error. Invest Ophthalmol Vis Sci. 2002 Dec;43(12):3633-40.
25. Ip JM, Saw SM, Rose KA, Morgan IG, Kifley A, Wang JJ, Mitchell P. Role of near work in myopia: findings in a sample of Australian school children. Invest Ophthalmol Vis Sci. 2008 Jul;49(7):2903-10.
26. Saw SM, Chua WH, Hong CY, Wu HM, Chan WY, Chia KS, Stone RA, Tan D. Nearwork in early-onset myopia. Invest Ophthalmol Vis Sci. 2002 Feb;43(2):332-9.
27. Jones-Jordan LA, Mitchell GL, Cotter SA, Kleinstein RN, Manny RE, Mutti DO, Twelker JD, Sims JR, Zadnik K, CLEERE Study Group. Visual activity before and after the onset of juvenile myopia. Invest Ophthalmol Vis Sci. 2011 Mar;52(3):1841-50.
28. Rose KA, Morgan IG, Ip J, Kifley A, Huynh S, Smith W, Mitchell P. Outdoor activity reduces the prevalence of myopia in children. Ophthalmology. 2008 Aug;115(8):1279-85.
29. Stambolian D. Genetic susceptibility and mechanisms for refractive error. Clin Genet. 2013 Aug;84(2):102-8.
30. Cheng D, Woo GC, Drobe B, Schmid KL. Effect of bifocal and prismatic bifocal spectacles on myopia progression in children: three-year results of a randomized clinical trial. JAMA Ophthalmol. 2014 Mar;132(3):258-64.
31. Swarbrick HA. Orthokeratology review and update. Clin Exp Optom. 2006 May;89(3):124-43.
32. Charm J, Cho P. High myopia-partial reduction ortho-k: a 2-year randomized study. Optom Vis Sci. 2013 Jun;90(6):530-9.
33. Cho P, Cheung SW. Retardation of myopia in Orthokeratology (ROMIO) study: a 2-year randomized clinical trial. Invest Ophthalmol Vis Sci. 2012 Oct 11;53(11):7077-85.
34. Chen C, Cheung SW, Cho P. Myopia control using toric orthokeratology (TO-SEE study). Invest Ophthalmol Vis Sci. 2013 Oct 3;54(10):6510-7.
35. Van Meter WS, Musch DC, Jacobs DS, Kaufman SC, Reinhart WJ, Udell IJ, American Academy of Ophthalmology. Safety of overnight orthokeratology for myopia: a report by the American Academy of Ophthalmology. Ophthalmology. 2008 Dec;115(12):2301-2313.e1.
36. Saw SM, Gazzard G, Au Eong KG, Tan DT. Myopia: attempts to arrest progression. Br J Ophthalmol. 2002 Nov;86(11):1306-11.
37. Chua WH, Balakrishnan V, Chan YH, Tong L, Ling Y, Quah BL, Tan D. Atropine for the treatment of childhood myopia. Ophthalmology. 2006 Dec;113(12):2285-91.
38. Tong L, Huang XL, Koh AL, Zhang X, Tan DT, Chua WH. Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. Ophthalmology. 2009 Mar;116(3):572-9.
39. Chia A, Chua WH, Cheung YB, Wong WL, Lingham A, Fong A, Tan D. Atropine for the treatment of childhood myopia: safety and efficacy of 05%, 01%, and 001% doses (Atropine for the Treatment of Myopia 2). Ophthalmology. 2012 Feb;119(2):347-54.
40. Chia A, Chua WH, Wen L, Fong A, Goon YY, Tan D. Atropine for the treatment of childhood myopia: changes after stopping atropine 001%, 01% and 05%. Am J Ophthalmol. 2014 Feb;157(2):451-457.e1.
41. Siatkowski RM, Cotter SA, Crockett RS, Miller JM, Novack GD, Zadnik K, U.S. Pirenzepine Study Group. Two-year multicenter, randomized, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. J AAPOS. 2008 Aug;12(4):332-9.
42. Siatkowski RM, Cotter S, Miller JM, Scher CA, Crockett RS, Novack GD, US Pirenzepine Study Group. Safety and efficacy of 2% pirenzepine ophthalmic gel in children with myopia: a 1-year, multicenter, double-masked, placebo-controlled parallel study. Arch Ophthalmol. 2004 Nov;122(11):1667-74.
43. Tan DT, Lam DS, Chua WH, Shu-Ping DF, Crockett RS, Asian Pirenzepine Study Group. One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. Ophthalmology. 2005 Jan;112(1):84-91.
44. Dörje F, Wess J, Lambrecht G, Tacke R, Mutschler E, Brann MR. Antagonist binding profiles of five cloned human muscarinic receptor subtypes. J Pharmacol Exp Ther. 1991 Feb;256(2):727-33.

Disclosure

None reported.

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Treating the Elite Athlete: Anti-Doping Information for the Health Professional

by Shikha Tandon, Larry D. Bowers, PhD & Matthew N. Fedoruk, PhD

USADA has developed an online educational tutorial to provide health professionals with information on anti-doping specific rules and resources.



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Abstract

Physicians and health professionals are a vital component in preserving the integrity of competition and the core principles of true sport. When treating an athlete, health professionals need to be cognizant of the anti-doping rules of the relevant sport organization. This review aims to provide an overview of the World Anti-Doping Agency Prohibited List, Therapeutic Use Exemptions, roles and responsibilities of the health professional, as well as provide resources that will guide their work with athletes.

Introduction

In sport, the second place is often viewed as the 'first loser'.[1] Athletes, and their coaches, are sometimes willing to make sacrifices and take risks, in an attempt to gain a competitive edge. Performance enhancement, with a 'win-at-all-costs' attitude, can be achieved by utilizing various physiological, mechanical, and pharmacological doping techniques.[1] Athletes and support personnel depend on the knowledge and expertise of health professionals to help guide them in making good medical decisions. Health professionals that work with athletes are often the first line of contact and it is important that they understand and comply with anti-doping policies and rules. Understanding the anti-doping rules can be challenging, but it is essential to ensuring success in program compliance, and avoiding potentially negative consequences – such as a positive anti-doping test or an adverse health event. Health professionals that fail to comply with anti-doping rules, run the risk of an anti-doping rule violation, which could lead to a possible period of ineligibility or lifetime ban from sport, for both the athlete and health professional.[2]

The U.S. Anti-Doping Agency and the World Anti-Doping Code

The U.S. Anti-Doping Agency (USADA) is the independent anti-doping agency for the Olympic and Paralympic movement in the United States.[3] USADA has the authority to execute a national anti-doping program encompassing testing, adjudication, education, and research; and to develop programs, policies, and procedures in each of these areas. USADA is a signatory to the World Anti-Doping Code (WADC) and is compliant with the WADC and all the accompanying WADC International Standards – The Prohibited List, International Standard for Testing,

International Standard for Therapeutic Use Exemptions, International Standard for Laboratories, and International Standard for Protection of Privacy and Personal Information.[3] In addition to the athlete, the actions of health professionals, in sport, are governed by the WADC and also by sport-specific anti-doping program rules.[2]

The World Anti-Doping Agency Prohibited List

The World Anti-Doping Agency (WADA) Prohibited List is a document that serves as the international harmonizing document and lists the substances and methods that are prohibited in Olympic sport.[4] The list is divided in to different categories and identifies which classes of substances and methods are prohibited at all times (in- and out-of-competition), in-competition only, as well as those substances that are prohibited in specific sports. WADA convenes an independent panel of international experts to consider the composition of the Prohibited List on an annual basis.[4]

A substance or method is considered for the Prohibited List if it meets any two of the following three criteria.[4]

- It has the potential to enhance sport performance;
- It represents an actual or potential health risk to the athlete;
- It violates the spirit of sport.

After the Prohibited List is revised each year by the WADA List Expert Group, it is sent to stakeholders for comment and finally approved by the WADA Executive Committee.[4] The revised list is approved and released each October for implementation the following January 1 to give opportunity to educate stakeholders on the revisions. For new substance additions, this may require changing a medication to non-prohibited alternatives or apply for a Therapeutic Use Exemption (TUE). While beta-blockers may be used in treating intra-ocular hypertension,[5] they also have the potential to steady nerves in competition.[6] Diuretics can be misused by athletes to rapidly excrete water from the body in order to meet weight categories, and also be used as a masking agent to dilute the urine such that lower concentrations of the prohibited substance is excreted from the body.[7] Stimulants can enhance performance by increasing energy and focus.[8] It is important to examine performance-enhancement broadly to consider the potential enhancement of not only speed, strength, and energy utilization, but also to include the enhancement of recovery, time to exhaustion, concentration and focus, pain tolerance, weight loss and maintaining optimal weight, thermoregulatory capacity, and confidence. Sidebar 1 outlines a case study on the use of thyroid hormone for performance enhancement.

The prohibited classes of substances that are prohibited at all times include non-approved substances (S0), anabolic agents (S1), peptide hormones, growth factors, related substances and mimetics (S2), beta-2 agonists (S3), hormone and metabolic modulators (S4), diuretics and masking agents (S5). Stimulants (S6), narcotics (S7), cannabinoids (S8), and glucocorticoids (S9) are prohibited in-competition only. Alcohol (P1) and beta-blockers (P2) are substances that are prohibited, in-competition only, in some sports. Methods that are prohibited at all times

Sidebar 1
Thyroid Hormone Case Study

Case:
A Tour de France cyclist admitted doping after having an adverse analytical finding. Among the prohibited substances he admitted using, were IV insulin, growth hormone, EPO. He also admitted using thyroxine. The reason that he gave for the use of thyroid hormone was:

A. Enhance muscle growth
B. Recover faster from training
C. Weight loss
D. Increased heart rate
E. Increased ventilation rate

Answer: C.
He claimed that the few additional kilograms that he lost, improved his climbing performance.

include manipulation of blood and blood components (M1), chemical and physical manipulation (M2), and gene doping (M3).[9] Substances, such as Tetrahydrogestrinone (THG), while not been proven through controlled studies to enhance athletic performance, are still prohibited. This is because these substances have the potential to cause adverse health effects due to their structural similarity with other anabolic agents. Oftentimes, it may not be ethical practice to conduct studies to test for human athletic performance enhancement using these unapproved substances. Table 1 lists examples of substances on the WADA Prohibited List for common medical diagnoses.

Table 1
Examples of substances on the WADA Prohibited List for common medical diagnoses. The WADA prohibited class is listed in parenthesis for each substance.

Medical Diagnosis	Examples of substances that are prohibited by WADA
Attention Deficit Hyperactivity Disorder	Methylphenidate (S6), Amphetamine (S6)
Asthma	Albuterol (S3), Salmeterol (S3), Formoterol (S3)
Androgen Deficiency/Male Hypogonadism	Testosterone (S1)
Arterial Hypertension	Hydrochlorothiazide (S5)
Diabetes Mellitus	Insulin (S4)
Post Infectious Cough	Pseudoephedrine (S6), Prednisone (S9)
Sinusitis/Rhinosinusitis	Pseudoephedrine (S6), Prednisone (S9)
Musculoskeletal Injuries	Methylprednisolone (S9), Oxycodone (S7)
Vitamin Deficiency	Intravenous infusion of vitamins (M2)
Allergies	Prednisone (S9)
Surgery	Oxycodone (S7)
Pain Management	Marijuana (S8)

It must be noted that the WADA prohibited list is an open list as it provides examples of prohibited substances and also prohibits any substances with similar biological effects. Agencies such as the National Collegiate Athletic Association (NCAA)[10] and Major League Baseball (MLB)[11] follow their own prohibited lists. Physicians should be aware of the competition status of the athlete, and consult the appropriate prohibited list, prior to prescribing any medication.

USADA's Global Drug Reference Online (GlobalDRO) resource provides athletes and support personnel with information regarding the prohibited status of medication as per the current WADA Prohibited List.[12] The user can search for specific pharmaceutical products as well as some over-the-counter medications that are sold in the United States, United Kingdom, Japan, and Canada. GlobalDRO does not provide information on dietary supplements or homeopathic medications. The USADA Wallet Card also provides a handy, quick reference summary guide to the common prohibited and permitted substances and medications under the WADA Prohibited List.[13] These resources can be accessed by athletes and health professionals via the USADA website.

Therapeutic Use Exemptions (TUEs)

In some situations, an athlete may have an illness or medical condition that requires the legitimate use of a substance that is listed on the WADA Prohibited List. In such situations, an athlete may be granted a Therapeutic Use Exemption (TUE).[14] USADA can grant a TUE for athletes, in compliance with the World Anti-Doping Agency International Standard for Therapeutic Use Exemptions (ISTUE).[15] The ISTUE document is a global standard and it should be noted that while some prescription of medication and treatment may be within the standard of care or common medical practice in the U.S., it may not be the normal standard within the international community. There are well established criteria, set by WADA, that need to be adhered to prior to approving a TUE[16] and a committee of experts reviews the diagnostic work-up much like an insurance review. These criteria are available in the ISTUE and have been designed to balance providing an unfair advantage with the need to provide athletes access to critical medication.[14] While the criteria for granting a TUE are listed in the ISTUE, it is the responsibility of the anti-doping organization to

appoint a team of qualified physicians that will serve as the TUE Committee (TUEC) and review each TUE application on an individual basis.[16] Physicians that are treating the athlete are responsible for providing and reporting accurate and complete medical information in the TUE application. The effectiveness of an alternative that is not prohibited should be evaluated, documented, and reported. A complete TUE file enables the TUEC to follow the diagnostic work-up process without ever seeing the athlete in-person and provide a thorough evaluation of the application.

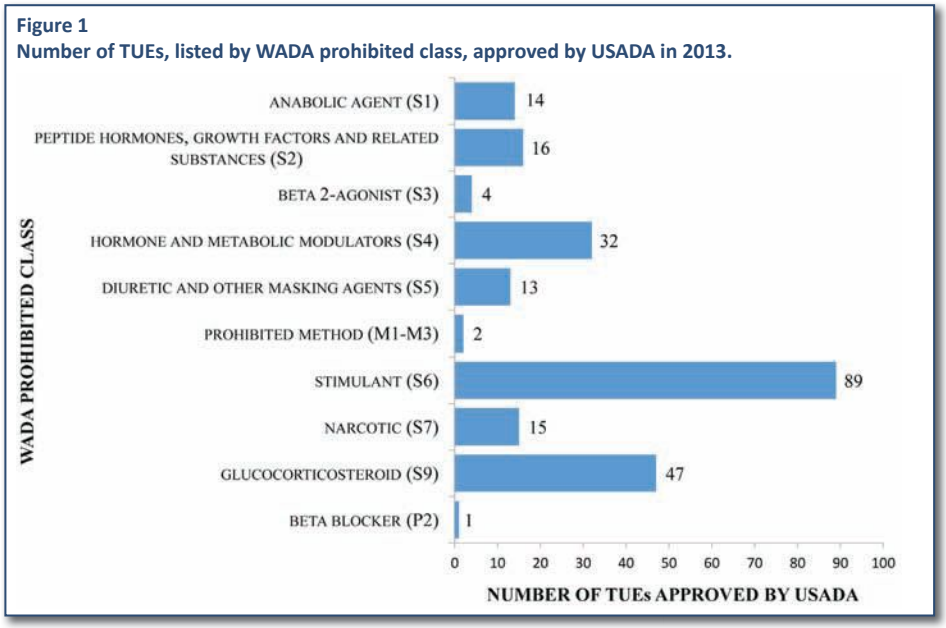
The criteria for granting a TUE, as outlined in the WADA ISTUE, is as follows:[16]

- The Athlete would experience a significant impairment to health if the prohibited substance or prohibited method were to be withheld in the course of treating an acute or chronic medical condition.
- The therapeutic use of a prohibited substance or prohibited method would produce no additional enhancement of performance other than that which might be anticipated by a return to a state of normal health following the treatment of a legitimate medical condition. The use of any prohibited substance or prohibited method to increase 'low-normal' levels of any endogenous hormone is not considered an acceptable therapeutic intervention.
- There is no reasonable therapeutic alternative to the use of the otherwise prohibited substance or prohibited method.
- The necessity for the use of the otherwise prohibited substance or prohibited method cannot be a consequence, wholly or in part, of the prior use, without a TUE, of a substance or method which was prohibited at the time of use.

As part of the TUE application process, the athlete is required to provide complete, and comprehensive medical documents and notes to support the diagnosis. There are WADA guideline documents,[17] written by physicians, available for Attention Deficit Hyperactivity Disorder (ADHD), adrenal insufficiency, anaphylaxis, androgen deficiency, arterial hypertension, asthma, diabetes mellitus, female to male transsexual athletes, growth hormone deficiency (childhood and adult), infertility and polycystic ovarian syndrome, inflammatory bowel disease, intravenous infusion, intrinsic sleep disorders, musculoskeletal injuries, post infectious cough, renal transplantation, and sinusitis and rhinosinusitis.[17] These documents are available on the USADA website and provide the treating physician with relevant information as well as lists out documentation that is required to support a TUE application. A TUE application that does not provide supporting medical documentation is returned to the athlete as incomplete and will not be processed. Figure 1 lists the number of TUEs approved by USADA in 2013.

It is important to keep in mind that the WADA TUE process may not be adopted by all sports organizations. For example, the National Collegiate

Figure 1
Number of TUEs, listed by WADA prohibited class, approved by USADA in 2013.



Athletic Administration (NCAA), the organization responsible for overseeing anti-doping in college level sports, reviews the Medical Exception for Banned Substances application, for some substances, retroactively if the athlete has an adverse test result.[18] USADA considers retroactive TUEs only in emergency circumstances, and generally requires 28 days of processing time for a TUE application.[15] When preparing for a surgery, the USADA website provides a to-do surgery checklist that covers anti-doping information that can be used by the athlete and the physician.[15]

Roles and Responsibilities of the Physician in Sport

Due to their focus on performance, athletes sometimes present their physicians with unique situations when compared to what is seen in the general population. Non-athletes are often motivated by the goal of prolonging a healthy life and seek reduced suffering and pain in an attempt to maintain long-term function.[19] Athlete patients, on the other hand, are performance driven and sometimes achievement, or the ability to compete, may take precedence in their mind over long term

Sidebar 2
Intravenous Infusions Case Study

Case:

An athlete that you are treating is competing in an upcoming event and must adhere to USADA anti-doping rules. There is some concern that on competition day the weather will be hot and humid, greatly increasing the chances of dehydration among the athletes. If there is a situation where the athlete is dehydrated and comes to you, as a health professional, and inquires about fluid replacement by IV for quick rehydration so that he/she may recover more quickly after the event. As a health professional, what would be your course of action?

Answer:

Intravenous infusions (IV) and/or injections of more than 50 mL per 6 hour period are prohibited, except for those legitimately received in the course of hospital admissions, surgical procedures or clinical investigations. The literature supports the position that drinking appropriate fluids may correct mild dehydration after exercise. IV infusions to aid in recovery are only warranted in severe cases of dehydration and gastrointestinal upset. When treating dehydration, if the athlete receives IV with saline and dextrose solution above 50 mL over 6 hours, the athlete/physician is required to apply to USADA for an emergency Therapeutic Use Exemption (TUE) by providing all relevant medical documentation and a complete TUE application form.

Table 2
Anti-Doping specific resources that are available to the health professional.

USADA Resources	Description	Weblink
GlobalDRO	Check the WADA status of medications by ingredient or brand name.	http://www.globaldro.com/us-en/
Wallet Card	List of medicines that are not prohibited by WADA in sport.	http://www.usada.org/substances/tue/
WADA Prohibited List	List of substances and methods that are prohibited in sport.	http://www.usada.org/substances/prohibited-list/
Supplement 411	Information on Dietary Supplements including a High-Risk List.	http://www.supplement411.org/supplement411/
Drug Reference Line	Speak to an expert to understand the Prohibited List, TUEs, and Dietary Supplements.	http://www.usada.org/substances/drug-reference-phone-line/
Ask the Scientist	Ask USADA's scientists and experts questions related to anti-doping science.	http://www.usada.org/science/ask-the-scientists/
Surgery Checklist	Information on anti-doping considerations in preparation for surgery.	http://www.usada.org/substances/tue/
HealthPro Advantage	Online anti-doping educational tutorial, specific to health professionals.	http://www.usada.org/resources/healthpro/
Athlete Express	Information on the basics of drug-testing.	http://www.usada.org/athletes/
Play Clean Tip Center	Anonymously report doping in sport.	http://www.usada.org/athletes/playclean/

health.[19] Post injury or illness, the main priority of an athlete is recovery such that they may return to competition and training at the earliest moment. This may cause them to be motivated to push the limits of their rehabilitation program. In some cases, the physician is responsible for making recommendations about when an athlete may resume certain activities. It is important that the physician is mindful of their obligations towards an athlete, or a sports team, and should carefully evaluate the motivation behind their actions. Sidebar 2 outlines a case study on intravenous infusions in sport.

As an example, as outlined in the College of Physicians and Surgeons of British Columbia, Professional Standards and Guidelines document, some of the responsibilities of a physician that is prescribing drugs to an athlete in sport, is as follows.[20]

- The physician should exercise caution when prescribing medications to athletes. The first responsibility of the physician is the health and safety of the patient.
- The physician should be mindful of the use of performance enhancing drugs (PEDs) in all levels of sport, be it high school or at an elite level. The physician should be knowledgeable about the possible dangers of PEDs and communicate directly with patients in an attempt to educate those that are engaging in these practices.
- The physician should not prescribe or advise patients about access to substances and services for the deliberate purpose of enhancing their sporting performance.
- The physician should not prescribe or administer any prohibited substance or assist with any method of doping, or succumb to pressure from patients, coaches or others to do so. The physician should be up to date in his knowledge on the WADA Prohibited List and consult it, and other anti-doping resources.
- The physician should prescribe to athletes and administer only those drugs which are medically indicated for established and bona fide medical conditions, in accordance with relevant clinical guidelines and the medical standard of care. The physician should also be aware of the TUE process and comply with the specific provisions contained in the ISTUE to provide only medically necessary drug treatment.

The WADA Code addresses the roles and responsibilities of athlete support personnel, who are defined as 'Any coach, trainer, manager, agent, team staff, official, medical, paramedical personnel, parent, or any other person working with, treating, or assisting an athlete participating in or preparing for sports competition'.[2] The Code has evolved to recognize the actions of athlete support personnel and also lists out possible sanctions for involvement with managing or participating in a doping program.

Resources for the Health Professional

USADA has developed a portal on their website which offers health professionals various anti-doping specific resources and documents, as listed in Table 2. HealthPro Advantage, USADA's online education tutorial, caters to health and medical professionals.[21] The goal of this 90-minute tutorial is to deliver practical, valuable, and directly applicable knowledge, specific to a health professional, who works with high-performance athletes. The tutorial features lessons on topics such as: Anti-Doping Roles and Responsibilities of Health Professionals, the WADA Prohibited List, the Sample Collection Process, Dietary Supplements, and the Therapeutic Use Exemption (TUE) process. Some of the benefits of completing the tutorial include:

- Learning to avoid errors which could contribute to an athlete testing positive and a possible anti-doping rule violation.
- Information on accessing various drug reference and educational resources.
- Determining the status of medication, including distinguishing substances prohibited at all times or only in-competition, or only in particular sports.

- Understanding the notification, sample collection, and anti-doping results management process.
- Understanding the roles and responsibilities of the athlete and team medical staff in the doping control process.
- Understanding the process for filing a TUE.
- Understanding Olympic Games and other major games specific anti-doping rules.
- Understanding and explaining the risks of dietary supplement use.

Conclusion

Physicians and health professionals that are treating athletes have an important role within the sporting community. Knowledge and understanding ensures that medical treatment provided to the athlete is in compliance with the anti-doping rules. Prior to prescribing any medication to the athlete, it is important to verify the prohibited status, in sport, of the medication. Therapeutic Use Exemption (TUE) procedures must be followed if the prohibited substance or method is medically necessary for the athlete. To enable a thorough evaluation of the TUE by the TUEC, it is important that the medical information provided by the health professional is detailed and accurate. The WADA Code states that those persons that are involved in doping of athletes, or covering up doping, should be subject to sanctions which are more severe than those given to athletes that test positive in a drug test. USADA has developed an online educational tutorial to provide health professionals with information on anti-doping specific rules and resources.

References

1. Baron DA, Martin DM, Magd SA. Doping in sports and its spread to at-risk populations: an international review. World Psychiatry. 2007; 6:118-123.
2. The World Anti-Doping Agency. 2015 World Anti-Doping Code. Available at: https://www.wada-ama.org/en/resources/the-code/2015-world-anti-doping-code#.VCWsVfldWAU. Accessed September 25, 2014.
3. The United States Anti-Doping Agency. About United States Anti-Doping Agency Page. Available at: http://www.usada.org/about/. Accessed September 25, 2014.
4. The World Anti-Doping Agency. World Anti-Doping Agency Prohibited List Page. Available at: http://list.wada-ama.org/. Accessed September 25, 2014.
5. Noecker RJ. The management of glaucoma and intraocular hypertension: current approaches and recent advances. Ther Clin Risk Manag. 2006; 2(2):193-206.
6. Lardon MT. Performance-enhancing drugs: where should the line be drawn and by whom? Psychiatry (Edgmont). 2008; 5(7):58-61.
7. Cadwallader AB, de la Torre X, Tieri A, Botrè F. The abuse of diuretics as performance-enhancing drugs and masking agents in sport doping: pharmacology, toxicology and analysis. Br J Pharmacol. 2010; 16(1):1-16.
8. Docherty JR. Pharmacology of stimulants prohibited by the World anti-Doping Agency (WADA). Br J Pharmacol. 2008; 154(3):606-622.
9. The World Anti-Doping Agency. The 2015 Prohibited List International Standard. Available at: https://wada-main-prod.s3.amazonaws.com/resources/files/wada-2015-prohibited-list-en.pdf. Accessed October 01, 2014.
10. The National Collegiate Athletic Association. 2013-2014 NCAA Banned Drugs. Available at: http://www.ncaa.org/health-and-safety/policy/2013-14-ncaa-banned-drugs. Accessed September 25, 2014.
11. Major League Baseball. MLB Players Association Joint Drug Agreement Page. Available at: http://mlbplayers.mlb.com/pa/info/cba.jsp. Accessed September 25, 2014.
12. The United States Anti-Doping Agency. USADA Global Drug Reference Online Page. Available at: http://www.globaldro.com/us-en/. Accessed September 25, 2014.
13. The United States Anti-Doping Agency. USADA Publications and Policies Page. Available at: http://www.usada.org/resources/publications-and-policies/. Accessed September 25, 2014.
14. Green GA. Doping control for the team physician – A review of drug testing procedures in sport. Am J Sports Med. 2006; 34:1690–1698.
15. The United States Anti-Doping Agency. USADA Therapeutic Use Exemptions Page. Available at: http://www.usada.org/substances/tue/. Accessed March 25, 2015.
16. The World Anti-Doping Agency. WADC International Standard for Therapeutic Use Exemptions 2011. Available at: https://www.wada-ama.org/en/resources/science-medicine/international-standard-for-therapeutic-use-exemptions-istue#.VCT-G_ldWAU. Accessed September 25, 2014.
17. The World Anti-Doping Agency. WADA Resources List Page. Available at: https://www.wada-ama.org/en/resources/search?f[0]=field_topic%3A24. Accessed September 25, 2014.
18. The National Collegiate Athletic Association. 2014 NCAA Drug Policies Brochure. Available at: http://www.ncaa.org/sites/default/files/Drug%20Policies%202014-15%2094256.pdf. Accessed September 25, 2014.
19. Murthy AM, Dwyer J, Bosco JA. Ethics in sports medicine. Bull NYU Hosp Jt Dis. 2012; 70(1):56-59.
20. College of Physicians and Surgeons of British Columbia. 2011 Professional Standards and Guidelines – Physician prescribing of performance enhancing drugs in sport. Available at: https://www.cpsbc.ca/files/pdf/PSG-Physician-Prescribing-of-Performance-Enhancing-Drugs-in-Sport.pdf. Accessed September 25, 2014.
21. The United States Anti-Doping Agency. USADA Health Professional Resources Page. Available at: http://www.usada.org/resources/healthpro/. Accessed September 25, 2014.

Disclosure

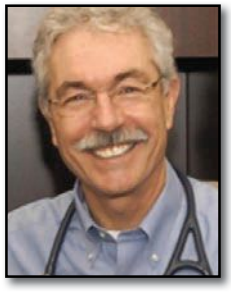
None reported.

MM

Telemedicine and Beyond

by David Voran, MD

Telemedicine shows us how technology can be used to actually intervene before diseases adversely affect the lives of our patients.



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Abstract

There is a resurgence of interest in telemedicine fueled by technology advancements and impending changes in reimbursement. Understanding various types of telemedicine helps separate hype from fact. This paper discusses the various forms of telemedicine; reviews telemedicine policy and regulatory status with emphasis in our [Missouri and Kansas] region; lists legislative, interstate licensing and reimbursement initiatives; and discusses future telemedicine trends with special attention to mobile devices.

Telemedicine: Definitions and Hype

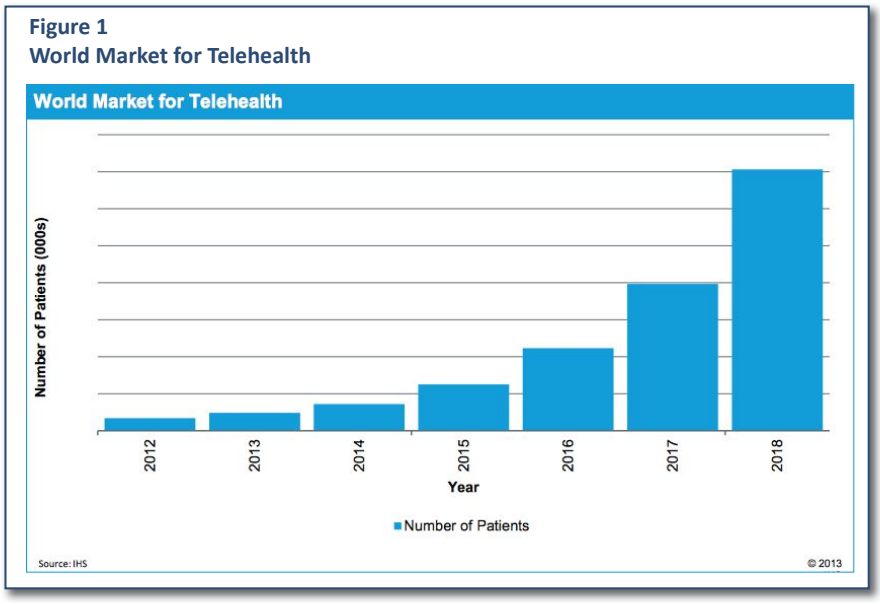
There has been a global logarithmic growth in telehealth encounters (see Figure 1).[1] Much of this growth is in the form of electronic visits or e-Visits. Lucas Mearin of *Computerworld* reports that e-Visits accounted for 75 million of 600 million appointments in the U.S. and Canada in 2013.[2] Most of these encounters are not what is considered traditional telemedicine where patients and providers communicate using special videoconferencing tools. Instead a large percentage of these visits are asynchronous store-and-forward messages using a variety of low-cost services. When synchronous e-Visits do occur, it is often in the form of regular telephone conversations, buttressed by the on-line information, rather than a virtual "face-to-face" visit.

Many case studies of well established, legacy telemedicine systems such as Avera eCare[3] for example, can be found online at the American Telemedicine Association web site in addition to the web sites of the system delivering these services. More recent and interesting uses of this technology occurred recently when the University of Nebraska used telemedicine equipment to treat an Ebola virus patient in their own facility.[4] Despite advances in technology, the utilization of these large systems has generally plateaued, primarily due to the cost, grant-driven funding models, and a host of other factors with reimbursement issues playing a big role.

Most of the growth in telemedicine is in the use of off-the-shelf technology in combination with cloud-based information services. In a recent survey of 1,000 U.S. employers, 37% reported they expected to offer telemedicine consultations for their employees as a low-cost alternative to emergency room or physician office visits. It has been reported that this use of telemedicine could yield six billion dollars per year in savings.[5]

The formal definition of

Figure 1
World Market for Telehealth



telemedicine according to the American Telemedicine Association is the "use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status."[6] Using this definition every phone call, electronic message or text to a patient could be defined as telemedicine.

The Centers for Medicare & Medicaid Services (CMS) defines telemedicine as the "provision of clinical services to patients by practitioners from a distance via electronic communications." But CMS significantly narrows the definition for Medicaid reimbursement to "two-way, real time interactive communication between the patient, and the physician or practitioner at the distant site … [with] the use of interactive telecommunications equipment that includes, at a minimum, audio and video equipment."[7] CMS explicitly does not consider any store-and-forward applications of this technology as telemedicine. This narrow definition of telemedicine excludes all of the asynchronous e-Visits that use standard e-mail, secure portal-based electronic messaging and phone conversations between the patient and the provider that doesn't include real-time two-way video. However by either definition the total number of telemedicine encounters still represent a very minute fraction of the total number of the 1.0 billion reimbursed physician encounters in the US.[8]

Why aren't their more virtual visits? Most physicians and patients use telemedicine-like technology daily in our communications with each other. We routinely conduct on-line virtual transactions with financial institutions, make travel and restaurant reservations, shop online and perform a host of other activities that in the past would've required a face-to-face encounter. Why don't we conduct a similarly significant share of our health transactions virtually? Despite all of the hype, why isn't telemedicine an integral part of any physician's practice?

It is my opinion the answers to these questions involve reimbursement and regulatory barriers that collectively discourage providers from using these tools to deliver medical care.

Telemedicine Stratification

I choose to arbitrarily stratify telemedicine into formal "big" and "intermediate" telemedicine services from "small" day-to-day uses of this technology by individual patients and providers.

- Big telemedicine is the result of many pilot projects that began in the early 1990s. They involve costly proprietary, high-end, high-resolution equipment in dedicated multimedia rooms connected together by a closed high-speed closed network. Each telemedicine room, or node, is located in a defined clinical setting such as a hospital, emergency room or clinic. Encounters are always synchronous based on two-way video encounters. They are scheduled in advance and involve several people in addition to the patient and the provider.
- Intermediate, specialty or service based services that utilize off-the-shelf cart-based mobile solutions to connect a provider to a patient. They can be found in clinical settings but can also be installed on a patient's own computer or tablets to be used in their homes. Encounters tend to be formalized, require some scheduling, documentation and billing analogous to face-to-face encounters.
- Small telemedicine is the use of inexpensive personal computers, smart phones, patient portals and/or other means of electronic communication we use in our day-to-day lives. Often this communication is asynchronous, does not involve a video component, is unscheduled, does not involve a support crew and uses public internet-based infrastructure.

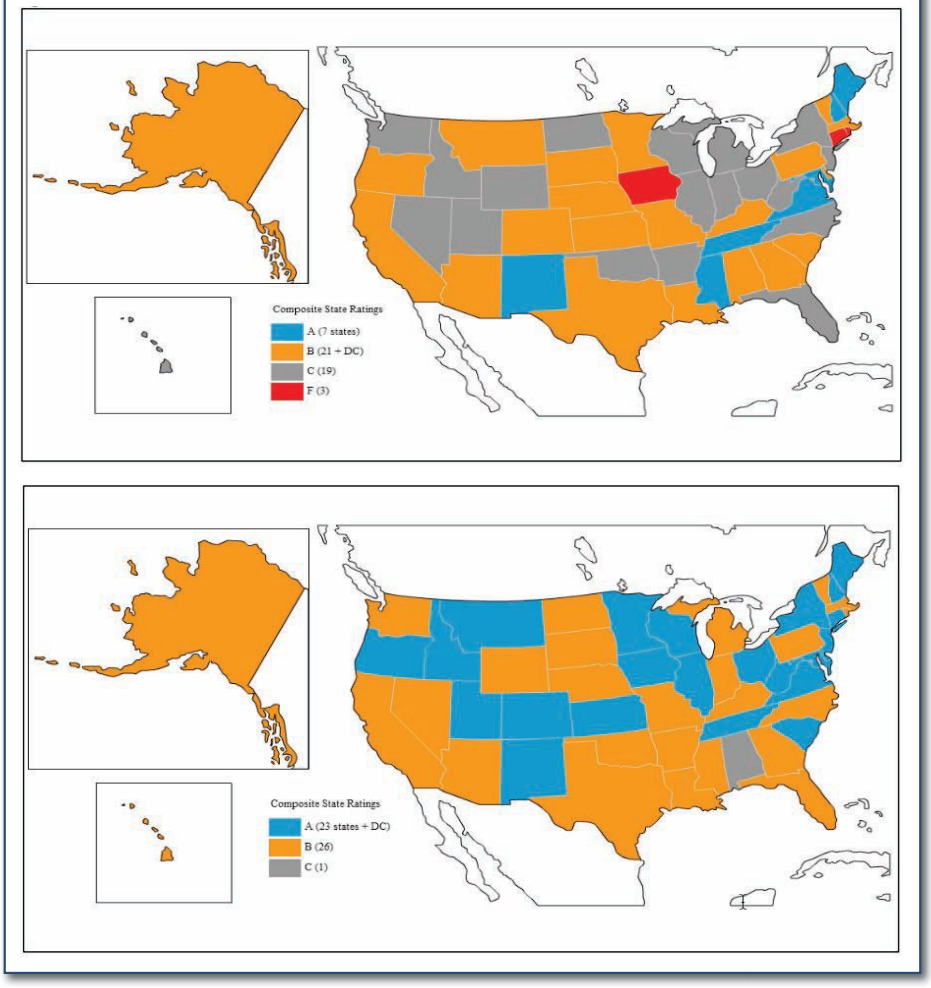
The purpose of this stratification helps understand regulatory language, differentiate reimbursement, calculate provider productivity as well as cut through many of

the confusing articles on telemedicine. Almost all of the formal regulatory and policy activity focuses on the "big" and "intermediate" telemedicine systems. Language effectively excluding personal technology restrains the ability of providers and patients to exploit these tools to deliver and receive healthcare leaving many questions unanswered.

Telehealth Coverage, Regulation and Reimbursement

Most states provide some reimbursement for telehealth encounters but coverage varies widely from state-to-state. The American Telemedicine Association maintains two up-to-date reports; one discusses state differences in Coverage and Reimbursement[9], the other is a Gaps Analysis of Physician Practice, Standards and Licensure.[10] Composite Maps provide an at-a-glance view of how each state's overall environment for telemedicine coverage (See Figure 2) and how they compare with regard to physician licensure (See Figure 3).

Figures 2 & 3
Composite Maps provide an at-a-glance view of how each state's overall environment for telemedicine coverage (Top - Figure 2) and how they compare with regard to physician licensure (Bottom - Figure 3).



A number of legislative initiatives intending to make it easier for physicians and patients to participate in virtual encounters are wending their way through various state and federal bodies. Though promising it is hard to predict which, if any, of these will be signed and enacted. Almost all of the legislative initiatives are directed towards the "big" and "intermediate" legacy telemedicine programs and all but ignore the "small" personal telemedicine services as defined above.

Federal level bills have been introduced in both the Senate and Congress to promote and improve telemedicine in the US include but are not limited to:

- S.596 - Fostering Independence Through Technology Act sponsored by John Thune (R-S.D.) introduced 3/18/2013[11].
- H.R.5380 – Medicare Telehealth Parity Act of 2014 sponsored by Rep. Mike Thompson (D-CA-5) introduced on 7/31/2014.[12]
- H.R.3306 – Telehealth Enhancement Act of 2013 introduced 10/22/2013 by Rep. Gregg Harper (R-MS-3).[13]
- S.2662 – Telehealth Enhancement Act of 2014 sponsored by Sen. Thad Cochran and introduced on 7/24/2014.[14]
- H.R.3750 Telehealth Modernization Act of 2013 sponsored by Rep. Doris Matsui (D-CA-6) and introduced on 12/12/2013.[15]

These initiatives point to a recognition by elected officials in both parties that telehealth has an important role in tackling high cost of healthcare, access deficiencies

and future methods of dealing with increasing needs as our population increases in size and age.

The Federation of State Medical Boards, spearheaded by the Wyoming State Board of Medicine is tackling the licensing barriers holding back telemedicine growth. This group is working to create an interstate expedited license that would be recognized by all member states.[16,17] The proposed telemedicine licensure would complement, not replace existing state licensure. It is early on in this process, dependent on a minimum of 7 participating states and expects to form this in 2016.

Telemedicine in Missouri and Kansas

Figure 4 shows side-by-side American Telemedicine Report Cards for Missouri and Kansas for Physician Practice Standards, Licensure, Coverage and Reimbursement. Both states have active programs.

Medicaid has covered some telemedicine services in Kansas since 2004. These included physician, psychotherapy, pharmacological management with – GT modifiers and requires the patient to be present at the originating site. Providers must have an active license to practice in order to provide services.

Figure 4
Side-by-side American Telemedicine Report Cards for Missouri and Kansas for Physician Practice Standards, Licensure, Coverage and Reimbursement.

Telemedicine in Missouri

PHYSICIAN PRACTICE STANDARDS & LICENSURE:	
Physician-patient encounter	F
Telepresenter	A
Informed Consent	A
Licensure & Out-of-State Practice	C
POLICY OR STATEMENT ON INTERNET PRESCRIBING:	✔

- Last policy revision: August 2013.
- Requires in-person exam and an in-person visit to establish physician-patient relationship.
- Requires full license and allows P2P exemption.

Telemedicine in Kansas

PHYSICIAN PRACTICE STANDARDS & LICENSURE:	
Physician-patient encounter	A
Telepresenter	A
Informed Consent	A
Licensure & Out-of-State Practice	C
POLICY OR STATEMENT ON INTERNET PRESCRIBING:	✔

- Requirements for telemedicine are on par with requirements for in-person services, not including prescribing. No unique practice standard requirements for telemedicine.
- Requires full license and allows P2P exemption.

Telemedicine in Missouri

PARITY:	
Private Insurance	A
Medicaid[132]	C
State Employee Health Plan[133]	A
MEDICAID SERVICE COVERAGE & CONDITIONS OF PAYMENT:	
Patient Setting	C
Eligible Technologies	F
Distance or Geography Restrictions	A
Eligible Providers	F
Physician-provided Services	B
Mental/behavioral Health Services[134-136]	B
Rehabilitation	F
Home Health	F
Informed Consent	F
Telepresenter	B
INNOVATIVE PAYMENT OR SERVICE DELIVERY MODELS:	
State-wide Network[137]	✔
Medicaid Managed Care	
Medicare-Medicaid Dual Eligibles	
Health Home	
HCBS Waiver	
Corrections	✔
Other	

- MO's private insurance parity law was enacted in 2013 and included coverage for state employee health plans.[130]

Medicaid

- Coverage for telemedicine under Medicaid is about average. The agency imposes restrictions on covered services and designates certain patient settings (excluding the home and school) and eligible distant site providers (physicians, advanced registered nurse practitioners, and psychologists as a condition of payment.
- Coverage for interactive audio-video only.
- Requires written informed consent and telepresenter on premises.[131]

Innovation

- Missouri Telehealth Network offers clinical, educational, emergency and disaster preparedness, and technical assistance via telemedicine across the state.

Telemedicine in Kansas

PARITY:	
Private Insurance	F
Medicaid	B
State Employee Health Plan	F
MEDICAID SERVICE COVERAGE & CONDITIONS OF PAYMENT:	
Patient Setting	A
Eligible Technologies	C
Distance or Geography Restrictions	A
Eligible Providers	A
Physician-provided Services	B
Mental/behavioral Health Services	B
Rehabilitation	F
Home Health	B
Informed Consent	A
Telepresenter	A
INNOVATIVE PAYMENT OR SERVICE DELIVERY MODELS:	
State-wide Network	
Medicaid Managed Care	✔
Medicare-Medicaid Dual Eligibles	
Health Home	
HCBS Waiver	✔
Corrections	✔
Other	

- Bordered by CO, MO, and OK which have private insurance parity laws. No telemedicine parity law.
- 2014 legislation introduced to provide parity coverage for telemental health[86] and telehealth-provided diagnosis and treatment for autism spectrum disorders.[87]

Medicaid

- No coverage for therapies via telemedicine under home health benefit.

Innovation

- Coverage for RPM and medication management available through approved HCBS waiver.[88-89]

The Center for TeleMedicine and TeleHealth is operated out of the University of Kansas Medical Center. This network has 60 nodes. The network provided 4,500 visits with 1,500 unique patients in 2013. It is more research than clinical in orientation and is dependent on grants for most of its operation. The Center is now exploring using the system to provide urgent care for the whole state.

A very innovative and promising use of telemedicine is the Kansas iCare, a pilot in mobile health clinic appointments using iPad Minis between multiple professionals and complex patients in their homes.

Missouri's coverage for telehealth is quite good when compared to other states. HB 986 prohibits plans from denying telehealth coverage and reimbursement and covers any services that would have been delivered in person. There are no regulatory restrictions on the type of technology being used but reimbursement is not available for any store-and-forward (asynchronous) services. A prior face-to-face physical exam is a necessary requirement for any reimbursement.

Missouri's Telehealth Network, directed by Rachel Mutrux, manages Missouri's system. Mo-Healthnet, run out of the University of Missouri, Columbia is a 202 node network running over MOREnet, a 2 gigabit backbone. The nodes are all located in defined clinical facilities that include most large and Critical Access Hospitals, Rural Health Clinics, Federally Qualified Health Centers, Nursing Homes, Dialysis Centers, Missouri State Rehab Center and Community Mental Health centers.

The primary benefit of these programs is to reduce the cost of travel for both specialist to rural areas and patients to distant centers where specialist care is located. Interestingly Psychiatric visits dominate the total telemedicine encounters in both states.

Future Directions

CVS' MinuteClinic is deploying telemedicine technology in a very novel way in California and Texas that might apply to many primary care offices and connected urgent care centers. Minute Clinics located in CVS pharmacies consist of two small adjacent exam room units built into a section of a CVS store. Most stores are staffed by a single nurse practitioner and patients self-register using a kiosk and wait their turn to be seen. In this pilot a typical self-contained telemedicine cart similar to those provided by IMED II[18] (See Figure 5) and Clinical Assist™ [19] (See Figure 6) is placed in the second exam room. This "telemedicine room" is then used when a waiting line develops. The nurse ushers one of the waiting patients into the "telemedicine room" where they can be seen by another nurse practitioner located in distant Minute Clinic who is not seeing patients at the time. This allows increased throughput at one location without having to change staffing models. In the first year of this pilot over 4,000 telemedicine encounters have been documented.[20] This model will undoubtedly spread throughout it's operations nation-wide as a key strategy in reducing local overhead and improving productivity and could very well suit many multispecialty groups with multiple locations.

Figures 5 & 6
Top, typical self-contained telemedicine cart similar to those provided by IMED II[18] and bottom, Clinical Assist™.

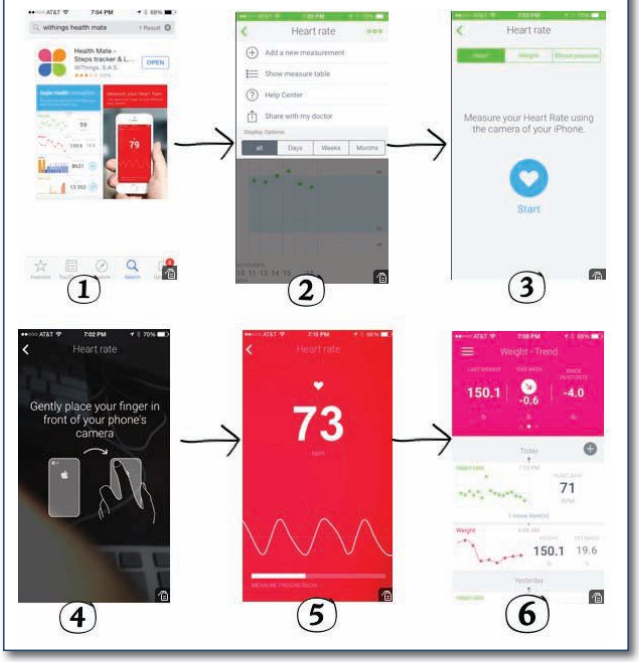




National network telemedicine services (Teladoc[21], MDlive[22], Doctor On Demand[23], MeMD[24], InteractiveMD[25], Specialists On Call[26] and many others similar systems) enroll physicians across the country to use their cloud-based infrastructure to field calls from patients located in the same state as the enrolled physician. When a subscriber calls a participating physician either near the patient or licensed in the patient's state is notified. The physician logs into the system to provide an asynchronous or synchronous visit depending on the urgency of the request. Many of the above mentioned national networks have corresponding Apps that enable their subscribing patients to initiate and conduct telemedicine/virtual visits from their phones.

These innovative uses of telemedicine are possible because of the shift from 3rd party reimbursement to direct consumer payment or subscription-based rmodels which

Figure 7
A composite screen capture of just one of many apps using only the built in camera and flash to relatively accurately measure pulses and though even the user's oxygen levels.



free the provider of telehealth services from the restrictions on what and how technology can be used to provide health care.

This brings us to the most promising trend in telemedicine, or what I call personal telemedicine. One of the biggest problems of virtual care is the need at some point to collect information that is normally obtained by directly touching or interacting with the patient to make diagnostic and treatment decisions. It is this need that is keeps regulators locked into the requirement of synchronous video interaction. This barrier is now beginning to be overcome by the use of technology embedded in many smart phones.

Current smartphones are brimming with a growing array of sensors designed primarily for non-medical uses. We consciously and unconsciously use apps relying on these motion, photometric and biometric sensors to give us directions, inform us about our activity, take photographs and connect and share information with others. These same sensors are now being used for clinical decision-making by a growing number of healthcare related apps. For example, Figure 7 is a composite screen capture of just one of many apps using only the built in camera and flash to relatively accurately measure pulses and though even the user's oxygen levels,[27,28]. In the last year we have witnessed many inexpensive attachments that are enabling clinicians and patients to capture single-lead EKGs,[29] obtain 20X to 80X magnification dermoscopic photos[30] and images of ear drums.[31] Each new smartphone iteration comes with ever increasing computing power that enable the owner to measure many physical parameters that in the past were only possible within health care settings.

Many other household devices are being connected to wi-fi and cellular networks and available for clinical use. For example, Withings Smart Body Analyzer[32] automatically uploads weight, body fat percentage and pulse to Withings web site or shared seamlessly with a growing number of apps to help an individual track health related personal parameters.

Apple's latest iOS 8 operating system contains HealthKit, an application framework, and Health App (See Figure 8) an application enabling other apps and hardware developers to distribute data with Apple's programs and each other.[33] Individuals can now choose to upload a wide range of personal health care information to their physician's patient portals and even into the shared medical record. Some health care and private organizations are experimenting with using these devices to automatically track patients and employees with chronic conditions to eliminate the need for costly face-to-face encounters for medical interventions.

Making sense of this mass of data becomes problematic for app developers, patients and clinicians. Cloud-based intelligent software services like IBM's Watson[34] are now available to any app developer to convert this data into meaningful information. We're starting to see apps designed to combine a users data with real-time queries against the world's medical literature to constantly inform the patient and the patient's physician on their immediate status. New start-up companies are being formed with the

Figure 8
Apple's latest iOS 8 operating system contains HealthKit, an application framework, and Health App, an application enabling other apps and hardware developers to distribute data with Apple's programs and each other.



intent on delivering a 24x7x365 "telemedicine" doctor in every person's hand.

Spurring much of this development is Qualcomm's Tricorder X Prize, a $10 Million dollar award to the first company to develop a portable, wireless hand-held device that not only monitors but diagnoses a patient's health conditions. Launched in October 2012, the contest is down to 10 finalists with the award tentatively scheduled for January 2016.[35]

These advancements open up an vast new area based on telemedicine tools enabling physicians to manage many more patients at a time than possible in the face-to-face model of care we are in today.

Summary and Conclusions

Formal "big" telemedicine continues to grow but will continue to be restrained without significant changes in reimbursement. In the meantime informal use of technology is spreading widely based on alternative reimbursement models. The explosion of hand-held technologies over the last few years with all of the capability as high end systems has surrounded traditional telemedicine services to the point they are becoming high-cost copies of what every person carries in their hand. Every physician recognizes that a growing number of patients are equipped with an array of tools that, if exploited, could be used to enhance the delivery of health care and improve access.

Apps on these phones can be supported in the background by extremely robust knowledge management systems like IBM's Watson to radically alter our ability as physicians to diagnose and treat diseases beyond the jail-cell exam room walls. Most importantly we can see how this technology can be used to actually intervene before these diseases adversely affect the lives of our patients. But in order for medicine writ large to exploit these technologies, payment reform must to take place.

References

1. A Dedicated Study on Telehealth that Provides Detailed Analysis of the World Market. Roashan, Roeen; Analyst. HIS Telehealth Report 2014. (http://info.imsresearch.com/lz/Instances/lz/documents/InMedica/Brochures/Abstract%20-%20World%20Market%20for%20Telehealth%202014%20Edition.pdf)
2. "Almost one in six doctor visits will be virtual this year." Mearian, Lucas. Computerworld Aug 8, 2014.
3. Avea eCARE Supports 675 Rural Clinicians in the Delivery of Highest Quality Care. American Telemedicine Association. http://www.americantelemed.org/about-telemedicine/telemedicine-case-studies/case-study-full-page/avera-ecare-supports-675-rural-clinicians-in-the-delivery-of-highest-quality-care#.U-cBLoBdWt
4. Nebraska Medical Center uses telemedicine to treat Ebola Patient. Baum, Stephanie. MedCityNews, September 15, 2014. (http://medcitynews.com/2014/09/nebraska-medical-center-uses-telemedicine-treat-ebola-virus-patient/)
5. Telemedicine could yield $6B per year in savings. Pedulli, laura. Clinical Innovation+Technology. August 11, 2104. (http://www.clinical-innovation.com/topics/mobile-telehealth/telemedicine-could-yield-6b-year-savings)
6. What is Telemedicine. http://www.americantelemed.org/about-telemedicine/what-is-telemedicine#.U-b7gIBdWt0
7. http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Delivery-Systems/Telemedicine.html
8. FastStats Homepage. Centers for Disease Control and Prevention. (http://www.cdc.gov/nchs/fastats/physician-visits.htm)
9. Thomas, Latoya and Capistrant, Gary. State Telemedicine Gaps Analysis: Coverage & Reimbursement. American Telemedicine Association. September 2014. (http://www.americantelemed.org/docs/default-source/policy/50-state-telemedicine-gaps-analysis---coverage-and-reimbursement.pdf?sfvrsn=6)
10. Thomas, Latoya and Gapistrant, Gary. State Telemedicine Gaps Analysis. American Telemedicine Association. September 2014. (http://www.americantelemed.org/docs/default-source/policy/50-state-telemedicine-gaps-analysis--physician-practice-standards-licensure.pdf?sfvrsn=6)
11. https://www.congress.gov/bill/113th-congress/senate-bill/596
12. https://www.congress.gov/bill/113th-congress/house-bill/5380
13. https://www.congress.gov/bill/113th-congress/house-bill/3306
14. https://www.congress.gov/bill/113th-congress/senate-bill/2662
15. https://www.congress.gov/bill/113th-congress/house-bill/3750
16. Interstate Medical Licensure Compact. Federation of State Medical Boards New Release. http://www.fsmb.org/state-medical-boards/interstate-model-compact/news
17. GRPOL Telemedicine Licensure. Telemedicine Overview Board-by-Board Approach. Federation of State Medical Boards. http://www.fsmb.org/Media/Default/PDF/FSMB/Advocacy/GRPOL_Telemedicine_Licensure.pdf
18. http://www.amdtelemedicine.com/telemedicine-equipment/imeds-telemedicine-system.html
19. http://www.amdtelemedicine.com/telemedicine-equipment/clinical-assist-system.html
20. Private conversation with Dr. Tobias Barker, Senior Medical Director for MinuteClinic
21. http://www.teladoc.com
22. https://www.mdlive.com
23. http://www.doctorondemand.com
24. http://www.memd.me
25. http://www.interactivemd.com
26. Specialists On Call, Joint Commission-accredited provider of emergency telemedicine consultations providing 24/7/365 speciality on-call coverage for neurology, cardiology, intensivists and psychiatry. http://www.specialistsoncall.com/en/index.php/about-us
27. Pulse Oximeter – Heart and Oxygen Monitor App by digiDoc Technologies AS available on iTunes. https://itunes.apple.com/app/pulse-oximeter-heart-oxygen/id775632066?ign-mpt=uo%3D8
28. Withings Health Mate – Steps Tracker & Life Coach. WiThings, S.A.S. Withings.Com
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31. Cellscope, Inc. www.cellscope.com
32. Smart Body Analyzer http://www.withings.com/us/smart-body-analyzer.html
33. HealthKit, Apple, Inc. https://developer.apple.com/healthkit/
34. IBMWatson. http://www.ibm.com/smarterplanet/us/en/ibmwatson/what-is-watson.html
25. Qualcomm Tricorder XPRIZE. http://tricorder.xprize.org

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Disclosure

None reported.

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Updates on Management of Anoxic Brain Injury after Cardiac Arrest

by Joanna Isabelle Ramiro, MD & Abhay Kumar, MD

The core of the management in anoxic brain injured patients from cardiac arrest is prompt application of hypothermia in appropriate settings, treatment of seizures, hemodynamic maintenance, and supportive care.





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Abstract

Brain injury is a leading cause of mortality and morbidity among cardiac arrest survivors. Management of these patients in the acute phase is challenging as is predicting their outcomes especially with the application of hypothermia. Therapeutic hypothermia has been proven beneficial but target temperature, timing, and duration that produce the best outcome are unclear and the subject of on-going research. We review the recent advances in therapy and update the guidelines for management of these patients.

Introduction

More than 400,000 people suffer from cardiac arrest each year in the United States.[1] Overall survival rates remain dismal: 22% in in-hospital cases and 10% in out-of-hospital cases, respectively.[1] A significant cause of mortality is secondary to brain injury, which is a reflection of the brain's intolerance to ischemia and its complex response to reperfusion.[2, 3] Over the past decades, several studies have been performed to better understand the process, prognosis, and management of anoxic brain injury after cardiac arrest in the hopes of improving outcome. Our aim is to update the reader about management of anoxic brain injury in the acute setting in these patients.

Pathophysiology of Neuronal Injury

Cessation of cerebral circulation leads to depletion of oxygen stores within 20 seconds and manifests as loss of consciousness.[4] At five minutes, glucose and oxygen are lost causing a disruption in ATP production and subsequent dysfunction of ATP-dependent membrane pumps, which maintain cellular membrane integrity.[4, 5] This eventually leads to influx of calcium ions into the ischemic brain cells with the release of glutamate, an excitotoxic neurotransmitter, to NMDA receptors. Elevated intracellular calcium amplifies injury by activating secondary messengers that further promote calcium influx and interfering with the mitochondrial electron transport energy chain leading to formation of oxygen free radicals.[5] These free radicals cause further cell damage that can trigger cell death.[4-6] Secondary injury, which can occur hours or days after the initial event, results from other causes of oxygen compromise such as hypotension, brain edema and cerebrovascular dysregulation.[2]

Neurologic Manifestations of Anoxic Brain Injury

The hippocampus, cerebral cortex, thalamus, and cerebellum are regions especially susceptible to hypoxic injury and could cause clinical symptoms such as alteration

of awareness, coma, seizures and strokes.[2, 5] Long-term outcomes due to damage to thalamo-cortical networks or bilateral cortical regions can range from memory deficits to persistent vegetative state.[2, 5] Involvement of the basal ganglia leads to movement disorders such as myoclonus, Parkinsonism, chorea and tics. The brainstem, on the other hand, is more tolerant of global ischemia; hence, the preserved function or early recovery of cranial nerves.[2,5] Disruption of the autonomic centers such as the hypothalamus or its connections to cortex, subcortical regions or brainstem can result in paroxysmal autonomic instability with dystonia or PAID syndrome, which is characterized by agitation, diaphoresis, hypertension, tachycardia, tachypnea, and extensor posturing.[7]

Defining Neurologic Outcome

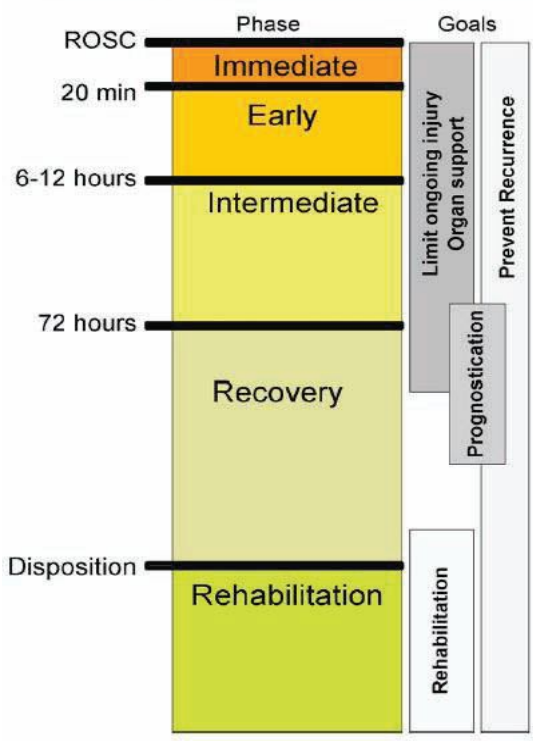
The Glasgow Outcome Scale (GOS) and the Cerebral Performance Category (CPC) are both five-point scales widely used in assessing neurologic outcome.[8] In the GOS, a score of 5 is associated with good cerebral performance with mild or no disability. Lower scores are indicative of more severe disabilities with a score of 1 associated with death or brain death. In CPC, the scoring system is reversed where lower scores are more favorable. Poor outcome (death, coma or vegetative state) is defined as GOS of 1-2 or CPC of 4-5 according to established guidelines.[8]

Prognostication: Clinical Manifestations, Timing and Tools

Cardiac arrest can cause significant neurological injuries leaving patients cognitively disabled and in a dependent state. (See Figure 1.) Very few patients recover neurologically intact.[9] Financial implications for families, insurers and health care systems are substantial.[9] The direction of care is dependent on accurate prognostic information, which relies mainly on clinical examination and other ancillary tests. The prognostication algorithm as suggested by American Academy of Neurology can be affected by application of hypothermia in cardiac arrest patients due to delayed clearance of sedatives and paralytics, which can mask their neurological examination.[9] Predicting prognoses early in these patients may lead to premature withdrawal of life-sustaining measures in about 20% of patients who would otherwise have good recovery.[8] Neurological examination for prognostication purposes should be delayed for 72 hours after normothermia is achieved in the absence of sedation and paralysis. The presence of some prognostic signs such as myoclonic status epilepticus occurring within 24 hours after arrest or absence of all brainstem reflexes may justify earlier evaluation for prognostication than recommended 72 hours.[10]

Figure 1
Phases of Post-Cardiac Arrest Syndrome

Reproduced from Nolan JP et al. Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication. Resuscitation 2008; 79:350—379 with permission from Elsevier.



Brainstem Reflexes and Motor Response

The loss of all brainstem functions, even during the early phase of recovery, is associated with poor outcome.[9, 10] The absence of bilateral pupillary light reflex 72 hours after cardiac arrest may be the most accurate predictor of poor outcome.[9, 11] Further information can be obtained from checking corneal reflexes, although it may be less reliable if paralytic medication effects persist in the system.[11] The reliability of the presence or absence of other brainstem reflexes such as the vestibulo-ocular, cough and gag reflexes has not been well documented.[10]

The motor component of the Glasgow Coma Scale (GCS) also provides additional prognostic information. At 48-72 hours after cessation of sedatives and paralytics, a motor response that localizes to pain (GCS motor

score ≥5) is suggestive of a favorable outcome while extension to painful stimuli (GCS motor score ≤2) is a poor prognostic sign.[9, 11]

Myoclonus and Seizures

Post-hypoxic myoclonic seizures are common following cardiac arrest. These are abrupt, irregular, muscle twitches that can be focal or generalized (involving the face, limbs, and trunk).[9] These can be sporadic and have little prognostic value.[8, 9] Status myoclonus, on the other hand, manifested as repetitive, unrelenting, generalized myoclonic seizures is highly associated with poor outcome even in patients with intact brainstem reflexes and good motor response, especially if it occurs within the first 24 hours of the cardiac event.[8-11] The occurrence of early status myoclonus has decreased since the advent of therapeutic hypothermia. This is likely from concurrent use of sedatives and paralytics, which can mislead physicians during prognostication.[10, 11]

Tonic-clonic and focal epileptic seizures frequently occur during the re-warming process but do not carry the same negative prognostic implication as early myoclonic status.[10]

Electroencephalography (EEG)

The predictive value of EEG is limited since it can be affected by factors such as timing of recording and interference from sedatives and hypothermia.[11] Seizures occur in 10–40% of cardiac arrest patients.[8] Electrographic seizures consist of epileptiform discharges occurring repetitively and continuously for at least 10 seconds.[11] Prolonged or recurrent electrographic seizures or electrographic status epilepticus (ESE), which can occur with or without clinical seizures is associated with poor outcome especially if it develops from a burst suppression pattern.[11] Other patterns associated with poor outcome such as alpha-coma, burst suppression or generalized suppression have been reported.[8]

Besides seizure detection, EEG can also be used to assess nervous system reactivity. Reactivity is confirmed when there is a reproducible change in the amplitude or frequency of the EEG background after stimulation, such as eye opening, clapping, vocal sounds, touch or pain.[8, 11] The absence of reactivity during and after hypothermia is strongly associated with poor outcome in some studies,[8,11] but the evidence about EEG reactivity in post-anoxic coma is limited and there need to be further studies before it can be reliably used in clinical settings.[8]

Somatosensory Evoked Potentials (SSEP)

In contrast to EEG, SSEPs are not affected by hypothermia or sedation. It is a non-invasive test that involves electrical stimulation of a peripheral nerve. For purposes of prognostication, the median nerve is typically tested at the level of the wrist.[10] In intact nervous systems, an electrical response (N20 potential) is recorded over the contralateral sensory cerebral cortex approximately 20 milliseconds after median nerve stimulation.[8,10] Bilateral absence of N20 SSEP at 24 hours after cardiac arrest is one of the most accurate predictors of poor outcome with specificity nearing 100%.[10] The use of SSEP is limited by its low sensitivity, unavailability in smaller institutions, and moderate inter-observer variation.[8-10] Despite these limitations, a recent review reveals that among all predictors, absence of N20 SSEP had the most influence on decision-making, including withdrawal of life-sustaining therapies, among physicians and families.[11]

Bio-Markers

Two of the most extensively studied serum biomarkers of brain injury are neuron-specific enolase (NSE) and S-100B.[8] Previous data suggested that a serum NSE level above 33μg/L at 24-72 hours after cardiac arrest is a good indicator of poor outcome.[9] However, this cut-off value could not be confirmed in more recent studies, especially in patients treated with hypothermia. Higher NSE cut-offs (>50-80μg/L) are necessary to reliably predict poor outcome.[8] S-100B levels are even more variable with cut-off values ranging from 0.2-1.5mg/L.[8] The presence of these biomarkers in extra-cerebral sources is a major cause of variability.[11] NSE-producing tumors (e.g. small-cell lung carcinoma and neuro-endocrine tumors) and hemolysis cause increased NSE levels.[11] In addition, fat and muscle breakdown, which may occur during prolonged chest compressions, can cause erroneously elevated S100-B levels.[8-10] Despite its ease of use and independence from sedative drug effects, the wide variability limits its role in decision-making.[8,9,11]

Neuro-Imaging

During the early phase of cardiac arrest, neuro-imaging results are typically not useful in prognostication as they may be normal or demonstrate subtle abnormalities.[12] The purpose of obtaining a head computed tomography (CT) scan immediately after arrest is to exclude any primary brain injury that can result in cardiac arrest or coma.[8,9] The main CT finding of anoxic brain injury is brain edema, which appears as sulcal effacement and decreased grey-white matter differentiation.[11,13] However, current data are

insufficient to support its use as a prognostication tool in post-cardiac arrest.[8]

Magnetic resonance imaging (MRI) offers more promise in predicting outcome. Disruption of cell membranes due to oxygen depletion restricts cell membrane water diffusion and results in cytotoxic edema.[9,14] This is responsible for the symmetrical grey matter hyper-intensities in diffusion-weighted imaging (DWI), which provides a qualitative measure of brain injury.[9,12,14] Different patterns of brain injury relate to clinical outcome. They include isolated cortical injury, isolated deep grey nuclei injury (e.g. caudate nucleus, putamen, and thalamus), and mixed cortical and deep grey nuclei involvement.[12,15] The mixed pattern correlates with the most severe form of injury.[15]

A standardized quantitative assessment of brain injury can be made by measuring the apparent diffusion co-efficient (ADC).[12] Patients with >10% of brain volume with a decreased ADC value between $650x10^{-6}$ mm^2/s to $700x10^{-6}$ mm^2/s had poor outcome (See Figure 2).[16] Most of the decrease in ADC values occur during a certain time period and involve specific brain regions.[13,14] The cortical grey matter was most profoundly affected between three to five days after arrest in patients who had a poor outcome.[14] Favorable outcome was noted in those with increased diffusion in the occipital and temporal cortices, hippocampus, putamen, and corona radiata.[14]

More recent advances in brain MRI techniques are being utilized for prognostication among comatose survivors mostly for research purposes. Diffusion Tensor Imaging (DTI) and functional MRI are among emerging areas of investigation. These measure changes in micro-structural and functional connectivity, respectively, with more disruptions associated with worse outcomes.[17] As we understand these technological advances are understood further, it may be possible to use them to improve prediction of neurologic recovery and outcomes among patients with anoxic brain injury in the future.

Management of Anoxic Brain Injury

Therapeutic hypothermia (TH)

Induced hypothermia as a therapy for acute brain injury was first described by Fay in the 1940s.[5] Subsequent use remained limited to small pre-clinical and clinical studies until the findings of Hypothermia After Cardiac Arrest trial conducted in Europe and a concurrent trial from Australia showed that maintenance of temperature between 32°C and 34°C for 12-24 hours increased survival as well as chances of favorable neurologic outcomes in patients with cardiac arrest due to ventricular fibrillation.[18,19]

Following these two studies, the International Liaison Committee on Resuscitation (ILCOR) and the American Heart Association (AHA) published an interim scientific statement recommending the use of therapeutic hypothermia in comatose survivors of cardiac arrest.[5] Since then, TH has been adopted as a standard of care for post-cardiac arrest cases including cases of pulseless electrical activity. It should be initiated as soon as possible with a target temperature ranging from 32-34°C.[2,5] Rapid intravenous infusion of ice-cold 0.9% saline, external cooling blankets or pads with water-filled circulating systems, and intravascular cooling are some of the methods utilized to achieve TH.[2,5]

There has been much debate regarding the recommended temperature of 32°- 34°C since similar results have been observed with milder cooling. A recent multi-center, randomized trial that compared target body temperature controlled at 33°C vs 36°C in patients who were resuscitated after cardiac arrest showed similar mortality rates and neurologic recovery in the two groups.[21] The study, however, emphasized the importance of actively controlling the temperature and fever prevention during the first three days of cardiac arrest.

Optimal timing of induction of TH also remains unclear but the current consensus is to start cooling as soon as possible.[2,5] Whether benefits of TH could be gained by applying it in pre-hospital settings was the subject of a recent study in cardiac arrest patients. Results showed that pre-hospital cooling reduced core temperature by hospital arrival and reduced the time to reach a temperature of 34°C but did not improve survival or neurological status in these patients.[22]

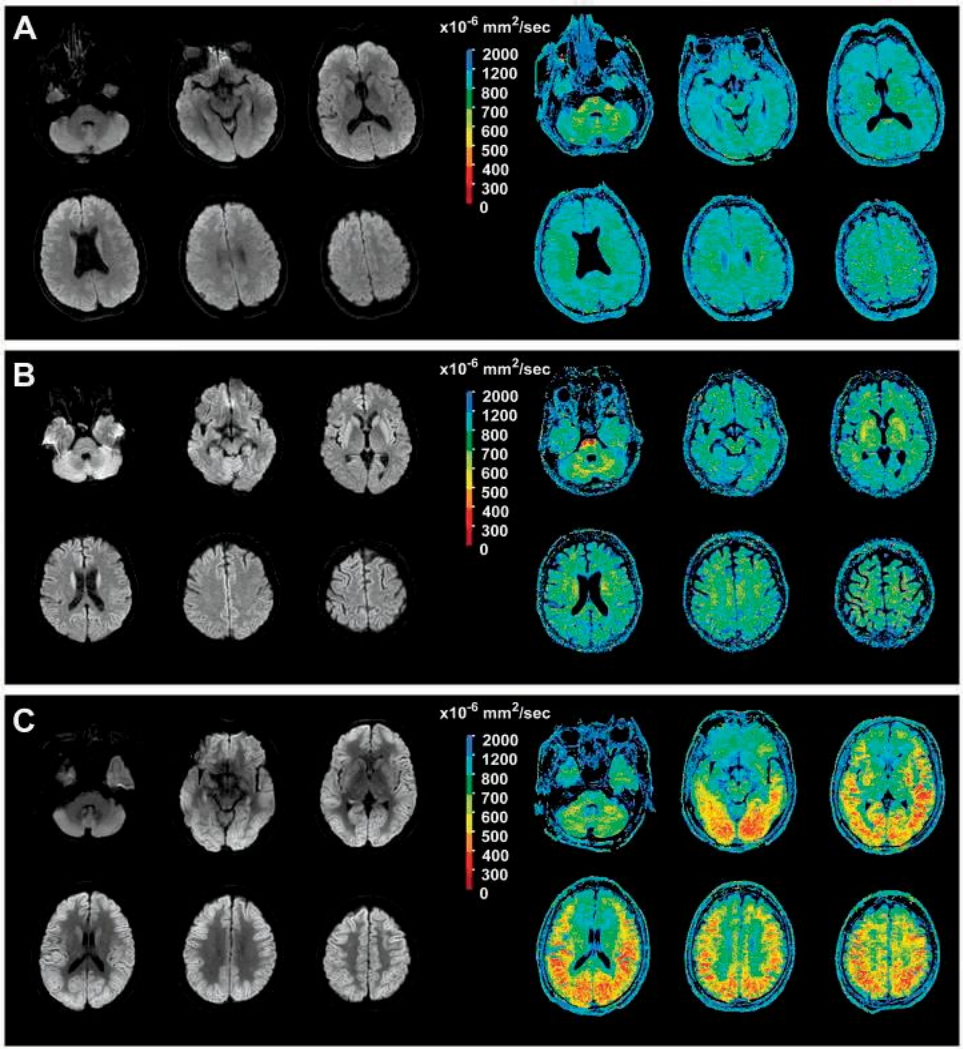
Current guidelines recommend application of TH as part of post-resuscitation care although subtle differences in protocols exist. Target temperature, timing, duration, and method of cooling that leads to the best neurologic outcome are still unknown and the subject of on-going, and possibly future, research.

Fever Management

It has been well documented that hyperthermia exacerbates acute neurological injury and contributes to poor outcomes.[23] Each degree over 37°C is correlated with an increased risk for severe disability, coma, or persistent vegetative state.[5] Development of fever after cardiac arrest is common. However, fevers are less common in those treated with TH. Fever does not appear to carry the same detrimental consequences in TH-treated patients as compared to those not receiving TH.[23] It is possible that the earlier hyperthermia occurs, the greater its consequences.[23]

Figure 2
Brain DWI and Corresponding ADC maps
(legend modified from original article)

The color ADC map shows pixels with an ADC value of 300–400 in red, 400–500 in orange, 500–600 in yellow, 600–700 in light green, 700–800 in dark green, 800–1200 in light blue, and 1200–2000 in dark blue.



Panel A: Twenty-two year-old man 64 hours after cardiac arrest who awoke after 3 days and had good neurological recovery at 6 months. Only subtle areas of restricted diffusion are seen in the thalami and cerebellum bilaterally.

Panel B: Thirty-seven year-old woman 52 hours after cardiac arrest who had impaired neurologic outcome. Note the widespread areas of restricted diffusion are seen in the cerebellum, thalami, basal ganglia, sub-cortical white matter, and cortex bilaterally.

Panel C: Sixty-six year-old man 67 hours after cardiac arrest who had poor outcome. Widespread areas of severely restricted diffusion are seen in the cortex, subcortical white matter, internal capsule, thalamus, basal ganglia, brainstem, and cerebellum bilaterally.

Reproduced from Wijman CAC et al. Prognostic Value of Brain Diffusion Weighted Imaging After Cardiac Arrest. Ann Neurol 2009; 65(4): 394–402 with permission from John Wiley and Sons.

Pre-clinical studies reveal that hyperthermia 24 hours after arrest, but not at 48 hours worsens brain injury, which suggests the time-dependent vulnerability of neurons to hyperthermia.[23] In both treatment subgroups, antipyretics and surface or invasive cooling measures should be used aggressively to ensure that the body temperature is less than 38°C.[5]

Seizure Control and Prevention

Prophylactic anti-epileptic drugs (AEDs) are not used commonly in post-cardiac arrest patients. In those who were treated with hypothermia, seizures are commonly observed during the re-warming phase and weaning of sedation.[5] An EEG should be performed on any patient who is suspected of having seizures, and those who do not regain consciousness after re-warming to exclude non-convulsive status epilepticus.[5, 20] Standard AEDs should also be started but no comparative studies provide guidance as to choice of therapy.[10] In cases of status epilepticus, anti-epileptic drugs are combined with sedatives, and the combination suppresses both clinical and electrographic seizures quite well. Data regarding suppression of status epilepticus using conventional AEDs alone are less convincing.[10] Myoclonic status, on the other hand, is difficult to treat. Clonazepam

is the most effective drug, but sodium valproate, levetiracetam, and propofol may also be effective.[2]

Cerebral Perfusion

Hypotension after ROSC should be avoided since it worsens cerebral ischemia.[5] Cerebral perfusion can be further compromised by dysregulation of cerebral vasculature, which can occur in the acute phase of recovery.[5] It may be necessary to maintain the mean arterial blood pressure (MAP) at higher levels to ensure adequate cerebral blood flow.[5] A MAP greater than 65mmg Hg is adequate for coronary perfusion but maybe insufficient to provide adequate cerebral blood supply unless therapies are implemented to decrease cerebral metabolic activity, such as sedation and hypothermia.[5] MAP values of 80 to 100 mm Hg have been suggested to be beneficial, at least for the first 24 hours after arrest.[5]

Neuroprotective drugs

Few neuroprotective drugs have been tested in clinical trials. There is inadequate evidence to recommend any pharmacological neuroprotective strategies to reduce brain injury in post-cardiac arrest patients.[2]

Conclusion

The core of the management in anoxic brain injured patients from cardiac arrest is prompt application of hypothermia in appropriate settings, treatment of seizures, hemodynamic maintenance, and supportive care. The previously established prognostic tools still hold, but TH has influenced the reliability and the timing of clinical evaluation and supportive tests. Prognostication should be done 72 hours after achievement of normothermia, in the absence of sedating or paralyzing drugs, to ensure that the information gathered is accurate in order to avoid premature withdrawal of life-sustaining measures in patients who would otherwise have good outcomes. In addition, certainty of predicting outcomes improves by utilizing a multi-modal approach to prognostication, where information from both clinical examination and supportive tests are taken together to guide decision-making. Lastly, certain areas of management such as target temperature, timing of initiation, and method of cooling require standardization and are currently under investigation.

References

1. Go AS et al. Heart Disease and Stroke Statistics—2014 Update: A Report From the American Heart Association. Circulation 2013; 129: e28-e292.
2. Nolan JP et al. Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication. Resuscitation 2008; 79:350—379
3. Laver S et al. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med. 2004; 30(11):2126-2128.
4. Madl C et al. Brain function after resuscitation from cardiac arrest. Curr Opin Crit Care 2004; 10:213–217.
5. Geocadin RG et al. Management of Brain Injury After Resuscitation From Cardiac Arrest. Neurol Clin. 2008 May; 26(2): 487 – 503.
6. Harukuni I et al. Mechanisms of brain injury after global cerebral ischemia. Neurol Clin. 2006 Feb;24(1):1-21.
7. Blackwell JA, Patrick PD, Buck ML et al. Paroxysmal Autonomic Instability With Dystonia After Brain Injury. Arch Neurol. 2004;61(3):321-328.
8. Horn J et al. Prognostication after Cardiac Arrest. Current Opin Crit Care. 2014; 20:280-286.
9. Wijdicks EFM, Hijdra, A., Young, G. B., Bassetti, C. L. & Wiebe, S. Practice Parameter: Prediction of outcome in comatose survivors Report of the Quality Standards Subcommittee of the American after cardiopulmonary resuscitation (an evidence-based review): Academy of Neurology. Neurology 2006;67:203–210.
10. Cronberg T et al. Neurological prognostication after cardiac arrest—Recommendations from the Swedish Resuscitation Council. Resuscitation 2013; 84: 867–872.
11. Sandroni C et al. Predictors of poor neurologic outcome in adult comatose survivors of cardiac arrest: A systematic review and meta-analysis.Part 2: Patients treated with therapeutic hypothermia. Resuscitation 2013; 84:1324 – 1338.
12. Bhattia M. Hypoxic Ischemic Injury in adult patients post cardiac arrest: A Pictorial essay. European Society of Radiology. www.my ESR.org.
13. Mylnash M et al. Temporal and Spatial Profile of Brain Diffusion-Weighted MRI After Cardiac Arrest. Stroke 2010;41:1665-1672.
14. Greer D et al. Serial MRI Changes in Comatose Cardiac Arrest Patients. Neurocrit Care 2011;14:61–67.
15. Choi SP et al. Diffusion-weighted magnetic resonance imaging for predicting the clinical outcome of comatose survivors after cardiac arrest: a cohort study. Critical Care 2010, 14:R17
16. Wijman CAC et al. Prognostic Value of Brain Diffusion Weighted Imaging After Cardiac Arrest. Ann Neurol 2009; 65(4): 394–402.
17. Greer DM, Rosenthal ES, Wu O. Neuroprognostication of hypoxic–ischaemic coma in the therapeutic hypothermia era. Nat. Rev. Neurol. advance online publication 11 March 2014; doi:10.1038/nrneurol.2014.36
18. Holzer M et al. Therapeutic hypothermia after cardiac arrest. Curr Opin Anaesthesiol. 2005; 18(2):163-168.
19. Bernard SA et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia.N Engl J Med. 2002; 346: 557-563.
20. Peberdy MA et al. Part 9: Post-Cardiac Arrest Care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122:S768-S786.
21. Nielsen N et al. Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest. N Engl J Med 2013;369:2197-206.
22. Kim F et al. Effect of Prehospital Induction of Mild Hypothermia on Survival and Neurological Status Among Adults With Cardiac Arrest: A Randomized Clinical Trial. JAMA. 2014;311(1):45-52.
23. Gebhardt K et al. Prevalence and effect of fever on outcome following resuscitation from cardiac arrest. Resuscitation 2013; 84: 1062– 1067.

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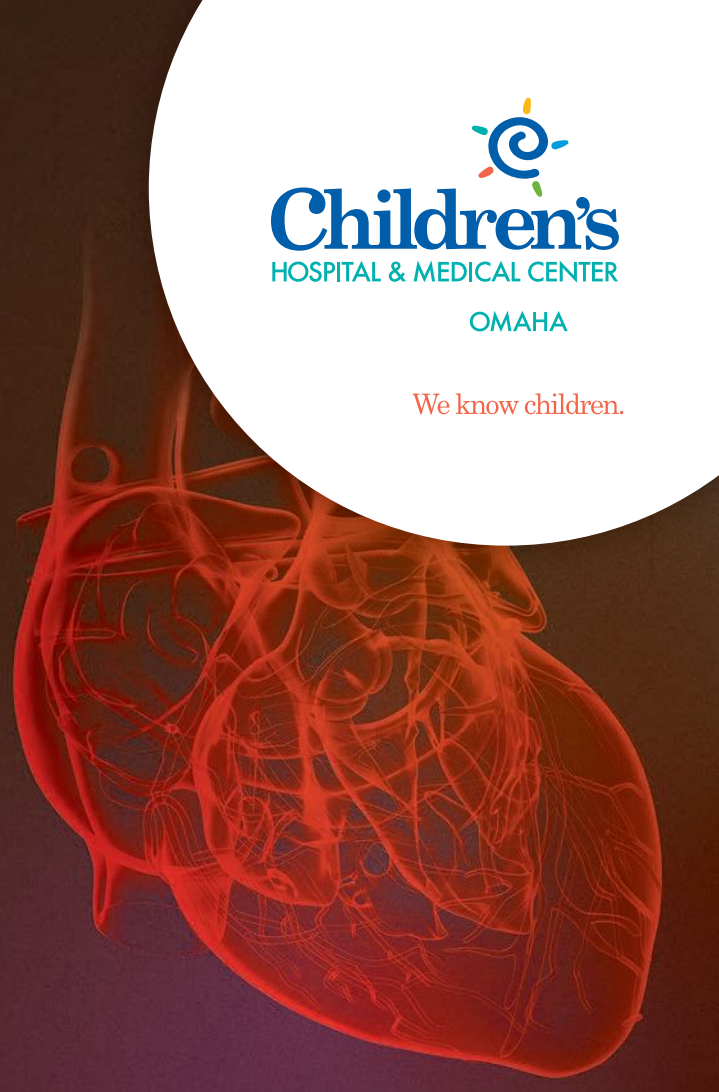
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Missouri State Medical Association Balance Sheet 2014

ASSETS		LIABILITIES AND NET ASSETS	
CURRENT ASSETS:		**CURRENT LIABILITIES:**	
Cash and Cash Equivalents	$ 724,583	Accounts Payable and Accrued Expenses	$ 20,985
Certificates of Deposit	104,226	Accrued Vacation	58,823
Short-Term Investments	8,989,279	Deferred Revenue	28,538
Interest Receivable	152	Deferred Dues	810,608
Accounts Receivable	10,312		
Prepaid Expenses	26,125	Total Current Liabilities	918,954
Total Current Assets	9,854,677		
FIXED ASSETS:		**NON-CURRENT LIABILITIES:**	
Land	83,000	Non-Qualified Deferred Compensation Agreement	358,210
Building and Improvements	605,077	Pension Benefit Liability	895,830
Furniture and Equipment	278,317		
Less: Accumulated Depreciation	(842,362)	Total Non-Current Liabilities	1,254,040
Total Net Fixed Assets	124,032	Total Liabilities	2,172,994
OTHER ASSETS:			
Note Receivable - MSMA Ins. Agency	209,610		
Investment in Subsidiary - MSMA Insurance Agency	(95,846)	**NET ASSETS:**	
Certificates of Deposit	104,932		
Long-Term Investments	2,559,453	Unrestricted	10,583,764
Total Other Assets	2,778,149	Total Net Assets	10,583,764
TOTAL ASSETS	$ 12,756,858	**TOTAL LIABILITIES AND NET ASSETS**	$12,756,758

Missouri State Medical Foundation 2014

ASSETS		LIABILITIES AND NET ASSETS	
CURRENT ASSETS:		**LIABILITIES:**	
Cash	$ 419,655	Funds Held for Others	$ 155,994
Investments	34,367		
Notes Receivable - Current	344,297	**TOTAL LIABILITIES**	155,994
Accrued Interest	157,580		
Total Current Assets	955,899		
EQUIPMENT:			
Office Equipment	1,091		
Software	10,692		
Less: Accumulated Depreciation	(10,837)		
Total Net Fixed Assets	946		
NON-CURRENT ASSETS:			
Investments	3,313,852		
Total Non-Current Investments	3,313,852		
Notes Receivable - Long Term	2,191,784	**NET ASSETS:**	
Allowance for Doubtful Accounts	(193,880)	Unrestricted	6,112,607
Notes Receivable - Long Term (Net)	1,997,904		
TOTAL ASSETS	$ 6,268,601	**TOTAL LIABILITIES AND NET ASSETS**	$ 6,268,601

Missouri Physicians Health Foundation 2014

ASSETS

CURRENT ASSETS:		
Cash and Cash Equivalents		
Cash - Checking	$	119,139
Cash - McIntosh Fund		34,657
Mutual Funds - McIntosh Fund		8,326
Certficates of Deposit		180,000
Accounts Receivable		172,944
Allowance for Doubtful Accounts		(13,450)
Accrued Interst		37
Total Current Assets		501,653
NON-CURRENT ASSETS:		
Investments - McIntosh Fund		16,272
Property and Equipment		
Office Furniture and Equipment		54,319
Less: Accumulated Depreciation		(34,625)
Net Property and Equipment		19,694
Total Non-Current Assets		35,966
TOTAL ASSETS	$	537,619

LIABILITIES AND NET ASSETS

CURRENT LIABILITIES:		
Accounts Payable	$	8,703
Total Current Liabilities		8,703
NET ASSETS:		
Unrestricted		528,916
Total Liabilities and Net Assets	$	537,619

MISSOURI PHYSICIANS HEALTH PROGRAM
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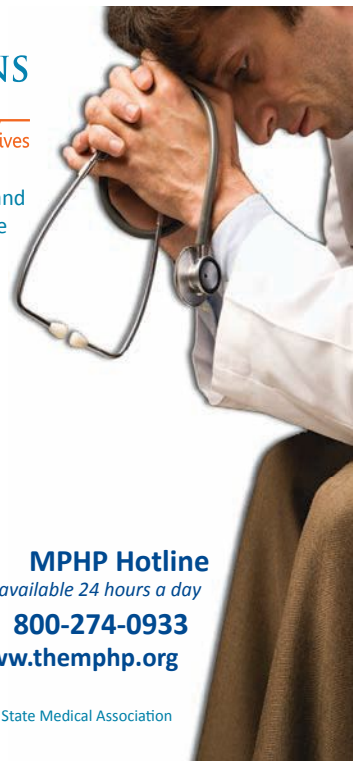
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- Physical Illness

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- Intervention
- Referral for Treatment
- Monitoring
- Advocacy



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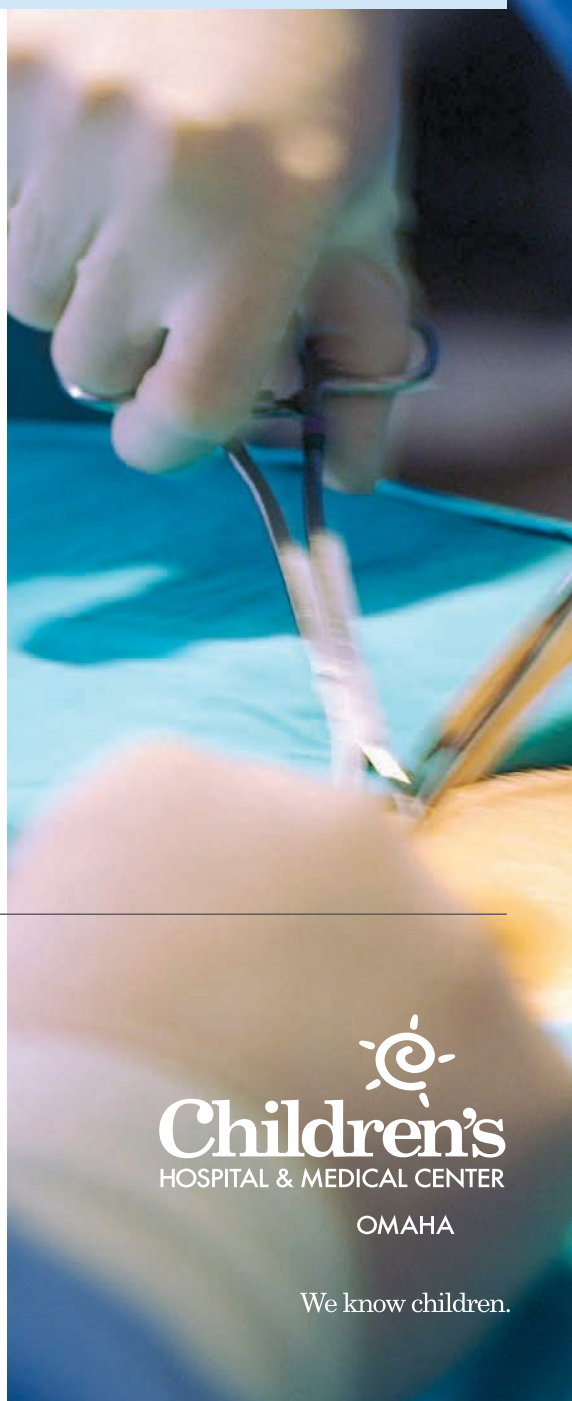
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